ORIGINAL ARTICLE

Prevention of Negative Symptom Psychopathologies in First-Episode Schizophrenia

Two-Year Effects of Reducing the Duration of Untreated Psychosis

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Background: The duration of untreated psychosis (DUP)—the time from onset of psychotic symptoms to the start of adequate treatment—is consistently correlated with better course and outcome, but the mechanisms are poorly understood.

Objective: To report the effects of reducing DUP on 2-year course and outcome.

Design: A total of 281 patients with a *DSM-IV* diagnosis of nonorganic, nonaffective psychosis coming to their first treatment during 4 consecutive years were recruited, of which 231 participated in the 2-year follow-up. A comprehensive early detection (ED) system, based on public information campaigns and low-threshold-psychosis–detecting teams, was introduced in 1 health care area (ED area), but not in a comparable area (no-ED area). Both areas ran equivalent 2-year treatment programs.

Results: First-episode patients from the ED area had a significantly lower DUP, better clinical status, and milder negative symptoms at the start of treatment. There were no differences in treatment received for the first 2 years between the groups. The difference in negative symptoms was maintained at the 1-year follow-up. There was a statistically significant difference in the Positive and Negative Syndrome Scale negative component, cognitive component, and depressive component in favor of the ED group at the 2-year follow-up. Multiple linear regression analyses gave no indication that these differences were due to confounders.

Conclusion: Reducing the DUP has effects on the course of symptoms and functioning, including negative symptoms, suggesting secondary prevention of the negative psychopathologies in first-episode schizophrenia.

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DESPITE MODERN TREATments, schizophrenia is one of the most incapacitating and costly mental disorders. Course and outcome are heterogeneous; several predictors have been identified, but few are malleable to interventions. One exception is the duration of untreated psychosis (DUP)—the time from onset of psychotic symptoms to the start of adequate treatment. A shorter DUP has consistently been shown to correlate with better course and outcome across symptom domains.[1,2]

While the significance of this correlation is clear, the underlying direction is not.[3] We do not know whether untreated psychosis generates poorer prognosis, or whether persons who are at risk for a poor prognosis enter treatment via pathways generating longer DUPs. The only way of disentangling the causal direction is to manipulate the DUP and then measure the outcome. Delaying treatment through a randomized clinical trial would be unethical in acute first-episode psychosis. The optimal and ethical way to isolate the influence of DUP is through a "service-systems" design intended to reduce DUP in 1 health care area (experimental) but not in another (control), and track the outcomes of the shorter vs longer DUP groups. The control population can be "parallel in time" and consist of patients from a geographically distinct area who are assessed and treated in the same time period as the experimental area patients. The control population could also be "historical" and consist of patients from the experimental area at another point in time. A combination of both approaches in 1 study would compensate for methodological problems inherent in the design, such as unknown but systematic sample differences between contrasting populations, or cohort effects.[4]

The current study uses the "parallel control" approach to study the effects of reducing DUP. A comprehensive early detection (ED) system based on low-threshold psychosis–detecting teams and public information campaigns was created in 1 area (ED area),[5] and first-episode patients from this area were compared with first-episode patients from a parallel area without early detection (no-ED area). The chosen areas had nearly indistinguishable sociodemographic

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and treatment service characteristics. Both ran equivalent 2-year comprehensive first-episode treatment programs consisting of antipsychotic psychopharmacology, assertively oriented individual outpatient treatment, and psychoeducational family work. This parallel control study was combined with 2 historical control studies of first-episode patients from the ED area, the first being from before the introduction of the ED program, and the second from after its completion.[6,7]

The study was designed to test the following core hypotheses: (1) ED programs can reduce DUP, (2) reducing DUP will be related to a comparative reduction in positive and negative symptoms displayed at the beginning of the first treatment, and (3) the initial ED area vs no-ED area differences in these parameters will be maintained for the first 2 years of standardized treatment, indicating ED-related secondary prevention. We have previously shown that first-episode patients from the ED area indeed had a significantly lower DUP, significantly lower symptom levels (including negative symptoms), and lower rates of severe suicidal behaviors at first treatment contact, compared with patients from the no-ED area.[8-10] Patients from both areas entered the 2-year integrated treatment program consisting of psychopharmacological treatment, assertively oriented outpatient treatment, and psychoeducational family work. The 1-year follow-up showed no differences in any outcome measures related to positive symptoms, but found a consistent and statistically significant difference in both negative symptoms and social functioning in favor of the ED group, indicating that the difference in negative symptoms had clinical significance.[7,11]

