



A randomised multicentre trial of integrated versus standard treatment for patients with a first episode of psychotic illness

Lone Petersen, Pia Jeppesen, Anne Thorup, Maj-Britt Abel, Johan Øhlenschläger, Torben Østergaard Christensen, Gertrud Krarup, Per Jørgensen and Merete Nordentoft

BMJ 2005;331;602-; originally published online 2 Sep 2005;
doi:10.1136/bmj.38565.415000.E01

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Contributors: See bmj.com

Funding: Camden and Islington Health Authority and the Department of Health. The contributors are independent of these bodies, except that several of us have contracts with a Mental Health Trust whose services have been commissioned by Camden and Islington Health Authority.

Competing interests: None declared.

Ethical approval: Camden and Islington community research ethics committee (reference 00/23).

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(Accepted 8 June 2005)

doi 10.1136/bmj.38519.678148.8F

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BMJ 2005;331:602-5

Abstract

Objectives To evaluate the effects of integrated treatment for patients with a first episode of psychotic illness.

Design Randomised clinical trial.

Setting Copenhagen Hospital Corporation and Psychiatric Hospital Aarhus, Denmark

Participants 547 patients with first episode of schizophrenia spectrum disorder.

Interventions Integrated treatment and standard treatment. The integrated treatment lasted for two years and consisted of assertive community treatment with programmes for family involvement and social skills training. Standard treatment offered contact with a community mental health centre.

Main outcome measures Psychotic and negative symptoms (each scored from 0 to a maximum of 5) at one and two years' follow-up.

Results At one year's follow-up, psychotic symptoms changed favourably to a mean of 1.09 (standard deviation 1.27) with an estimated mean difference between groups of -0.31 (95% confidence interval -0.55 to -0.07 , $P = 0.02$) in favour of integrated treatment. Negative symptoms changed favourably with an estimated difference between groups of -0.36 (-0.54 to -0.17 , $P < 0.001$) in favour of integrated treatment. At two years' follow-up the estimated mean difference between groups in psychotic symptoms was -0.32 (-0.58 to -0.06 , $P = 0.02$) and in negative symptoms was -0.45 (-0.67 to -0.22 , $P < 0.001$), both in favour of integrated treatment. Patients who

received integrated treatment had significantly less comorbid substance misuse, better adherence to treatment, and more satisfaction with treatment.

Conclusion Integrated treatment improved clinical outcome and adherence to treatment. The improvement in clinical outcome was consistent at one year and two year follow-ups.

Introduction

Certain psychosocial treatments, such as assertive community treatment and family intervention, have been shown to have beneficial effects on clinical and social outcomes for patients with schizophrenia.^{1,2} It has also been suggested that early treatment after the onset of psychotic illness provides the best chance of preventing relapse.^{3,4}

Our study (the OPUS trial) is the first large randomised clinical trial of integrated treatment versus standard treatment for patients who had experienced a first episode of psychosis.⁵

Participants and methods

Patients

Patients were included from all inpatient and outpatient mental health services in Copenhagen and Aarhus County. From January 1998 until December 2000, 547 patients aged 18-45 years with a diagnosis in



This is the abridged version of an article that was first posted on bmj.com on 2 September 2005: <http://bmj.com/cgi/doi/10.1136/bmj.38565.415000.E01>

the schizophrenia spectrum who had not been given antipsychotic drugs for more than 12 weeks of continuous treatment were included in the trial. Patients were centrally randomised to integrated treatment or standard treatment (see bmj.com for details).

Interventions

The trial was pragmatic, comparing integrated treatment defined by a set of protocols with usual treatment.

Integrated treatment

This was assertive community treatment enhanced by better specific content via family involvement and social skills training, and was provided by two multi-disciplinary teams in Copenhagen and one in Aarhus. Caseload reached a level of about 10. Each patient was offered treatment for two years. A primary team member, designated for each patient, was responsible for maintaining contact and coordinating treatment. Patients were visited in their homes or other places in their community or at their primary team member's office according to their preference. During hospitalisation, treatment responsibility was transferred to the hospital, but a team member visited the patient once a week. Office hours were Monday to Friday, 8 am to 5 pm. Outside office hours, patients could leave a message and be sure that the team would respond the next morning. A crisis plan was developed for each patient. If the patient was reluctant about treatment, the team stayed in contact with the patient and tried to motivate the patient to continue treatment.

