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Are multi family groups appropriate for patients with first episode psychosis? A 5-year naturalistic follow-up study

Rossberg JI, Johannessen JO, Klungsoyr O, Opjordsmoen S, Evensen J, Fjell A, Haahr U, Joa I, Langeveld J, Larsen TK, Melle I, Rund BR, Simonsen E, ten Velden W, Vaglum P, Friis S, McGlashan T. Are multi family groups appropriate for patients with first episode psychosis? A 5-year naturalistic follow-up study.

Objective: To compare outcome over 5 years for patients who participated in multi family groups (MFGs) to those who refused or were not offered participation.
Method: Of 301 first episode psychotic patients aged 15–65 years, 147 participated in MFGs. Outcome was measured by drop-out rates, positive and negative syndrome scale (PANSS) symptom scores, and duration of psychotic episodes during the follow-up period.
Results: Multi family group participants had a significantly lower drop-out rates at 5-year follow-up than patients who did not participate. However, the MFG participants had significantly less improvement in PANSS positive and excitative symptoms and had significantly longer duration of psychotic symptoms during the follow-up period.
Conclusion: Multi family groups appear to increase the chance of retaining patients in a follow-up study, but adjustment of the programme may be necessary with first episode psychosis patients to meet their needs better.

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Key words: family therapy; psychosis; first episode; outcome

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Significant outcomes

- First episode psychotic patients who participated in a psychoeducational multi family group (MFG) intervention had lower drop-out rates than patients who refused or where not offered participation.
- Multi family group participants improved less than patients who refused or where not offered participation concerning positive and negative syndrome scale positive and excitative symptoms and they had longer duration of psychotic symptoms in the follow-up period.
- The differences remained statistically significant even when controlling for confounding variables.

Limitations

- The present study was not a randomized controlled trial.
- There could be unknown confounders influencing the results.
- Absence of selection bias from differential loss to follow-up relies on the missing at random assumption.

Introduction

It is well established that family interventions are beneficial for patients with a severe mental disorder. A recent Cochrane review concludes that family interventions seem to decrease relapse rates and hospital admissions, and improve compliance with medication. They also seem to improve general social impairment and the levels of expressed emotion (EE) within the family (1). However, family interventions differ as to whether they are multi family, single family or mixed. They also differ in the duration of intervention and whether or not the patients participate in the intervention (2). The interventions usually involve education about the disease, stress reduction strategies, communication training and problem solving enhancement, but we still lack firm empirical evidence of what the key effective ingredients are (3–9).

Furthermore, very few studies have examined the effect of family interventions in pure samples of patients with a first episode psychosis. In a recent literature search we found only four studies of single family interventions for this patient group (10–13). Goldstein et al. (10) randomly assigned 104 acute young schizophrenic subjects having their first or second admission to one of four aftercare conditions. Conditions involved one of two dose levels of a depot antipsychotic and presence or absence of crisis-oriented family therapy. The aim of the programme was to help families accept the psychosis, identify probable problems precipitating the psychosis, and to attempt to foresee and minimize similar stress in the future. Relapse rates at 6 months follow-up were the least in patients receiving high doses of antipsychotics and family intervention and the greatest among patients receiving low doses of antipsychotics and no family intervention. The family intervention group showed a significant reduction in psychotic symptoms at 6 weeks but a sustained effect was only seen among patients who also received high doses of medication.

Leavey et al. (11) randomized relatives of 106 first episode psychoses patients to usual care or to a seven session intervention with education and advice from a support team. At 4 and 9 months after the intervention, there was no significant effect of the intervention either on rehospitalization rates or carer satisfaction. Less than half of the intervention group completed the intervention, and a number complained to the support team that they would have preferred more practical help.

Linszen et al. (12) studied 76 first episode psychosis patients who were given 3 months in-patient treatment followed by a 12-month outpatient psychosocial programme. Patients and their parents were stratified according to high and low EE and then randomly assigned to presence or absence of an additional 18 session behaviour family intervention programme over 1 year. The main components were psychoeducation, communication training and development of problem solving skills. The study found no additional benefit from the family intervention on relapse rates. In fact, patients from families with low EE tended to get worse after the intervention. A 5-year follow-up study (13) showed that patients who were assigned to the intervention had no better course of the illness than the control group, but they spent fewer months in hospital probably due to better family support.

Rund et al. (14) studied the outcome of a 2-year psychosocial treatment programme including a single-family intervention with education and problem solving. They compared the 2-year outcome for 12 adolescent patients with early onset schizophrenia and high EE relatives and 12 carefully matched historical control patients who were given standard treatment. The found that in the intervention group 58% of the relatives changed from high to low EE compared to none in the control group and the number of relapses was lower than in the control group.