Reviews suggest a stronger relationship between DUP and negative symptoms than between DUP and positive symptoms.[2] The literature also suggests that longer durations of untreated illness may reduce the treatment responsiveness of negative symptoms.[2] Two types of negative symptoms have been described for schizophrenia: primary negative symptoms that are central to the core neurobiological deficits of the disorder, and secondary negative symptoms that are generated in response to positive symptoms (eg, social isolation secondary to paranoia) or that emerge in the context of unremittingly demoralizing realities (eg, institutionalization).[12,13] Persistent negative symptoms are an unmet therapeutic need.[14] There is an apparent effect of antipsychotic medication on negative symptoms secondary to positive symptom amelioration, but the effect on primary negative symptoms is minor.[13] Given the limited effects of current treatments, the potential effect of reducing DUP on negative symptoms is of considerable clinical interest, and may also expand our knowledge of the mechanisms involved in the development of stable negative symptoms and chronicity.[15]

The main aim of this article is thus to investigate whether the initial differences in negative symptoms found at the start of treatment in the ED area are maintained for the entire 2 years of standardized active treatment.

METHODS

SETTING

The study was carried out on the basis of the specialized psychiatric services in 4 Scandinavian health care sectors. The ED area consisted of: (1) the North Rogaland and (2) South Rogaland health care sectors in Rogaland County, Norway, with a combined total population for the 2 sectors of 370 000 inhabitants. The no-ED area consisted of (3) the Ullevaal health care sector of Oslo County, Norway, and (4) the mid-sector, Roskilde County, Denmark, with a combined total population for the 2 sectors of 295 000 inhabitants. The populations of all 4 health care sectors lived mainly in urban and suburban areas (84% of the ED population were 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 mean income levels and unemployment rates. Patients from the ED area were less likely to be immigrants from a non-Western country (4% vs 12%) and less likely to have postsecondary education (21% vs 31%) ($P < .001$, Fisher exact test for both).

In all sectors the treatment systems were catchment area–based and publicly funded, with no differences in utilization of inpatient psychiatric services. Treatment of first-episode patients was considered a task for the specialized psychiatric treatment system, with rapid transfer of recognized cases from primary care. From January 1, 1997, to December 31, 2000, all first-episode patients in all sectors of both areas were assessed by trained personnel at first contact and assigned to the first-episode treatment programs without delay. The programs adopted a standard treatment algorithm for antipsychotic medication, individual psychosocial treatment, and psychoeducational multifamily groups. In the ED area, an extensive ED program was added that was not carried out in the no-ED area. The ED program consisted of educational campaigns about psychotic symptoms and their treatment directed at the general population through newspaper advertisements, and targeted information campaigns directed at schools and general practitioners. Specialized low-threshold early detection teams were established that could be reached by a single phone call from potential patients, families, or friends from their social networks.

PARTICIPANTS

The study included all eligible patients meeting study criteria for the period of January 1, 1997, to December 31, 2000. Eligibility criteria were: living in one of the participating health care areas, being 18 to 65 years old, meeting *DSM-IV* criteria for schizophrenia, schizophreniform disorder, schizoaffective disorder (narrow schizophrenia spectrum disorders) or a brief psychotic episode, delusional disorder, affective psychosis with mood-incongruent delusions, psychotic disorder not otherwise specified, or active psychosis (Positive and Negative Syndrome Scale [PANSS][16] score of ≥ 4 on positive scale items 1, delusions; 3, hallucinatory behavior; 5, grandiosity; 6, suspiciousness/ persecution; or general scale item 9, unusual thought content), not previously adequately treated for psychosis (no antipsychotic medication greater than 3.5 haloperidol equivalents for more than 12 weeks, or remission if earlier), no neurological or endocrine disorders, no contraindications to treatment, speaks a Scandinavian language, has an IQ higher than 70, and able to give informed consent.

