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Early intervention and a five year follow up in young adults with a short duration of untreated psychosis: ethical implications

Don Linszen*, Peter Dingemans, Marie Lenior

Academic Medical Center/De Meren, University of Amsterdam, Tafelbergweg 25, 1105 BC Amsterdam, The Netherlands

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Abstract

In a Dutch treatment intervention study of patients ($n = 76$) with first psychotic episodes of schizophrenia the hypothesis tested was whether early differential treatment after an acute psychotic break improved outcome as compared with other studies. Patients had a relatively short duration of untreated psychosis. No significant effect between two treatment conditions on relapse rate was found. The 15-month intervention program kept the psychotic relapse rate as low as 15%; lower than comparable studies. Thus, the initial results were in support of the hypothesis.

After completion of the 15 months study, patients were referred to other agencies and followed for five years. Results of the follow up study showed that the low relapse rate could not be maintained. Of the remaining 71 patients of the initial sample, 52% had one or more psychotic relapses, 25% developed chronic positive symptoms and 23% did not have another psychotic episode. In addition, the level of social functioning turned out to be low: the majority of patients were dependent upon their parents, few held down a skilled or paid job and also their quality of life seemed low, results indicate that early intervention may improve short term but not long term outcome in schizophrenia.

Our results also suggest that referral to other mental health agencies after intervention is not sufficient. Continuity of outpatient care, including continuity of a professional relationship, continuity of support for the family, and the continuity in management of illness, medication and stress may be a key issue in the first five years after the onset of psychosis in schizophrenia. Early recognition and intervention may not nearly be as important for outcome as continuity in care and caregivers. At present, however, it remains questionable whether early intervention programs in first-episode patients with a short duration of untreated psychosis can offer the prospect of altering the course of schizophrenia without a sustained comprehensive treatment program.

Keywords: Ethical issues; Early recognition and intervention; First-psychotic episode; Schizophrenia; Relapse

1. Introduction

Effective intervention in first-episode schizophrenia and related disorders strongly calls for recognition at the earliest possible stage of florid psychosis, i.e. the prodromal period (Häfner and Maurer, 1995). Interventions should contribute to symptom remission, delay of psychotic relapse and prevention of psychosocial deterioration (Birchwood and MacMillan, 1993; McGlashan, 1996) Furthermore, it should alter the heterogeneous, but predominantly unfavorable course of schizophrenia into a more benign type. Objections made against early recognition programs from an ethical point of view, such as induction of fear of psychosis and stigmatization, would then be outweighed by the beneficial effect of early intervention.

* Corresponding author. Tel.: +31-20-5662246.
E-mail address: d.h.linszen@amc.uva.nl (D. Linszen).

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Some research evidence supports this claim. Patients with first-episode schizophrenia respond well to treatment in the first year, especially a subgroup of patients with a short duration of untreated psychosis (Loebel et al., 1992; Crow et al., 1986). Duration of untreated psychosis (further abbreviated as DUP) longer than one year has been associated with more severe forms of schizophrenic illness, such as a delay in symptom remission. Beyond the first year psychotic relapse rates increased over time (Crow et al., 1986; Leff et al., 1990). In the seminal Northwick Park first episode group, 76% of the patients had been readmitted at least once at five year follow up (Geddes et al., 1994).

In this paper the question is addressed whether enough evidence and thus ethical justification exists to claim that early recognition and treatment of first-episode patients with a relatively short DUP will enhance outcome and thus prognosis. For that reason we will summarize the main findings of the initial project (Linszen et al., 1996) and the five year follow up data which recently became available (Lenior et al., 2001).

2. The Amsterdam psychosis project, initial phase

In a Dutch study the impact of a 15 months combined drug and differential transmural intervention program was evaluated in a sample ($n = 97$) of adolescent and young adult patients with early onset, and first psychotic episode of schizophrenia and related disorders.

The intervention program consisted of an outpatient treatment with day hospital and community care, preceded by a period of in-patient treatment. During in-patient treatment patients participated in a highly structured program including psycho-education for all relatives of the patients (Anderson, 1977). The study investigated the effectiveness of two intervention programs in preventing psychotic relapse and increasing the functional level of the patients. The first intervention program entailed, after the in-patient program, a behavioral family intervention program with a duration of one year (Falloon et al., 1982) in combination with a patient oriented psychosocial intervention including maintenance drug, disease and stress management (Liberman, 1986). The second program consisted of the patient oriented intervention only (best clinical care).

