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Effectiveness of targeted intervention and maintenance pharmacotherapy in conjunction with family intervention in schizophrenia

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Abstract A sample of 85 patients with schizophrenia, of whom 34 later dropped out, received randomised treatment. There were no significant differences between treatment-takers and drop-outs in the variables assessed. Patients received either standard-dose maintenance neuroleptic treatment or targeted maintenance pharmacotherapy and all patients received behavioural family therapy. Measures of psychopathology, social adjustment, side-effects, family burden, and expressed emotion were assessed at baseline and then periodically over an 18-month period. The study was designed to compare the two alternative pharmacological maintenance approaches, each of them supported by psychosocial intervention. Any evaluation of the impact of behavioural family treatment on relapse rates and other outcome criteria is exclusively descriptive. A significantly higher rate of relapse was observed at 18 months in patients randomised to targeted treatment compared to those randomised to standard-dose treatment (35 % vs 4 %). Although patients assigned to the targeted maintenance group received significantly lower mean doses of neuroleptics, there were no significant differences between the two groups with regard to side-effects, global measures of social function, and overall psychopathology. Family burden was higher in the targeted-treatment group at six months, but did not differ at the one-year and eighteen-month time points. However, both groups improved significantly from baseline to 12 or 18 months in almost all variables assessed. Thus, the behavioural family approach did not compensate for the problems associated with the targeted medication strategy.

Key words Schizophrenia · Relapse prevention · Targeted intervention · Intermittent medication · Psychoeducational family therapy · Behavioural family management

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Introduction

Alternative neuroleptic dosage strategies

Concerns about the adverse effects of neuroleptic medication, in particular the development of tardive dyskinesia, have led to the search for alternative long-term medication regimens, in particular low-dose and targeted (= intermittent or early intervention) treatment. In low-dose therapy patients receive about 20 % of the usual standard dose, while in targeted treatment medication is, in most cases, gradually discontinued. If clinical deterioration is noted, e. g. prodromal signs occur (Herz and Melville, 1980), medication is promptly reinstated

Low-dose strategies

Neuroleptic low-dose treatment strategies have been demonstrated to be feasible and to compare favourably with standard-dose pharmacotherapy (Schooler, 1991) as long as very low doses are avoided and the patients are in a stable, remitted phase of their illness (Goldstein et al., 1978; Hogarty et al., 1988; Johnson et al., 1987; Kane et al., 1983; Kane et al., 1985; Kane et al., 1986; Kane and

Marder, 1993; Marder et al., 1984; Marder et al., 1987). Most studies found reduced side-effects, fewer negative symptoms, and a reduced family burden. However, low-dose strategies may increase the risk of relapse depending on the stage of illness, dose level, manner in which minor exacerbations are treated, and the length of time that this regimen is used.

Targeted intervention (TI)

Contrary to earlier findings (Carpenter and Heinrichs, 1983; Carpenter et al., 1987; Herz et al., 1982), most recently completed controlled studies on targeted treatment could not confirm that this strategy is as effective as standard-dose maintenance pharmacotherapy (standard intervention, SI) in preventing relapse (Carpenter Jr. et al., 1990; Herz et al., 1991; Jolley et al., 1989; Jolley et al., 1990; Mueller et al., 1992; Pietzcker et al., 1993; Schooler et al., 1997). However, the patients with targeted pharmacotherapy received less medication and experienced fewer side-effects, particularly extrapyramidal symptoms. Nevertheless, there were no clear and consistent benefits in terms of tardive dyskinesia or social functioning.

Neuroleptic withdrawal

In their review of the literature of 66 studies on neuroleptic withdrawal, Gilbert et al. (1995) found a mean cumulative relapse rate of 53 % in patients withdrawn from neuroleptic treatment and 16 % in those maintained on medication over a mean follow-up period of 10 months. The authors recommend a gradual reduction to the lowest effective dose as the preferred strategy. In the reply commentary several authors state some caveats to this. Wyatt et al. (1995) predict that breakthroughs would be less severe and relapse more easily treated if neuroleptic medications were tapered over a period extending from months to years. The speed at which medication should be reduced is still unknown, although from the review study of Viguera et al. (1997) it seems that patients discontinuing treatment gradually (> 3 weeks) have a lower risk of relapse than those being withdrawn from oral neuroleptic therapy abruptly. The question of how much of a neuroleptic dose can be removed safely at what rate and under what conditions is still not resolved. Nonetheless, Wyatt et al. state that many patients can do well on lower doses of neuroleptic medication, as long as psychosocial treatments are provided in addition. This question is addressed in our study by applying targeted medication and family treatment.