A Chinese study has examined the effect of family intervention combining multi family groups (MFGs) and individual counseling sessions every 1–3 months during 18 months (15). The study randomized 78 male first admission patients with schizophrenia to the intervention or to standard care. The intervention group had a significantly lower rate of hospital readmissions and a significantly higher level of functioning. The study had no follow-up after the intervention and the patients had been suffering from psychosis for almost 3 years before inclusion in the study.

In line with this overview, review papers have concluded that the evidence of the efficacy of family intervention for patients with a first episode psychosis is limited and conflicting (7, 8, 16, 17).

However, none of the studies cited above, have evaluated Psychoeducational MFG treatment developed by McFarlane et al. This intervention has been reported to be highly effective for first episode patients (18, 19), as it 'i) allays anxiety and exasperation; ii) replaces confusion with knowledge, direct guidance, problem solving, and coping skill training; iii) reverses social withdrawal and rejection by participation in a MFG that counters stigma and demoralization; and iv) reduces anger by providing a more scientific and socially

acceptable explanation for symptoms and functional disability'.

McFarlane and colleagues have reported excellent results in several studies where patients were randomized to a multi family psychoeducational group intervention or one or more control interventions (standard care, single family treatment or family dynamic MFGs) (20–24). All studies indicated superior results for the psychoeducational MFG intervention. However, all studies have included both patients with chronic and with first episode psychosis and the mean duration of psychosis is between 4 and 10 years. None of the studies have reported the percentage of first episode psychosis patients or specified the outcome for this patient group. In a book (18), McFarlane reports that one of the studies (20) showed that patients with a first episode psychosis receiving the MFG intervention had superior outcome concerning relapse rates at 2 years [19% for MFG vs. 44% for single family groups (SFG)]. However, the number of first episode psychosis patients is not reported, and McFarlane underlines that the MFG is particularly superior for Caucasian patients with high EE families and poor acute response to antipsychotic medication. For patients with none of these risk factors the relapse rate was actually higher for MFG than for SFG patients (42% vs. 22%) (18, pp. 55–56).

To our knowledge, the OPUS trial is the only study that has evaluated MFG for groups where all patients had first episode psychosis. This study randomized 547 first episode psychotic patients to either an integrated treatment programme or standard care (25). The integrated treatment consisted of assertive community treatment, psychoeducational MFGs and social skills training. Relatives in integrated treatment felt less burdened and were significantly more satisfied with treatment than relatives in standard treatment, but there were no significant effects of intervention groups on knowledge of illness and EE level. However, only half the key relatives of the intervention group had more than six sessions of family treatment, and the study does not specify if outcome was related to number of sessions.

To sum up, we still lack empirical knowledge as to whether the MFG approach improves patient outcome for patients with a first episode psychosis. Given that existing studies question the advantage of MFG in patients with low EE and good acute response to antipsychotic patients, it is especially important to evaluate the outcome of MFG for samples of first episode psychotic patients with a short duration of untreated psychosis and fairly rapid remission.

Aims of the study

To explore if patients who participated in psychoeducational MFGs had greater improvement in symptom level, shorter duration of psychotic symptoms, fewer admissions and shorter duration of hospitalization during the follow-up period compared to patients who refused or were not offered participation.

Material and methods

This study is part of the TIPS (early Treatment and Intervention in PSychosis) study, a multi-site project with the principle aim of examining the relationship between reduced duration of untreated psychoses (DUP) and outcome among patients with a first episode psychosis. A total of 161 patients were recruited from an Early Detection (ED) treatment catchment area and 140 patients from no Early Detection (No-ED) treatment area. Details of the study are described elsewhere (26, 27). In this study, we have merged the data from the ED and No-ED areas.

Subjects

Patients with a first episode of psychosis were recruited from all psychiatric in- and out-patient clinics in four catchment areas over four consecutive years. Inclusion criteria were: 15–65 years of age and meeting the DSM IV criteria for schizophrenia, schizophreniform disorder, schizoaffective disorder, brief psychotic episode, delusional disorder, affective psychosis with mood incongruent delusions or psychotic disorder not otherwise specified. The patients included were actively psychotic and had never been adequately treated for psychosis and had no neurological or endocrine disorders with relationships to the psychosis. Furthermore, they presented with no contraindications to antipsychotic medications, were able to speak one of the Scandinavian languages, had an IQ over 70 and were willing and able to give informed consent.

A total of 301 patients were included, out of which 246 were invited to participate in the MFGs. Fifty-four patients and families were not invited MFG participation (28 had no family within reasonable distance, two were not recommended due to language problems, 23 were not recommended due to other reasons (a key family member suffered from a serious psychiatric or medical illness, or there was a recent history of sexual abuse within the family) and one patient died before start of MFG). One patient received a single-family

intervention and was consequently excluded from the study. Ninety-nine were lost to MFG participation due to refusal (79 of the patients denied us contact with the families, and for 20 more the families refused to participate).

