Five-Year Follow-up of a Randomized Multicenter Trial of Intensive Early Intervention vs Standard Treatment for Patients With a First Episode of Psychotic Illness

The OPUS Trial

Mette Bertelsen, MSc; Pia Jeppesen, MD, PhD; Lone Petersen, PhD; Anne Thorup, MD, PhD; Johan Øhlenschlæger, MD, PhD; Phuong Le Quach, MD; Torben Østergaard Christensen, PhD; Gertrud Krarup, MD; Per Jørgensen, MD; Merete Nordentoft, MD, PhD, MPH

Context: Intensive early treatment for first-episode psychosis has been shown to be effective. It is unknown if the positive effects are sustained for 5 years.

Objective: To determine the long-term effects of an intensive early-intervention program (OPUS) for first-episode psychotic patients.

Design: Single-blinded, randomized, controlled clinical trial of 2 years of an intensive early-intervention program vs standard treatment. Follow-up periods were 2 and 5 years.

Setting: Copenhagen Hospital Corporation and Psychiatric Hospital, Aarhus, Denmark.

Patients: A total of 547 patients with a first episode of psychosis. Of these, 369 patients were participating in a 2-year follow-up, and 301 were participating in a 5-year follow-up. A total of 547 patients were followed for 5 years.

Interventions: Two years of an intensive early-intervention program vs standard treatment. The intensive early-intervention treatment consisted of assertive community treatment, family involvement, and social skills training. Standard treatment offered contact with a community mental health center.

Main Outcome Measures: Psychotic and negative symptoms were recorded. Secondary outcome measures were use of services and social functioning.

Results: Analysis was based on the principles of intention-to-treat. Assessment was blinded for previous treatment allocation. At the 5-year follow-up, the effect of treatment seen after 2 years (psychotic dimension odds ratio [OR], −0.32; 95% confidence interval [CI], −0.58 to −0.06; P = .02; negative dimension OR, −0.45; 95% CI, −0.67 to −0.22; P = .001) had equalized between the treatment groups. A significantly smaller percentage of patients from the experimental group were living in supported housing (4% vs 10%, respectively; OR, 2.3; 95% CI, 1.1–4.8; P = .02) and were hospitalized fewer days (mean, 149 vs 193 days; mean difference, 44 days; 95% CI, 0.15–88.12; P = .05) during the 5-year period.

Conclusions: The intensive early-intervention program improved clinical outcome after 2 years, but the effects were not sustainable up to 5 years later. Secondary outcome measures showed differences in the proportion of patients living in supported housing and days in hospital at the 5-year follow-up in favor of the intensive early-intervention program.

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Psychosis is related to great stress and is a burden for society; the personal consequences of relapse and the fear of future relapse are often overwhelming for patients. Birchwood and colleagues have hypothesized that there exists a critical period just after the debut of psychosis in which a window of opportunity exists to intervene and improve the long-term course of illness. Previous studies have shown that it is possible to intervene during the early course of illness to secure a better outcome, but there is no evidence that indicates how long early interventions need to be active to prevent relapse. Rosenheck et al have shown that for a large population of homeless people with severe mental disorders, the advantages of assertive community treatment (ACT) can be sustained after transfer to other services if clinicians are allowed the flexibility to decide at which stage a patient is ready for such a transfer. This study (the OPUS trial) is the largest randomized clinical trial comparing the...
intensive early-intervention program (OPUS) with standard treatment (community mental health centers) for patients experiencing their first episode of psychosis and the first to report outcome after 5 years of follow-up. The intensive early-intervention program consisted of ACT, psychoeducational family treatment, and social skills training. The experimental treatment was carried out for 2 years.

The intensive early-intervention program has shown significant positive effects on psychotic and negative symptoms, secondary substance abuse, treatment adherence, success with lower dosages of antipsychotic medication, and a higher satisfaction with treatment after 2 years of treatment. It is unknown if these positive effects are sustainable after the experimental treatment ends and patients are referred to standard treatment according to their needs.

The 3 core elements in the intensive early-intervention program aim to provide the patient with the skills to cope with the illness, manage their own medication, and reduce stress. If patients have learned to use these skills independently or with support from their families, they will theoretically help them to continue medication and buffer stress during the course of illness and when the experimental treatment is no longer active. The positive effects of ACT, psychoeducational family intervention, and social skills training for patients with psychosis are well documented separately during the time when treatment is active, but follow-up studies indicate that the effects disappear when treatment ends.

This 5-year follow-up assesses the patients 3 years after the transition to standard treatment and offers the opportunity to investigate whether the intensive early-intervention treatment is able to sustain its positive effects.

