ORIGINAL ARTICLE

Reducing the Duration of Untreated First-Episode Psychosis

Effects on Clinical Presentation

Ingrid Melle, MD; Tor K. Larsen, MD; Ulrik Haahr, MD; Svein Friis, MD; Jan Olav Johannessen, MD; Stein Opjordsmoen, MD; Erik Simonsen, MD; Bjørn Rishovd Rund, PhD; Per Vaglum, MD; Thomas McGlashan, MD

Context: Most studies on first-episode psychosis show an association between a long duration of untreated psychosis (DUP) and poorer short-term outcome, but the mechanisms of this relationship are poorly understood.

Objective: To determine whether it is possible to reduce the DUP for first-episode patients in a defined health care area through the introduction of an early detection (ED) program, compared with parallel health care areas without an ED program (No-ED).

Setting and Patients: We included consecutive patients with a *DSM-IV* diagnosis of nonorganic, nonaffective psychosis coming to their first treatment in the study health care areas between January 1, 1997, and December 31, 2000. A total of 281 patients (76% of the total) gave informed consent.

Interventions: The ED and No-ED health care areas offered an equivalent assessment and treatment program for first-episode psychosis. The ED area also carried out an intensive ED program.

Results: The DUP was significantly shorter for the group of patients coming from the ED area, compared with patients from the No-ED areas (median, 5 weeks [range, 0-1196 weeks] vs 16 weeks [range, 0-966 weeks]). Clinical status measured by the Positive and Negative Syndrome Scale and the Global Assessment of Functioning Scale was significantly better for patients from the ED area at start of treatment and, with the exception of Positive and Negative Syndrome Scale positive subscale, at 3 months. Multiple linear regression analyses gave no indication that confounders were responsible for these differences.

Conclusions: It is possible to reduce the DUP through an ED program. The reduction in DUP is associated with better clinical status at baseline that is maintained after 3 months.

Arch Gen Psychiatry. 2004;61:143-150

From the Division of Psychiatry, Ullevaal University Hospital (Drs Melle, Friis, and Opjordsmoen), and the Institute of Psychology (Dr Rund) and Department of Behavioral Medicine (Dr Vaglum), University of Oslo, Oslo, Norway; Rogaland Psychiatric Hospital, Stavanger, Norway (Drs Larsen and Johannesen); Roskilde Psychiatric University Hospital Fjorden, Roskilde, Denmark (Drs Haahr and Simonsen); and Department of Psychiatry, Yale University School of Medicine, New Haven, Conn (Dr McGlashan).

THE PERIOD FROM THE onset of frank psychotic symptoms to the start of adequate treatment, the duration of untreated psychosis (DUP), varies considerably in patients with first-episode psychosis. Several studies have shown mean DUPs of 1 year or more.[1] Staying psychotic for months or years will obviously influence social, occupational, and interpersonal functioning. Most studies on first-episode psychosis show an association between a long DUP and poorer short-term outcome,[2-9] although some newer studies have questioned this finding.[10-13]

The mechanism(s) of this association is poorly understood,[14] and the correlational designs of all existing studies make it impossible to draw any conclusions regarding the direction of the relationship. A long DUP may only be an epiphenomenon or a marker of preexisting common factors that contribute to the poor outcome.[1,15] The increasing psychosocial problems and stigma associated with the untreated psychosis may also serve as an indirect link between the DUP and outcome. A long DUP might also contribute directly to a poorer prognosis through destructive biological and psychological processes.[1] If the DUP is causally related to outcome, it may be one of the few known prognostic factors in schizophrenia that theoretically can be modified by interventions. This has sparked a number of studies on the early phases in psychosis, including several on early treatment. No study has managed to reduce DUP significantly,[16] but some have been good models for the development of early-intervention programs.[6]

A study that aims at disentangling the effects of the DUP from confounding factors requires modifying the DUP differentially across patient groups. The most

promising way to change the timing of initial treatment in psychosis (ie, the DUP) is to introduce early detection (ED) programs into an intervention service. The ideal design to test whether there is a DUP effect would be a randomized controlled study assigning a group of first-episode patients to delayed treatment, but this has major ethical and practical difficulties. An alternative design is quasi-experimental, in which patients from one health care sector serving an entire population receive an experimental approach, in this case the ED program, and are compared with patients from another health care sector who do not receive the experimental approach. The control population can be parallel and consist of patients from a geographically distinct health care sector, or it can be historical and consist of patients from the experimental health care sector before the experimental approach was introduced.[17,18] A combination of the parallel and historical control designs in a single study would compensate for several of the methodological problems inherent in quasi-experimental designs. No previous studies have attempted to modify the DUP with a parallel control design.

The present report originates from the Early Treatment and Intervention in Psychosis Study, a prospective longitudinal study of first-onset psychosis from 4 Scandinavian health care sectors with equivalent first-episode treatment programs. Two of the sectors carried out an extensive ED program (ED area) and the other 2 did not (No-ED area) in a parallel control design.[19] A historical control comparison between patients treated within the first 2 years of the ED program and patients treated within the same health care sector 4 years previously showed that the DUP was significantly shorter for ED program patients.[20] This strongly indicated that the program had an ability to reduce the DUP,[20] most probably through a reduced threshold for detection. The historical control design cannot control for any cohort effects, such as the possibility of a general increase in attention to first-episode patients, or the local effects of introducing an ambitious research program. This effect is minimized by the parallel control design. The present report addresses the following 2 main hypotheses of the parallel control study: (1) Adding an ED program will reduce the DUP for ED-area patients compared with No-ED–area patients. (2) The decrease in the DUP is related to a reduced threshold for entering treatment and will be paralleled by less severe symptom levels at baseline, ie, from start of treatment throughout the acute phase, in ED-area patients compared with No-ED–area patients. The present study does not deal with the question of differences in treatment outcome during the first year of treatment; this issue will be addressed in later communications.

