ORIGINAL ARTICLE

Two-year outcome in first-episode psychosis treated according to an integrated model. Is immediate neuroleptisation always needed?

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Summary – In this multicentre study the two-year outcome of two groups of consecutive patients (total $N = 106$) with first-episode functional non-affective psychosis, both treated according to the 'need-specific Finnish model', which stresses teamwork, patient and family participation and basic psychotherapeutic attitudes, was compared. No alternative treatment facilities were available in the study sites. The two study groups differed in the use of neuroleptics: three of the sites (the experimental group) used a minimal neuroleptic regime whilst the other three (the control group) used neuroleptics according to the usual practice. Total time spent in hospital, occurrence of psychotic symptoms during the last follow-up year, employment, GAS score and the Grip on Life assessment were used as outcome measures. In the experimental group 42.9% of the patients did not receive neuroleptics at all during the whole two-year period, while the corresponding proportion in the control group was 5.9%. The overall outcome of the whole group could be seen as rather favourable. The main result was that the outcome of the experimental group was equal or even somewhat better than that of the control group, also after controlling for age, gender and diagnosis. This indicates that an integrated approach, stressing intensive psychosocial measures, is recommended in the treatment of acute first-episode psychosis. © 2000 Éditions scientifiques et médicales Elsevier SAS

first-time psychosis / follow-up study / integrated treatment / outcome / use of neuroleptics

INTRODUCTION

There seem still to be controversies concerning the most appropriate and effective treatment of first-episode non-affective psychoses, although several practice guidelines [6, 17] and consensus statements, especially concerning schizophrenic psychoses [16, 19], have been published. The right balance between psychological and biological modes of treatment, in particular, is still under debate. Nevertheless, an integrated approach has usually been recommended. One example is the comprehensive or need-adapted (the so-called Finnish) model, which is based on the more than 30 years of research and development work of Professor Yrjö Alanen and his coworkers [2-5]. The basic principles of this model are teamwork, basic psychotherapeutic attitude, family-centredness and 'need-specificity'.

Because there are many controlled studies showing that neuroleptic drugs are superior to placebo in reducing positive psychotic symptoms [13, 15], their routine

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use in the treatment of non-affective psychoses, especially acute schizophrenia, is seldom questioned. There seems to be more controversy concerning the usefulness and efficacy of psychosocial modes of treatment, although their effect has also been demonstrated in several studies in recent years [24]. There is also some evidence in the literature that the role of neuroleptics is more relative if intensive effort is laid on the psychosocial modes of treatment [10, 12, 20, 26, 28].

However, there is wide agreement that the use of neuroleptics is not without problems. Approximately 30–40% of the acute patients do not benefit sufficiently from these drugs. Up to 30% of the patients experience clearly disturbing acute side effects. For many patients the effect on their 'sense of living' seems to be particularly unpleasant. Some of the (fortunately rare) side effects can be really severe, such as malignant neuroleptic syndrome, or agranulocytosis in the case of clozapine. The irreversible long-term side effect, tardive dyskinesia, has affected up to 20% of patients who have used these drugs for several years. Although the launching of the new-generation neuroleptics has diminished these problems, alternatives to the routine use of neuroleptics have been sought. Examples in recent years are the recommendations for intermittent [9] or minimal-dose [21] use of neuroleptics.

A multicentre research and development project, called Acute Psychosis Integrated Treatment (API), was started in Finland in 1992 [18]. The main objective of this project was to test the feasibility of the Finnish treatment model [3] in ordinary psychiatric service systems. The other objective was to evaluate the role of neuroleptic drug treatment when psychosocial measures are applied maximally in the treatment of first-episode psychoses. The specific aims of this paper are to 1) describe the overall two-year outcome of the project patients; 2) compare the outcome of the experimental group (minimal use of neuroleptics) with that of the control group (use of neuroleptics as usual); and 3) describe the role of some confounding variables (sex, age, duration and course of illness prior to treatment, diagnosis) on the outcome.

