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RESEARCH

Five years of specialised early intervention versus two years of specialised early intervention followed by three years of standard treatment for patients with a first episode psychosis: randomised, superiority, parallel group trial in Denmark (OPUS II)

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Abstract

Objective To compare the effects of five years of specialised early intervention (SEI) treatment for first episode schizophrenia spectrum disorder with the standard two years of SEI plus three years of treatment as usual.

Design Randomised, superiority, parallel group trial with blinded outcome assessment. Randomisation was centralised and computerised with concealed randomisation sequence carried out at an external site.

Setting Participants were recruited from six OPUS teams in Denmark between 2009 and 2012. OPUS teams provide SEI treatment to all patients diagnosed with a schizophrenia spectrum disorder in Denmark.

Participants 400 participants (51% women) with a mean age of 25.6 (standard deviation 4.3) were randomised to five years of SEI (experimental intervention; n=197) or to two years of SEI plus three years of treatment as usual (control; n=203).

Interventions OPUS treatment consists of three core elements—modified assertive community treatment, family involvement, and social skill training—with a patient-case manager ratio of no more than 12:1. For participants randomised to five years of OPUS treatment, the treatment was largely unchanged. Participants randomised to the control group were mostly referred to community health centres after two years of SEI treatment.

Main outcomes Follow-up assessments were conducted five years after start of OPUS treatment. Primary outcome was negative symptoms measured on the scale for assessment of negative symptoms (avolition-apathy, anhedonia, alogia, and affective blunting). Secondary outcomes were remission of both negative and psychotic symptoms, psychotic symptoms, suicidal ideation, substance abuse, compliance with medical treatment, adherence with treatment, client satisfaction, days in hospital care, and labour market affiliation.

Results Levels of negative symptoms did not differ between the intervention group and control group (1.72 *v* 1.81 points; estimated mean difference –0.10 (95% confidence interval 0.33 to 0.13), P=0.39). Participants receiving five years of OPUS treatment were more likely to remain in contact with specialised mental health services (90.4% *v* 55.6%, P<0.001), had higher client satisfaction (estimated mean difference 2.57 points (95% confidence interval 1.36 to 3.79), P<0.001), and had a stronger working alliance (estimated mean difference 5.56 points (95% confidence interval 2.30 to 8.82), P=0.001) than the control group.

Conclusions This trial tests SEI treatment for up to five years for patients with first episode schizophrenia spectrum disorder; previous trials have found treatment effects for programmes lasting from one to three years. The prolonged SEI treatment had few effects, which could be due to the high level of treatment provided to control participants and the late start of specialised treatment.

Trial registration Clinicaltrial.gov NCT00914238.

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Introduction

The most successful addition to the treatment of schizophrenia and other psychotic illnesses seen over recent decades has been the introduction of specialised early intervention (SEI).[1][2] The SEI teams combine assertive community treatment,[3][4] psychoeducation,[5] and family involvement,[6][7] with a low case load of patients for case managers. The early intervention paradigm from which the SEI teams grew is based on the hypothesis of a critical period in the disorder.[8-10] This hypothesis suggests that the more fluctuating course seen early in psychotic disorders should be more receptive to intervention, which could have long term effects if patients could be stabilised at a lower level of disability. This led early intervention advocates to argue that treatment resources and research should be directed toward the early phase of illness.

SEI teams are now well established as standard treatment for first episode psychosis in many developed countries.[11][12] A meta-analysis of the effect of SEI teams published in 2014[13] identified four randomised clinical trials testing multidisciplinary teams providing assertive treatment combined with psychoeducation and family interventions for one to two years. This analysis showed that the SEI teams had positive effects on hospital admission rates and use of bed days as long as patients were in treatment. For the trials with long term follow-up after the end of the intervention period, the results were more contradictory.[14-16] The largest randomised clinical trial of SEI treatment, the OPUS I trial,[3-17] found that participants in the intervention group relapsed to the psychopathological and functional levels of the control participants three years after the end of the intervention.[15] In a naturalistic study from Canada, researchers testing the effect of five years of SEI treatment found that they could sustain and further reduce the psychopathology and increase the functional level of the participants.[18]

There is currently a gap in knowledge regarding how to improve the long term effects of SEI programmes. Based on current evidence, it seems fair to hypothesise that SEI teams have an effect as long as patients are in treatment. We therefore aimed to test whether the positive results seen in patients receiving SEI treatment can be sustained if the treatment is prolonged. Given the previous findings of positive effect of the SEI treatment[17][19] and the limited pharmacological treatment options for negative symptoms, we tested whether negative symptoms are reduced in a patients receiving prolonged SEI treatment compared with those treated in community health centres after termination of two years of SEI treatment.

Methods

Participants

All participants were recruited from six Danish OPUS teams (five in Copenhagen and one in Aarhus) between 2009 and 2012. They were recruited an average of 19 months into their 24 month treatment programme. OPUS teams are part of the adult psychiatric services treating patients aged 18-35 at the time of their first diagnosis of schizophrenia spectrum disorder (ICD-10 (international classification of diseases, 10th revision): schizophrenia F20, schizotypal disorder F21, persistent delusional disorders F22, acute and transient psychotic disorders F23, induced delusional disorder F24, schizoaffective disorders F25, other non-organic psychotic disorders F28, and unspecified non-organic psychosis F29).[20] Participants had to meet the diagnostic criteria for one of the above mentioned diagnoses at time of inclusion. Patients with an IQ below 70 points are not

treated in OPUS teams and therefore were not part of the study population.