The fidelity of the programme⁶ was 70% in both Copenhagen and Aarhus. Factors responsible for reduced fidelity were time-limited treatment, 24 hour coverage in other settings, and about two contacts weekly with each patient, patient's family, and collaborating partners.

Psychoeducational family treatment was offered,⁷ which included 18 months of treatment, 1.5 hours twice weekly, in a multiple family group with two therapists and four to six patients with their families. The multiple family group focused on problem solving and development of skills to cope with the illness.

Patients' social skills were assessed,⁸ and those with impaired social skills were offered training focusing on medication, coping with symptoms, conversation, and problem solving skills in a group of a maximum of six patients and two therapists.

Standard treatment

Standard treatment usually offered the patient treatment at a community mental health centre. Each patient was usually in contact with a physician, a community mental health nurse, and in some cases also a social worker. Home visit was possible, but office visits were the general rule. A staff member's caseload in the community mental health centres varied between 1:20 and 1:30. Outside office hours, patients could refer themselves to the psychiatric emergency room.

Antipsychotic drugs

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 use of second generation antipsychotic drugs as first choice.

Assessments

Only independent investigators were involved in follow-up interviews. They were not blind to treatment allocation. At study entry and at the one and two year follow-ups, the following information was collected (see bmj.com for details):

- Main diagnosis and comorbidity based on the schedule for clinical assessment in neuropsychiatry (SCAN)
- Scale for assessment of positive symptoms (SAPS) and scale for assessment of negative symptoms (SANS)
- Sociodemographic factors
- Global assessment of functioning, function and symptoms (GAF)
- Social network schedule
- Client satisfaction questionnaire
- Suicide attempts and suicidal ideation based on self reporting
- Duration of untreated psychosis, assessed with the interview for retrospective assessment of onset of schizophrenia (IRAOS).

We used algorithms to investigate whether patients fulfilled the general criteria for depression in ICD-10. Inter-rater reliability among investigators found moderate or very good agreement.

Other data sources

Information about use of bed days was available from official registers for all patients, and service use, use of antipsychotic drugs, and treatment adherence from patients' full medical records.

Statistical methods

Attrition to the two year follow-up interview was skewed: 75% of the patients randomised to integrated treatment attended the interview compared with only 60% of control patients (see fig on bmj.com). To manage the skewed attrition we carried out sensitivity analyses. We also assessed the influence of missing data on the one and two year outcome measures, by subjecting the data on SAPS, SANS, and GAF to further analysis which assumed that the distribution of missing data could be estimated from the information from previous interviews. (See bmj.com for full details of statistical analysis.)

Power calculation

When the trial was planned, we considered relapse to be the primary outcome measure, and we intended to assess each patient every third month for positive symptoms with SAPS interviews. However, since participation in these interviews was only about 60%, we decided in September 1999 to use psychotic and negative symptoms at one and two year follow-up as the primary outcome measures. From our power calculation we calculated that 178 patients should be included in each group.

Results

Baseline characteristics

The two treatment groups had no significant differences in their baseline characteristics (see table 1 on bmj.com).

Attrition from study

We found no significant difference in baseline measures between those patients who participated in

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Clinical outcomes and user satisfaction of patients with a first episode of psychotic illness who received integrated treatment or standard treatment. Values are means (SD) unless stated otherwise