The remaining 147 participated in the psychoeducational MFG treatment. Details about the treatment are given elsewhere (28), and will only briefly be described here briefly. The contact with the patients and families started with three alliance meetings.

After the alliance meetings, all families met every second week with one of the group leaders on a single-family basis until start of the MFG. Group participation was offered as quickly as possible, but the start of new groups had to wait until a sufficient number of families accumulated. Therefore, patients had to wait a median of 37 weeks from admission before the start of their groups (25 percentile: 27 weeks; 75 percentile: 46 weeks).

Sixteen of the MFG patients did not participate in any session. A total of 66 patients participated in less than 50% of the group meetings, 27 participated in 50–74% and 38 participated in ≥75%. Forty two relatives participated in <50% of the group meetings, 40 in 50–74% and 65 in ≥75%.

As seen from Table 1, 94 patients had no Positive and Negative Syndrome Scale (PANSS) scores at 5-year follow-up. The loss from follow-up was 22% among those participating in the MFG, compared to 33% among those not offered and 43% among the refusers. This difference is strongly statistically significant ($\chi^2 = 12.23$, d.f. = 2, $P < 0.003$), indicating that the MFG-participants had a high probability to stay in the study, while the MFG-refusers had a high probability to drop-out. Furthermore, the table shows that MFG-participation seems to be particularly important for keeping patients who did not remit from their psychosis in the study, while patients in the refuser group had a stronger tendency to drop-out of the study without having remitted.

Table 1. Patients with or without positive and negative syndrome scale scores at 5-year follow-up by remission and multi family group participation

		Completed PANSS scores at 5-year follow-up		No PANSS scores at 5-year follow-up	
MFG participation	*N*	Remitted before 5 years	Continuously psychotic first 5 years	Known remission before drop-out	No known remission before drop-out
Not offered	54	32	4	14	4
Refused	99	52	4	29	14
Participated	147	100	14	29	4
Total	300	184	22	72	22

MFG, multi family group; PANSS, Positive and Negative Syndrome Scale.

Clinical measures

The Structured Clinical Interview for DSM IV Axis I Disorders was used for diagnostic purposes at baseline (29). Symptom levels were rated at baseline, 3 months, 1 year, 2 years, and 5 years. Symptom levels were measured with PANSS and divided into Positive, Negative, Excitative, Depressive, and Cognitive Components based on the five-factor model (30). Global functioning was measured by the Global Assessment of Functioning (GAF), which was split into symptom scores and function scores to improve reliability (31). The PANSS score on the positive items 1, 3, 5, 6 or on the general subscale item 9 were used to define remission and relapses. Remission was defined as at least 1 week of symptoms with a PANSS score of <4 on all the five items above. Relapse was defined as at least 1 week with symptoms corresponding to a PANSS score ≥4 on one or more of the five items.

Premorbid adjustment was measured by the Premorbid Adjustment Scale (PAS) (32, 33) To ease interpretation the PAS scores were dichotomized into a Social Dimension (PAS Social) and an Academic Dimension (PAS Academic) (34).

Quality of Life was measured by Lehman's Quality of Life Interview (L-QoLI) (35). In this study, we used the item 'Satisfaction with life in general' to measure subjective quality of life at baseline. To measure objective quality of life we used the results from a previous factor analysis that revealed four factors; Financial adequacy, Daily activities, Social contacts, and Family contacts (36).

Drug and alcohol abuse at baseline was assessed by the Alcohol and Drug Use Scale (37). Social functioning (number of friends and work functioning) at baseline was measured with the Strauss–Carpenter scale (38).

Durations of medical treatment (in weeks) and durations of psychotherapy (in weeks) were assessed during the 5-year follow-up period.

Treatment conditions

All patients were provided a standard treatment protocol. The treatment protocol also included antipsychotic medication (for most patients low dose second generation antipsychotic medication) and once a week individual assertive outreach psychotherapy. Details of the psychoeducational MFG intervention are described elsewhere (28). To

ensure fidelity of the MFG intervention all the group leaders had regular supervision (monthly). For every session the group leader completed a fidelity form ad modem McFarlane. This questionnaire comprised questions concerning number of sessions with problem solving (e.g. medications, symptoms, treatment, work-school issues etc.) as well as deviation from the manual. The extent to which the group leaders followed the manual was reported to the supervisors every sixth month together with a more descriptive fidelity report. The main foci of the group meetings were problem solving and communication training. The mean percentage of sessions with problem solving strategies was 62% (SD = 18). The programme was organized in three stages: i) Separate sessions to engage families and patients, ii) Separate educational workshops for patients and family members, and iii) MFG meetings every second week during 2 years.