Psychosocial factors in relapse

Long-term neuroleptic treatment has been shown to be effective in delaying relapse, but even with continuous and assured injectable long-acting medication about 25–40 % of patients relapse during the first year of discharge from hospital, compared to about 70 % of patients taking placebo (Hogarty, 1984). The high rate of relapse has stimulated research on contributing factors: apart from medication non-compliance and social stressors, life events or a family environment high on "expressed emotion" (EE, Leff and Vaughn, 1985), or both, seem to be particularly important. The predictive validity of the EE rating has been investigated in 27 studies world-wide resulting in a median relapse rate nine months after discharge of 48 % for patients living with an high EE relative in contrast to 21 % for patients living in a low EE family (Butzlaff and Hooley, 1998; Kavanagh, 1992). Thus, in order to modify the behaviour of all family members simultaneously the patient should be included in the family management.

Family intervention in preventing relapse

Several intervention programs have been developed that combine different variants of family intervention and neuroleptic medication as a means of delaying or preventing relapse in schizophrenia. Mari and Streiner (1994) conducted a meta-analysis of the impact of family interventions in a small number of strictly selected studies in schizophrenia (Falloon et al., 1982; Falloon et al., 1984; Goldstein et al., 1978; Hogarty and Anderson, 1986; Hogarty et al., 1991; Leff, 1982; Leff and Vaughn, 1985; Tarrier et al., 1988; Tarrier et al., 1989; Vaughan et al., 1992). Overall, the authors found the effects of family therapy to be favourable. Two to five patients needed to be treated to avert one episode of relapse in a nine-month follow-up period.

The results from the different studies are very consistent in showing a marked reduction in relapse for patients in family treatment when compared with patients in standard psychiatric care (for reviews see Dixon and Lehman, 1995; Falloon et al., 1990; Kavanagh, 1992; Lam, 1991; Penn and Mueser, 1996; Shadish, 1994). However, the recently completed multisite study by Schooler et al. (1997) used a less intensive, once-monthly control condition for the more intensive family management approach, and found no differences in relapse rates between these two conditions.

Goals of the study

This study is designed to assess the relative effectiveness of standard-dose pharmacotherapy versus targeted maintenance treatment, each enriched by special psychosocial intervention. Any statement about the assessment of the impact of behavioural family treatment on relapse rates and other outcome criteria is exclusively descriptive.

Additionally, we wanted to investigate the feasibility of the targeted approach in combination with behav-

ioural family treatment as suggested by Jolley et al. (1990) and introduce the behavioural family therapy approach of Falloon et al. (1984) in Germany. Furthermore, we hypothesised that over the study period patients with targeted medication would receive less medication and experience fewer side-effects than patients with a standard dose.

Subjects and methods

Design

An open 18-month clinical trial was used in order to investigate the clinical feasibility of these treatment approaches using the existing lines of treatment. In Germany the treatment of patients with schizophrenia is primarily carried out by psychiatrists in private practice. Therefore, the private practitioner model was adopted for the treatment approach.

In contrast to previous psychoeducational studies, both high and low EE families were included. As the effectiveness of behavioural family management in everyday clinical practice was the focus of the study, inclusion of low EE families appeared to be appropriate. Originally our study was planned as a controlled two-by-two design, but the study design had to be changed to compare the two alternative pharmacological maintenance approaches, each of them enriched by special psychosocial intervention. The inclusion of behavioural family treatment constitutes a marked difference to most other studies except that of Schooler et al. (1997), which was planned and conducted at about the same time. In the Pietzcker et al. study for instance, apart from the particular pharmacological strategies, there were only routine treatments consisting of regular contacts with the study physician, the study nurse, and social counselling if necessary. In our study, in comparison to previous studies of targeted versus continuous pharmacotherapy (and of family intervention), there is a broader range of outcomes assessed including outcomes of the family (e. g. family burden, family interaction etc.) thus complying with demands frequently made in the literature (e. g. Mari and Streiner, 1994) for the inclusion of measures of distress among relatives, subjective reports of patients and relatives, assessment of family burden etc.