METHODS

SETTING

The study was carried out on the basis of the specialist psychiatric services in 4 Scandinavian health care sectors (the 2 health care sectors in Rogaland County, Norway, with a total of 370 000 inhabitants, and the Ullevaal health care sector, Oslo County, Norway, and the midsector, Roskilde County, Denmark, with a combined total of 295 000 inhabitants). The populations of the health care sectors lived mainly in urban and suburban areas (Stavanger, Norway, with suburban areas; parts of Oslo, Norway, with suburban areas; and parts of greater Copenhagen, Denmark, suburban areas), with 84% of the ED population living in urban areas vs 96% of the No-ED population ($P<.001$, Fisher exact test). There were no differences in age and sex distribution between the 2 areas and no differences in main income levels and unemployment rates in the total population. Patients from the ED area were less likely to be immigrants from a nonwestern country (4% vs 12%) and to have education after high school (21% vs 31%) ($P<.001$ for both, Fisher exact test).

In all 4 health care sectors, the treatment systems were catchment area based and publicly funded. The core basis of the psychiatric specialist treatment system was subsector catchment area–based outpatient units, with the addition of short-term, acute-care inpatient units and a restricted number of specialized long-term wards (4 different outpatient units and 2 hospitals in the ED area and 5 outpatient units and 2 hospitals in the No-ED area). The treatment system was based on referral from general practitioners, but the assessment and treatment of first-episode psychosis were considered a task for the specialized psychiatric treatment system, with immediate transfer of recognized cases as standard practice. There were no differences in the use of inpatient psychiatric services across the areas.

From January 1, 1997, the specialized psychiatric services of the 4 health care sectors established equivalent treatment programs for patients with first-episode psychosis. All first-episode patients from all 4 sectors underwent assessment by trained personnel as soon as possible after first contact with the specialized treatment system and were assigned to the treatment program without delay. The program consisted of defined treatment algorithms for antipsychotic medication (low-dose second-generation antipsychotic medication), individual psychosocial treatment (a trained psychiatric case worker offering weekly sessions), and psychoeducational family work (multifamily groups). The program was based on experiences from other first-episode treatment programs and the recommendations of the Schizophrenia Patients Outcomes Research Team.[21] In 2 of the health care sectors (Rogaland County), an extensive ED program was added that was not performed in the 2 other participating health care sectors (Oslo and Roskilde counties).

The ED program consisted of educational campaigns about psychotic symptoms and their treatment directed at the general population through newspaper, radio, and cinema advertisements and targeted information campaigns directed at general practitioners, social workers, and high school health care personnel. In addition, specialized low-threshold ED teams were established that could be reached by a single telephone call from potential patients, family, and friends, and the telephone number was made part of the information campaign. The organization of the ED program was based on the idea that treatment could be delayed owing to lack of awareness or to prejudices about psychotic disorders and their treatments in the psychotic person, in the person's network, and/or among first-line health care and social welfare personnel. Treatment could secondarily be delayed owing to difficulties in accessing psychiatric services. A tertiary delaying factor could be delays in identifying cases and/or resource limitations in assigning adequate treatment for first-episode patients at the level of the specialized psychiatric services. The ED program addressed the first 2 factors, with the intention of bringing first-episode patients earlier into the specialized psychiatric services assessment and treatment programs.[19] Establishing equivalent treat-

ment programs in the ED and No-ED areas would necessarily reduce delays on the level of the specialized services equally and thus carried the possibility of shortening the DUP in the No-ED area.

The study included all eligible patients meeting study criteria for the period of January 1, 1997, through December 31, 2000. Participants were followed up with personal interviews after 3 months and 1 and 2 years. Five-year follow-up has started, and 10-year follow-up is planned. Only data from baseline and the 3-month follow-up are parts of this report. The Regional Committee for Research Ethics approved the study. All patients entering the study gave written informed consent. Information regarding nonparticipants is based on data gathered anonymously for the purpose of bias testing.

SUBJECTS

Inclusion criteria consisted of living in the catchment area of 1 of the 4 health care areas (south and north sectors, Rogaland County [ED area], and Ullevaal sector, Oslo County, and midsector, Roskilde County [No-ED area]); age 18 to 65 years; meeting the *DSM-IV* criteria for schizophrenia, schizophreniform disorder, schizoaffective disorder (narrow schizophrenia spectrum disorders) or brief psychotic episode, delusional disorder, affective psychosis with mood-incongruent delusions, or psychotic disorder not otherwise specified; being actively psychotic, as measured by a Positive and Negative Syndrome Scale (PANSS)[22] score of 4 or more on at least 1 of positive subscale items 1 (delusions), 3 (hallucinatory behavior), 5 (grandiosity), or 6 (suspiciousness/persecution) or general subscale item 9 (unusual thought content); not receiving previous adequate treatment for psychosis (defined as antipsychotic medication of >3.5 haloperidol equivalents for >12 weeks or until remission of the psychotic symptoms); having no neurological or endocrine disorders with relationship to the psychosis; having no contraindications to antipsychotic medication; understanding and/or speaking a Scandinavian language; having an IQ score of above 70; and being willing and able to give informed consent.

The length of the study recruitment period (4 years) was based on a predefined estimate of the expected number of first-episode patients (15/100 000 per year, with 25% refusal of informed consent) and a power analysis of patients necessary to demonstrate clinically significant differences in outcome (a minimum of 100 patients in each of the 2 study groups).