	1 year follow-up (n=419)				2 year follow-up (n=369)			
	Integrated treatment (n=227)	Standard treatment (n=192)	Estimated mean difference (95% CI)	P value of difference	Integrated treatment (n=205)	Standard treatment (n=164)	Estimated mean difference (95% CI)	P value of difference
Psychopathology*:								
Psychotic dimension	1.09 (1.27)	1.35 (1.39)	-0.31 (-0.55 to -0.07)	0.02	1.06 (1.26)	1.27 (1.40)	-0.32 (-0.58 to -0.06)	0.02
Negative dimension	1.68 (1.10)	2.02 (1.12)	-0.36 (-0.54 to -0.17)	<0.001	1.41 (1.15)	1.82 (1.23)	-0.45 (-0.67 to -0.22)	<0.001
Disorganised dimension	0.40 (0.59)	0.42 (0.56)	-0.04 (-0.14 to 0.07)	0.5	0.37 (0.56)	0.50 (0.73)	-0.12 (-0.25 to 0.00)	0.06
GAF, symptom	48.2 (14.9)	44.9 (16.0)	3.00 (0.37 to 5.63)	0.03	51.18 (15.01)	48.67 (15.92)	2.45 (-0.32 to 5.22)	0.08
GAF, function	51.7 (15.1)	49.4 (14.6)	2.61 (0.11 to 5.15)	0.04	55.16 (15.15)	51.13 (15.92)	3.12 (0.37 to 5.88)	0.03
User satisfaction†	24.9 (4.5)	23.0 (7.2)	1.88 (0.73 to 3.02)	0.001	26.1 (3.7)	22.9 (5.2)	3.09 (2.10 to 4.04)	<0.001

GAF=global assessment of functioning.

*Estimated mean differences are based on a repeated measurements model with treatment site, sex, substance misuse, diagnosis at baseline, and baseline values of the scale included as covariates (see text for details).

†Based on client satisfaction questionnaire score. Estimated mean differences calculated by analysis of variance with treatment site as covariate.

the follow-up interviews and those who did not, except that patients from Aarhus and patients with a relative attending the baseline interview in both treatment groups were more likely to attend the follow-up interview. In the control group, patients who had not completed high school and those with substance misuse diagnosed at baseline interview were less likely to participate in the follow-up interviews.

Main outcomes

Integrated treatment was significantly better than standard treatment with regard to both psychotic symptoms and negative symptoms (see table). The estimated effect of integrated treatment versus standard treatment on the psychotic symptoms was equal to every third patient in the integrated treatment group gaining one point (from "severe" to "marked" or from "moderate" to "mild") when measured with the SAPS scale. The effect on negative symptoms is equal to every second patient in integrated treatment gaining one point compared with standard treatment. This is of clinical importance.

Integrated treatment also resulted in significantly greater patient satisfaction, and this difference between treatment groups was larger at two year follow-up than at one year. Cohen's *d* standardised effect size for client satisfaction was 0.69, which is fairly large.

Sensitivity analyses of psychotic and negative symptoms

We tested two different assumptions about the patients who did not participate in the two year follow-up interview. The less favourable prognostic factors among non-participants compared with participants suggest that non-participants as a group fared worse. Carrying forward the non-participants' baseline values and one year values (if available) for the psychotic and negative dimensions to the two year follow-up resulted in integrated treatment having an even greater positive effect on both psychotic and negative symptoms.

The other (less likely) assumption was that non-participants had experienced a total remission of psychotic and negative symptoms. On this basis, we set their psychotic and negative dimensions at two years to zero, and the positive effect of integrated treatment on the psychotic and negative dimensions became non-significant.

Comorbidity and social outcomes

Integrated treatment significantly reduced substance misuse both at one year and two year follow-up, but it

had no significant effect on depression or suicidal behaviour and ideation (see bmj.com).

A significantly smaller proportion of patients given integrated treatment did not live independently at one year follow-up compared with patients given standard treatment (10% *v* 17%), but not at two year follow-up (13% *v* 14%). At one year follow-up significantly more of the patients given integrated treatment than those given standard treatment were attending a rehabilitation programme (14% *v* 7%), but at two years the difference was not significant (17% *v* 12%).

Non-adherence to treatment

During the first year, patients were significantly less likely to discontinue integrated treatment for at least a month than standard treatment (8% *v* 22%). Integrated treatment was also clearly superior to standard treatment when non-adherence was measured in terms of treatment discontinued in spite of need (3% *v* 15%) or in terms of not making any outpatient visits (3% *v* 15% in first year, 7% *v* 31% in second year) (see bmj.com).

Use of health services and antipsychotic drugs

Patients given integrated treatment spent significantly fewer days in hospital in the first year than did patients given standard treatment (mean 62 days *v* 79 days). For the total intervention period, patients given integrated treatment used 22% fewer bed days than those given standard treatment (mean 89 days *v* 114 days; difference -25.0, 95% confidence interval -51.0 to 1.1, *P*=0.06).