Design and randomisation

The study was a randomised, superiority, parallel group trial with blinded outcome assessment, comparing five years of SEI treatment versus the standard two year SEI treatment (clinicaltrial.gov NCT00914238). All participants received two years of SEI treatment in an OPUS team. Nineteen months into the programme, participants were assessed for inclusion into the present trial. After assessment, the participants were randomised to continue in the OPUS team for three additional years (that is, five years in total) versus discontinuation after the standard two years.[21] The randomisation was centralised and computerised with concealed randomisation sequence carried out by the Copenhagen trial unit (CTU). Block sizes ranging between 10 and 6 were concealed to clinicians and investigators. Randomisation was stratified according to treatment site and negative symptoms. Negative symptoms were assessed for the four negative global domains (avolition-apathy, anhedonia, alogia, and affective blunting) on the scale for assessment of negative symptoms,[22] and stratified by one or more domains with a score of 3 or above, compared with no scores of 3 or above. The full study protocol is published elsewhere.[21]

OPUS treatment

The SEI treatment provided in Denmark is named OPUS. OPUS treatment is a psychosocial treatment programme provided to all patients diagnosed with a schizophrenia spectrum disorder in Denmark. The treatment is provided for the first two years after initial diagnosis. The treatment programme was established after the OPUS I trial proved the treatment's effectiveness in reducing both negative and psychotic symptoms.[17][19]

The treatment had three main pillars: modified assertive treatment,[23] family involvement,[24][25] and social skill training.[5] In addition, the patient could, in groups or individually, receive different recovery programmes tailored to personal need. At the start of treatment, the teams tried to establish contact with at least one family member who would then be invited to attend educational workshops and psychoeducational groups.[7] The multidisciplinary teams include psychiatrists, psychologists, nurses, social workers, physiotherapists, and vocational therapists. All team members, except for the psychiatrist, function as case managers. The ratio of patients to case managers must not exceed 12:1. For the participants randomised to extended OPUS treatment, there were no major changes in their treatment programmes. More participants were expected to be in remission, so the ratio of patients to case managers was raised to 15:1. All treatment and group programmes were available for the participants, and the families were invited back for a psychoeducational booster session.

Treatment as usual (years 2-5)

Patients randomised to treatment as usual after two years of OPUS treatment would most often be referred to a community health centre. Alternatively, if they no longer were considered in need of specialised treatment, participants could be referred to the primary care of their general practitioner or to assertive community treatment if they were in need of more intensive treatment than the community health centres could provide. The assertive community teams treat patients who are unable to attend office meetings. Estimates from the capital region, where three quarters of the participants were treated, found that 19% (n=31) of participants randomised to treatment as usual were

in contact with an assertive community team at some point during follow-up. In community health centres, home visits were possible; however, owing to the higher ratio of patients to case managers (typically between 20:1 and 30:1), the standard was office meetings at outpatient treatment facilities.

Antipsychotic treatment

Participants in both intervention groups were treated in accordance with national and regional guidelines recommending low doses of antipsychotic drugs in monotherapy for patients with first episode schizophrenia spectrum disorder and second generation antipsychotic drugs as first line of treatment.[26 27] The medical treatment was not part of the intervention and no fixed protocol exists. A national quality database monitors the use of antipsychotic drugs, but data on individual participants were not accessible.

Outcomes

Primary and secondary outcomes are listed at clinicaltrial.gov NCT00914238. Interviews were conducted either at research facilities in Copenhagen and Aarhus or at the patient's home. Follow-up interviews were conducted five years after the start in OPUS treatment, from November 2012 to June 2015. The intervention group had then received five years of OPUS treatment while the control group had received two years of OPUS treatment followed by three years of treatment as usual. Outcome assessors were blind to treatment allocation and high priority was given to keeping the investigator blinded during the follow-up interview. Thus, all questions regarding the treatment were presented in self-rated questionnaires.

Main diagnoses and comorbidity were based on the schedule for clinical assessment in neuropsychiatry (SCAN2.1),[28] sections 6-8, 11, 12, and 17-19. Duration of untreated psychosis was assessed at baseline by use of an adjusted version of the interview for the retrospective assessment of the onset of schizophrenia.[29] In addition to study outcomes, data on sociodemographic and previous psychiatric illness were collected. Educational level was split into short and long education. Short education included upper secondary education, post-secondary non-tertiary education, and short cycle tertiary education; long education included all education levels from university graduate level and above.

Primary outcome

The primary outcome was negative symptoms measured on the scale for assessment of negative symptoms.[22] The scale contains five domains, but in line with later factor analyses,[30] we only included the four global domains considered the most robust and most used in proposed criteria for remission in schizophrenia[31]: avolition-apathy, anhedonia, alogia, and affective blunting. The average of these four scores yielded a composite negative dimension score ranging from 0 to 5 points.[30]

Secondary outcomes

1. Remission of both positive and negative symptoms, reflected as no global scores on the scale for assessment for positive symptoms[22] and exceeding 2 on the scale for assessment of negative symptoms (that is, mild symptoms) over the past three months.

2. Similarly to negative symptoms, psychotic symptoms were measured as the average of two of the four global domains on the scale for assessment for positive symptoms (global hallucination and global delusion).[22 30]

3. Substance abuse was estimated as a reduction in participants fulfilling criteria for a diagnosis of harmful use or dependency syndrome diagnosed with ICD-10 (F1x.1 and F1x.2).[20] Diagnoses were established using the schedule for clinical assessment in neuropsychiatry,[28] sections 11 and 12.