Statistical analyses

To describe differences between the three groups at baseline we used one-way ANOVA with Scheffe as the *post hoc* test.

Longitudinal analyses were performed to assess whether the participants and non-participants changed differently over time. To account for missing data and confounding variables, we used a linear mixed model, which has been the recommended method for repeated measures (39). Linear splines were used to describe the main features in the observed outcomes (Fig. 1) with random intercept and random slopes included, when proven to enhance model fit. Due to the lack of randomized treatment, various baseline measures were considered to be potential confounders for the relation between treatment and outcome, and adjusted for. Model selection was based on maximum likelihood (and restricted maximum likelihood) and non-significant covariates were excluded.

The following equation describes the model (with adjustment for one baseline confounder X_{1i}):

$$\begin{aligned} Y_{ij} = {} & (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})t^* \times I\big(\text{time}_{ij} \geq t^*\big) \\ & + (\beta_2 + b_{2i})\big(\text{time}_{ij} - t^*\big)_+ + \beta_3 \text{MFG}_i + \beta_4 t^* \\ & \times I\big(\text{time}_{ij} \geq t^*\big) \times \text{MFG}_i + \beta_5\big(\text{time}_{ij} - t^*\big)_+ \\ & \times \text{MFG}_i + \beta_6 X_{1i} + e_{ij} \end{aligned}$$

Where Y_{ij} is the outcome for patient $i = 1, \ldots, 301$ at time point $j = 1, \ldots, 5$, e_{ij} is the error-term,

$$I\big(\text{time}_{ij} \geq t^*\big) = \begin{cases} 0, & \text{for time}_{ij} < t^* \\ 1, & \text{for time}_{ij} \geq t^* \end{cases}$$

$$\big(\text{time}_{ij} - t^*\big)_+ = \begin{cases} 0, & \text{for time}_{ij} \leq t^* \\ \text{time}_{ij} - t^*, & \text{for time}_{ij} > t^* \end{cases}$$

$\beta_0, \ldots, \beta_5$ are the fixed effects (population averages) and b_{0i}, b_{1i}, b_{2i} are the individual specific random intercept and slopes prior and following t^* respectively. Two linear splines are modeled with a knot at $t^* = 3$ months for outcomes in Table 3, and $t^* = 3$ years for outcomes in Table 4. The parameters of main interest are the interaction terms between the treatment group variable MFG_i and time that describes whether or not the treatment groups change differently over time. For example, with the specific parametrization above, a β_5 significantly different from 0 means that the treatment

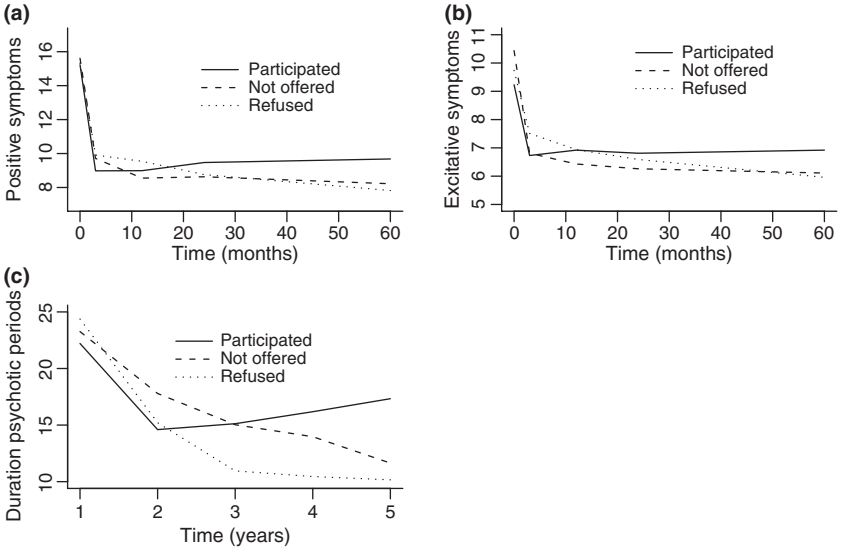

Fig. 1. The development of the positive and negative syndrome scale (PANSS) positive symptoms (a), PANSS excitative symptoms (b), and the total durations of psychotic episodes (c) in the 5-year follow-up period for patients who participated in psychoeducative multi family groups and for patients who refused or were not offered participation. The Figure displays the raw scores of the different outcome measures.

groups change differently from t^* and onwards. Predictions of individual-specific trajectories were performed by empirical best linear unbiased prediction (EBLUP) in order to identify individuals with poor benefit from the treatment. Residual analysis was carried out to assess model adequacy. All statistical analyses were performed with the statistical package, SPSS (version 16; SPSS Inc., Chicago, IL, USA).