Two hypotheses were tested; the first was linked to the primary outcome measure, and the second to the secondary outcome measure. (1) Patients who were allocated to the intensive early-intervention program for 2 years and then transferred to standard treatment have a better clinical outcome, measured by the level of psychotic and negative symptoms, global functioning, substance abuse, depression, and suicidal behavior, compared with patients allocated to standard treatment throughout the first 5 years of treatment. (2) Patients who were allocated to the intensive early-intervention program for 2 years and then transferred to standard treatment have a better social outcome compared with patients allocated to standard treatment; social outcome is measured as more patients living independently, fewer hospitalizations (less use of supported housing and days in hospital), and more patients with a competitive job or studying.

### Methods

#### Participants

A total of 547 patients were included in the trial during the period from January 1998 until December 2000. Patients were included from both inpatient and outpatient mental health services in Copenhagen and Aarhus. At the time of inclusion, patients were aged between 18 and 45 years and came in contact with mental health services for the first time with a diagnosis within the schizophrenia spectrum (measured using the F2-category codes of the International Statistical Classification of Diseases, 10th Revision [ICD-10][20]), and none of them had received antipsychotic medication for more than 12 continuous weeks. Patients were followed and reassessed after 2 and 5 years.

The basic characteristics of the cohort are shown in Table 1. Representativity was good. A total of 90% of the patients in Aarhus and 63% in Copenhagen were registered in the psychiatric case registers as having had their first contact with psychiatric services in the same period, and they were diagnosed within the same diagnostic spectrum. The official registers revealed that patients who were not included were significantly...
older and fewer of the patients had a diagnosis of schizophrenia (66% in the trial compared with 42% in the register). Of the eligible patients, only 3% refused to participate.

**RANDOMIZATION**

Patients were centrally randomized to the intensive early-intervention program or standard treatment. In Copenhagen, randomization was carried out through centralized telephone randomization at the Copenhagen Trial Unit. The allocation sequence was a computer-generated ratio of 1:1 in blocks of 6, and stratified for each of 5 centers. In Aarhus, the researchers contacted a secretary by telephone when they had finished the entry assessment of each patient. The secretary then drew 1 lot from among 5 red and 5 white lots out of a black box. When the block of 10 was used, the lots were redrawn. Block sizes were unknown to the investigators.

**TREATMENTS**

The trial was pragmatic, comparing the intensive early-intervention program, which was defined by a set of protocols, with treatment as usual.

**INTENSIVE EARLY-INTERVENTION PROGRAM**

The intensive early-intervention program consisted of 3 core elements: ACT,8,9 family treatment,12,21 and social skills training.13,22 Two multidisciplinary teams were established and trained to provide the intensive early-intervention program for 2 years. The caseload ratio was 1 researcher for every 10 patients. The patients were designated a primary staff member who was responsible for maintaining contact and coordinating the treatment within the team and across social services and other involved institutions. Patients were visited at their homes or other places in the community, or seen at their primary team member’s office, according to the patients’ preferences. During hospitalization, responsibility for the patient was transferred to the hospital, but the primary staff member maintained contact with the patient at least weekly. Office hours were Monday to Friday, from 8 AM to 5 PM. Outside of office hours, patients could leave messages on the staff’s cell phone and be assured that the team would respond the next morning. A crisis plan was developed and trained for with each patient. The aim of the intensive early-intervention program was to offer an individual plan of treatment for each patient. If patients were reluctant to be treated, the team stayed in contact with the patient and tried to find a common focus for collaboration to thereby motivate the patient to continue treatment.

The team always tried to get in contact with at least 1 family member and motivate the family to participate in a psychosocial treatment. Family treatment followed the McFarlane manual for psychoeducational treatment11 for multiple family groups and included 18 months of treatment for 1.5 hours every second week in a multiple-family group with 2 therapists and 4 to 6 patients with their families. The focus was on problem-solving and development of skills to cope with the illness.

Patients with impaired social skills were offered social skills training focusing on medication, coping with symptoms, conversation, and problem-solving skills in a group with a maximum of 6 patients and 2 therapists.

The fidelity of the treatment program, measured with the index of fidelity of assertive community treatment,23 was 70% in Copenhagen and Aarhus. The factors responsible for the reduced fidelity were time-limited treatment, 24-hour coverage in other settings, and about 2 contacts weekly with each patient, the patient’s family, and collaborating partners.

The intensive early-intervention program was phase specific, meaning that the primary team member carefully assessed when patients were ready for a specific treatment modality.