4. To assess user satisfaction during the study, participants answered the client satisfaction questionnaire.[32]

5. Adherence to treatment was assessed first by use of the Danish National Patient Registry[33] to establish whether the participant had attended a meeting with the case manager within the last three months of the study. If so, the participant was considered to be in adherence with treatment, or still in contact with specialised psychiatric services. For those participants where the register did not find any contacts within the last three months before the follow-up assessment, the medical files were assessed by an independent investigator. If the registers were found to be wrong, the adherence status was changed. Owing to organisational differences, this assessment could be made only for participants from the five teams in Copenhagen (n=319).

6. Compliance with medical treatment was measured as the percentage of full prescribed doses taken in the past week. Answers were then categorised as 0-25%, 25-50%, 50-75%, and 75-100% of prescribed doses.

7. Suicidal behaviour, defined as suicidal thoughts in the past year, was assessed by participant report.

8. By use of data from the Danish National Patient Registry,[33] numbers of days in hospital care were calculated.

9. Based on the DREAM database[34] from the Danish Ministry of Employment, the labour market affiliation was assessed. The database contains data on both employment and use of social welfare.

The ability to live independently was defined as a secondary outcome in our trial protocol, but the registers on supported housing have not been updated yet and this outcome will be reported later.

Exploratory outcomes

1. Contrary to most SEI treatment programmes, most OPUS teams also treat patients diagnosed with a schizotypal disorder. Therefore, for comparability, we also explored psychotic symptoms after exclusion of participants with this diagnosis.

2. Disorganised dimension is measured as the average of two global domains on the scale for assessment for positive symptoms (global rating of bizarre behaviour and global rating of positive formal thought disorder) and one item from the scale for assessment of negative symptoms (inappropriate affect).[30]

3. Remission of psychotic symptoms in the past two years was assessed with the life chart schedule.[35]

4. Global cognitive functioning was reflected in the brief assessment of cognition in schizophrenia.[36] The raw scores from this assessment were transformed to z scores at baseline and follow-up, based on the mean and standard deviation of the healthy controls from a different Danish trial,[37] and are reported as total z scores.

5. Functional level, on both the global assessment of functioning[38] and personal and social performance scale,[39]

were assessed at the follow-up and baseline interview and the results were the same for both scales. The total score of the personal and social performance scale is reported.

6. Based on the assessment of compliance with medical treatment, the proportion of participants receiving antipsychotic treatment could be evaluated.

7. Doses of antipsychotic drugs were calculated into chlorpromazine equivalents using Gardner's consensus article from 2010.[40] For those drugs for which the article does not provide an algorithm, the World Health Organization's defined daily doses were used.[41] There is no consensus regarding the best way to calculate chlorpromazine equivalents[42] and, for sensitivity analyses, the minimal effective doses were used.[43]

8. Participants assessed their working alliance with their contact person using the working alliance inventory.[44]

9. Self-efficacy was assessed by participant self-report using the general self-efficacy scale.[45]

10. Participant's quality of life was measured on four domains (physical health, psychological, social relationship, and environment) in the WHO Quality of Life-BREF (WHOQOL-BREF).[46]

11. Outpatient contacts and psychiatric emergency contacts per year were calculated by use of the Danish National Patient Registry.[33]

At the follow-up assessment, the blind was broken in 9.0% (n=26) of interviews: 7.7% (n=11) in the treatment as usual group and 10.2% (n=15) in the intervention group.

Inter-rater reliability

All investigators were trained in conducting interviews for the schedule for clinical assessment in neuropsychiatry at the Copenhagen University's PhD course. Similarly, all investigators were trained in manuals for the scale for assessment for positive symptoms and scale for assessment of negative symptoms, and there were regular reliability interviews at the baseline investigations and during follow-up. The intraclass correlation coefficients varied from 0.63 to 0.77 for the negative dimension, indicating good agreement, although still below the study protocol's aim of 0.7. For the psychotic dimension, intraclass correlation coefficients ranged from 0.70 to 0.90, indicating good to very good agreement.[47]

Statistical methods

Power calculations

At the two year follow-up in the OPUS I trial, we found a mean difference of 0.40 points (standard deviation 1.20) on the negative dimension between the experimental intervention group and control group.[17] In the present trial, we aimed to detect the same difference, five year after initiation of treatment, and three years after end of the standard two year SEI treatment. This meant that we had to recruit 142 participants to each study group to be able to reject the null hypothesis that the population means of the two groups were equal with a probability (power) of 0.80. The type 1 error probability associated with the test of this null hypothesis is 0.05. Expecting approximately 30% attrition, we included 200 patients in both the intervention and control groups.

Analysis

All analyses were conducted according to the intention to treat principle, with a statistician blinded for treatment allocation.

To compensate for missing data, we analysed the data using multiple imputations, predictive mean matching with nearest neighbour for the medicine data, linear regression for the rest of the continuous outcomes, and binary logistic regression for the dichotomous outcomes. Based on attrition analysis, the data were not missing completely at random, and assuming that the rest of the data were missing at random, the multiple imputation command in SPSS was set to use the baseline values of primary and secondary outcomes and age, sex, disorganised dimension, treatment site, and diagnosis as predictor variables when imputing missing data. The imputed data were all those used to establish the outcome variables.