The length of the recruitment period was based on a power analysis indicating that we needed a minimum of 100 patients per group to ascertain clinically significant outcome differences (20% improvement in central symptom measures).[10] Given that incidence estimates were 15 patients per 100 000 per year, and expecting a 25% rejection of informed consent, the length of recruitment was calculated to be 4 years. During these 4 years, 186 patients from the ED area and 194 from the no-ED area met the study criteria (both figures are within the expected incidence range for schizophrenia spectrum disorders).[17] Of these, a total of 141 patients from the ED area and 140 patients from the no-ED area gave informed consent to enter the study (74% of eligible participants).

Table 1. Patient Demographics and Clinical Characteristics

	Not From ED Area (n=113)	From ED Area (n=118)
Mean (SD) age at study entrance[a]	30.73 (9.97)	26.43 (7.83)
Men, No. (%)	66 (58)	69 (58.50)
Nordic origin, No. (%)[b]	101 (89.38)	116 (98.31)
Mean (SD) premorbid social functioning at the childhood level	0.99 (1.03)	0.93 (1.15)
Mean (SD) change in premorbid social functioning	0.81 (1.33)	0.89 (1.62)
Mean (SD) premorbid academic functioning at the childhood level	1.89 (1.34)	1.70 (1.13)
Mean (SD) change in premorbid academic functioning	0.46 (1.27)	0.66 (1.20)
Mean (SD) length of education at study entrance, y	11.99 (2.71)	12.10 (2.02)
Median duration of untreated psychosis, wk (range)[c]	16 (0-966)	5 (0-1196)
Narrow schizophrenia spectrum diagnosis, No. (%)	84 (73)	96 (81)
Drug or alcohol abuse, No. (%)	19 (16.96)	20 (17.09)

Abbreviation: ED, early detection.
[a] $P<.01$, t test.
[b] $P<.01$, Fisher exact test.
[c] $P<.01$, Mann-Whitney U test.

The participants were followed up after 3 months, 1 year, and 2 years. At the 2-year follow-up, 231 patients had completed the full follow-up, with data sets including demographics, diagnostics, and symptoms (ED n=118, no-ED n=113). The ED area patients were more likely to be non-Nordic than the no-ED area patients; they were also younger and had a shorter DUP (**Table 1**). Between 2-year follow-up participants and dropouts, there were no significant ED vs no-ED differences at baseline. At the 1-year follow-up, the 2-year dropouts from both the ED and no-ED areas were less likely to be in remission, were more likely to abuse drugs ($P<.05$, Pearson χ^2 test for both), more likely to have longer durations of disruption of individual treatment and medication ($P<.05$, independent sample t test for both), and less likely to improve in positive and excitement symptoms from baseline ($P<.05$, independent sample t test for both). Also, ED area dropouts between the 1-year and 2-year follow-ups worsened, while no-ED area dropouts showed improvement in negative symptoms from baseline to the 1-year follow-up (both not statistically significant).

The Regional Committee for Research Ethics approved this study. All patients entering the study gave written informed consent.

INSTRUMENTS

Clinically experienced and trained research personnel carried out the assessments. The Structured Clinical Interview for the *DSM-IV* was used for diagnosis.[18] Symptom levels were measured by the PANSS,[16] and symptom domains are represented by the corresponding PANSS components (positive, negative, excitement, cognitive, and depressive).[19] Global functioning was measured by the Global Assessment of Functioning Scale (GAF)[20] (split into symptom [GAFs] and function scores [GAFf] to improve psychometric properties),[21] drug and alcohol abuse by the Drake scale,[22] and quality of life by the Lehman Quality of Life scale.[23] The DUP was measured retrospectively, based on all available sources, as weeks from onset of psychosis (the first week with symptoms corresponding to a PANSS score of ≥ 4 on positive scale 1, 3, 5, 6, or general scale 9) until start of adequate treatment (structured treatment with antipsychotic medications or hospitalization in a highly staffed psychiatric ward to manage psychotic symptoms). In the rare cases of previous self-remitting psychotic episodes, these were added to the DUP. All available data were used to ascertain the DUP. Premorbid functioning was measured by the Premorbid Adjustment Scale.[24] The last year before onset of psychosis was not taken into account, to avoid scoring functional loss due to prodromal symptoms as being premorbid. The Premorbid Adjustment Scale covers 2 discrete domains: academic (school performance and school adaptation) and social (social accessibility/isolation and peer relationships). We used childhood level and change (difference between last premorbid score and childhood level) for each domain in our analyses.[25]