The proportion of patients receiving first or second generation antipsychotic drugs was not significantly different in the two treatment groups. To establish whether differences in antipsychotic medication in the two groups were responsible for the differences in psychotic and negative dimension, we analysed drug use by treatment allocation, treatment site, baseline value of scale, and use of second generation antipsychotics (or first and second generation, or first generation only). All analyses showed a significant positive effect of integrated treatment on psychotic and negative symptoms. Patients given integrated treatment received significantly lower doses of second generation antipsychotics.

Discussion

Patient outcomes

The results of this large randomised trial favour integrated treatment, consisting of the assertive community treatment model enhanced by specific

protocols for family involvement and social skills training, with regard to psychopathology, adherence to treatment, comorbid diagnosis of harm and dependence, client satisfaction, social outcomes (only first year), and use of health services. The positive effects on psychotic symptoms were not explained by differences in use of antipsychotic drugs. The results from the first year with regard to psychotic and negative symptoms were replicated in the second year, indicating robustness.

The effect of integrated treatment on psychotic and negative symptoms was smaller than the minimum effect we had assumed when calculating the sample size needed for the trial. If we calculate standardised measures of effect size such as Cohen's *d*, we find a medium effect size for psychotic symptoms and negative symptoms. Calculations of Cohen's *d* are based only on assessment of interviewed patients, and therefore possibly underestimate the difference between integrated treatment and standard treatment.

Analyses of differential attrition in the two treatment groups indicate that more patients with poor outcome (such as substance misusers) were interviewed in the integrated treatment group, so the effect of integrated treatment on substance misuse may be larger than in our results. This might explain why the patients receiving integrated treatment did not have a significantly better social outcome than the patients given standard treatment in the two year follow-up.

The results concerning suicide attempts and suicidal ideation are not encouraging, and it is likely that specialised interventions such as 24 hour support and cognitive behaviour therapy might be required to get better results.

Comparison with other studies

Our findings are in accordance with the results from a meta-analysis of assertive community treatment for people with severe mental illness,¹ with findings from naturalistic studies of integrated treatment,⁹⁻¹¹ and with the results of the only other published randomised clinical trial of specialised care for patients with early psychosis.¹²

Limitations of the study

It was necessary to change our outcome measure from relapse to psychotic and negative symptoms, but this decision was made before the analyses of one year outcome were started.

Interviewers were not blind to which treatment patients had been assigned, which may be associated with a biased rating of psychopathology. However, our findings about psychopathology are coherent with several other outcome measures that are less likely to be biased—such as health service use. Our analyses of use of bed days were not influenced by the differential attrition. Our trial might be biased because of skewed attrition, but our analyses indicate that patients who did not attend two year follow-up interviews constituted a negatively selected subpopulation. This would be more likely to bias our results against integrated treatment than in favour of it.

Conclusion

Integrated treatment reduced psychotic and negative symptoms more than standard treatment. The effect was small but of clinical importance. Integrated

What is already known on this topic

Patients with non-affective, first episode psychosis constitute a high risk group for several negative outcomes

Psychoeducational multi-family groups are effective in preventing relapse in populations of patients with chronic schizophrenia

Assertive community treatment of patients with severe mental illness has positive effects on independent living, labour market affiliation, satisfaction with treatment, and use of hospital beds

What this study adds

Integrated treatment (assertive community treatment enhanced with psychoeducational family intervention and social skills training) can be modified to focus on elements of special relevance to patients with a first episode of psychotic illness

Integrated treatment reduced psychotic and negative symptoms more than standard treatment

Integrated treatment also reduced comorbid alcohol and drug misuse and increased adherence to treatment and user satisfaction

treatment improved adherence to treatment. It also adds substantial costs to treatment, but these would be counterbalanced by the reduced use of other health services that we found with this intervention.

Contributors: See bmj.com.

Funding: The project received grants from the Danish Ministry of Health (jr.nr. 96-0770-71), Danish Ministry of Social Affairs, University of Copenhagen, Copenhagen Hospital Corporation, Danish Medical Research Council (jr.nr. 9601612 and 9900734), and Slagtermester Wørzners Foundation.

Competing interests: None declared.

Ethical approval: The local ethics committee approved the trial (KF 01-387/97).