A total of 100 datasets were imputed. We analysed the data using binary logistic regression for the dichotomous variables (remission, suicidal ideation, diagnosis of substance abuse, compliance with medical treatment, adherence to treatment, remission of psychotic symptoms in the last two years of the study, antipsychotic treatment in the last month, antipsychotic treatment in the last two years, competitive employment, and disability pension). We also used linear regression for the continuous variables (negative dimension, psychotic dimension, client satisfaction, number of months employed, bed days, working alliance, general self-efficacy, disorganised dimension, psychotic dimension excluding schizotypal disorder, total z score for the brief assessment of cognition in schizophrenia, personal and social performance scale, doses of antipsychotic drugs, quality of life, outpatients contacts, and psychiatric emergency contacts). The stratification variables (treatment site and negative symptoms) were included as covariants in the analyses. Owing to uneven distribution of sex and client satisfaction at baseline, we conducted a sensitivity analysis with these variables included as covariates. We did all analyses using SPSS version 22.

Patient involvement

During the development of the trial protocol, the design and outcomes of the study were discussed with the OPUS user panel, a panel of former service users in OPUS. Participants will receive written information about the results of the study.

Results

A total of 468 participants were eligible for assessment at the time of recruitment. After exclusion of those not meeting inclusion criteria, who moved too far away, or who died, 440 participants were truly eligible for the study and the 400 recruited therefore represents 90.9% of the eligible population. Baseline characteristics showed a higher proportion of women in the treatment as usual group and higher client satisfaction among the participants randomised to extended OPUS treatment. Baseline values are reported in table 1⇓. Of those participants for whom we were able to assess adherence to treatment (the 319 patients treated in Copenhagen), 90.4% randomised to prolonged treatment remained in OPUS treatment until the end of the intervention versus 55.6% who remained in contact with either community health centres or assertive community teams in the treatment as usual group (P<0.001).

Attrition

The overall attrition of participants can be seen in figure 1⇓. Of the 400 patients included, 289 were seen at the follow-up interview. The primary outcome was assessed in 286 participants. Because of attrition at the follow-up interview, sources for attrition bias had to be considered. We found a statistically significant difference between participants attending

follow-up and those not at the negative dimension, disorganised dimension, treatment site, client satisfaction, and diagnosis. Those not attending the follow-up interview had higher negative dimension and disorganised dimension scores and lower client satisfaction at baseline than those attending. This difference was corrected for using multiple imputations.

Primary outcome

Both study groups were able to maintain treatment effects from baseline to follow-up. We found no significant difference between the intervention group and control group regarding negative symptoms. Mean negative dimensions for OPUS participants versus treatment as usual participants were 1.72 versus 1.81 points (estimated mean difference −0.10 (95% confidence interval −0.33 to 0.13), P=0.39). In sensitivity analyses of the observed data, the mean was slightly lower, corresponding to the lower level of baseline negative symptoms of patients attending the follow-up interview, but the estimated mean difference and 95% confidence interval was similar.

Secondary and exploratory outcomes

Results for secondary and exploratory outcomes are shown in tables 2 and 3⇓. Sensitivity analyses of the observed data or including sex and baseline client satisfaction did not significantly change the mean difference and 95% confidence interval for any of the variables.

In the primary analyses, we found no statistically significant differences between the two treatment groups on mean scores on the psychotic dimension or on the proportion of participants in remission. For the psychotic dimension, the mean scores were 1.72 for the OPUS group versus 1.94 for the treatment as usual group (estimated mean difference −0.23 (95% confidence interval −0.52 to 0.06), P=0.12; table 2⇓). Exploratory analyses excluding patients with a schizotypal disorder did not affect the estimated mean difference substantially (−0.26 (−0.56 to 0.05), P=0.10; table 3⇓).

In fact, 22.3% of OPUS participants and 21.7% of treatment as usual participants were in remission of both negative and psychotic symptoms (odds ratio 1.08 (95% confidence interval 0.65 to 1.80), P=0.76; table 2⇓). The rates of participants with a dual diagnosis of substance abuse were lower at the follow-up assessment than at the baseline interview, but there was no difference between the OPUS (16.8%) and treatment as usual (17.2%) groups (0.95 (0.53 to 1.72), P=0.87). Of those participants receiving antipsychotic treatment, 83% in the OPUS group versus 79% in the treatment as usual group reported taking at least 75% of their prescribed doses (odds ratio 1.34 (95% confidence interval 0.61 to 3.0), P=0.47). For the working alliance exploratory outcome (estimated mean difference 5.56 (95% confidence interval 2.30 to 8.82), P=0.001; table 2⇓) and the client satisfaction secondary outcome (2.57 (1.36 to 3.79), P<0.001; table 3⇓), we found a significant difference favouring OPUS treatment.

For the register data (tables 2 and 3⇓), all data were available for all patients. We did not find any significant differences for number of months employed (estimated mean difference −0.11 (95% confidence interval −2.67 to 2.44), P=0.93) or mean number of bed days between the OPUS group (9.1 (standard deviation 21.9)) and treatment as usual group (11.8 (34.1); estimated mean difference −2.79 (95% confidence interval −8.40 to 2.82), P=0.33). For exploratory outcomes, we did not find any differences in disability pensions (28.4% OPUS treatment *v* 25.6% treatment as usual; odds ratio 1.18 (95% confidence interval 0.72 to 1.92), P=0.52)), labour market

affiliation at end of study (23.4% in competitive work or study *v* 25.1%; odds ratio 0.92 (95% confidence interval 0.56 to 1.50), P=0.73), or number of psychiatric emergency contacts (0.48 (standard deviation 1.11) *v* 0.40 (0.84); estimated mean difference 0.08 (95% confidence interval −0.11 to 0.27), P=0.43). As expected, we saw a significantly higher use of outpatient services in the OPUS group (18.4 (standard deviation 12.0)) contacts per year versus the treatment as usual group (14.6 (11); estimated mean difference 3.78 (95% confidence interval 1.56 to 6.01), P=0.001).