All raters were trained to reliability by rating preprepared audio/videotapes before entering the study assessment teams. For PANSS, we used actual videotaped interviews. For diagnosis, GAF, and DUP, clinically experienced raters who had not participated in the assessments scored the case notes. Written vignettes were used here because the multiple sources for DUP ascertainment could not be covered by a taped interview, and because the raters thus could be blinded to patients' place of origin. Reliability of the scales was fair to very good: DUP, 0.99; GAFs, 0.63; GAFf, 0.75; PANSS components: positive, 0.80; negative, 0.79; depressive, 0.59; excitement, 0.58; cognitive, 0.48; alcohol use, 0.75; illicit drug use, 0.86 (Intraclass Correlation Coefficients [1, 1]); for diagnostic categories, κ was 0.76.[26]

STATISTICAL ANALYSIS

Analyses were made with SPSS 14.0 (SPSS Inc, Chicago, Illinois), except for growth curve analyses that were made with Mplus 4.0.[27] All tests are 2-tailed with a level of significance of 0.05. For the bivariate group comparisons, the P values are corrected for multiple testings (15 tests). Nonsignificant findings are marked *ns*. For skewed data, either nonparametric tests or a transformed variable was used; DUP was substituted in the multivariate analyses with ln (DUP+1).

The multiple linear regression analyses were done to rule out the possibility that group differences in outcome were due to confounders. These analyses were done hierarchically, with "Coming from the ED area" entered last. Independent variables were chosen based on their hypothetical potential to influence and mediate the relationship between the dependent variable and "Coming from the ED area," as indicated by group differences in the distribution of this variable between the ED and the no-ED sample, through a significant relationship with the dependent variable, as indicated by a significant bivariate relationship to the dependent variable in the current material, or by demonstrated predictive power regarding the dependent variable from previous studies. We assumed that the differences in baseline symptoms were related to earlier detection and intervention. Furthermore, the hypothesis tested here was that these initial differences would persist up to the 2-year follow-up, indicating prevention of negative symptom escalation over time, rather than an intervention-induced reduction in negative symptoms over time. Because of this, we did not enter (ie, correct for) baseline symptom levels in the regression analyses.

The final models were examined for violation of the assumptions underlying linear models through residual plots, and for interaction effects between "coming from the ED area" and the other independent variables, and finally for the effects of outliers and influential observations. To exclude the possibility that group differences were based on differential attrition between the 1-year and 2-year follow-ups, the main multiple linear regression analyses were repeated including patients lost between these time points, and substituting missing 2-year data with the corresponding 1-year data for these. This procedure did not influence the main results.

Table 2. Symptomatic and Functional Status at 2-Year Follow-up

	Not From ED Area (n=113)	From ED Area (n=118)
Mean (SD) PANSS positive component at 2 y	9.06 (4.02)	9.13 (4.97)
Mean (SD) PANSS negative component at 2 y[a]	19.19 (9.06)	15.54 (6.48)
Mean (SD) PANSS cognitive component at 2 y[a]	5.58 (2.52)	4.31 (1.86)
Mean (SD) PANSS depressive component at 2 y[a]	9.94 (3.76)	8.08 (2.92)
Mean (SD) PANSS excitement component at 2 y	6.82 (2.55)	6.57 (2.75)
Median time to first remission (95% CI)	12.00 (9.23-14.77)	10.00 (7.67-12.31)
In remission at 2-y follow-up, No (%)	85 (75.22)	81 (68.64)
In relapse at 2-y follow-up, No (%)	13 (11.50)	17 (14.41)
Continuously psychotic to 2-y follow-up, No (%)	15 (13.27)	20 (16.95)
Median time to first remission (95% CI)	12.00 (9.23-14.77)	10.00 (7.67-12.31)
Mean (SD) GAF symptoms for 2 y	50.81 (14.54)	53.64 (17.68)
Mean (SD) GAF functioning for 2 y	49.47 (14.78)	53.80 (17.32)
Mean (SD) No. of social contacts for 2 y[b]	3.18 (1.03)	3.33 (0.99)
Mean (SD) No. of daily activities for 2 y[b]	1.18 (0.33)	1.25 (0.34)
Mean (SD) No. of family contacts for 2 y[b]	3.92 (0.82)	4.00 (0.69)