A total of 874 persons with psychosislike symptoms seeking help from the specialized psychiatric services underwent screening by the study's assessment teams (131/100 000). As expected, because of campaigns that encouraged patients with possible psychotic symptoms to seek help, the number of persons undergoing screening was higher in the ED area. However, slightly fewer patients met the study criteria in the ED area (186 [50/100 000] vs 194 [66/100 000] from the No-ED area). The yearly incidence varied considerably from study year to study year across and within the 2 study areas (ED area highest, 17/100 000 [year 1]; ED area lowest, 10/100 000 [year 3]; No-ED area highest, 18/100 000 [year 4]; No-ED area lowest, 13/100 000 [year 1]). These incidence rates are within the expected range for schizophrenia and related disorders.[23] These observed differences in incidence may be due to natural variations in the base rate of relatively rare disorders. Alternatively, the trend toward a higher incidence in the No-ED areas may be accounted for by the higher degree of urbanization.[24]

Most patients (n=249 [66%]) meeting study criteria were hospitalized at first contact; there were no significant differences for the ED area (n=113 [61%]) vs the No-ED area (n=136 [70%]) ($P=.07$). Of the 380 eligible patients, 284 gave informed consent to enter, but 3 later withdrew this, leaving 281 patients aged 18 to 65 years who gave informed consent (141 in the ED area and 140 in the No-ED area [74% of all patients meeting study criteria]). As reported elsewhere,[25] patients who did not enter the study had significantly longer DUPs than patients who entered (median, 26 weeks [range, 0-936 weeks] and 10 weeks [range, 0-1196 weeks], respectively; $P<.001$, Mann-Whitney test). This finding was replicated in both areas when they were examined separately. We found no other significant differences between patients who did and did not enter the study.

MEASURES

Assessment teams in Rogaland County; the Ulleval sector, Oslo County; and the midsector, Roskilde County, consisted of clinically experienced and trained research personnel who performed all evaluations.[26] Difficult evaluations were discussed in regular team meetings to arrive at consensus ratings. The Structured Clinical Interview for the *DSM-IV* Axis I Disorders was used for diagnostic purposes.[27] Symptom levels were measured by means of the PANSS.[22] Global functioning was measured by the Global Assessment of Functioning Scale (GAF),[28] and the scores were split into symptom (GAFs) and function (GAFf) scores to improve psychometric properties. Misuse of alcohol and other drugs was measured by the Drake Scale.[29]

The DUP was measured as the time from onset of psychosis until the start of adequate treatment. Onset of psychosis was equated with the first appearance of positive psychotic symptoms, defined as the first week with symptoms corresponding to a PANSS score of 4 or more on positive subscale items 1, 3, 5, or 6 or on general subscale item 9. Adequate treatment was defined as the start of structured treatment with antipsychotic medications or the start of hospitalization in highly staffed psychiatric wards organized to manage disturbing psychotic symptoms. All available sources, including semistructured personal interviews with patients and relatives, were used to ascertain the length of this period. In the rare case of previous short, self-remitting psychotic episodes, the lengths of these episodes were added to the DUP.

Premorbid functioning was measured by the Premorbid Adjustment Scale (PAS).[30] The PAS subdivides the premorbid period into the following: childhood (age, <11 years), early adolescence (age, 12-15 years), late adolescence (age, 16-18 years), and adulthood (age, ≥19 years). The last year before onset of psychosis was not taken into account in the PAS evaluation to avoid interference by functional loss in the prodromal phase. Scores for adulthood are not reported here, since a relatively large group of patients had onset of psychosis before 18 years of age. The PAS results are most often reported as an index for each period. Recent reports indicate that the PAS covers the following 2 discrete areas of functioning: academic (school performance and school adaptation) and social (social accessibility/isolation, peer relationships, and capacity to establish sociosexual relationships [the last item was not rated for childhood]).[31] A division of the PAS into academic and social adaptation (mean scores across childhood and early and late adolescence) were used in the statistical analyses.

All raters were trained to reliability in the use of study instruments by rating previously prepared case notes and audiotapes/videotapes before entering the study assessment teams.[26] Reliability for the PANSS scores was measured by the rating of actual videotaped interviews of first-episode patients by all raters. Reliability for the diagnosis, GAF scores, and DUP was measured by the rating of actual case notes by masked raters (S.F. and S.O.) with long clinical research experience who had not participated directly in the patient assessments. Written vignettes were used because the multiple sources for the DUP ascertainment could not be covered fully by a taped interview. Reliability of measurements ranged from fair to very good (DUP,

Table 1. Patient Characteristics at Start of First Treatment

	No-ED Area (n = 140)	ED Area (n = 141)
Age, mean (SD), y*	31.1 (10.5)	26.2 (7.6)
Females, No. (%)	61 (44)	54 (38)
Scandinavian background, No. (%)†	123 (88)	137 (97)
Marital status, No. (%)†‡		
Single	88 (63)	103 (75)
Divorced, separated, or widowed	21 (15)	9 (7)
Married or cohabiting	31 (22)	20 (14)
Education§		
Length, mean (SD), y	12.0 (2.8)	12.1 (2.9)
High school examination, No. (%)	76 (55)	89 (68)
College examination, No. (%)	14 (10)	12 (9)
University examination, No. (%)	12 (9)	11 (8)
Diagnostic distribution, No. (%)		
Schizophrenia	41 (29)	39 (28)
Schizophreniform disorder	30 (21)	31 (22)
Schizoaffective disorder	12 (9)	22 (16)
Brief psychosis	6 (4)	13 (9)
Delusional disorder	9 (6)	6 (4)
Affective psychosis MID	21 (15)	19 (13)
Psychosis NOS	21 (15)	11 (8)
Narrow schizophrenia spectrum diagnosis, No. (%)†	83 (59)	92 (65)
Alcohol or other drug abuse, No. (%)†	38 (27)	54 (38)
Premorbid adjustment, mean (SD) score‖		
Academic, across childhood and early and late adolescence	2.1 (1.2)	2.1 (1.1)
Social, across childhood and early and late adolescence	1.3 (1.0)	1.3 (1.1)