MATERIAL AND METHODS

Design

Six psychiatric hospitals and their outpatient facilities, covering catchment areas with 70,000–200,000 inhabitants from different parts of Finland, participated in

the API Project [18]. All the centres agreed to conduct the treatment of their API cohorts (consecutive patients with first-episode schizophrenia-type psychosis) according to the psychotherapeutic and family-centred principles of the Finnish treatment model [3]. Three of the centres that had the most training and experience in the use of psychosocial measures agreed to apply the 'minimal neuroleptics use' regime developed for the API project. This meant that during the period of the intensive 'initial examination' (the first three weeks after admission) neuroleptic drug treatment was, whenever possible, not started. If the patient's condition had clearly improved during this initial phase, the neuroleptisation of the patient was postponed even further or avoided totally. The other three centres used neuroleptics as was their usual practice, which in most cases meant immediate neuroleptisation (the control group).

So far, follow-up surveys have been conducted at six months, one year and two years after the basic survey. The specific project teams, established in every centre from their ordinary staff, have been responsible for the assessments and other data collection. This paper will focus on the two-year outcome.

The study protocol was approved by the ethics committee of the Medical Faculty of the University of Turku as well as by the ethics committees of each participating centre. All patients in the study gave informed consent.

Subjects

The subjects of this study were consecutive patients with a first-episode psychosis and without any previous psychiatric treatment. No other treatment facilities were available in these catchment areas. The specific inclusion criteria were formulated in the following way: 1) new patient with an admission diagnosis of functional non-affective psychosis according to DSM-III-R (295, 297, 298); 2) residency in the catchment area; 3) 15 to 44 years of age; 4) admission for treatment between 1 April 1992 and 31 December 1993; and 5) patient was able to give informed consent and was willing to participate; if the patient was less than 18 years old, informed consent from the guardian was also needed.

The specific exclusion criteria included earlier treatment with neuroleptics, earlier psychotherapy (more than 30 visits), serious physical illness, pregnancy and serious threat of suicide or violence.

All together, 165 patients (107 in the experimental centres and 58 in the control centres) were originally

considered to fulfill the inclusion criteria. The greater number of patients from the experimental centres is explained by the bigger size of their catchment areas. Thirty (18.2%) of these patients (experimental: 23 [21.5%]; control: 7 [12.1%]) were not, however, included in the final study population (χ^2= 2.247; $P > 0.05$). Most of the dropouts refused to participate. The effect of the specific exclusion criteria was nonexistent. However, one should take into consideration that five patients from one experimental site were sent in the initial phase of their treatment to other hospitals outside the catchment area because this centre had no facilities to treat involuntarily admitted patients. These patients were also dropouts. The possible bias caused by this fact will be considered in the discussion.

Thus, 135 patients (experimental: 84; control: 51) were included in the study population. Of these, 80 (59.3%) were men and 55 (40.7%) were women. Those between 25 and 34 years of age formed the largest age group (41%); the mean age was 28.7 years. Of the original study population, 106 (78.5%) could be evaluated at the two-year follow-up survey. Most of the dropouts at this phase were not willing to participate. Three patients were excluded because their diagnosis at the six-month follow-up rechecking was affective disorder. Five patients (three from the experimental and two from the control group) had died during the two-year follow-up period. Four of these deaths were suicides, and all these patients had received neuroleptic medication.

The demographic and clinical characteristics of those who did and those who did not participate in the two-year follow-up are presented in *table I*. It is evident that those who participated had a higher frequency of more serious disorders as their initial diagnoses were more often schizophrenia and less often unspecified psychosis.

Study instruments

The patients were evaluated personally at all phases of the study by specific project teams who participated in joint training before the study started. Cross-validation between the project teams of the different centres, however, was not conducted. The patients' family members took part in these interviews whenever possible. The following study instruments were used:

A semi-structured interview form to collect information on the patient's history, his family and family relations, outbreak of the illness, symptoms, clinical

Table I. Demographic and clinical characteristics of the follow-up sample and of the dropouts.