**STANDARD TREATMENT**

Standard treatment usually consisted of offering the patient treatment at a community mental health center. Each patient was in contact with a physician, a community mental health nurse, and in some cases, a social worker. Home visits were possible, but office visits were the general rule. A staff member’s caseload in the community mental health centers varied between 20 and 30 patients. Outside of office hours, patients could refer themselves to the psychiatric emergency department. Such psychosocial treatments as supported counseling, psychoeducation, and family contact were provided infrequently and in a less intensive and unsystematic way, and only in a minority of cases. For more details see Petersen et al.4

**TRANSITION FROM INTENSIVE EARLY-INTERVENTION PROGRAM TO STANDARD TREATMENT**

After 2 years of the intensive early-intervention program, patients from the intervention group were transferred to standard treatment. For a few patients, this consisted of a transfer to only their general practitioner. The transition to standard treatment was carried out as gradually and gently as possible, but naturally the break in the relationship with the contact person in the intensive early-intervention program could cause feelings of loss for the patient. Introduction to standard treatment was a high priority, and the transition period could last up to 2 months.

**ANTIPSYCHOTIC MEDICATION**

Patients in both treatment groups were offered antipsychotic drugs according to guidelines from the Danish Psychiatric Society, which recommend a low-dose strategy for patients with a first episode of psychotic illness and the use of second-generation antipsychotic drugs as a first choice.

**ASSESSMENTS**

Independent investigators conducted the 5-year follow-up interviews. All investigators were blind to previous treatment allocation. For practical reasons, independent investigators at the 2-year follow-up could not be blinded.4

At entry, the 2-year follow-up, and the 5-year follow-up, information on the following topics was collected: (1) main diagnosis and substance abuse, based on the Schedule for Clinical Assessment in Neuropsychiatry ([SCAN] version 2.0 in 1998 and SCAN 2.1 since 1999); (2) symptoms according to the Scale for Assessment of Psychotic Symptoms (SAPS) and Scale for Assessment of Negative Symptoms (SANS)20 (data are analyzed according to the 3 dimensions: psychotic, negative, and disorganized, with values ranging from 0-5); (3) sociodemographic factors;27 (4) course of illness with Life Chart Schedule; (5) global assessment of functioning and symptoms (GAF); (6) duration of untreated psychosis, assessed at entry to the trial with the Interview for Retrospective Assessment of Onset of Schizophrenia; and (7) suicidal behavior, measured by self-reporting of suicide attempts and suicidal ideation.31

The algorithms from the SCAN interview were used to investigate whether patients fulfilled the general criteria for depression according to the ICD-10.
Figure 1. Flowchart of patients through study. OPUS indicates intensive early-intervention program; ST, standard treatment.

OTHER DATA SOURCES

Using the unique Danish official registers, it is possible to accomplish a complete follow-up of all patients regarding a range of relevant process and outcome measures. Information about days spent in hospital, emergency department visits, outpatient contacts, housing situation, and vocational situation were collected from the registers for all patients (100% follow-up rate) included in the trial, except those who had died or emigrated. A list of all supported housing institutions was made manually, so that all institutions were captured. A great effort was made to ensure that all institutions used are supported housing facilities for patients with mental health problems. Most of the institutions are staffed 24 hours daily.

The following information was gathered: (1) In the Danish Civil Registration System, all persons alive and residing in Denmark are registered and assigned a 10-digit personal identification number. The register contains continuously updated information. (2) Information about days in hospital, emergency department contacts, and outpatient contacts was collected from the Danish Psychiatric Central Register. (3) A database with department contacts, and outpatient contacts was collected from the institutions. (4) Information about days in hospital, emergency department contacts, and outpatient contacts was collected from the Integrated Database for Labour Market Research. (5) Mortality and cause of death were drawn from the Integrated Database for Labour Market Research.33 (5) A database with information extracted from entry and 2-year follow-up interviews was combined with address information in the Civil Status Register, thereby providing information about independent living and supported housing.32 (4) Employment, family situation, sick leave, and early-age pension were extracted from the Integrated Database for Labour Market Research.27 (5) Mortality and cause of death were drawn from the Cause of Death Register.34

INTRARATER RELIABILITY

All investigators were trained in conducting the SCAN interview at the World Health Organization collaborating center and trained in the SCAN, SAPS, and SANS with live interviews. Twenty live SCAN interviews were conducted. During the 5-year follow-up period, all raters from the 2-year follow-up and the 5-year follow-up did reliability interviews with SANS and SAPS. The intraclass correlation coefficient was 0.90 for the negative dimension and 0.92 for the psychotic dimension; both are classified as very good agreement.33

BLINDING

Raters at the 5-year follow-up were blinded to patients’ previous treatment allocation. After each interview, raters made a guess as to which treatment they believed the patient had most likely received. The reliability between the guessed and true treatment allocation were measured as a k coefficient, 0.23, indicating poor reliability, which means that a fair level of blinding was obtained.36

OUTCOME MEASURES

The primary outcome measures were psychotic and negative symptoms (SANS and SAPS) and social functioning (functional GAF). Secondary outcomes included secondary diagnosis of substance abuse, medication and use of services, depressive symptoms, suicidal behavior, housing situation, and vocational situation.