3. Method

3.1. Subjects

All patients were admitted to the adolescent clinic, a facility for young patients with an inpatient unit of the psychiatric center of the Academic Medical Center (AMC) in Amsterdam during an acute episode of psychosis. At admission patients were screened for the presence of schizophrenia or related disorders and the need for continuous antipsychotic medication. Inclusion criteria for the study were a diagnosis of schizophrenia, schizophreniform, schizoaffective and related psychotic disorders according to DSM-III-R (American Psychiatric Association, 1987). Patients of either sex had to be between 15 and 26 years of age. In addition, for the design of the controlled trial, patients had to live with, or to be in close contact with their parents or other relatives. Parents or relatives had to speak Dutch. Patients with primary alcohol dependence, drug dependence and or brief drug-related psychoses were excluded.

After informed consent was obtained from both patients and parents, 97 patients were included in the in-patient treatment program. From the initial sample ($n = 97$) 76 patients entered the outpatient phase of the clinical trial. The non-participating group (21 patients) and the group that completed (most of) the outpatient trial showed no statistically significant differences in illness variables. Also no difference was found when the two intervention groups, the individual and the individual plus behavioral family intervention, were compared.

The remaining patients were diagnosed (DSM-III-R) as suffering from: schizophrenia (55%), schizoaffective disorder (21%), schizophreniform disorder (13%) and other psychotic disorders (e.g. delusional disorder and atypical psychosis; 11%). Patients were predominantly of Caucasian origin (80%) and unmarried (98%). The mean age of onset of psychosis of the participating sample was 19.3 ($SD = 2.3$). An important finding was the (relatively) short duration of untreated psychosis (mean 5.4 months, $SD = 11.0$) in this large sample of young patients (Linszen et al.,

1996). 65% of the patients never had a profession. Of the patients who held a job at admission, 71% worked at an unskilled level. The patients' families lived predominantly in urban areas (79%), 60% of the parents were married.

3.2. Treatment

From admission onwards, an intervention program was carried out in two phases: a) an inpatient phase of three months with a highly structured program, in which all patients participated, complemented with a psychoeducational approach for all relatives of the patients, followed by b) an outpatient phase of twelve months [with two forms of psychosocial intervention including anti-psychotic medication].

In both phases two types of interventions were carried out in accordance with written protocols. All patients received an individually oriented intervention during all phases of the program. For half of the sample a behavioral family intervention was added to the individual intervention of the patients in the outpatient phase. Patients and their families were randomly assigned to both intervention conditions. The duration of the assessment period was identical for both treatment conditions (for a full description of the study and the intervention regimen see: Linszen et al., 1996).

3.3. Instruments

During intake, parents or relatives of the patients were interviewed with the psychiatric and social history schedule (PSHS), a UCLA-family project variant of the life chart schedule (Susser et al., 2000). In this interview data were obtained about present and past illness as well as prognostic factors and pre-morbid social attainment (Kokes et al., 1977), substance abuse, medication and family history of mental disorder. Expressed Emotion (EE) in the families of the patients was assessed with the Five-Minute Speech Sample (Magana et al., 1986).

Clinical status was, independently from treatment, monthly assessed with the expanded version of the brief psychiatric rating scale (BPRS-E; Ventura et al., 2000), and rated by an independent and reliable (>91% agreement with UCLA criterion group) research psychologist (PD). On the basis of the BPRS-E scores two different criteria of relapse were used in the intervention study, one based on a) monthly assessed BPRS-ratings, done blindly by the research psychologist and the second based on b) the clinical psychiatric notes (Linszen et al., 1994a).

Medication compliance was indexed by the treating psychiatrist and the social psychiatric nurse in their regular contacts. Both interviewed the patient about his or her compliance; compliance estimates of both raters were recorded separately. The social psychiatric nurse did occasional pill counts. A research assistant, blind to the study design, reviewed these data for each month of the study and made ratings on a four point scale: 1 (0–24% compliance: no or irregular), 2 (25–49%: rather irregular), 3 (50–74%: rather regular), 4 (75–100%: regular, including depot medication).

4. Results

Using the BPRS-E criteria, 20 of the 76 patients relapsed (26%), whereas according to the clinical psychiatric criteria, 22 were so classified (29%). Since each criterion contained possible false positive and false negative instances of relapse, we decided that a conservative strategy would require that both sources, i.e. the independent BPRS-E and clinical psychiatric evaluations, agreed that a relapse had concurred. This combined relapse criterion was used in the subsequent analyses and results.