Phase	Participated N = 106	Dropouts N = 29	P
Gender (male)	56.6 %	69.0 %	0.230
Age			0.673
15–24	34.9	27.6	
25–34	39.6	48.3	
35–44	25.5	24.1	
Marital status			0.709
Never married	71.8 %	79.3 %	
Married	22.3 %	17.2 %	
Ex-married	5.8 %	3.5 %	
Social class (white collar)	32.4 %	44.8 %	0.214
Diagnosis (DSM-III-R)			0.012
Schizophrenia or delusional psychosis	45.0 %	19.3 %	
Schizophreniform psychosis	23.9 %	26.9 %	
Unspecified psychosis	31.2 %	53.8 %	
Mean age (years)	29.4	30.9	0.284
Mean age at 1st psychiatric symptoms	25.9	28.7	0.161
Mean age at 1st psychotic symptoms	28.8	30.6	0.239
GAS at baseline (mean)	4.17	4.62	0.852

state and diagnosis on the basis of the DSM-III-R. The form also contained items concerning the detailed treatment plan for the patient.

A corresponding form, excluding the history, was used at the follow-up surveys. Furthermore, the follow-up form included detailed questions about service use during the follow-up period. The final diagnosis was confirmed at the six-month follow-up

The psychosis items from the Comprehensive Psychological Rating Scale, CPRS [7], as well as two family assessment scales [1, 22] were filled in at every phase of the study.

The Brief Psychiatric Rating Scale, BPRS [23], was mainly used for short-term monitoring of the patients in the beginning of the treatment, but this form was also completed at the follow-up surveys of the study.

Outcome measures

The two-year outcome of the API patients was assessed with the following measures: 1) Total time spent in hospital treatment during the two-year study period, including the possible initial hospitalisation (fewer than 14 days/14 days or more); 2) occurrence of psychotic symptoms according to the CPRS during the last

follow-up year (no symptoms/at least one symptom); 3) engagement in paid employment at the two-year follow-up survey (yes/no); 4) the Global Assesment Scale (GAS) score [14] at the two-year follow-up survey (7 or more/less than 7); and 5) the Grip on Life Assessment [27] at the two-year follow-up survey (maintained/at least partly lost).

Statistical methods

In most of the analyses cross-tabulations with the χ^2 test as the statistical method were used. Analysis of variance was used to test the difference of means. The effect of several independent variables on the outcome measures was tested by logistic regression analysis.

RESULTS

Initial assessment of the groups

In the initial evaluation of the patients, there were no significant differences between the experimental and control groups in the measures used to assess the outcome, namely number of psychotic symptoms, GAS or the Grip on Life assessment. However, the duration from onset of active psychotic symptoms to admission was longer for the experimental group (mean 49 days) than for the control group (mean 24 days; t = 2.299, P = 0.024).

The initial diagnoses were rechecked at the six-month follow-up survey to ensure the needed follow-up time for diagnosing schizophrenia. Two-fifths of the total follow-up group received a diagnosis of schizophrenia (2950-2953, 2955-2959) or delusional psychosis (297), and one-fourth schizophreniform psychosis (2954). For about 30% the diagnosis was unspecified psychosis (298). There were more patients with schizophrenia and delusional psychosis, and fewer with schizophreniform psychosis in the experimental group in comparison to the control group (difference of the distributions: χ^2 = 6.582; P < 0.05) *(table II)*.

Treatment received

The experimental group and the control group differed clearly in the use of neuroleptic drug treatment. In the experimental group 42.9% of the patients had not received neuroleptics at all during the total two-year follow-up period, including the initial phase of the treatment, while the corresponding figure in the control group was 5.9% (χ^2= 17.343; P < 0.001). The mean total duration of neuroleptic treatment for those who had received these drugs was 42.6 weeks in the experimental group, and 56.5 weeks in the control group (F = 1.53; P = 0.212). The neuroleptic dosage used was usually rather low in both groups. The dose exceeded 450 mg of chlorpomazine equivalent at some phase of the treatment for only 3.0% of the patients in the experimental group, and for 12.8% of the patients in the control group (χ^2 = 3.866; P < 0.05).

Within the experimental group, those patients who received neuroleptics did not differ statistically significantly from those who did not according to the assessments made at the initial examination. These assessments included premorbid adjustment, employment, number of psychotic symptoms, duration of untreated psychosis and diagnosis. On the other hand, those who had received neuroleptics had a significantly worse outcome, suggesting a more severe type or course of illness in comparison to those who had not received neuroleptics.