Discussion

Principal findings

The ability to affect the negative symptoms in schizophrenia spectrum disorders has been one of the main accomplishments of the OPUS treatment, as shown in the OPUS I trial.[17] In the present OPUS II trial, both treatment models compared were able to maintain the level of negative symptoms, observed at baseline, and we were not able to find any effects of the prolonged OPUS intervention on the negative symptoms, nor on any other psychopathological dimensions, functional level, labour market affiliation, cognitive function, or hospital admissions. We did find a positive effect of prolonged OPUS on the working alliance exploratory outcome, and a higher client satisfaction in the intervention group. The high rate of discontinuation from the community health centres is not considered a central finding because we were unable to properly assess the reasons for discontinuation.

The lack of treatment benefits of the prolonged treatment could either be interpreted to mean that the beneficial effects of two years of treatment can be sustained without needing further SEI treatment, or that three additional years of treatment do not improve the outcome of illness. The fact that all participants improved on their psychopathological scores, cognitive levels, and functional scores suggests that the first interpretation is the most accurate (fig 2⇓).

The continued improvement in symptoms is contradictory to the OPUS I trial,[15] in which patients who received OPUS treatment had a mean relapse of symptoms after the end of SEI treatment. A plausible explanation for the lack of beneficial treatment effects and the general improvements seen in the OPUS II trial could be the high quality of the treatment provided to the control group. The fact that participants in the control group had a surprisingly high number of contacts with their case managers suggests that the treatment provided in both the intervention and the control group is beneficiary. Furthermore, elements introduced by SEI services as family involvement and psychoeducation are now mandatory in the community health centres. Finally, as many as 19% of participants randomised to treatment as usual in OPUS II had been in contact with an assertive community team during follow-up. The caseload in these teams was 10 patients to one case manager, indicating that we compared two treatment programmes with equivalent treatment intensity for the most ill participants. The difference in symptom improvement between the two studies could also be due to changes in the treatment provided or the symptoms of the participants recruited.

One could question whether SEI treatment was provided early enough to affect the course within the critical period. The mean duration of untreated psychosis was more than three years (median 52 weeks). We were aware that some patients were on waiting lists in the community health centres for up to one year before starting their OPUS treatment. A patient who had untreated psychosis for two years and then waited one year

before starting treatment would be at end of the critical phase after the regular two years of treatment. Thus, the prolonged treatment given would mostly have been provided in the plateau phase,[48] which is when the effect of SEI teams is more questionable. Other studies have found a relation between duration of untreated psychosis and outcome,[49] and one randomised controlled trial found that shortening the duration of untreated psychosis had an effect on the long term functional outcome.[50]

There are various explanations for the effects seen on the working alliance and client satisfaction questionnaire, which indicates a more positive patient experience. In a media climate where psychiatry is often accused of providing suboptimal treatment, it is important to state that patients are content with the treatment that they receive. However, it is also possible that participants were more interested in being randomised to the intervention group and, consequently, might have scored these items better because they received the desired intervention, even if there was no benefit on the other outcomes.

Strengths and limitations of study
Strengths
We used central randomisation stratifying for important predictive factors,[51-54] used blinded outcome assessors,[51-54] assessed several register based outcomes that are likely less influenced by knowledge about intervention group affiliation than other outcomes, included stratification factors in our main analyses,[55 56] conducted our main analyses on the data where missingness was controlled by multiple imputation,[57 58] conducted our analyses blinded for intervention group,[59] and drew our conclusions without knowledge of intervention group.[59] Moreover, although we based our sample size calculation on a power of 80%, by inflating our sample by 30% and analysing all participants using multiple imputations, we actually had a power of 91% to detect the a priori defined least significant difference regarding the primary outcome.

Limitations
Owing to the nature of psychosocial interventions, participants and clinical staff were not blinded. The primary outcome was negative symptoms, but because the study included participants with non-psychotic disorder (schizotypal disorder), it was underpowered to detect small differences on the psychotic dimension. Furthermore, the need to randomise patients six months before the start of the intervention could have affected the last part of the OPUS treatment for the treatment as usual group. Of 468 participants eligible for inclusion in the study, 11 were transferred to specialist teams such as a dual diagnosis team or forensic team, or lived in supported housing facilities with a high staff-to-patient ratio and therefore did not continue in OPUS treatment. Another 23 eligible participants declined to participate, and we do not know how these two groups differed from the studied population.

Follow-up was 72%, which was sufficient, but there was substantial attrition bias with regard to treatment site, negative and disorganised dimension, diagnosis, and client satisfaction. We corrected these differences by using multiple imputations, setting the number of imputations as high as 100, and calculating sensitivity analyses for the missing data. However, we do not know whether the results would have changed without this attrition. We have no measurement of family or carers' experience of the intervention, and we believe that inclusion of their experiences would have provided valuable information. No measurement of fidelity was included in the study which

makes us unable to report on the treatment actually provided in the study period, neither were we able to thoroughly assess the treatment provided to the treatment as usual group.