The relapse rate in these young patients in both treatment conditions turned out to be low during intervention. Using the conservative criterion, 12 of the 76 patients (16%) relapsed.

The addition of a behavioral family intervention program failed to have a significant beneficial effect on psychotic relapse, neither in high nor in low EE family environments. Two patients from 'low EE' families relapsed in the individual plus family intervention, compared with no relapsing patients from low EE families in the individual intervention alone.

Patient and environmental variables in this sample, including DUP, were examined as a risk factor for relapse. EE emerged to have strong predictive value and turned out to be a predictor, when a conservative measure of relapse was used. Cannabis abuse was the only major predictor in the group of patients with high EE families (Linszen et al., 1997). This finding is in concordance with an earlier study of a larger sample

of the population under study, in which cannabis abuse turned out to be the main stressor eliciting relapse in patients with schizophrenia (Linszen et al., 1994b).

5. The Amsterdam psychosis project, five year follow up

The aim of the present study was to investigate whether the favorable effect on the relapse rate would last after the end of the intensive 15-month intervention program. The follow up period was 60 months, i.e. the time span of the critical period.

6. Method

6.1. Subjects

Of the original sample of 76 families 13 parents refused further cooperation. As a group they did not differ on demographic parameters, although participating patients ($n = 63$) had a shorter duration of psychotic episodes at initial admission and also showed less positive and negative symptoms (BPRS-E) at the end of discharge from the clinic. Seventy-three patients participated in the follow up study.

6.2. Instruments

During follow up, expressed emotion (EE) was assessed with the Five-Minute Speech Sample (Magana et al., 1986). In addition, the life chart schedule was administered (LCS; WHO, 1992; see also: Susser et al., 2000) for reliability data of the LCS). We will only report on the LCS follow up data here since EE-data are reported extensively elsewhere (Lenior et al, 2001).

The LCS is an instrument eliciting data about symptoms, treatment and social conditions (work, study, living arrangement) during a given period. Clinical trained interviewers carried out the LCS interviews. At the start of the interview, respondents were requested to indicate points in time when changes concerning symptoms, treatment, etc. had occurred since discharge. The data were filled in on a time schedule. During the rest of the interview, this schedule served as a memory aid to answer the more detailed questions of the structured interview. The LCS was also used to collect data from other informants, mostly one or two parents. The LCS covered the period between discharge from the intervention study and the date of the interview.

A patient was regarded to have a relapse when a clear statement about recurrence or exacerbation of florid positive psychotic symptoms (hallucinations, delusions and/or formal thought disorders) was made, with or without rehospitalisation. The LCS data were clinically reviewed with regard to relapse and rated by one of the authors (DL). Relapse data were reviewed again by a psychiatrist who had not been involved with the patients. There was disagreement for six patients (8%) about the clinical status (no relapses, one or more relapse(s), chronic). For the six patients about whom disagreement existed, consensus was reached.

7. Results

7.1. Relapse

One fourth ($n = 19$) of the patients had no psychotic relapse during the follow up period, half ($n = 36$) had one or more psychotic episodes and the remaining 25% showed chronic psychotic (positive) symptoms. Across a time span of 60 months the average amount of being psychotic was 19.2 months with a wide range (S.D. = 24.5). The median survival time for the 55 patients who were not rated as chronic turned out to be 34 months. Of the 55 non-chronic patients 65% was considered to have relapsed (at least once) in five years.

The type of intervention-patients were initially randomized over two treatment conditions-did not differentially affect duration of psychosis during follow up.

During follow up the average stay was eight months in a psychiatric hospital and 10 months in a sheltered living arrangement. Homelessness occurred ($n = 7$) but was of a short duration (range: few days up to two months). One patient was in prison for one month. With regard to diagnostic subgroups patients with a diagnosis of schizophrenia, as opposed to schizo-affective or schizophreniform, were found to stay on average nine months longer in psychiatric institutions.

7.2. Social functioning

During follow up patients had 'structural activities' for about half the time (26 months with an SD = 20). About half of the patients ($n = 34$) held a paid job (unskilled or semi skilled) for at least some time, but for most of them (65%) the educational level of the job was lower than their own educational level. There were six patients who did household chores for the greater part of the follow up.

During follow up 34% of the patients lived for the greater part with their parents and 40% lived alone, 12% lived with a partner and 7% was chronically hospitalized.

The parents predominantly took care of the patients in the follow up period, and helped them with daily chores such as housekeeping (69%). Parents accompanied their children to an ambulatory appointment (44%), checked their medication on a regular basis (34%), and helped them with making decisions about treatment (37%).