According to the treatment model of the API project, most of the patients received some form of psychological treatment *(table III)*. As can be seen, psychological therapies were used more often in the experimental group than in the control group. The use of family therapy (mainly systemic-analytic) was especially abun-

Table II. The final diagnoses of the two-year follow-up material by site (%).

Diagnosis	Experiment N = 67	Control N = 39	Total N = 106
Schizophrenia	49.3	25.6	40.6
Schizophreniform psychosis	16.4	38.5	24.5
Delusional psychosis	3.0	10.3	5.7
Unspecified psychosis	31.3	25.6	29.2
Total	100.0	100.0	100.0

Table III. The psychological treatments used during the follow-up period by site, proportions by percentage.

Mode of treatment	Experiment N = 67	Control N = 39	Total N = 106	P
Intensive individual psychotherapy	25.4	28.2	26.4	0.750
Family therapy	67.2	38.5	56.6	0.004
Group therapy	4.5	15.4	8.5	0.052
Any form of psychological treatment	73.1	53.9	66.0	0.043

dant in the experimental group, and there was a clear difference in comparison to the control group. Group therapy, on the other hand, was used more often at the control sites.

Overall outcome

The overall two-year outcome of the API series is shown in *table IV*. There was no significant difference between the sexes in any of the outcome measures. About two-fifths of the patients had spent fewer than 14 days in hospital treatment during the whole study period. Eleven-point-nine percent of the patients had not been hospitalised at all, 17.4% had been in hospital treatment altogether for at least three months and 7.3% had been hospitalised for six months or longer.

Generally, the situation of the patients at the two-year follow-up was relatively good. A little over half of them had been totally free from psychotic symptoms during the last follow-up year, and only one-fifth of the patients had had five symptoms or more. Two-fifths of patients had a fairly high GAS score (7 or more), and three-fifths had been able to maintain their 'grip on life'. The mean GAS score was 6.0. On the other hand, fewer than one-third were employed. As many as 22% of the patients were unemployed at the two-year follow-up, and 31% were on sick leave or disability pension.

As expected, the overall outcome varied greatly according to diagnosis *(table V)*. The outcome was clearly poorer for those diagnosed with schizophrenia (2950-3, 2955-9) than for the other diagnostic groups. In the delusional psychosis group (297) there were fewer patients with a high GAS score than in the other groups. The time from first psychiatric symptoms as well as the time from first active psychotic symptoms were not associated with the outcome measures *(tables VI and VII)*.

Table IV. Two-year outcome by sex; proportions by percentage.

| Outcome measure | Sex | | | P |
	Men	Women	Total	
Less than 2 weeks in hospital during 2 years	36.7	47.8	41.5	0.248
No psychotic symptoms during last year	48.3	56.5	51.9	0.178
Employed	35.0	28.3	32.1	0.574
GAS score 7 or more	35.2	46.5	40.2	0.179
Retained grip on life	59.3	65.2	61.9	0.537

Table V. Two-year outcome by diagnosis; proportions by percentage.

| Outcome measure | Diagnosis | | | | P |
	2950–3 2955–9	2954	297	298	
Less than 2 weeks in hospital during 2 years	30.2	42.3	66.7	51.6	0.163
No psychotic symptoms during last year	34.9	65.4	50.0	64.5	0.048
Employed	9.3	46.2	66.7	45.2	0.002
GAS score 7 or more	23.1	47.8	16.7	62.1	0.005
Retained grip on life	44.2	72.0	83.3	74.2	0.019

Table VI. Two-year outcome by time from first psychiatric symptoms; proportions by percentage.

| Outcome measure | Time (years) | | | P |
	< 1 N = 38	1–2 N = 39	2 + N = 29	
Less than 2 weeks in hospital during 2 years	44.7	41.0	37.9	0.852
No psychotic symptoms during last year	55.3	56.4	41.4	0.412
Employed	31.6	41.0	20.7	0.206
GAS score 7 or more	41.7	46.0	29.2	0.416
Retained grip on life	62.2	64.1	58.6	0.899

Table VII. Two-year outcome by time from first psychotic symptoms; proportions by percentage.

| Outcome measure | Time (days) | | | P |
	0–6 N = 38	8–31 N = 34	31+ N = 34	
Less than 2 weeks in hospital during 2 years	42.1	47.1	35.3	0.613
No psychotic symptoms during last year	52.6	52.9	50.0	0.965
Employed	39.5	35.3	20.6	0.204
GAS score 7 or more	36.1	35.5	50.0	0.420
Retained grip on life	62.2	58.8	64.7	0.882

Comparison between the groups

One aim of this paper was to compare the outcome between the experimental group (minimal neuroleptics use) and the control group (normal neuroleptics use). It was shown that the experimental group in comparison to the control group had a somewhat better two-year outcome: it had less hospital treatment during the

Table VIII. Two-year outcome by site; proportions by percentage.