Results

Baseline

Table 2 displays characteristics at baseline of patients who participated in the MFG treatment and those who did not. As revealed in the table, patients who attended MFG treatment were younger and more often diagnosed with a narrow schizophrenia spectrum disorder than the not offered group. Patients who participated in the MFG intervention had significantly better social relations, more contact with friends, better work functioning and were more satisfied with life in general than the refuser group. Patients who participated had more weeks with medical treatment and psychotherapy in the follow-up period than those who refused to participate. As we recently have found that patients who were involuntarily had more severe psychopathology and poorer functioning at baseline (40) we also calculated the distribution of involuntarily admitted patients. The overall percentage was 54, and nearly identical for the three groups.

As displayed in Table 3 the symptom levels in all three groups were quite similar.

Follow-up

By using PANSS scores, we calculated time to remission and cumulative relapse rates. The 50 percentile (median) time to remission was 10 weeks for all patients, and the 75 percentile was 28 weeks. The results were nearly identical for the three groups.

We then calculated the cumulative relapse rates for the three groups. As seen from Table 4, the relapse rate was moderately higher among the MFG participants than in the two other groups. To make a more sophisticated test for group differences linear mixed models with five different PANSS outcomes were fitted (Table 5). Candidate covariates were selected from the baseline characteristics (Table 1) and kept in the model when significant. The two PANSS components, positive

Table 2. Patient characteristics and covariates used in the linear mixed model

MFG	Participated (N = 147)	Refused (N = 99)	Not offered (N = 54)
Age, Mean (SD)	23.6 (6.4)	30.3 (10.10)*	34.80 (10.70)*
Female, *n* (%)	56 (38)	38 (38)	31 (57)*
Scandinavian background, *n* (%)	143 (97)	93 (94)	43 (80)
Years of education, Mean (SD)	11.7 (2.0)	11.8 (2.6)	12.92 (2.86)*
Narrow schizophrenia spectrum disorder, *n* (%)			
No	44 (30)	38 (38)	31 (57)*
Yes	103 (70)	61 (62)	23 (43)*
Duration of untreated psychosis in weeks, Median (range)	10 (0–416)	12 (0–966)	4.50 (0–1196)
Alcohol use at baseline (Drake), Mean (SD)	1.93 (0.64)	2.0 (0.75)	1.93 (0.75)
Drug use at baseline (Drake), Mean (SD)	1.82 (1.03)	1.58 (0.97)	1.57 (1.02)
PAS. Social level, Mean (SD)			
Childhood	1.07 (1.17)	0.97 (1.13)	0.94 (1.04)
Last score	1.84 (1.45)	2.09 (1.58)	1.57 (1.32)
PAS. Academic level, Mean (SD)			
Childhood	1.77 (1.17)	1.79 (1.37)	1.74 (1.36)
Last score	2.50 (1.38)	2.34 (1.35)	2.23 (1.45)
Strauss–Carpenter, Mean (SD)			
Friends at baseline	3.08 (1.20)	2.52 (1.45)*	2.79 (1.30)
Work at baseline	2.25 (1.63)	1.67 (1.75)*	2.37 (1.69)
Satisfaction with life in general (Lehman), Mean (SD)	4.25 (1.56)	3.96 (1.76)	4.08 (1.65)
Social contacts. (Lehman), Mean (SD)	3.49 (0.91)	2.96 (1.05)*	3.20 (0.89)
Daily activities. (Lehman), Mean (SD)	0.57 (0.27)	0.58 (0.27)	0.58 (0.28)
Family contacts. (Lehman), Mean (SD)	4.10 (0.68)	3.85 (0.88)	3.59 (0.98)*
Financial adequacy. (Lehman), Mean (SD)	0.82 (0.27)	0.74 (0.33)	0.71 (0.31)
Durations of medical treatment (in weeks) first 5 years	168 (86)	135 (92)*	144 (92)
Durations of psychotherapy (in weeks) first 5 years	179 (81)	126 (84)*	168 (84)

MFG, multi family group; PAS, Premorbid Adjustment Scale.
*$P < 0.05$. Significant differences between patients who participated and those who refused or were not offered participation.