Furthermore, a longer duration of psychosis was significantly correlated with longer psychiatric admittance, shorter periods of structural activities, and more help from parents.

8. Discussion

A main weakness of this study is that the follow up part of the project did not establish data for a control group. That may limit the generalisability of the rather sobering follow up results. Our conclusions may be far reaching for some readers, while for others the longitudinal tracking of this cohort may be seen as a strong asset of this project. When the first part of the study ended, the treatment results strongly suggested that the basic treatment program, including a family approach modeled after Anderson et al. (1986) was quite effective. The findings were in agreement with those of the Schooler study (1995) that found no differential effects between two family treatments with an educational (Anderson et al., 1986) and a behavioral approach with psycho-education, communications training and problem solving skills training (Falloon et al., 1982). In our study, continuity of care in time, place and person during inpatient, day and outpatient treatment may have been a very effective ingredient. This was also reflected in the medication compliance. Compliance was found to be high throughout the study, as the mean rating during day treatment was 3.84 (SD = 0.52) and during community care 3.76 (SD = 0.59) on a four point scale. At that time no outcome differences were present between patients who received an individual intervention versus the group which received individual and behavioral family intervention. The main conclusion after the first part of our intervention study was, that an early intensive psychosocial and drug treatment program had a favorable effect on the relapse rate of schizophrenia and related disorders within a 12-month period (Linszen et al., 1996). Combined with the relatively short duration of untreated psychosis these findings are in concordance with the Loebel et al. (1992) results. In that study a delay in treatment of psychosis of more than one year was associated with poor outcome, e g. with a delay in symptom remission, and thus with a longer time to recover.

The difference between the relapse rate of the combined family/individual and the individual condition was too small to conclude that the addition of the behavioral family intervention induced stress. However, it can still be labeled as a side effect induced by an increase in stress of the behavioral family intervention in low EE families by focusing on unnecessary communications training and could have interfered with early adjustment patterns centered around loss and mourning (Linszen et al., 1996; Birchwood, 1999).

However a change for the worse became apparent in the second part of the study, i.e. a follow up of a period of five years. We could only conclude that relapse levels had reverted to the ones mentioned in the long-term course studies: about 70%. A large group of patients did not return to initial levels of functioning but had become dependent on psychiatric and parental care. These results left us with the question of whether it is evidence based and ethically justified to inform patients and parents that early recognition and adequate intervention in first-episode psychosis with a relatively short duration of untreated psychosis, enhances the prognosis.

Considering our findings, the answer is affirmative with respect to the results of the initial phase intervention: the early course of schizophrenia can be altered

with beneficial results. One may also assume that the favorable effects of the intervention program would last after the intensive 15-month treatment program. However, the results of the follow up study clearly show that the favorable effects on psychotic relapse disappeared rapidly, underlining that early onset schizophrenia is associated with a poor symptomatic and functional outcome (Häfner and Maurer, 1995). Other recent five-year follow up studies have revealed the same pattern: after an initial and beneficial low relapse rate, rates returned to the familiar heterogeneous course. In the Hillside study in New York, for instance, a high rate of one or more relapses (81.9%) occurred within five years after recovery from a first psychotic episode, with a diminished relapse risk when maintenance antipsychotics were used (Robinson et al., 1999). In a Scottish study, 78% of a first admission sample relapsed after five years (Scottish Schizophrenia Research Group, 1992). In the Amsterdam follow up study, a decline in social functioning in many patients occurred as well (Lenior et al., 2001). These findings during follow up underline McGlashan (1996) remark that interventions in schizophrenia seem to be effective as long as they are active. One may add for first episode patients, that effective interventions need to be active, long-term and comprehensive .

Long term treatment programs are needed to evaluate this hypothesis, that the only way to prevent poor outcome in early-recognized first episode schizophrenia is sustained case management. Active ingredients have to include disease-, medication- and stress management in combination with a family oriented approach with support, information and problem solving for a minimum period of five years. That period approaches the critical period in which the severity of schizophrenia is established (Birchwood and MacMillan, 1993).

The final answer to the ethical question of whether early intervention has a beneficial long-term effect on the course of schizophrenia will be dependent on the outcome of these longer intervention programs.

At present it remains questionable whether early intervention programs in first-episode patients with a short duration of untreated psychosis can offer the promise of altering the course of schizophrenia without a sustained comprehensive treatment program.

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