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(Accepted 19 July 2005)

doi 10.1136/bmj.38565.415000.E01

What is already known on this topic

It is generally assumed that the more explicit and meticulous the search strategy, the more likely a systematic review is to pick up all the important papers

In systematic reviews of clinical treatments, most high quality primary studies can be identified by searching four standard electronic databases

What this study adds

In systematic reviews of complex and heterogeneous evidence (such as those undertaken for management and policymaking questions) formal protocol-driven search strategies may fail to identify important evidence

Informal approaches such as browsing, "asking around," and being alert to serendipitous discovery can substantially increase the yield and efficiency of search efforts

"Snowball" methods such as pursuing references of references and electronic citation tracking are especially powerful for identifying high quality sources in obscure locations

We initially scanned over 6000 electronic abstracts and book titles, and selected 1004 full-text books or papers for further analysis. After appraising all these for quality and relevance, we cited 495 (of which 213 were empirical studies and 21 were systematic or quasi-systematic reviews) in the final report. We classified each according to its origin, using the taxonomy above.

Results

The table shows the origins of our 495 sources. Twenty three per cent of the sources were known to us or were recommended by colleagues when we approached them by email, which took little time. Electronic searching, including developing and refining search strategies and adapting these to different databases, took about two weeks of specialist librarian time and yielded only about a quarter of the sources—an average of one useful paper every 40 minutes of searching. It took a month to hand search a total of 271 journal-years, from which we extracted only 24 papers that made the final report—an average of one paper per nine hours of searching.

Overall, the greatest yield was from pursuing selected references of references. It was impossible to isolate the time spent on reference tracking since this was done in parallel with the critical appraisal of each paper. Electronic citation tracking of selected papers took around a day in total and uncovered many important, recent sources, including five systematic reviews (three of which were not identified by any other method) and 12% of all empirical studies—around one useful paper for every 15 minutes of searching. Five

papers came our way by chance, including a major systematic review that was passed to one of us in a coffee queue by someone who did not know about this research.

Discussion

Systematic review of complex evidence cannot rely solely on predefined, protocol driven search strategies, no matter how many databases are searched. Strategies that might seem less efficient (such as browsing library shelves, asking colleagues, pursuing references that look interesting, and simply being alert to serendipitous discovery) may have a better yield per hour spent and are likely to identify important sources that would otherwise be missed. Citation tracking is an important search method for identifying systematic reviews published in obscure journals.

This study builds on extensive secondary research by all the authors on the systematic review (see reference list), whose input we gratefully acknowledge. We also thank Jeanette Buckingham for comments on a previous draft of this paper.

Competing interests: None declared.

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(Accepted 14 September 2005)

Corrections and clarifications

A randomised multicentre trial of integrated versus standard treatment for patients with a first episode of psychotic illness

An error crept into this paper by Lone Petersen and colleagues during editing and subsequently evaded detection (*BMJ* 2005;331:602-5, 17 Sep). In the methods section, the description of integrated treatment should have stated that psychoeducational family treatment was offered in 1.5 hour sessions twice a month (not twice weekly).

Dutch experience of monitoring euthanasia

Poor editorial communication led to the omission of a figure that should have accompanied this Education and Debate article by Bregje D Onwuteaka-Philipsen and colleagues (*BMJ* 2005;331:691-3, 24 Sep). Readers can now see the figure on [bmj.com](http://bmj.com/bmjournals.com/cgi/content/full/331/7518/691/DC1) (<http://bmj.com/bmjournals.com/cgi/content/full/331/7518/691/DC1>).

Delays in publication of cost utility analyses conducted alongside clinical trials: registry analysis

For some reason that we have been unable to establish, the final author (Peter J Neumann) of this paper by Dan Greenberg and colleagues did not appear in the full text version and the contents page on bmj.com, although it did appear in the pdf version and in the printed journal (*BMJ* 2004;328:1536-7). The online omissions have been corrected.

Penicillin should remain the standard treatment for early syphilis—for now

Despite managing to cite azithromycin correctly three times in the text of this Short Cut item, compiled by Alison Tonks (*BMJ* 2005;331:721-2, 1 Oct), we failed in our fourth attempt. Towards the end of the item, we called it azathioprine (which we misspelt).