Table 3. Baseline symptom scores for those patients who participated and those who refused or were not offered participation

MFG	Participated (*N* = 147)	Refused (*N* = 99)	Not offered (*N* = 54)
PANSS			
Positive component	15.23 (4.29)	15.33 (3.99)	15.61 (4.78)
Negative component	20.67 (9.44)	20.98 (8.89)	19.59 (7.29)
Excitative component	9.23 (4.33)	9.74 (4.23)	10.44 (4.60)
Depressive component	11.94 (4.09)	12.30 (4.07)	12.54 (3.85)
Cognitive component	7.04 (3.32)	7.49 (3.32)	7.17 (3.42)
GAF			
Function	32.72 (10.46)	30.00 (9.60)	31.50 (10.85)
Symptoms	29.79 (7.02)	28.77 (6.87)	28.91 (6.97)
No. hospitalization 1. Year	1.33 (1.04)	1.29 (0.86)	1.26 (0.94)
Duration of hospitalization 1. Year	18.61 (18.06)	15.10 (14.94)	12.12 (14.62)
Duration of psychotic periods 1. Year	22.21 (18.91)	24.37 (19.21)	23.26 (20.26)

Values are expressed as Mean (SD).
GAF, global assessment of functioning; MFG, multi family group; PANSS, Positive and Negative Syndrome Scale.
*$P < 0.05$. Significant differences between patients who participated and those who refused or were not offered participation.

Table 4. Cumulative relapse rates of patients who have relapsed

MFG participation	*N**	1 year *N* (%)	2 years *N* (%)	3 years *N* (%)	4 years *N* (%)	5 years *N* (%)
Not offered	46	5 (11)	7 (15)	9 (20)	9 (20)	10 (22)
Refused	81	10 (12)	15 (19)	18 (22)	19 (23)	20 (25)
Participated	129	17 (13)	30 (22)	37 (29)	41 (32)	45 (35)
All patients	256	32 (13)	52 (20)	64 (25)	69 (27)	75 (29)

MFG, multi family group.
*Only patients who have remitted.

and excitative, showed significantly different development between treatment groups during the follow-up period. The participators showed significantly more positive symptoms than the non-participators from 3 months an onwards (0.04 units more per month of follow-up, than both refusers and not offered groups). The participators also had significantly more excitative symptoms than the refusers (0.03 units per month of follow-up for excitative symptoms).

A non-significant treatment group effect showed similarity among the treatment groups with respect to symptom levels at baseline (Table 3). For all outcomes and treatment groups, a significant improvement in the initial 3 months' period was observed (significant effects of time before 3 months and non-significant interaction with time). This was followed by a small change in time for the rest of the follow-up period (Table 3 and Fig. 1a,b).

A model similar to that for PANSS was fitted for number and duration of hospitalizations and psychotic episodes (in weeks per year of follow-up) (Table 6). The participators had significantly longer psychotic periods during follow-up compared to both the refuser group and the not offered group (1.59 weeks per year more for the refuser group and 2.72 for the not offered group). A large improvement in the initial year was observed in all groups (no differences), followed by smaller changes over time (Worse among the participation group (Table 6 and Fig. 1c). The patients were examined at baseline, 3 months, 1 year, 2 years, and 5 years. As revealed in Fig. 1a,b, there was a major symptom improvement the first 3 months. Concerning duration of psychotic episodes each year, Fig. 1c, shows a major decrease the first year.

As the patients were not randomly recruited to the groups, group differences might be due to confounding variables. We therefore made several additional analyses of the effect of potential confounders. We adjusted for medications received during the follow-up, psychotherapy received during the follow-up and number of sessions the patients attended the MFG. The differences still remained statistically significant. We still cannot exclude the possibility that unmeasured confounding variables may have influenced both treatment utilization the outcome. We therefore did not include treatment variables in the final model (41).

To control for the fact that the MFG groups kept a higher percentage of the severely ill patients, we reran all analyses including only patients who had remitted. The differences still remained statistically significant.

As a last test, we excluded the 20 patients with highest predicted PANSS scores. Even then only minor changes were observed and the differences still remained significant.

Discussion

Contrary to expectation, the main finding of this study was that MFG participation did not improve outcome. During the follow-up period the MFG participants actually had higher relapse rates, longer duration of psychotic episodes, and higher levels of PANSS positive and excitative symptoms than those who did not participate.

How can we explain these results? A tempting explanation is that the results represent an artifact due to methodological limitations. Patients were not randomly selected to the groups, and differences in outcome might be due to sample differences. At baseline, the MFG participants were significantly younger, than both the other groups, and we have previously shown that patients with adolescent onset have a more insidious onset than patients whose psychosis start in adult age (42). Compared

Table 5. Fixed effect estimates in the linear mixed model for five positive and negative syndrome scale dimensions