Subjects

Consecutive admissions to the Max Planck Institute of Psychiatry were recruited for the study. Inclusion criteria were 1) an ICD–9 (World Health Organization, 1978) diagnosis and the Research Diagnostic Criteria (RDC, Spitzer et al., 1978) of schizophrenia and schizoaffective (mainly schizophrenic) disorder (including ICD 295.0–295.3, 295.6 and 295.7), 2) an age range of 17 to 55 years, 3) living with, or being in close contact with a relative (defined as at least 10 hours per week) for at least three months before admission, and being likely to return to that household after discharge, 4) living close enough to the clinic to permit at least one home visit, and 5) informed consent from the patient and family members to participate in both medication and family treatment. Exclusion criteria were 1) evidence of an organic central nervous system disorder, 2) unequivocal liver damage, 3) mental retardation, 4) an ICD–9 diagnosis of psychoactive substance abuse or dependence, 5) a history of more than three relapses per year after the withdrawal of maintenance neuroleptic medication and 6) pregnancy.

Criteria for withdrawal from the study were, among others, patient refusal or unsatisfactory treatment co-operation, intercurrent somatic illnesses, but not as in the ANI study (German Neuroleptic Treatment Study, Pietzcker et al., 1993) the impossibility of withdrawing the neuroleptics within six months or of maintaining the patient without drugs for a minimum of four weeks in the targeted strategy.

Procedures

After the patient had satisfied the diagnostic criteria, the Camberwell Family Interview (CFI, Leff and Vaughn, 1985) was conducted with the closest relatives in order to establish the EE status of the family. Following consent, patients were randomly assigned to receive either continuous standard dose or targeted medication, both in combination with behavioural family treatment. Stratified block randomisation was applied with EE and sex as strata.

Treatment

Family intervention

We conducted the well-specified form of behavioural family treatment developed by Falloon and colleagues (Falloon et al., 1984). This treatment involves psychoeducation about the illness, its course and treatment, the improvement of communication as well as problem-solving skills within the family, and stress reduction. Detailed information about this kind of treatment may be found in the specified descriptions (Falloon et al., 1984; Hahlweg et al., 1995; Hahlweg and Wiedemann, 1999).

While the patient was hospitalised, an extensive assessment of the patient and the family was carried out including the videotaping of the family's interaction when discussing a family problem.

One of the team of ten therapists (six female, four male) treated a family. All therapists were assigned an equivalent number of cases in both conditions. Sessions following a detailed treatment manual (Falloon et al., 1988; Hahlweg et al., 1995) were held weekly for three months, biweekly for another three months, and monthly until at least the end of the first year, according to the family's needs. In contrast to Falloon et al., the family treatment sessions were conducted in the out-patient clinic. Whenever possible, at least one home visit was conducted during the first phase of treatment, although there is no evidence that home-based interventions are superior to clinic-based treatment, particularly in light of the study by Randolph et al. (1994) who performed family treatment according to Falloon et al. successfully in the clinic.

All therapists were experienced clinical psychologists and had received extensive training in behavioural family treatment consisting of an initial two-day workshop followed by weekly skills training sessions over at least a ten-week period. Each new therapist had acted as co-therapist in the treatment of at least two families before treating families in the study. All received a written treatment manual and weekly to biweekly supervision.

Neuroleptic treatment

Neuroleptic treatment was conducted predominantly by psychiatrists in private practice. The type of neuroleptic drugs used throughout the study was not restricted. As in the Pietzcker et al. study, dosages were converted into milligrams of chlorpromazine (mg CPZ) equivalents according to conversion rules adopted from the relevant literature (Ortiz and Gershon, 1986).

Psychiatrists were asked to maintain the recommended dose for three months after hospital discharge. In the standard care condition psychiatrists were asked to maintain the same dose level for the 18-month period, but as in the Pietzcker et al. study (1986) were allowed to adjust the dosage provided they maintained a minimum dosage of 100 mg CPZ equivalents.

In the targeted condition the psychiatrists were asked to gradually decrease the drug after three months (step-by-step discontinuation of 50 % of neuroleptics every two weeks). If subjects showed prodromal signs, neuroleptic treatment was reintroduced. When restabilisation was attained, pharmacotherapy was again tapered off. Patients were seen by the study psychiatrist at least once a month for the first year of treatment, thereafter by request or whenever a relapse occurred. Relapsed patients were kept in the study.

Assessments

Major assessments were done at admission, on discharge and then 6, 12, and 18 months later. In addition, monthly assessments were conducted during the first year.