Abbreviations: ED, early detection; MID, mood-incongruent delusions; NOS, not otherwise specified.
*$P<.01$, 2-tailed, unpaired t test.
†$P<.05$, Pearson χ^2/Fisher's exact test.
‡For the ED area, n = 138.
§For the no-ED area, n = 138; for the ED area, n = 131.
‖Measurement by the Premorbid Adjustment Scale.[30]

0.99; GAFs score, 0.63; GAFf score, 0.75; PANSS positive sum score, 0.88; PANSS negative sum score, 0.76; and PANSS general sum score, 0.56 [all intraclass correlations, 1.1]; for diagnostic categories, $\kappa = 0.76$). Measurements of the duration of the prodromal phase did not achieve sufficient reliability, and duration of untreated illness (including the prodrome) was taken out of the analyses.

STATISTICAL PROCEDURES

Analyses were performed with the statistical package SPSS (version 11.0; SPSS Inc, Chicago, Ill). The applied methods are reported for all group comparisons. All tests were 2-tailed. We used nonparametric tests for data without normal distribution. As noted in several other studies, the DUP does not have a normal distribution, whereas its natural logarithm does.[14] All analyses that included the DUP were nonparametric, with the exception of multiple linear regression analyses. In these, the DUP was transformed to its natural logarithm. The multiple linear regression analyses were performed for 2 explicit reasons. The first was to find a statistical model with a good prediction of the DUP. The second and most important reason was to investigate whether differences between ED and No-ED areas were due to confounding factors. The multiple linear regression analyses were thus performed hierarchically in several steps, with coming from the ED area entered last. First, all variables were entered that showed group differences between the ED and No-ED samples, that had a significant bivariate relationship to one of the dependent variables in the present study, or that demonstrated potential predictive power from previous studies. The variable of coming from the ED area was entered last. Because this procedure included a large number of variables, they were organized into different domains or blocks (eg, demographics, premorbid adjustment, diagnostics, personality factors and social integration, and ED status).

Most independent variables were known predictors of outcome in schizophrenia spectrum psychosis. The personality factors and social integration domain included variables that might be indicators of differences in help seeking or detection. The PANSS baseline items of lack of insight, poor volition, hostility, withdrawal, passive/apathetic withdrawal, and active social avoidance were chosen as signs of personality factors that could be related to reluctance to seek treatment. The variables of being married, frequency of family contact, frequency of family telephone contact, frequency of contact with others, frequency of telephone contact with others, working the last year before first treatment, and studying the last year before first treatment were chosen as signs of contacts with other persons who might intervene and aid help seeking.

In most cases, we found multiple intercorrelations among variables within a domain, and we chose a subset of variables to represent the domain on the basis of the strength of their relationship to the dependent variable and the goodness of fit of the model. This implies that slightly different subsets were possible, but changing the number and content of subsets did not have any influence on the main findings regarding differences between areas. Continuous independent variables were examined for nonlinear relationships with the dependent variable and transformed (to its natural logarithm or to a binary variable at identified thresholds) if necessary. The final model was examined for interaction effects and the effects of outliers and influential observations, including leverages. The strength of prediction of an individual domain or variable was based on a judgment of changes in R^2 and F for blocks and by the adjusted β coefficient for individual variables. Only the final models are presented herein.

The GAFs score was chosen as the dependent variable representing clinical status, owing to the high correlations with GAFf and PANSS scores measured simultaneously. There were no differences regarding main results if the GAFs score was exchanged with the PANSS positive or the PANSS total symptom scores in complementary analyses. These analyses are not presented herein.

RESULTS

The main differences between study participants from the ED and No-ED areas were that ED-area patients more often were Scandinavian, younger, and single and misused alcohol or other drugs (**Table 1**).

The DUP was short in both areas, with a combined median of 10 weeks (range, 0-1196 weeks; mean, 49.1 weeks; SD, 120.6 weeks). The DUP was significantly shorter in the ED area than in the No-ED area, with a median of 5 weeks (range, 0-1196 weeks) compared with 16 (range, 0-966 weeks) ($P = .003$, Mann-Whitney test). Symptom levels were high and global functioning was low at the start of first treatment, but patients from the ED area had significantly lower symptom levels and higher functioning across all measured clinical domains. These differences in clinical status were still present but less prominent after 3 months (**Table 2**).

There was a high level of intercorrelation between the DUP, ED area, and important demographic and clini-

cal variables (**Table 3**). All potentially significant variables were thus entered in a hierarchical stepwise multiple linear regression analysis with the DUP as the dependent variable (**Table 4**). Sex, premorbid adjustment (academic), a narrow schizophrenia spectrum diagnosis, PANSS active social avoidance, weekly telephone contacts with family, and working during the last year before contact each had a significant relationship to the DUP. The direction of relationships were that female sex, good premorbid functioning, the absence of a diagnosis of narrow schizophrenia spectrum disorder, less social avoidance, more family contacts, and working during the last year before treatment start were associated with a shorter DUP. Coming from the ED area retained its statistically significant influence (coming from ED area associated with shorter DUP) when entered on the last step of the analysis.

Concerning clinical status at the start of first treatment, only a narrow schizophrenia spectrum diagnosis, the DUP, and coming from the ED area had a significant influence so that the absence of a narrow schizophrenia spectrum diagnosis, a longer DUP, and coming from the ED area were associated with a better clinical status at start of treatment (**Table 5**). Coming from the ED area was the strongest predictor, even when entered at the last step.