STATISTICAL ANALYSIS

Because of the attrition from the follow-up interviews (Figure 1), the influence of missing data on the 2- and 3-year outcome measures had to be considered. Hence, data from the SANS, SAPS, and GAF were subjected to further analysis using a mixed-model analysis with a repeated-measurements model with unstructured variance matrix (Table 2). This approach assumed that the distribution of missing data could be estimated from the information from previous interviews. The condition for using this method is the assumption that data were missing at random when taking into consideration the information extracted from entry and 2-year follow-up interviews.37-39 The following covariates were entered in the repeated measurements model: treatment, substance abuse at entry, sex, and age. The values from entry for the respective outcome measures (SAPS, SANS, and GAF) were included automatically, because they are included in the model and no treatment effect was allowed for at entry. Alternative approaches to managing the skewed attrition are sensitivity analyses and multiple imputations. According to Little et al,37 multiple im-
Odds ratios for treatment effects were calculated using logistic regression analysis, and mean differences were estimated through analysis of variance for continuous variables.

In accordance with the intention-to-treat principle, all patients were analyzed in the treatment groups to which they were randomly allocated, regardless of whether they had completely followed the scheduled design. All statistical analyses were done with the Statistical Package for the Social Sciences 11.0 (SPSS, Inc, Chicago, Illinois).

POWER CALCULATION

It was expected that the mean (SD) reduction in psychotic symptoms measured by SAPS would be 1 (1.3) point for the patients allocated to standard treatment. At a minimum, it should be possible to detect a 50% greater reduction in psychotic symptoms in the experimental group at the .05 level of significance and with power of 0.9. Using the Pocock formula,10 142 patients would be required for each study group to detect a 50% greater reduction in psychotic symptoms measured by SAPS would be 1 (1.3) point for the experimental group at the .05 level of significance and with power of 0.9. Using the Pocock formula,10 142 patients would be required for each study group.

Sensitivity analyses of psychotic symptoms, negative symptoms, and substance abuse

Owing to the large attrition from the study (Figure 1), 2 assumptions were tested regarding patients who did not participate in the 5-year follow-up interview. The first assumption was that the nonparticipants’ level of psychotic and negative symptoms and substance abuse would be the same as the last observation; therefore, the nonparticipants’ entry values and 2-year values (if available) for the psychotic and negative dimensions and substance abuse were carried forward to the 5-year follow-up. The second assumption was that nonparticipants had experienced a total remission of psychotic and negative symptoms and substance abuse. On this basis, their values at the 5-year follow-up were set at 0. Data were analyzed using both assumptions, but it was found that neither of the 2 possibilities showed any significant differences between the 2 groups regarding level of symptoms or substance abuse.

Although no selection bias could be detected, it is still necessary to be cautious about possible bias with a follow-up rate of only 57%.

Table 2. Clinical Outcome of Patients With a First Episode of Psychotic Illness Who Participated in the Intensive Early-Intervention Program or Standard Treatment

<table>
<thead>
<tr>
<th></th>
<th>2-Year Follow-up (n=389)</th>
<th>5-Year Follow-up (n=301)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OPUS (n=205)</td>
<td>ST (n=164)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>Estimated Mean Difference (95% CI)</td>
<td>Estimated Mean Difference (95% CI)</td>
</tr>
<tr>
<td>Psychotic dimension</td>
<td>1.06 (1.26)</td>
<td>1.27 (1.40)</td>
</tr>
<tr>
<td>Negative dimension</td>
<td>1.41 (1.15)</td>
<td>1.82 (1.23)</td>
</tr>
<tr>
<td>Disorganized dimension</td>
<td>0.37 (0.56)</td>
<td>0.50 (0.73)</td>
</tr>
<tr>
<td>GAF symptoms</td>
<td>51.18 (15.01)</td>
<td>48.67 (15.92)</td>
</tr>
<tr>
<td>GAF function</td>
<td>55.16 (15.15)</td>
<td>51.13 (15.92)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; GAF, global assessment of functioning (scale); OPUS, intensive early-intervention program; ST, standard treatment.

a Estimated mean differences are based on a repeated measurement model in unstructured variance matrix. Treatment site, sex, substance abuse, and age were included as covariates.
2- and 5-year follow-ups, when the experimental treatment was no longer active. This development is illustrated in Figure 2.