Adherence to treatment was only measured at the end of the study and therefore was not a fully adequate measurement during follow-up. To assess the use of outpatient services, we found the use of registers an inaccurate method to assess adherence during follow-up, and therefore supplemented our register data with registrations from the medical files for the last three months of follow-up. We abstained from using any measurements of adherence in the follow-up interview because of the risk of breaking the blind. Finally, the reliance on only two time points restricted our ability to analyse the course of illness. We chose only one follow-up point owing to previous problems with high attrition rates with frequent follow-up points. To compensate for this, we supplemented our survey data with register data, which to some degree can be used to analyse the entire follow-up period.

Comparison with other studies
To our knowledge, this is the first randomised clinical trial testing prolonged early intervention beyond three years. One trial compared the effect of three years of SEI with two years and showed positive effects on functional levels and depressive and negative symptoms,[60] but it was conducted in a low resource setting. Therefore, the treatment offered in the treatment as usual group might not be comparable to the service level in Denmark. A Canadian trial is currently testing five years of SEI treatment compared with two years,[61] but results are not yet published.

Conclusion and policy implications
Our data showed a general improvement for both treatment groups, confirming findings from earlier follow-up studies that patients diagnosed with schizophrenia do not have an overall deteriorating course.[62-65] Our results differ from previous long term follow-up studies of SEI treatment where participants seem to relapse after end of the intervention treatment. But we did not find an effect of prolonged treatment on our primary outcome, and therefore the results of the main trial outcomes cannot serve as a basis for recommending SEI treatment for five years. However, our results do not contradict the critical phase hypothesis.

Given the intensity of treatment provided to the treatment as usual group, we may have found two ways to uphold the beneficial effects of the two year SEI programme. Either prolonged early intervention or treatment as usual with assertive community treatment were provided to the most ill group of patients. Further trials into prolonged early intervention should include interventions to reduce treatment delays within the treatment system and with detection teams to shorten the duration of duration of untreated psychosis. Further subgroup analyses of the effect of delay on the treatment effect will be conducted and published. Secondary economic analyses might also show no increased cost to the prolonged treatment—if so, the higher client satisfaction might in itself be an argument for implementation.

What is already known on this topic

Previous studies of specialised early intervention (SEI) for patients with first episode psychosis have found beneficiary effects of the treatment as long as participants are in treatment

Some long term effects of the treatment were found in 2008, but there has been no evidence of such an effect on clinical outcomes

The OPUS II study investigates whether the positive effects seen in shorter SEI programmes can be sustained if treatment is prolonged up to five years

What this study adds

The two models compared (five years of SEI *v* two years of SEI and three years of treatment as usual) were equally successful in maintaining effects on negative symptoms

Prolonged SEI treatment had no significant effect on other clinical outcomes, but those participants receiving prolonged treatment had higher client satisfaction and stronger working alliances than controls

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Tables

Table 1| Baseline characteristics for 400 participants with disorders in the schizophrenia spectrum, included in the Danish OPUS II trial. Data are number (%) of participants unless stated otherwise

Characteristics	OPUS treatment (n=197)	Treatment as usual (n=203)
Sociodemographic characteristics		
Female	89 (46.2)	115 (56.7)
Age (mean (SD))	25.6 (4.3)	25.5 (4.2)
Being a parent	12 (6.1)	18 (8.9)
Completed high school	81 (41.1)	78 (38.4)
Employed or enrolled as a student	33 (16.8)	44 (21.7)
Disability pension	17 (8.6)	19 (9.4)
Education		
None	85 (43.1)	86 (42.6)
Under education	28 (14.2)	20 (9.9)
Short education, skilled	51 (25.9)	57 (28.2)
Long education	33 (16.8)	39 (19.3)
Living conditions		
Living alone	110 (55.8)	122 (60.1)
Living with partner, children, or both	42 (21.3)	38 (18.7)
Living with parents	31 (15.7)	23 (11.3)
Living in supervised setting	11 (5.6)	15 (7.4)
Homeless	2 (1)	5 (2.5)
Clinical		
Diagnosis		
Schizophrenia	147 (74.6)	152 (74.9)
Schizotypal disorder	39 (19.8)	44 (21.7)
Delusional disorder	5 (2.5)	5 (2.5)
Brief and transient psychotic disorder	1 (0.5)	1 (0.5)
Schizoaffective disorder	4 (2)	0 (0)
Unspecified non-organic psychosis	1 (0.5)	1 (0.5)
Non-psychotic psychiatric illness before psychosis and OPUS	180 (91.4)	188 (92.6)
Duration of untreated psychosis (weeks, mean (SD))	121 (173)	164 (196)
Duration of untreated psychosis (weeks, median (range))	52 (0-962)	69 (0-879)
Negative dimension (mean (SD))	1.89 (0.93)	1.86 (0.97)
Psychotic dimension (mean (SD))	1.92 (1.19)	1.82 (1.26)
Psychotic dimension, excluding F21 (mean (SD))	2.15 (1.17)	2.04 (1.28)
Disorganised dimension (mean (SD))	0.52 (0.60)	0.44 (0.58)
Total z scores in brief assessment of cognition in schizophrenia (mean (SD))	–2.47 (1.66)	–2.32 (1.92)
Substance abuse*	48 (24.4)	45 (22.2)
Chlorpromazine equivalents (mg, mean (SD))	463 (332)	420 (293)
Suicide ideation and behaviour		
Suicide attempt ever	71 (36)	89 (43.8)
Suicide attempt in last year of study	17 (8.6)	16 (7.9)
Suicidal ideations in last year of study	94 (47.7)	105 (52)
Social functioning		
Personal and social performance scale (score, mean (SD))	48.4 (11.7)	48.8 (13.5)
Treatment		
Client satisfaction at baseline (mean (SD)), CSQ	27.3 (3.9)	26.3 (4.4)

Table 1 (continued)

Characteristics	OPUS treatment (n=197)	Treatment as usual (n=203)
Duration from start of OPUS treatment to inclusion interview (weeks, mean (SD))	85.6 (11.1)	84.7 (10.5)

F21=schizotypal disorder; OPUS treatment=psychosocial treatment programme (specialised early intervention) provided to all patients diagnosed with a schizophrenia spectrum disorder in Denmark, column named OPUS show participants randomised to five years of OPUS treatment; SD=standard deviation, CSQ=client satisfaction questionnaire.