At 3 months, premorbid functioning (social), working the previous year, and DUP emerged as statistically significant predictors (**Table 6**). The direction of the association was that better premorbid adjustment, employment, and a shorter DUP were associated with higher 3-month GAFs scores. Coming from the ED area retained its significant relationship with a better clinical status, even with correction for baseline differences in the GAFs score and when entered at the last step of the analysis.

COMMENT

The results of the present study demonstrate that it is possible to influence the DUP by means of a comprehensive ED program. The study design ensures that the DUP differences are not caused by general or specific cohort effects such as changes in awareness of psychotic disorder or effects on recruitment through better assessment and treatment programs in the psychiatric services. These factors are probably important, as the median DUP observed in this study's No-ED group is among the shorter DUPs registered.[14]

There are some group differences between ED and No-ED patients. The larger number of patients with a non-Scandinavian origin in the No-ED group is probably based on real population differences. The difference in age at first contact and the associated differences in marital status and misuse of alcohol and other drugs (single status and misuse are significantly more common in younger patients) are more difficult to explain, since there are no observed differences in the age distribution of catchment area populations. The median age at first contact is within the expected range insofar as several large studies report these medians in the first half of the fourth decade of life,[32,33] even if medians in the middle of the third decade are more common epidemiologically. As first-episode schizophrenia spectrum psychoses are relatively rare, these differences could reflect random variations in small annual samples. This could pose a problem if there were interactions between age at onset and the effect of the ED program, but to our knowledge there are no studies that indicate differences in help-seeking behavior between people in their second and third decades of life. The results of this study indicate that demo-

Table 2. Clinical Status at Start of First Treatment and 3-Month Follow-up

Clinical Status	No-ED Area (n = 140)	ED Area (n = 141)
At start of treatment, mean (SD) score		
PANSS positive symptoms*	21.7 (5.6)	18.8 (4.9)
PANSS negative symptoms*	16.6 (7.5)	13.9 (5.7)
PANSS general symptoms*	38.4 (10.4)	31.6 (7.6)
GAF symptoms*	27.1 (6.9)	31.0 (6.4)
GAF function*	28.8 (9.7)	33.6 (10.0)
At 3-month follow-up, mean (SD) score		
PANSS positive symptoms	12.4 (4.4)	11.7 (4.9)
PANSS negative symptoms†	14.3 (6.7)	12.8 (5.6)
PANSS general symptoms*	28.1 (9.5)	25.1 (7.5)
GAF symptoms*	45.0 (11.3)	50.4 (14.0)
GAF function*	45.1 (12.1)	51.2 (12.7)

Abbreviations: ED, early detection; GAF, Global Assessment of Functioning Scale[28]; PANSS, Positive and Negative Syndrome Scale.[22]
*$P<.01$, *t* test.
†$P<.05$, *t* test.

Table 3. The Bivariate Relationships Between ED Area, DUP, and Significant Demographic and Clinical Variables*

Variable	ED Area	DUP
Age	–0.26*	–0.01
Sex	–0.05	–0.17†
Scandinavian background	–0.20†	–0.01
Marital status	–0.15‡	–0.12‡
Length of education	0.07	–0.17†
Narrow schizophrenia spectrum diagnosis	0.06	0.32†
Alcohol and/or other drug misuse	0.12‡	–0.04
Conduct disorder	–0.04	0.15‡
Premorbid adjustment score, mean		
Premorbid school adaptation	0.01	0.24†
Premorbid social adaptation	–0.64	0.16†
Clinical status at start of first treatment		
PANSS positive symptoms	–0.25†	–0.04
PANSS negative symptoms	–0.18†	0.12‡
PANSS general symptoms	–0.34†	0.08
GAF symptoms	0.27†	0.18†
GAF function	0.26†	0.15‡
Clinical status at 3-month follow-up		
PANSS positive symptoms	–0.13‡	0.40†
PANSS negative symptoms	–0.12	0.22†
PANSS general symptoms	–0.16†	0.22†
GAF symptoms	0.18†	–0.41†
GAF function	0.25†	–0.30†

Abbreviations: DUP, duration of untreated psychosis; ED, early detection; GAF, Global Assessment of Functioning Scale[28]; PANSS, Positive and Negative Syndrome Scale.[22]
*Data are expressed as Spearman correlations (ρ).
†$P<.01$, nonparametric correlations.
‡$P<.05$, nonparametric correlations.

Table 4. Multiple Linear Regression Analysis of the Effect of Independent Variables on the DUP*†

Block No., Variable	Model Summary for Each Step		Contribution of Separate Variables for Last Step		
	R^2 Change	F Change	β (SD)	*t*	*P* Value (95% CI)
Constant			1.33 (1.22)	1.09	.28 (–1.07 to 3.72)
1					
Female	0.03	2.69	–0.46 (0.20)	–2.40	.02 (–.84 to –.07)
Age in years†			0.33 (0.36)	0.81	.42 (–.38 to .92)
Scandinavian origin			0.33 (0.36)	0.90	.37 (–.39 to 1.04)
2					
Premorbid academic adaptation	0.05	15.20	0.19 (0.08)	2.24	.03 (.02 to .35)
3					
Narrow schizophrenia spectrum	0.09	13.24	0.92 (0.18)	4.78	<.001 (.54 to 1.30)
Alcohol or other drug misuse			–0.23 (0.21)	–1.12	.26 (–.64 to .18)
4					
PANSS active social avoidance‡	0.06	5.99	0.48 (0.18)	2.61	.01 (.12 to .84)
Weekly telephone calls with family			–0.52 (0.20)	–2.57	.01 (–.93 to –.12)
Working year before contact			–0.43 (0.19)	–2.27	.02 (–.81 to –.06)
5					
Coming from ED area	0.03	9.60	–0.59 (0.19)	–3.09	.002 (–.99 to –.22)

Abbreviations: CI, confidence interval; DUP, duration of untreated psychosis; ED, early detection; PANSS, Positive and Negative Syndrome Scale.[22]
*Final model, $R^2 = 0.253$; model F = 8.552; $P<.001$.
†Transformed to its natural logarithm.
‡Transformed to a binary variable (score of ≤2 = 0; score of ≥3 = 1).