Functional GAF also demonstrated an effect of the intensive early-intervention program after 2 years of treatment (55.16 vs 51.13; mean difference, 3.12; 95% CI, 0.37-5.88; \(P=0.03\)), but this difference was also not present after 5 years (55.36 vs 54.16; mean difference, 1.34; 95% CI, −2.65 to 5.34; \(P=0.51\)).

**SECONDARY OUTCOME MEASURES**

**Depression, Substance Abuse, and Suicidal Behavior**

The intensive early-intervention program significantly reduced substance abuse at the 2-year follow-up, but not at the 5-year follow-up (Table 3). No effect was found of the intensive early-intervention program on depression and suicidal behavior after 2 or 5 years.

**Antipsychotic Medication**

The proportion of patients receiving first- or second-generation antipsychotic medication was not significantly different in the 2 treatment groups after 2 or 5 years. Patients in the intensive early-intervention program received significantly lower doses of second-generation antipsychotic medication after 2 years, but not after 5 years (Table 3).

**Use of Services**

When analyzing data from the registers, it was found that patients who had participated in the intensive early-intervention program during the first 2 years spent significantly fewer days in hospital than patients who had received standard treatment (mean, 96 vs 123 days; mean difference, 27.4 days; 95% CI, 0.57-54.32; \(P=0.05\)) (Table 4). From 2 to 5 years, there was no significant difference in mean days in hospital between patients in the 2 groups (58 vs 71 days; mean difference, 13.1 days; 95% CI, −12.5 to 38.7; \(P=0.31\)). Because days in hospital decreased in this period, lack of power makes it impossible to say that the difference is not coincidental; hence, the result may be a type II error. Investigating the entire period of 5 years, patients in the intensive early-intervention program had 20% fewer mean days in hospital than patients in standard treatment (149 vs 193 days; mean difference, 44 days; 95% CI, 0.15-88.12; \(P=0.05\)) (not shown).

**Social Outcomes**

All data on social outcome are derived from the registers that made it possible to follow up all patients except those who had died (Table 4). During the 5 years, 16 patients had died. A total of 7 patients died of suicide, 3 of unexplained causes, 1 by accident, and 1 of natural causes. Standard mortality rate was 11 compared with the general population in Copenhagen and Aarhus Counties, aged 18 to 45 years.

The proportion of patients living in supported housing did not differ between treatment groups after 2 years of treatment, but at the 5-year follow-up, only 4% of the patients in the experimental group were living in supported housing, whereas 10% from the standard treatment group were (OR, 2.3; 95% CI, 1.1-4.8; \(P=0.02\)). The mean (SD) days spent in supported housing for the patients from the experimental group in the time period from 2 to 5 years was 57 (213) vs 102 (282) in the standard treatment group (mean difference, 45.1 days; 95% CI, 0.31-89.9; \(P=0.05\)). The range of days spent in supported housing from entry to the 5-year follow-up was 5 to 1094 days for the experimental group and 27 to 1094 days for the standard group (not shown).

When analyzing the proportion of patients working or being educated, it was found that after 5 years, 61% of patients from the intensive early-intervention program and 59% from the standard treatment group were not working or studying. In this age range in the general population, 20% are not working or studying. There were no significant differences between the 2 treatment groups.
REMISSION

The Life Chart Schedule\textsuperscript{28} offered an opportunity to analyze the course of illness during the previous 2 years up to the 5-year follow-up (Table 5). Results showed that there were no significant differences between the 2 groups as to whether the course had been continuous or episodic, or if the patient had not been psychotic at all during the past 2 years.