Outcome measure	Experiment	Control	Total	P
Less than 2 weeks in hospital during 2 years	50.8	25.6	41.5	0.011
No psychotic symptoms during last year	58.2	41.0	51.9	0.088
Employed	32.8	30.8	32.1	0.826
GAS score 7 or more	49.2	25.0	40.2	0.019
Retained grip on life	65.7	55.3	61.9	0.291

two-year period, had psychotic symptoms somewhat less often during the last year, and a high GAS score was more common (table VIII).

Finally, stepwise logistic regression analyses of the outcome measures were conducted using age, sex, diagnosis, time from first psychiatric symptoms, time from first psychotic symptoms and site (experimental or control) as explanatory variables. The clearest difference between the experimental and control groups (in favour of the experimental group) appeared again in the length of hospital treatment and occurrence of psychotic symptoms. The analysis of the last-mentioned outcome measure is shown in *table IX*. As can be seen, only the diagnosis and the site came into the model as significant explanatory variables. The most remarkable finding from this analysis is that the difference between the experimental and control group became even more pronounced when the other (confounding) variables were taken into consideration. The risk of showing psychotic symptoms during the last follow-up year was more than threefold for the control group in comparison to the experimental group. What is noteworthy is that time from first psychiatric symptoms and time

Table IX. Predictors of psychotic symptoms at two-year follow-up; step-wise logistic regression analysis using sex, age, diagnosis, time since first psychiatric symptoms, time since first psychotic symptoms and site as independent variables.

Variable	Relative risk	95 % confidence low	high	P
Diagnosis				.029
2954	1.0			
2950–3, 2955–9	5.88	1.82	19.61	
297	1.79	0.27	11.76	
298	1.45	0.43	4.76	
Site				.009
experimental	1.0			
control	3.33	1.28	9.09	

from first psychotic symptoms were not associated with the outcome.

DISCUSSION

Weaknesses of the study

There are some weaknesses in this study that must be taken into consideration when interpreting its results. Among them belong the lack of information on the reliability in diagnostics, the heterogeneity of the diagnoses and the possible bias caused by the fact that the project teams who also participated in the treatment of the patients made all the outcome assessments. The fact that there were dropouts both in the initial recruiting phase and in the follow-up may also have some effect on the results.

Concerning the diagnostics, the DSM-III-R diagnoses have been in official use in the Finnish psychiatric services since 1987, so the diagnostic criteria, which are translated into Finnish, were familiar to the project teams. The slight difference in the diagnostic composition between the groups could be controlled for with the logistic regression analysis. Actually, the patients in the experimental group had somewhat more severe diagnoses than patients in the control group, so it is unlikely that the difference in the diagnostic mix could explain the better outcome in the former group.

The heterogeneity of the diagnostic composition may, of course, also be seen as a problem. Perhaps the interpretation of the results would be easier if the groups had consisted only of patients with a clear diagnosis of schizophrenia. This had, on the other hand, brought problems in this acute first-episode cohort because of the required six-month time period of active symptoms by the DSM-III-R system for that diagnosis.

The fact that the outcome measures were assessed by persons who participated in the treatment of the patients may be seen as a more serious problem. The credibility of the results would be increased if an independent researcher had made the assessments as well. However, before the project started, persons who made the outcome assessments were trained in their use. Furthermore, during the whole project joint training days, where problems in the assessments could be discussed, were organised twice a year for the project teams in all the centres. There is no reason to believe that the staff of the experimental centres would have been more biased in their assessments than those of the control centres. The use of independent evaluators is not without prob-

lems. For example, concerning the occurrence of psychotic symptoms during the last follow-up year, the outsider does not have that knowledge about the patient's situation which is needed to make a proper assessment. In our experience, patients are often also unwilling to meet an outsider for evaluation, resulting in an even bigger loss. The length of the hospital stay, on the other hand, which showed a clear difference in favour of the experimental group, is clearly an outcome measure which is not dependent on the evaluator.