Abbreviations: CI, confidence interval; ED, early detection; GAF, Global Assessment of Functioning Scale; PANSS, Positive and Negative Syndrome Scale.
[a] $P<.001$, *t* test.
[b] n=203 for quality of life measures.

Table 3. Correlations Between the Positive and Negative Components, Demographics, and Clinical Characteristics

	Positive Component	Negative Component
From ED area	0.007	–0.228[a]
Age at baseline	–0.299[a]	–0.019
Sex	–0.203[a]	–0.299[a]
Nordic origin	0.043	0.019
Premorbid social functioning at the childhood level	0.496[a]	0.068
Premorbid academic functioning at the childhood level	0.139[b]	0.245[a]
Premorbid academic functioning, change	0.017	–0.070
Premorbid social functioning, change	0.117	0.236[a]
Length of education	–0.146[b]	–0.274[a]
Duration of untreated psychosis, natural logarithm	0.226[a]	0.217[a]
Time to first remission	0.437[a]	0.232[a]
Narrow schizophrenia spectrum diagnosis	0.365[a]	0.349[a]
Drug or alcohol abuse	0.229[a]	0.060
Family group participation	0.099	–0.011
Duration of antipsychotic medication, first 2 y	0.111	0.120
Duration of structured individual treatment, first 2 y	0.131[b]	0.022
Duration of all hospital admissions, first 2 y	0.345[a]	0.224[a]
GAF functioning	–0.558[a]	–0.632[a]
GAF symptoms	–0.771[a]	–0.574[a]
Satisfaction with life in general	–0.179[b]	–0.268[a]
Daily activities for 2 y	–0.271[a]	–0.448[a]
Social contacts for 2 y	–0.101	–0.462[a]
Family contacts for 2 y	0.029	–0.222[a]

Abbreviations: ED, early detection; GAF, Global Assessment of Functioning Scale.
[a] $P<.01$, Pearson correlation.
[b] $P<.05$, Pearson correlation.

Five latent growth curves were used to model change in symptoms (PANSS components) over time.[28] Parameterization of the growth factors was coded as the number of months since first measurement, reflecting the uneven time intervals; data from all time points were used. The intercept reflects the initial status, whereas the slope measures change throughout all time points. The slope was regressed on the intercept to control for potential symptom differences in the 2 groups at the first time point (T1). A robust maximum likelihood estimation procedure was used, owing to possible nonnormal distribution of the PANSS. Missing data were accounted for by the Full Information Maximum Likelihood approach. Squared terms indicative of nonlinear change were tried out in the models, but were not significant for any subscale.

RESULTS

There were no statistically significant differences in the amount of treatment received by the 2 groups in the first 2 years. This includes weeks in which patients received antipsychotic treatment (no-ED group median, 95 weeks [range, 0-104 weeks] vs ED group median, 84 weeks [range, 0-104 weeks], $P=.42$), weeks with systematic individual treatment (no-ED group median, 102.5 weeks [range, 6-104 weeks] vs ED group median, 96 weeks [range, 4-104 weeks], $P=.13$), weeks hospitalized (no-ED group median, 12.5 weeks [range, 0-104 weeks] vs ED group median, 16.0 weeks [range, 0-104 weeks], $P=0.9$) (all Mann-Whitney *U* tests, uncorrected for multiple testings), and number of patients participating in multifamily groups (no-ED group, 56 patients [46.3%] vs ED group, 65 patients [53.7%], $P=.43$).