\begin{table}[h]
\centering
\caption{Substance Abuse, Use of Antipsychotic Drugs, and Suicidal Ideation and Behavior of Patients With a First Episode of Psychotic Illness Who Participated in the Intensive Early-Intervention Program or Standard Treatment}
\begin{tabular}{lccc}
\hline
\multicolumn{4}{c}{2-Year Follow-up (n=436)} \tabularnewline
Parameter & OPUS (n=243) & ST (n=193) & Difference in Percentages (95% CI) & OR (95% CI)/Parameter Estimate (95% CI) & P Value \tabularnewline \hline
Substance abuse and suicidal behavior and ideation & & & & & \\
Diagnosis of substance abuse\textsuperscript{b} & 43 (17) & 40 (21) & 4 (−3 to 11) & 0.5 (0.3 to 1.0) & .04 \tabularnewline
Diagnosis of depression\textsuperscript{b} & 37 (15) & 35 (18) & 3 (−4 to 11) & 0.8 (0.5 to 1.5) & .47 \tabularnewline
Attempted suicide during follow-up\textsuperscript{b} & 20 (8) & 20 (10) & 2 (−3 to 7) & 0.8 (0.4 to 1.7) & .51 \tabularnewline
Suicidal thoughts during last 2 y\textsuperscript{b} & 113 (56) & 86 (53) & 3 (−0.1 to 0.07) & 0.9 (0.7 to 1.6) & .82 \tabularnewline
Any antipsychotic drugs at follow-up data\textsuperscript{b} & 146 (60) & 107 (55) & −5 (−14 to 4) & 1.2 (0.9 to 1.8) & .23 \tabularnewline
First-generation drugs only\textsuperscript{b} & 25 (17) & 21 (20) & 3 (−4 to 10) & 0.9 (0.5 to 1.4) & .51 \tabularnewline
Second-generation drugs only\textsuperscript{b} & 72 (49) & 45 (42) & −7 (−16 to 2) & 1.3 (0.9 to 1.9) & .15 \tabularnewline
Mean (SD) equivalents of haloperidol, mg\textsuperscript{c} & 4.3 (2.8) & 5.3 (3.4) & −0.7 (−1.4 to 5.6) & 0.7 (3.2) & .07 \tabularnewline
First- or second-generation drugs\textsuperscript{c} & 3.3 (2.7) & 3.0 (3.4) & 0.29 (−1.01 to 1.6) & 1.9 (4.6) & .66 \tabularnewline
First-generation drugs only\textsuperscript{c} & 4.0 (2.4) & 4.9 (2.9) & −0.91 (−1.5 to −0.32) & 2.1 (2.1) & .01 \tabularnewline
Second-generation drugs only\textsuperscript{c} & & & & & \\
\hline
\multicolumn{4}{c}{5-Year Follow-up (n=301)} \tabularnewline
Parameter & OPUS (n=151) & ST (n=150) & Difference in Percentages (95% CI) & OR (95% CI)/Parameter Estimate (95% CI) & P Value \tabularnewline \hline
Substance abuse and suicidal behavior and ideation & & & & & \\
Diagnosis of substance abuse\textsuperscript{b} & 44 (25) & 36 (23) & 8 (−5 to 21) & 1.1 (0.6 to 2.0) & .71 \tabularnewline
Diagnosis of depression\textsuperscript{b} & 37 (25) & 29 (19) & 8 (−5 to 21) & 1.1 (0.6 to 2.0) & .71 \tabularnewline
Attempted suicide during follow-up\textsuperscript{b} & 20 (8) & 13 (9) & 7 (−4 to 18) & 1.3 (0.7 to 2.4) & .43 \tabularnewline
Suicidal thoughts during last 2 y\textsuperscript{b} & 113 (56) & 86 (53) & 3 (−0.1 to 0.07) & 0.9 (0.7 to 1.6) & .82 \tabularnewline
Any antipsychotic drugs at follow-up data\textsuperscript{b} & 146 (60) & 107 (55) & −5 (−14 to 4) & 1.2 (0.9 to 1.8) & .23 \tabularnewline
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Second-generation drugs only\textsuperscript{c} & & & & & \\
\hline
\end{tabular}
\end{table}

Abbreviations: CI, confidence interval; OPUS, intensive early-intervention program; OR, odds ratio; ST, standard treatment.

\textsuperscript{a}Results from 2-year follow-up are presented in a previous article.\textsuperscript{4}

\textsuperscript{b}Odds ratios and P values based on logistic regression analyses.

\textsuperscript{c}In calculating equivalence, 100 mg of chlorpromazine was estimated to be equivalent to 2 mg of haloperidol. P values are based on analysis of variance.

COMMENT

The results of this large randomized controlled trial disprove our first hypothesis; 2 years in the intensive early-intervention program showed no effect on the clinical outcome at the 5-year follow-up, nor on psychotic or negative symptoms, global functioning, substance abuse, depression, or suicidal behavior. The positive effects on psychotic and negative symptoms and global functioning seen after 2 years of treatment were, in other words, not sustainable after the experimental treatment ended.