	PANSS outcome									
	Positive		Negative		Excitative		Cognitive		Depressive	
Covariate	Estimates	(95% CI)	Estimates	(95% CI)	Estimates	(95% CI)	Estimates	(95% CI)	Estimates	(95% CI)
Main effects groups (MFG)										
Refused	0.77	(−0.86, 2.40)	−0.79	(−3.21, 1.63)	0.27	(−1.00, 1.53)	0.27	(−0.67, 1.21)	−0.30	(−1.40, 0.81)
Not offered	−0.52	(−1.89, 0.85)	−0.46	(−3.30, 2.39)	1.30	(−0.21, 2.81)	0.22	(−0.89, 1.33)	0.23	(−1.08, 1.53)
Participated	0 (Ref)		0 (Ref)		0 (Ref)		0 (Ref)		0 (Ref)	
Main effect time										
Time ≤3 months	−2.17	−2.46, −1.88)	−1.17	(−1.65, −0.68)	−0.88	(−1.16, −0.60)	−0.76	(−0.94, −0.57)	−0.93	(−1.17, −0.69)
Time >3 months	0.01	(−0.01, 0.02)	−0.01	(−0.03, 0.02)	0.01	(−0.00, 0.02)	−0.00	(−0.01, 0.01)	−0.02	(−0.04, −0.01)
Interaction, group × time ≤3 months										
Refused	0.42	(−0.04, 0.88)	0..41	(−0.37, 1.19)	0.05	(−0.39, 0.49)	0.05	(−0.25, 0.35)	0.06	(−0.34, 0.45)
Not offered	0.07	(−0.47, 0.60)	−0.03	(−0.94, 0.89)	−0.40	(−0.93, 0.13)	−0.11	(−0.46, 0.24)	−0.08	(−0.55, 0.38)
Participated	0 (Ref)		0 (Ref)		0 (Ref)		0 (Ref)		0 (Ref)	
Interaction, group × time >3 months										
Refused	−0.04#	(−0.07, −0.01)	−0.03	(−0.08, 0.01)	−0.03#	(−0.05, −0.01)	−0.02#	(−0.03, −0.01)	0.00	(−0.02, 0.02)
Not offered	−0.04#	(−0.07, −0.01)	−0.01	(−0.06, 0.04)	−0.02	(−0.04, 0.01)	0.01	(−0.00, 0.27)	0.01	(−0.01, 0.04)
Participated	0 (Ref)		0 (Ref)		0 (Ref)		0 (Ref)		0 (Ref)	

Adjustment for significant covariates; Positive symptoms: Gender, Core diagnosis, Drug use, Durations of untreated psychosis, Financial adequacy (Lehman Quality of Life) and Work baseline (Strauss–Carpenter).
Adjustment for significant covariates; Negative symptoms: Gender, PAS social scale (last score), Work baseline (Strauss–Carpenter).
Adjustment for significant covariates; Excitative symptoms: Gender and Work baseline (Strauss–Carpenter).
Adjustment for significant covariates; Cognitive symptoms: Core diagnosis. PAS Academic scale (last score) and Work baseline (Strauss–Carpenter).
Adjustment for significant covariates; Depressive symptoms: Satisfaction with Life in General (Lehmans Quality of Life) and Financial adequacy (Lehmans Quality of Life).
PANSS, positive and negative syndrome scale.
#Significant differences during the follow-up period between attenders and non-attenders after 3 months, in units per month.

to the not offered group the MFG participants had a fewer years of education and a higher percentage of males and of patients with a narrow spectrum schizophrenia disorder. However, the differences remained statistically significant even after adjustment for these confounders, and all other possible confounders in Table 1.

Table 6. Fixed effect estimates in the linear mixed model for number and duration of hospitalizations and psychotic episodes in the follow-up period

Covariate	Estimates	(95% CI)	Estimates	(95% CI)
Main effects groups (MFG)				
Refused	3.90	(−2.93, 10.73)	0.01	(−0.25, 0.27)
Not offered	8.50	(−0.12, 17.11)	0.02	(−0.31, 0.34)
Participated	0 (Ref)		0 (Ref)	
Main effect time				
Time ≤2 years	−4.00	(−5.65, −2.34)	−0.38	(−0.47, −0.29)
Time >2 years	0.62	(−0.26, 1.51)	−0.05	(−0.10, −0.00)
Interaction, group × time ≤2 years				
Refused	−1.09	(−3.80, 1.60)	−0.03	(−0.18, 0.12)
Not offered	1.17	(−2.10, 4.43)	0.02	(−0.17, 0.20)
Participated	0 (Ref)		0 (Ref)	
Interaction, group × time >2 years				
Refused	−1.59#	(−3.12, −0.05)	−0.02	(−0.10, 0.07)
Not offered	−2.72#	(−4.52, −0.92)	−0.06	(−0.17, 0.04)
Participated	0 (Ref)		0 (Ref)	

Adjustment for significant covariates; Duration of psychotic periods: Age, Core diagnosis, Duration of untreated psychosis and Work baseline (Strauss–Carpenter).
Adjustment for significant covariates; Number of hospitalizations: Core diagnosis and Work baseline (Strauss–Carpenter).
Adjustment for significant covariates; Durations of hospitalizations: Age and Core diagnosis.
#Significant differences during the follow-up period between attenders and non-attenders after 2 years, in units per weeks/number per year.