The patient's history and information on potential predictor variables were collected at admission by structured interviews and by using the Phillips scale of premorbid adjustment (Harris, 1975), and the prognosis scale developed by Strauss et al. (1977). Prodromal symptoms were recorded at admission and thereafter routinely at each contact with a specifically developed documentation list containing items selected from those reported by Herz and Melville (ESS, 1980) and further idiosyncratic early warning signs. Out of these 29 most common prodromal symptoms and the idiosyncratic early warning signs, each scoring between 1 (=nonexisting) and 5 (=extreme), three to five individual items were selected by patients and relatives that constituted the very personal early warning signs for this patient and the family. At admission all patients and their families were asked about the prodromal symptoms they had experienced before this or previous breakdowns. Worsening of prodromal signs was defined as a rating of "moderate" (= 3) or greater, representing an increase of at least 2 scale points on any one of the warning signs given that the patient had previously had no warning sign (a rating of 1 in the scoring). Patients and relatives were instructed in the course of family therapy to report these signs as early as possible during the study treatment and also afterwards. If necessary, the individual list of signs and symptoms was updated after each relapse. Patients who showed persistent warning signs (continuing ratings of 2 ("mild") or above on at least one of the warning signs) were classified as having a significant worsening when they showed an increase to a rating of 4 ("strong") or 5 ("very strong") that involved a 2-point change in at least one of the warning signs. A thorough examination and discussion of these signs took place at each contact with the patient and the family (Wiedemann et al., 1994 b).

Psychopathological symptomatology was recorded throughout the study using the Brief Psychiatric Rating Scale (BPRS, Lukoff et al., 1986; Overall and Gorham, 1962), the Inpatient Multidimensional Psychiatric Scale (IMPS, Hiller et al., 1986; Lorr and Klett, 1967), the Intentionality Scale that specifically measures a broad range of negative symptoms (Intentionalitäts-Skala, InSka, Mundt et al., 1985), and the Global Assessment Scale (GAS, Endicott et al., 1976) as outside observer ratings, as well as the Symptom Checklist 90 (SCL–90-R, Derogatis, 1977), the subjective Well-being Scale (Befindlichkeitsskala, Bf-S, von Zerssen, 1976), and the Paranoid-Depression Scale (PD-S, von Zerssen and Koeller, 1976) as self-rating scales.

Side-effects were monitored by means of the Extrapyramidal Symptom Scale (EPS, Simpson and Angus, 1970), and our own scale that was developed to assess the full range of possible side-effects (including salivation as well as akathisia and tardive dyskinesia), partly modifying the Abnormal Involuntary Movement Scale (AIMS, Guy, 1976) and the Dosage Record and Treatment Emergent Symptom Scale (DOTES, CIPS – Internationale Skalen für Psychiatrie, 1986).

Social adjustment was recorded by the Social Adjustment Scale (SAS, Weissman and Bothwell, 1976) including work and household roles, social and leisure activities, and personal well-being.

The relatives' EE was assessed by means of the semi-structured and audiotaped CFI (Vaughn and Leff, 1976). In every household all parents and spouses, and in several households also the closest sibling(s) were interviewed. EE ratings were assessed by two raters who were trained to sufficient reliability by C. Vaughn (interrater reliability 91 %).

Family burden was assessed using a 10-item rating scale covering possible family conflict areas (internal consistency 0.89). Additionally, the Family Assessment Measure (FAM, Skinner et al., 1983) represented a global measure of the general functioning of the family, and the BEB questionnaire (Kasielke and Hänsgen, 1987) assessed the bodily complaints of the individual (internal consistency r=0.92).

Psychotic relapse was defined as a reoccurrence of psychotic symptoms with or without subsequent hospitalisation and operationalised following the recommendations of Nuechterlein et al. (1986): A rating of "moderately severe" (= 5) for significant exacerbation or a rating of "severe" (= 6) or greater for relapse, representing an increase of at least 2 scale points in any one of the psychosis items of the BPRS (unusual thought content, conceptual disorganisation, suspiciousness, and hallucinations), given that the patient was previously in remission (a rating of 3 or below on the scales). Patients who showed persistent symptoms (continuing ratings of 4, "moderate", or above on at least one of the psychotic scales) were classified as having a significant exacerbation when they showed an increase to a rating of 6 or 7 that involved a 2-point change on one of the psychotic scales. Patients were classified as nonrelapsers if they showed neither relapse nor significant exacerbation, unless their psychotic symptoms persisted at such a high level as to preclude these states.