The second hypothesis regarding social outcome was partly confirmed; the results demonstrated that patients from the experimental group were living more independently (less use of supported housing), and spent significantly fewer days in hospital during the 5-year period. These results indicate that, to some extent, patients from the experimental treatment group fared better with regard to adapting to normal life outside institutions. It is debatable how much attention should be paid to the statistically significant result regarding independent living. On one hand, data on supported housing are a secondary outcome measure, but are very robust, reliable, and valid, especially considering that the number of days spent in supported housing after 2 and 5 years also differ significantly. These results offer unique insight into the patients’ social abilities and capability to live alone without support, and are the best proxy measure for social functioning in our study. Further, Marshall et al\textsuperscript{9} showed that ACT had an effect on adherence, days in hospital, employment, and housing situation, meaning that even though housing situation is a secondary outcome measure, it is highly relevant.

On the other hand, if a Bonferroni correction had been applied to the figures, the significant difference between the 2 groups regarding independent living would have disappeared. According to Schulz et al,\textsuperscript{41} caution should be exercised when there are more than 15 end points and only 1 turns out to be statistically significant. Because we have fewer end points, a Bonferroni correction of the data was not chosen.

The intensive early-intervention program added substantial cost to treatment, but this was counterbalanced by the reduced cost of other health services during this
intervention, especially the savings on supported housing after 5 years.

The external validity of the trial was high owing to good representativity. Dropout analyses showed that patients not participating in the 2-year follow-up had a poorer prognosis, but the same analysis of patients participating in the 5-year follow-up revealed that it was not a select group of patients who were participating. Even though it is not possible to detect a possible attrition bias at the 5-year follow-up, it cannot be refuted that the large attrition at the 5-year follow-up may have biased the results.

Power calculations showed that 142 patients were required in each arm, and this requirement was fulfilled; hence, it is not likely that the 5-year follow-up results are subject to a type II error, but a 50% reduction in symptoms is possibly a very optimistic expected difference.

In the 5-year follow-up, performance bias may have influenced the results, owing to the fact that the patients from the experimental group, unlike the patients from the standard group, experienced a shift in treatment continuity when they were transferred to standard treatment after 2 years.

The raters at the 5-year follow-up were blinded to previous treatment allocation, and data from the registers offered 100% follow-up of patients, thus minimizing the risk of our results being biased. On the other hand, assessment at the 2-year follow-up may have been associated with a biased rating owing to the lack of blinding; therefore, these results may have been subject to detection bias.

Our findings are in accordance with findings from other studies regarding outcome after 2 years of early intensive treatment, but these studies do not investigate the effect of the experimental treatments for an extended time period.

In strict terms, it must be concluded that the benefits of the intensive early-intervention program after 2 years

| Table 4. Use of Health Services and Social Outcome for Patients With a First Episode of Psychotic Illness Who Participated in the Intensive Early-Intervention Program or Standard Treatment† |
|-----------------------------------------------|----------------|----------------|----------------|----------------|----------------|----------------|
|                                             | OPUS (n=278) | ST (n=278) | Difference in Percentages (95% CI) | OR (95% CI) | Parameter Estimate (95% CI) | P Value |
| Use of services                             |              |              |                                |            |                               |         |
| Mean (SD) No. of days in hospitala           | 96 (146.7)   | 123 (170.6)  | 27.4 (0.57 to 54.32)           | .05        | 58 (145.1)                   | 71 (154.9) | 13.1 (-12.5 to 38.7) | .31 |
| Median No. of days in hospitalb              | 25           | 52           | 0.04                            | 0          | 0                             |         |
| Not hospitalized                              | 89 (32)      | 73 (27)      | -5 (-0.1 to 0.02)              | .01        | 157 (57)                     | 148 (54)  | -3 (-0.1 to 0.06)    | .66 |
| No outpatient contacts last yearc            | 20 (7)       | 85 (31)      | 24 (17 to 31)                  | .01        | 127 (46)                     | 133 (48)  | 4 (-0.04 to 0.13)    | .41 |
| Mean (SD) use of emergency department, No.d  | 1.43 (2.6)   | 1.71 (4.0)   | 0.28 (-0.28 to 0.87)           | .33        | 1.9 (4.6)                     | 2.2 (5.9)  | 0.3 (-0.6 to 1.2)    | .51 |
| Social outcome                               |              |              |                                |            |                               |         |
| Not living independentlyd                    | 19 (7)       | 18 (7)       | 0 (-0.04 to 0.04)              | .99        | 11 (4)                       | 26 (10)   | 6 (-0.09 to -0.06)   | .23 |
| Mean (SD) No. of days in protected homesb    | 30 (105)     | 35 (122)     | 5.2 (-24.6 to 14.3)            | .59        | 57 (213)                     | 102 (282) | 45.1 (0.31 to 89.9) | .05 |
| Not working or being educatedd              | 142 (52)     | 151 (56)     | 4 (-0.02 to 0.14)              | .8         | 159 (57)                     | 148 (54)  | -3 (-0.1 to 0.06)    | .57 |
| Mean (SD) No. of days absent from work owing to illnessb | 75 (125) | 80 (125) | -5.1 (-19.1 to 28.7) | .89 | 45 (115) | 40 (95) | -5.9 (-26.1 to 15.29) | .58 |
| Mean (SD) No. of days on early pensionb      | 58 (163)     | 75 (186)     | 16.9 (-15.9 to 49.1)           | .31        | 382 (437)                    | 430 (457) | 48.3 (-37.2 to 133.8) | .26 |
| Living alone or alone with childrend        | 243 (88)     | 219 (81)     | -7 (-0.1 to -0.00)             | .05        | 226 (82)                     | 206 (75)  | -7 (-0.1 to 0.01)    | .16 |