*Fulfilling criteria for harmful use or dependency syndrome diagnosed, ICD-10 (international classification of diseases, 10th revision, F1x.1 and F1x.2).

Table 2| Primary and secondary outcomes, assessed 3.5 years after inclusion in the OPUS II trial and five years after initiation of SEI intervention treatment

	Imputed and register data					
	No of participants	OPUS treatment	Treatment as usual	Estimated mean difference (95% CI)	Odds ratio (95% CI)	P difference
Primary outcome						
Negative dimension (mean (SD))	400	1.72	1.81	−0.10 (−0.33 to 0.13)	—	0.39
Secondary outcomes						
Psychotic dimension (mean (SD))	400	1.72	1.94	−0.23 (−0.52 to 0.06)	—	0.12
Remission	400	44 (22.3)	44 (21.7)	—	1.08 (0.65 to 1.80)	0.76
Suicidal ideation	400	58 (29.4)	69 (34.0)	—	0.80 (0.50 to 1.30)	0.37
Substance abuse*	400	33 (16.8)	35 (17.2)	—	0.95 (0.53 to 1.72)	0.87
Compliance with medical treatment†	229	89 (83)	97 (79)	—	1.34 (0.61 to 3.0)	0.47
Client satisfaction (mean (SD))	400	27.0	24.4	2.57 (1.36 to 3.79)	—	<0.001
No of months employed (mean (SD))‡	400	8.8 (14.1)	9.0 (14.0)	−0.11 (−2.67 to 2.44)	—	0.93
No of bed days (mean per year (SD))‡	400	9.1 (21.9)	11.8 (34.1)	−2.79 (−8.40 to 2.82)	—	0.33
Adherence to treatment§	319	142 (90.4)	90 (55.6)	—	8.6 (4.5 to 16)	<0.001

Data are number (%) of participants unless stated otherwise. OPUS treatment=psychosocial treatment programme (specialised early intervention) provided to all patients diagnosed with a schizophrenia spectrum disorder in Denmark, column named OPUS show participants randomised to five years of OPUS treatment; SD=standard deviation.

*Fulfilling criteria for harmful use or dependency syndrome diagnosed, ICD-10 (F1x.1 and F1x.2).

†Only analysed for participants receiving treatment with antipsychotic drugs.

‡Data based on registers and therefore not imputed.

§Outcome was operationalised as participants were still in contact with specialised psychiatric services at the time of follow-up interview. Data were obtained with a combination of registers and medical files, and therefore not imputed and only analysed for participants from Copenhagen.

Table 3| Exploratory outcomes (post hoc analyses), assessed 3.5 years after inclusion in the OPUS II trial and five years after initiation of SEI treatment

	Imputed data and register data					
	No of participants	OPUS treatment	Treatment as usual	Estimated mean difference (95% CI)	Odds ratio (95% CI)	P_{difference}
Disorganised dimension (mean (SD))	400	0.69	0.79	−0.11 (−0.29 to 0.084)	—	0.28
Psychotic dimension, excluding schizotypal disorders (mean (SD))	345	1.80	2.05	−0.26 (−0.56 to 0.05)	—	0.10
Remission of psychotic symptoms in last two years	400	87 (44.4)	84 (41.4)	—	1.19 (0.75 to 1.87)	0.46
Total z scores in brief assessment of cognition in schizophrenia (mean (SD))	400	−1.88	−1.89	0.03 (−0.33 to 0.39)	—	0.88
Personal and social performance scale (score, mean (SD))	400	54.2	54.5	−0.06 (−2.89 to 2.77)	—	0.97
Receiving antipsychotic treatment in last month	400	108 (54.9)	122 (59.9)	—	0.78 (0.49 to 1.25)	0.30
Receiving any antipsychotic treatment in last 2 years	400	140 (71.0)	148 (73.0)	—	0.88 (0.53 to 1.46)	0.63
Doses of antipsychotic drugs (mean (SD))*	229	423	398	—	21.8 (−68.3 to 112)	0.64
Working alliance (mean (SD))	400	65.6	60.1	5.56 (2.30 to 8.82)	—	0.001
General self-efficacy (mean (SD))	400	27.3	26.6	0.79 (−0.68 to 2.26)	—	0.29
Quality of life (four domains)						
Physical health	400	67.3	65.1	2.2 (−1.5 to 6.0)	—	0.25
Psychological	400	56.2	53.8	2.6 (−2.2 to 7.4)	—	0.29
Social relationship	400	62.2	61.3	0.99 (−3.3 to 5.3)	—	0.66
Environment	400	68.4	66.4	2.2 (−1.4 to 5.8)	—	0.23
No of months in some sort of employment (mean (SD))†	400	12.1 (15.2)	12.4 (14.8)	−0.16 (−2.78 to 2.45)	—	0.90
Patients in competitive employment or studying at follow-up (%)†	400	46 (23.4)	51 (25.1)	—	0.92 (0.56 to 1.50)	0.73
In study, competitive or non-competitive employment at follow-up (%)†	400	59 (29.9)	64 (31.5)	—	0.94 (0.59 to 1.48)	0.79
Patients on disability pension at follow-up (%)†	400	56 (28.4)	52 (25.6)	—	1.18 (0.72 to 1.92)	0.52
No of outpatient contacts (mean per year (SD))†	400	18.4 (12.0)	14.6 (11.0)	3.78 (1.56 to 6.01)	—	0.001
No of psychiatric emergency hospital contacts (mean per year (SD))†	400	0.48 (1.11)	0.40 (0.84)	0.08 (−0.11 to 0.27)	—	0.43