The second possible explanation is selective loss of patients. As shown in Table 1, nearly all the most seriously ill MFG-participants stayed in the study, while the two other groups (especially the MFG refuser group) had a considerable loss of such patients. This selective loss clearly violates the assumption of missing at random. It seems as if the MFG programme managed to retain the sickest in treatment, and thereby accumulate chronic psychotic patients. Patients, who were lost from the other groups without having remitted, might have just as serious course of illness. To eliminate this potential bias, we reran all our analyses including only patients who had remitted. The differences between the groups still remained statistically significant. Consequently, we are not able to explain our results either by selective sampling or selective loss of patients. We therefore have to assume that they have internal validity.

Evaluation of external validity is more difficult, as we lack adequate studies for comparison. The closest comparisons are two studies by McFarlane et al. (20, 21) that compare MFG and SFG. They report relapse rates of 25% and 28% at 2 years for MFG patients, and relapse rate of 50% at 4 years. Our MFG patients had only slightly lower relapse rates, 22% at 2 years and 32% at 4 years. However,

there were huge differences concerning the comparison groups. The SFG patients in McFarlane's studies had relapse rates of 44 and 42% at 2 years and 78% at 4 years, while our comparison groups had 15 and 19% at 2 years and 20 and 23% at 4 years. Even though such a comparison needs to be interpreted with caution, it seems as if the different conclusions between the McFarlane studies and ours are due mainly to differences in outcome of the comparison groups. By having comparison groups with a much better outcome, we have put the MFG intervention to a very hard test.

Nevertheless, our results remain surprising, and we have to search for other factors that can challenge the external validity of our results. One possible explanation could be poor quality of treatment. We based the family work of the TIPS project on the standard elements of a psychoeducational MFG programme. We used the manual developed by McFarlane et al. and under his direct supervision we modified the programme to try to meet the needs of first-episode patients and their families better as these needs may be quite different from those of more chronic psychotic patients and their families. Interventions for families with schizophrenia have traditionally focused on coping with the negative consequences of a chronic serious disease as part of the life for the patients and their families. In contrast, a first psychosis onset is an acute traumatic event that precipitates a crisis reaction with extreme pain, turmoil, and denial.

The psychoeducational family intervention was introduced to the Norwegian health care system for the first time in the present study and we may have had insufficient experience with meeting persons in that phase and establishing an alliance with them. We may also have stressed too much the seriousness of the disease and conveyed a less optimistic view than might be appropriate for the patients with a first episode psychosis with short DUP.

The group format might have become too demanding for at least some of patients who had recently experienced a psychotic breakdown. A demanding and standardized family intervention, as used in this study, might have interfered with the recovery process by introducing stress where stress-reduction was the goal. There might also have been situations of conflict between the needs of patients and the needs of relatives, with group leaders identifying themselves too much with the relatives' needs and wishes for change without inviting the patients to participate, for example, in a problem solving process.

An additional question is the timing and duration of treatment. The MFG treatment started later than recommended. However, the MFG participants did just as well as the other groups in the period prior to start of MFG. Therefore, delayed treatment probably did not strongly influence outcome. However, even if we followed the manual concerning duration of treatment, we cannot rule out the possibility that this factor was important. Our results indicate deterioration in the MFG participants during the last 3 years of the follow-up period, i.e. the period after the MFG intervention stopped. A longer treatment might have been useful for some patients.

This study was not originally designed to measure the effect of the MFG intervention. As a consequence it has several methodological weaknesses that threaten both internal and external validity of the results. We have controlled for confounders as far as possible, but acknowledge that even the best available statistical controls have their limitations. And, as described above, there were some variables for which we could not control. One additional variable deserves mention. We managed to measure Expressed Emotions (EE) only in a subgroup of patients. The data indicated that most patients came from low EE families, but missing data made it impossible to use this measure in the analyses. We therefore cannot exclude the possibility that the baseline EE-level might have influenced the outcome.

We these reservations in mind, we conclude that in our study the addition of MFGs to a structured treatment programme with medication and individual psychotherapy seems to have increased the probability that patients stayed in the study, probably because the MFG participation helped them to stay in the treatment. Besides this, however, we have to conclude that the study failed to demonstrate additional therapeutic benefit of MFG participation in our sample of first episode patients who mostly had a very short DUP. Reasons may be that most of our patients responded quickly to antipsychotic medication and most of them seemed to come from low EE families. McFarlane indicates that both of these factors reduce the superiority of MFGs (18, pp. 55–56). This study clearly needs replication before firm conclusions can be drawn, and further research is needed to examine what kind of first episode patients and families should be matched with what kind of family intervention for what length of time.

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