Concerning the primary outcome measures (**Table 2**), there was no statistically significant difference between the 2 groups in the PANSS positive components. The statistically significant difference for the PANSS negative component in favor of the ED group was maintained at the 2-year follow-up. There were no statistically significant differences between groups in time to first remission, number of patients in remission or relapse, number of relapses, PANSS excitement component, or GAFs at the 2-year follow-up (Table 2). There were statistically significant differences in the PANSS cognitive component and the PANSS depressive component. There was also a clear trend toward better functioning, reflected by better social activity and GAFf in favor of the ED group, but this did not reach statistical significance after correcting for multiple testing (Table 2).

There was a complex pattern of bivariate relationships between patient characteristics and symptoms measured by the PANSS (**Table 3**). Multiple linear regres-

Table 4. Multiple Linear Regression Analysis With Negative Component at 2-Year Follow-up as Dependent Variable

Variables	Standardized Coefficients	*t* Value	Significance	(95% CI)
Constant		4.343	0.000	(11.917 to 31.754)
Age at baseline	–0.007	–0.092	0.927	(–0.134 to 0.122)
Sex	–0.198	–3.044	0.003	(–5.274 to –1.127)
Nordic origin	0.033	0.531	0.596	(–3.075 to 5.340)
Length of education	–0.125	–1.940	0.054	(–0.834 to 0.007)
Premorbid social functioning, change	0.189	2.936	0.004	(0.345 to 1.757)
Duration of untreated psychosis	–0.007	–0.103	0.918	(–0.653 to 0.588)
Narrow schizophrenia spectrum diagnosis at 2 y	0.258	3.734	0.000	(2.193 to 7.103)
Drug or alcohol abuse	–0.026	–0.415	0.678	(–3.354 to 2.187)
Family group participation	–0.092	–1.246	0.214	(–3.819 to 0.863)
Duration of antipsychotic medication, first 2 y	–0.054	–0.710	0.479	(–0.051 to 0.024)
Duration of structured individual treatment, first 2 y	–0.031	–0.434	0.665	(–0.060 to 0.039)
Duration of hospital admissions	0.188	2.895	0.004	(0.017 to 0.089)
From ED area	–0.255	–3.860	0.000	(–6.185 to –2.002)

Abbreviations: CI, confidence interval; ED, early detection.
[a] Model R^2, 0.332.
[b] Model F, 7.234; $P<.001$.

Table 5. Development in the PANSS Positive and Negative Components During the Follow-up Period

	Positive Component		Negative Component	
	No-ED Area, Mean (SD)	ED Area, Mean (SD)	No-ED Area, Mean (SD)	ED Area, Mean (SD)
Baseline	16.35 (4.18)	14.46 (4.39)	22.74 (9.95)	18.64 (6.76)
3 mo	9.24 (3.54)	8.84 (4.15)	17.83 (7.81)	16.68 (6.56)
1 y	8.94 (4.02)	8.56 (4.71)	18.65 (7.14)	16.36 (7.40)
2 y	9.06 (4.02)	9.13 (4.97)	19.19 (9.06)	15.54 (6.48)

Abbreviations: ED, early detection; PANSS, Positive and Negative Syndrome Scale.

sion analyses did not indicate that the group difference in the negative component was mediated by confounders. The analysis showed that being male and having a decline in premorbid social functioning, a narrow schizophrenia-spectrum diagnosis, and longer hospitalizations in the follow-up period increased the risk for elevated levels of negative symptoms at the 2-year follow-up. Coming from ED area had a statistically significant effect in decreasing negative symptoms, even when entered at the last step of the analysis. The bivariate relationship between DUP and level of negative symptoms appeared to be mediated through premorbid functioning and diagnosis (**Table 4**). The differences between the ED and no-ED groups in the cognitive and depressive components did not appear to be mediated through differences in other variables.

The group difference in the negative component appeared to increase from the 1-year to the 2-year follow-up; here the ED groups showed a small but steady decrease, while the tendency for the no-ED group was the opposite (**Table 5**). This finding was strengthened by a growth curve analysis showing an interaction effect for group × time for the PANSS negative component. There were no group × time effects for the other symptom dimensions (**Table 6**).