Data are number (%) of participants unless stated otherwise. OPUS treatment=psychosocial treatment programme (specialised early intervention) provided to all patients diagnosed with a schizophrenia spectrum disorder in Denmark, column named OPUS show participants randomised to five years of OPUS treatment; SD=standard deviation.

*Only analysed for participants receiving antipsychotic medical treatment at five year follow-up.

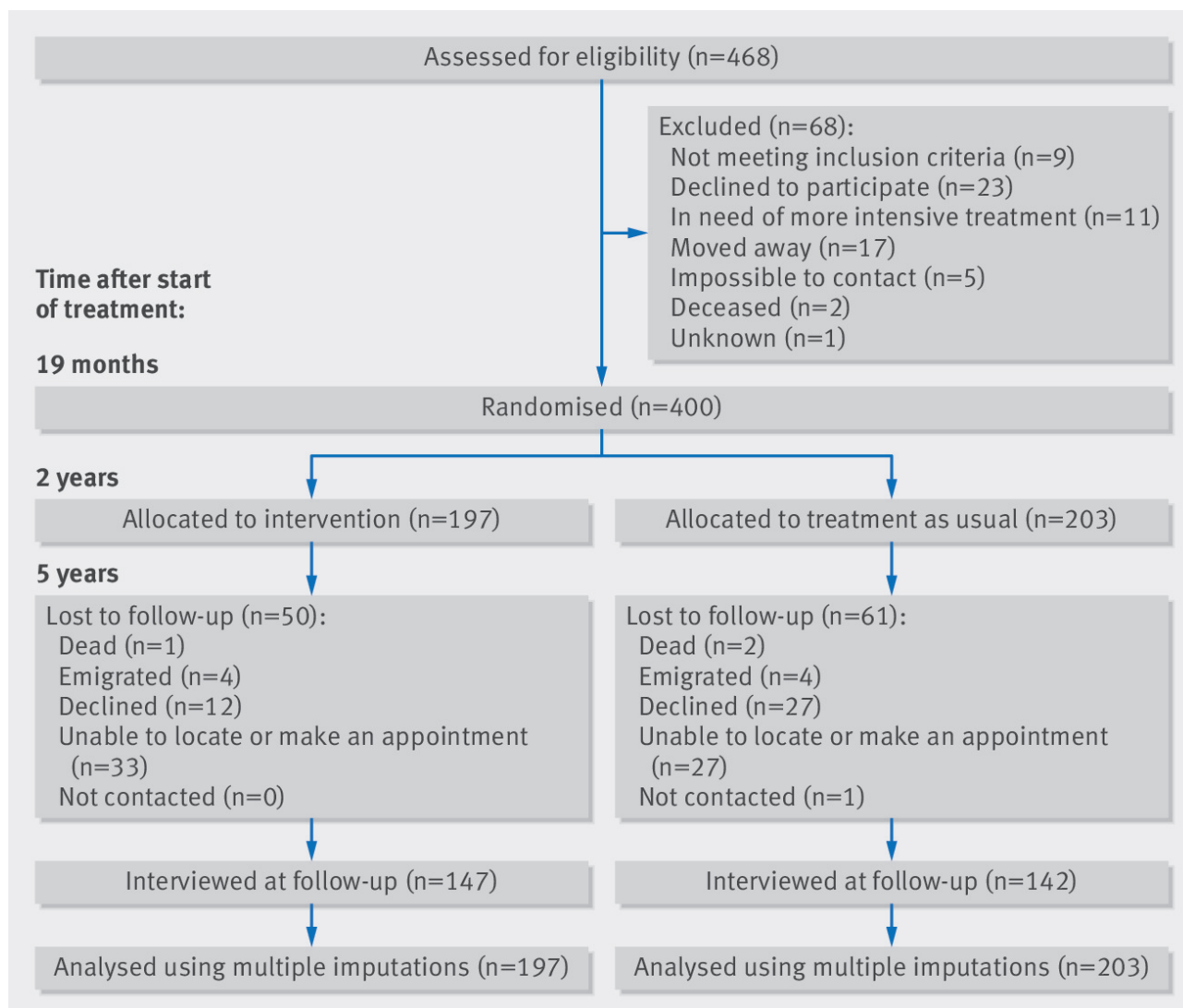†Numbers were based on registers and therefore not imputed.

Figures

Fig 1 Flowchart of participants in the OPUS II study

Fig 2 Psychopathological, functional, and cognitive development during the OPUS II study. From top to bottom, graphs show development of negative symptoms (mean score on the scale for assessment of negative symptoms (SANS)), psychotic symptoms (mean score on the scale for assessment for positive symptoms (SAPS)), functional level (mean score on the personal and social performance scale (PSP)), and cognitive functioning (mean total score on the brief assessment of cognition in schizophrenia (BACS)) from baseline to follow-up