Table 5. Multiple Linear Regression Analysis of the Effect of Independent Variables on Clinical Status (GAF Symptoms) at Start of First Treatment*

Block No., Variable	Block Model Summary for Each Step		Contribution of Separate Variables for Last Step		
	R^2 Change	F Change	β (SD)	*t*	*P* Value (95% CI)
Constant	. . .	. . .	30.28 (5.34)	5.67	<.001 (19.72 to 40.67)
1					
Female			–0.47 (0.86)	–0.55	.58 (–2.16 to 1.22)
Age in years†	0.04	3.26	–1.97 (1.45)	–1.36	.18 (–4.83 to .89)
Scandinavian origin			2.44 (1.60)	1.50	.34 (–.74 to 5.56)
2					
Premorbid social adaptation	0.001	0.17	0.09 (0.40)	0.23	.82 (–.69 to .88)
3					
Narrow schizophrenia spectrum	0.02	2.49	–3.27 (0.88)	–3.70	<.001 (–5.01 to –1.53)
Alcohol or other drug misuse		0.98	–0.49 (0.92)	–0.53	.60 (–2.30 to 1.33)
4					
Weekly telephone calls with family	0.01	0.89	–0.43 (0.91)	–0.47	.64 (–2.22 to 1.36)
Working year before contact			0.83 (0.84)	0.99	.32 (–.82 to 2.46)
5					
DUP†	0.04	11.64	1.21 (0.27)	4.46	<.001 (.67 to 1.74)
6					
Coming from ED area	0.08	24.32	4.17 (0.85)	4.93	<.001 (2.51 to 5.84)

Abbreviations: CI, confidence interval; DUP, duration of untreated psychosis; ED, early detection; GAF, Global Assessment of Functioning Scale.[28]
*Final model, $R^2 = 0.18$; model F = 5.613; $P<.001$.
†Transformed to its natural logarithm.

graphic, premorbid, diagnostic, and personality factors have separate influences on the DUP, in addition to the ED program, but that the effect of the ED program is strongest. We believe that it is reasonable to conclude that the observed shortening of the DUP does not appear to be based on confounding factors such as group differences in demographic or clinical characteristics between recruited patients.

The relationships among patient characteristics, the DUP, an ED program, and clinical status in the baseline period (at start of first treatment and at 3-month follow-up) are complex and warrant some comments. The DUP still varies considerably within both areas, as several ED patients have long DUPs and most No-ED patients have short DUPs. As differences in DUP are not fully explained by the ED program, we may still expect to find significant relationships between the DUP and clinical status. At 3 months, we find a strong negative correlation between the DUP and level of improvement, in line with most studies in this area. Few studies, however, have

Table 6. Multiple Linear Regression Analysis of the Effect of Independent Variables on Clinical Status (GAF Symptoms) at 3-Month Follow-up*

	Block Model Summary for Each Step		Contribution of Separate Variables for Last Step		
Block No., Variable	R^2 Change	F Change	β (SD)	*t*	*P* Value (95% CI)
Constant	. . .	. . .	29.80 (10.44)	2.86	.005 (13.14 to 54.53)
1					
GAFs at start of treatment	0.00	0.003	0.03 (0.12)	0.25	.80 (–.20 to .26)
2					
Female	0.05	3.99	2.48 (1.59)	1.56	.12 (–.65 to 5.61)
Age in years†			4.97 (2.69)	1.85	.07 (–0.33 to 10.28)
Scandinavian origin			2.64 (2.97)	0.89	.38 (–1.82 to 9.90)
3					
Premorbid social adaptation	0.04	11.58	–1.67 (0.74)	–2.26	.02 (–3.12 to –.22)
4					
Narrow schizophrenia spectrum	0.02	2.12	–0.90 (1.67)	0.54	0.59 (–4.20 to 2.39)
Alcohol or other drug misuse			–0.62 (1.70)	–0.37	0.71 (–3.97 to 2.73)
5					
Weekly telephone calls with family	0.38	5.34	0.71 (1.68)	0.42	.67 (–2.60 to 4.02)
Working year before contact			4.01 (1.55)	2.59	.01 (.96 to 7.07)
6					
DUP†	0.08	25.51	–2.18 (0.52)	–4.10	<.001 (–3.20 to –1.16)
7					
Coming from ED area	0.03	8.51	4.77 (1.64)	2.92	.004 (1.55 to 8.00)

Abbreviations: CI, confidence interval; DUP, duration of untreated psychosis; ED, early detection; GAF, Global Assessment of Functioning Scale.[28]
*Final model, $R^2 = 0.25$; model F = 7.32; $P<.001$.
†Transformed to its natural logarithm.

examined the relationship between the DUP and symptoms at start of treatment, and most of these have not found any significant associations.[34,35] The only exception found a weak positive correlation between the DUP and symptom levels,[36] whereas the present study found a weak negative correlation. A negative correlation makes some sense from a clinical point of view, as it is reasonable to expect that very symptomatic patients enter treatment more rapidly, but it is too early to draw any conclusions regarding the relationship between the DUP and symptoms at start of first treatment.