COMMENT

The Treatment and Intervention in Psychosis study[9] has already shown the clinical merits of early intervention, as ED area patients entered treatment with less severe clinical symptoms, less serious suicidality, and shorter total duration of their first-episode.[10,11] Persistently lower levels of negative symptoms in favor of the ED group throughout the first 2 years indicate a significant effect on subsequent course. A parallel trend toward better functional and social outcome in the ED group implies a functional impact.

An alternative explanation might be that first-episode patients from this area generally have shorter DUPs and better outcomes than first-episode patients elsewhere. This does not appear to be the case, because the ED group had shorter DUPs and lower symptom levels compared with first-episode patients from the same area before the Treatment and Intervention in Psychosis program started (pre-ED group)[29] and from the same area after the information campaigns ended (post-ED group).[7] The 1-year follow-up of the pre-ED group found negative symptoms of similar severity to the no-ED group, showing that the difference is a program-specific effect.[7]

Both groups in our study were provided with the same treatment package with well known effectiveness for psychotic symptoms. Treatment utilization was the same, and treatment appeared uniformly effective for the positive and excitement symptoms of psychosis across groups. It is unlikely that the ED vs no-ED difference in negative symptoms is secondary to differences in positive symptoms. Given this, and the fact that the difference in negative symptoms appears to be enduring (measured for 2 years), we consider it likely that we are seeing differences in persistent negative symptoms, as defined recently by Buchanan,[14] and perhaps even primary negative symptoms as defined previously by Kirkpatrick et al.[30,31] We cannot confidently assert this, because our design did not include the means to measure these deficit

Table 6. Growth Models for PANSS Components at Baseline, 3-Month, 1-Year, and 2-Year Follow-ups[a]

	Intercept			Slope		
Component	No-ED Area, Mean (SD)	ED Area, Mean (SD)	Difference, *t* Value	No-ED Area, Mean (SD)	ED Area, Mean (SD)	Difference, *t* Value
Positive	11.14 (.00)	11.85 (.86)	2.23[b]	−.07 (.13)	−.08 (.00)	1.57 (ns)
Negative	21.17 (4.60)	19.76 (4.63)	2.35[b]	.01 (.26)	−.13 (.24)	2.56[a]
Cognitive	6.10 (1.63)	4.80 (1.78)	3.58[c]	−.02 (.08)	.00 (.03)	1.67 (ns)
Depressive	11.33 (1.97)	9.27 (1.73)	4.82[c]	−.05 (.13)	−.06 (.06)	1.47 (ns)
Excitement	7.71 (.66)	7.63 (1.56)	1.53 (ns)	−.06 (.07)	−.02 (.10)	.12 (ns)

Abbreviations: ED, early detection; ns, not significant; PANSS, Positive and Negative Syndrome Scale.
[a] Sex, age, ethnicity, length of education, alcohol, drug or alcohol abuse, premorbid social adjustment (initial level and change), and diagnosis are included as covariates in the analysis.
[b] $P < .05$.
[c] $P < .01$.

phenomena. However, we can say with confidence that the ED patients did not show negative symptom deterioration during the first 2 years.

To understand our findings requires a shift in perspective from treatment to prevention. What appears to be happening in the ED sample between baseline and 2 years is not more robust treatment of negative symptoms, but a prevention of negative symptom escalation. That is, the intensity of deficits in the cases that were detected and treated earlier remains close to the level in which intervention was initiated. This finding provides prima facie evidence that early detection and treatment may affect the core neurobiological deficit process of schizophrenia, and through this alter the course and prognosis for the better. Our data provide no clue as to the mechanisms behind this phenomenon, but they do challenge the prevailing assumption that these deficit processes are immutable.

Two methodological shortcomings limit the extent of these conclusions. First, the 2 comparison samples cannot approximate the level of matching as well as randomization procedures. Given that adjustment for confounders goes only as far as confounding variables can be identified, our study may have underadjusted for unidentified site differences. Second, the clinical ratings of the PANSS interviews were not masked for ED vs no-ED status, thus rendering them vulnerable to assessment biases. We therefore offer these data as a possible first demonstration of secondary prevention of psychosis, one that can profit from continuing follow-up, and one that invites and requires replication.

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