Abbreviations: CI, confidence interval; OPUS, intensive early-treatment program; OR, odds ratio; ST, standard treatment.

†Two-year figures show the period from entry to 2-year follow-up; 5-year figures show the period from 2-year follow-up to 5-year follow-up. Data are from registers with 547 patients followed up after both 2 and 5 years. Patients who had died are not included in analysis.

P values based on analysis of variance.

P values based on Mann-Whitney U test for independent sample.

Odds ratios and P values based on logistic regression analyses.

Living alone or alone with children mean that the patient is either living totally by himself or herself or that he or she is a single mother or father raising his or her children alone, with no partner in the household.
were not sustainable, and no basic changes in illness were seen after 5 years from the start of the program.

Our results give rise to questions about how long early-intervention services should be offered to patients to maintain good clinical and social outcomes. Second, this trial pinpoints the intrinsic problem of early-intervention services, namely how to make the transition to normal life as gentle as possible for those patients who no longer need treatment, or who need a less intensive treatment program, while at the same time maintaining continuous treatment for those who develop a chronic course of illness.

There is a need to continuously investigate whether the short-term (12-24 months)\(^a\)\(^b\) outcome achieved with specialized early-intervention services can be sustained for a longer time period. There is also a need to investigate the consequences of a prolonged treatment program that lasts for the entire 5 years, which is hypothesized to cover the critical period.\(^2\) More randomized controlled trials are also needed that try to determine which specific elements from specialized early intervention, if not all, need to be offered for an extended time period. It would also be of great interest for future research to carry out analysis of the mediating factors of the different treatment modalities to determine whether some subgroups of the sample might be faring differently from others. This would give the field of research an indication of whether the experimental treatment is particularly beneficial for some groups of patients compared with other groups.

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**Correspondence:** Mette Bertelsen, MSc, Bispebjerg Hospital, Department of Psychiatry, Bispebjerg Bakke 23, 2400 Copenhagen NV, Denmark (mbe_76@yahoo.dk).

**Author Contributions:** Prof Ralf Hemmingsen and Prof Niels Reisby participated in designing the study and writing the initial application for funds. Prof Philip Hougaard supervised the statistical analysis. Copenhagen Trial Unit planned and conducted the randomization procedure for the Copenhagen patients. All authors participated in critical revision of drafts of the manuscript and approved the final version. Britt Morthorst and Lise Elgaard helped conduct research interviews.

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### Table 5. Remission and Relapse During Last 2 Years Before 5-Year Follow-up\(^4\)

<table>
<thead>
<tr>
<th></th>
<th>Intensive Early-intervention Program (n=151)</th>
<th>Standard Treatment (n=150)</th>
<th>Differences in Percentages (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Episodic course of illness(^b)</td>
<td>21 (14)</td>
<td>19 (13)</td>
<td>−2 (−0.06 to 0.1)</td>
</tr>
<tr>
<td>Continuous course of illness(^c)</td>
<td>67 (45)</td>
<td>65 (44)</td>
<td>−2 (−0.12 to 0.1)</td>
</tr>
<tr>
<td>Not psychotic(^d)</td>
<td>62 (41)</td>
<td>64 (43)</td>
<td>2 (−0.13 to 0.09)</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.

\(^a\)Based on Life Chart Schedule.\(^2\)

\(^b\)Episodic characterized as no psychotic episode lasting longer than 6 months.

\(^c\)Continuous characterized as no remission lasting longer than 6 months.

\(^d\)Not psychotic meaning no psychotic episode during last 2 years.

## References