The study's main finding is that with all other factors being equal, early detection efforts will bring people into treatment at lower symptom levels. It is thus reasonable to conclude that the threshold for seeking and/or entering treatment appears to have been lowered by the ED program, and that the differences in clinical states are not based on confounding factors and appear to be stable through the initial phase of treatment. Whether the main pivotal point for the lowered threshold resides with the patient, the family, the patient's network, or the general practitioner warrants further study.

From a methodological point of view, a randomized controlled trial would be a stronger design than the present quasi-experiment. A randomized controlled trial was discussed in the planning process of this study, but the idea was discarded for several reasons. It is not possible to randomize the effect of a mass media educational campaign or the detection of first-episode patients by professionals. Randomization would have to take place after detection, by experimentally delaying the start of adequate treatment. It was judged to be unethical to address the public with information on probable harmful effects of a long-standing psychosis, followed by a request to submit to the risk of delayed treatment. Most patients would in this situation probably refuse to give informed consent to enter the randomized controlled trial.

The strength of the study is its basis in a catchment area treatment system that constitutes all possible treatment services for first-episode patients from that particular geographical area. The study sample is thus an epidemiological sample. The publicly paid treatment system ensures that there are few major differences in quality of care offered in the participating sectors. This is strengthened by the introduction of a common treatment program for first-episode patients. If follow-up data confirm that the 2 patient groups have received equivalent treatments, the basis is provided for a study of the relationship between the DUP and outcome where it is possible to disentangle the effects of DUP from potential confounding factors for the first time.

Submitted for publication December 9, 2000; final revision received May 4, 2003; accepted August 26, 2003.

This study was supported by grant 133897/320 from the Norwegian National Research Council (Oslo); the Norwegian Department of Health and Social Affairs (Oslo); grant 1997/41 from the National Council for Mental Health/Health and Rehabilitation (Oslo); Rogaland County (Stavanger, Norway) and Oslo County (Oslo) (Drs Vaglum, Johannessen, Friis, Larsen, Melle, and Opjordsmoen); the Theodore and Vada Stanley Foundation (Bethesda, Md); the Regional Health Research Foundation for Eastern Region (Hilleroed, Denmark); Roskilde County (Roskilde, Denmark); Helsefonden Lundbeck Pharma (Hellerup, Denmark); Eli Lilly Denmark (Lyngby); Janssen-Cilag Pharmaceuticals Denmark (Birkeroed) (Drs Simonsen and Haahr); a National Alliance for Research on Schizophre-

nia and Depression (NARSAD) Distinguished Investigator Award (Great Neck, NY); grant MH-01654 from the National Institute of Mental Health (Rockville, Md) (Dr McGlashan); and a Young Investigator Award from NARSAD (Dr Larsen).

This study is part of the Early Treatment and Intervention in Psychosis Study project with the following research group: Thomas McGlashan, MD (principal investigator); Per Vaglum, MD (principal investigator); Svein Friis, MD; Ulrik Haahr, MD; Jan Olav Johannessen, MD; Tor K. Larsen, MD; Ingrid Melle, MD; Stein Opjordsmoen, MD; Bjørn Rishovd Rund, PhD; and Erik Simonsen, MD.

Corresponding author and reprints: Ingrid Melle, MD, Division of Psychiatry, Ullevaal University Hospital, Kirkeveien 166, N-0407 Oslo, Norway (e-mail: Ingrid.melle @psykiatri.uio.no).