The loss in this study was not exceptionally high: 18% both in the recruiting phase and in the follow-up. The majority of the dropouts were refusals. As was mentioned in the Subjects section, five of the patients of one experimental centre were excluded from the study population because this catchment area had no resources for treating involuntarily admitted patients. However, if one supposes that all these patients would belong to the poor outcome group the main result of this study would not change: the outcome in the experimental group would not be poorer than that in the control group.

One should, however, not consider our study design as a real experimental design because the experimental and control groups were recruited from different study sites. It is clear that they can differ, although they are comprised of consecutive patients of the participating centres, as already stated, e.g., the diagnostic mix differed somewhat between the groups. For all the reasons stated above the results of our study must be regarded as tentative, and they need replication with a more controlled design.

Strengths of the study

This study also has some strengths. The most important is that the study population consisted of all consecutive patients with previously untreated first-episode functional non-affective psychosis from geographically defined catchment areas (with the exception mentioned above). There were no other psychiatric treatment facilities in these catchment areas, so the coverage of the samples can be regarded as very good. It is also noteworthy that the patients had not received any treatment (including neuroleptics) before entering the study, meaning that differences in previous treatment cannot explain the result.

Main finding

The main finding of this study was that the two-year outcome of an unselected group of consecutive first-time psychotic patients who were treated by intensive psychosocial interventions combined with minimal use of neuroleptics was at least as good as the outcome of those whose treatment regime included the usual doses of neuroleptics. Concerning time spent in hospital during the follow-up period or occurrence of psychotic symptoms during the last follow-up year, the prognosis was, after controlling for confounding factors, especially the diagnosis, even better in the experimental than in the control group.

One must also take into consideration that more patients in the experimental group than in the control group received intensive family therapy. Therefore, the better prognosis in the experimental group can most probably be explained by this fact, not by the lack of neuroleptics. Anyhow, the finding can be interpreted so that routine use of neuroleptics in the treatment of these patients is not so essential as it usually has been considered.

The two-year outcome of our patients can also generally be seen as relatively good compared to that seen in other corresponding studies [25]. It is noteworthy that about half of the patients were totally free from psychotic symptoms during the second follow-up year. The good prognosis was also somewhat expected because the series consisted of other diagnostic groups than schizophrenia. It could also be seen that the outcome was poorer for those whose diagnosis was schizophrenia than for those in the other diagnostic groups.

Our result is not totally unique. It is in agreement with the few other studies which have used a neuroleptic-free treatment regime for patients with schizophrenia-type psychoses (see for example [10, 26, 28]). On the other hand, the result is in clear contradiction with the recent statements that routine neuroleptisation is essential in all acute/first-episode psychoses, and that delay in starting the drug treatment may be detrimental for the outcome because psychosis in itself may be neurotoxic [29, 30].

CONCLUSIONS

What do these results mean in practice? They clearly support the notion that psychosocial measures are useful and effective in the treatment of first-time psychotic patients. It also seems evident that in selected cases of

first-time psychosis neuroleptic treatment is not as essential as it has usually been considered, if intensive psychosocial treatment measures are provided. Unfortunately, our study did not give clues for picking out these cases at admission. The conclusion could be that in many cases it is possible and even desirable to wait at least for a couple of weeks after admission before starting neuroleptic treatment in first-episode psychotic patients.

The use of neuroleptic-free treatment regimes in psychiatric research has recently been discussed in a lively manner [8, 11, 31]. This discussion has mainly focused on the use of placebo in drug trials with patients suffering from schizophrenia or other non-affective psychoses. Our view is that this discussion should be widened to cover research where effective (psychosocial) alternatives to drug treatment, especially in first-episode psychoses, are sought. Our preliminary results indicate that this might be useful. However, one has to keep in mind that our results can only be seen as indicative, because many uncertainties are included in the study design. More rigorous research is still needed in the field of integrated treatment of psychotic conditions.

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