REFERENCES

1. McGlashan TH. Duration of untreated psychosis in first-episode schizophrenia: marker or determinant of course [published correction appears in *Biol Psychiatry.* 2000;47:473]? *Biol Psychiatry.* 1999;46:899-907.
2. Johnstone EC, Crow TJ, Johnson AL, MacMillan JF. The Northwick Park Study of first episodes of schizophrenia, I: presentation of the illness and problems relating to admission. *Br J Psychiatry.* 1986;148:115-120.
3. Loebel AD, Lieberman JA, Alvir JM, Mayerhoff DI, Geisler SH, Szymanski SR. Duration of psychosis and outcome in first-episode schizophrenia. *Am J Psychiatry.* 1992;149:1183-1188.
4. Szymanski S, Lieberman JA, Alvir JM, Mayerhoff D, Loebel A, Geisler S, Chakos M, Koreen A, Jody D, Kane J. Gender differences in onset of illness, treatment response, course, and biologic indexes in first-episode schizophrenic patients. *Am J Psychiatry.* 1995;152:698-703.
5. Waddington JL, Youssef HA, Kinsella A. Sequential cross-sectional and 10-year prospective study of severe negative symptoms in relation to duration of initially untreated psychosis in chronic schizophrenia. *Psychol Med.* 1995;25:849-857.
6. McGorry PD, Edwards J, Mihalopoulos C, Harrigan SM, Jackson HJ. EPPIC: an evolving system of early detection and optimal management. *Schizophr Bull.* 1996; 22:305-326.
7. Haas GL, Garratt LS, Sweeney JA. Delay to first antipsychotic medication in schizophrenia: impact on symptomatology and clinical course of illness. *J Psychiatr Res.* 1998;32:151-159.
8. Altamura AC, Bassetti R, Sassella F, Salvadori D, Mundo E. Duration of untreated psychosis as a predictor of outcome in first-episode schizophrenia: a retrospective study. *Schizophr Res.* 2001;52:29-36.
9. Black K, Peters L, Rui Q, Milliken H, Whitehorn D, Kopala LC. Duration of untreated psychosis predicts treatment outcome in an early psychosis program. *Schizophr Res.* 2001;47:215-222.
10. Linszen D, Lenior M, de Haan L, Dingemans P, Gersons B. Early intervention, untreated psychosis and the course of early schizophrenia. *Br J Psychiatry Suppl.* 1998;172:84-89.
11. Ho BC, Andreasen NC, Flaum M, Nopoulos P, Miller D. Untreated initial psychosis: its relation to quality of life and symptom remission in first-episode schizophrenia. *Am J Psychiatry.* 2000;157:808-815.
12. Craig TJ, Bromet EJ, Fennig S, Tanenberg-Karant M, Lavelle J, Galambos N. Is there an association between duration of untreated psychosis and 24-month clinical outcome in a first-admission series? *Am J Psychiatry.* 2000;157:60-66.
13. Barnes TR, Hutton SB, Chapman MJ, Mutsatsa S, Puri BK, Joyce EM. West London first-episode study of schizophrenia: clinical correlates of duration of untreated psychosis. *Br J Psychiatry.* 2000;177:207-211.
14. Norman RM, Malla AK. Duration of untreated psychosis: a critical examination of the concept and its importance. *Psychol Med.* 2001;31:381-400.
15. Verdoux H, Liraud F, Bergey C, Assens F, Abalan F, van Os J. Is the association between duration of untreated psychosis and outcome confounded? a two year follow-up study of first-admitted patients. *Schizophr Res.* 2001;49:231-241.
16. Larsen TK, Friis S, Haahr U, Joa I, Johannessen JO, Melle I, Opjordsmoen S, Simonsen E, Vaglum P. Early detection and intervention in first-episode schizophrenia: a critical review. *Acta Psychiatr Scand.* 2001;103:323-334.
17. McGlashan TH. Early detection and intervention in schizophrenia: research. *Schizophr Bull.* 1996;22:327-345.
18. Malla AK, Norman RM, Voruganti LP. Improving outcome in schizophrenia: the case for early intervention. *CMAJ.* 1999;160:843-846.
19. Johannessen JO, McGlashan TH, Larsen TK, Horneland M, Joa I, Mardal S, Kvebaek R, Friis S, Melle I, Opjordsmoen S, Simonsen E, Ulrik H, Vaglum P. Early detection strategies for untreated first-episode psychosis. *Schizophr Res.* 2001; 51:39-46.
20. Larsen TK, McGlashan TH, Johannessen JO, Friis S, Guldberg C, Haahr U, Horneland M, Melle I, Moe LC, Opjordsmoen S, Simonsen E, Vaglum P. Shortened duration of untreated first episode of psychosis: changes in patient characteristics at treatment. *Am J Psychiatry.* 2001;158:1917-1919.
21. Lehman A, Carpenter WT, Goldman HH, Steinwachs DM. Treatment outcomes in schizophrenia: implications for practice, policy and research. *Schizophr Bull.* 1995;21:669-675.
22. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull.* 1987;13:261-267.
23. Goldner EM, Hsu L, Waraich P, Somers JM. Prevalence and incidence studies of schizophrenic disorders: a systematic review of the literature. *Can J Psychiatry.* 2002;47:833-843.
24. Eaton WW, Mortensen PB, Frydenberg M. Obstetric factors, urbanization and psychosis. *Schizophr Res.* 2000;43:117-123.
25. Friis S, Melle I, Larsen TK, Johannessen JO, Simonsen E, Opjordsmoen S, Vaglum P, McGlashan TH. Does duration of untreated psychosis (DUP) bias schizophrenia study samples [abstract]? *Schizophr Res.* 2001;49:260.
26. Friis S, Larsen TK, Melle I, Opjordsmoen S, Johannessen JO, Haahr U, Simonsen E, Rund BR, Vaglum P, McGlashan T. Methodological pitfalls in early detection studies: the NAPE Lecture 2002: Nordic Association for Psychiatric Epidemiology. *Acta Psychiatr Scand.* 2003;107:3-9.
27. First MB, Spitzer RL, Gibbon M, Williams JBW. *Structured Clinical Interview for DSM-IV Axis I Disorders–Patient Edition (SCID I/P, Version 2.0).* New York: New York State Psychiatric Institute, Biometrics Research Dept; 1995.
28. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition.* Washington, DC: American Psychiatric Association; 1987.
29. Drake RE, Osher FC, Noordsy DL, Hurlbut SC, Teague GB, Beaudett MS. Diagnosis of alcohol use disorders in schizophrenia. *Schizophr Bull.* 1990;16:57-67.
30. Cannon-Spoor HE, Potkin SG, Wyatt RJ. Measurement of premorbid adjustment in chronic schizophrenia. *Schizophr Bull.* 1982;8:470-484.
31. Silverstein ML, Mavrolefteros G, Close D. Premorbid adjustment and neuropsychological performance in schizophrenia. *Schizophr Bull.* 2002;28:157-165.
32. Tohen M, Stoll AL, Strakowski SM, Faedda GL, Mayer PV, Goodwin DC, Kolbrener ML, Madigan AM. The McLean First-Episode Psychosis Project: six-month recovery and recurrence outcome. *Schizophr Bull.* 1992;18:273-282.
33. Hafner H, Maurer K, Loffler W, Riecher-Rossler A. The influence of age and sex on the onset and early course of schizophrenia. *Br J Psychiatry.* 1993;162:80-86.
34. Black K, Peters L, Rui Q, Milliken H, Whitehorn D, Kopala LC. Duration of untreated psychosis predicts treatment outcome in an early psychosis program. *Schizophr Res.* 2001;47:215-222.
35. Browne S, Clarke M, Gervin M, Waddington JL, Larkin C, O'Callaghan E. Determinants of quality of life at first presentation with schizophrenia. *Br J Psychiatry.* 2000;176:173-176.
36. Drake RJ, Haley CJ, Akhtar S, Lewis SW. Causes and consequences of duration of untreated psychosis in schizophrenia. *Br J Psychiatry.* 2000;177:511-515.