Data analysis

Treatment effects were tested using the Mann-Whitney U test for independent samples due to distributional problems with some of the outcome variables. The Kaplan-Meier analysis was used for the effects on the period of time to relapse. Linear rank statistics were used in the test for the longitudinal analysis of variables (development of values from discharge to 6, 12 and 18 months) (Akritas and Brunner, 1997; Brunner and Puri, 1996; Munzel, 1996). This recently developed test can be used not only for continuous, but also for ordinal data. If the basic assumptions of the Wilcoxons Signed Rank test or the paired t-test (symmetric distribution for Wilcoxons Signed Rank test, normal distribution of differences for the paired-t-test) are not fulfilled, linear rank statistics have been shown to be better suited than either of these. If the assumptions of the paired-t-test are met, the tests have comparable power. Linear rank statistics have already been used in psychiatric research by Bandelow et al. (1998).

Results

Recruitment

To be able to generalise the results it is important to know from which population the sample was drawn and which criteria for exclusion were used. During the study period a total of 411 patients with schizophrenia were consecutively admitted to the clinic and screened. Of these, 164 (40 %) were not living with a relative or did not intend to stay with a relative after discharge. The remaining 247 patients (60 %) were in principle eligible for psychoeducational family management. Of these, 162 were excluded because of further exclusion criteria such as additional substance abuse disorder or organic disorder (N=63), living too far away or not being fluent enough in German (N=40), or the patient's or relative's refusal (N=59). The remaining 85 patients entered the trial and were randomly assigned to the treatment groups. A detailed description of the recruitment procedure, the eligibility, the representativeness, and the drop-out results have been given in a previous paper (Wiedemann et al., 1994 a).

Drop-outs

Of the 85 patients, 51 were regarded as treatment takers, while 34 (40 %) dropped out after randomisation.

Assessment drop-outs were defined as those patients and families who were randomly allocated and took part in some of the assessment procedures, but dropped out before receiving any treatment (N=25, 29 %). Of these,

11 had been randomised to the standard dose condition and 14 to the targeted condition (difference not significant).

Treatment drop-outs (N=9, 11%) were defined as those families and patients who had entered the study and received a maximum of six treatment sessions (two psychoeducational sessions and four sessions of communication skills training; criteria as used in the Hogarty et al. study, 1986). Accordingly, treatment takers received at least seven sessions of behavioural family management and tried to solve one of the family conflicts using a structured problem-solving scheme. Of these, four patients had been randomised to standard dose and seven to targeted medication (difference not significant).

There were no significant differences between treatment-takers and drop-outs in the variables assessed. The two drop-out groups did not differ significantly in any of the sociodemographic, illness, or symptom variables (Wiedemann et al., 1994a).

Patient characteristics

Demographic characteristics, treatment history and psychopathologic symptoms at baseline are presented in Table 1. The 51 patients had an average age of 30 years. 90% met ICD–9 criteria for schizophrenia, 10% for schizoaffective psychosis, mainly schizophrenic, at study entry. Psychopathologic symptoms were in the minimal to mild range for all of the measures examined including negative symptoms assessed on the Intentionality Scale (Mundt et al., 1985). Twenty-seven patients were randomly allocated to the standard medication group and 24 to the targeted intervention group. There were no significant differences between the two groups with regard to treatment history, sociodemographic and symptom variables. Only the GAS showed a trend (standard versus targeted = 70 versus 77, $p < .10$). Although this may well be a chance finding, it tends to favour the targeted group given that this variable indicates a better prognosis the higher the score. However, on the Strauss-Carpenter prognosis scale there was no difference. Moreover, without this difference, there would have possibly been the same result or an even greater difference between the two groups, as there would have been more relapses in the targeted group.

Family characteristics

In total, 73 relatives (49% males) were included with a mean age of 49 years (SD=11.3). Of these, 36 relatives were in the targeted group and 37 in the standard group. They did not differ significantly in sociodemographic, clinical or family variables and belonged mainly to the middle class.

Family intervention took place with partners in 23 cases (45%), with one parent in 7 cases (14%), and with both parents in 21 cases (41%). There were no differences in the proportion of parental versus spouse family members in the two medication groups (25 parents versus 10 spouses in the targeted, and 24 parents versus 13 spouses in the standard group).

Table 1 Demographic characteristics, treatment history and psychopathologic symptoms at start of treatment (standard intervention, SI, versus targeted intervention, TI)

	SI (N=27)		TI (N=24)		U
	mean	SD	mean	SD	p=
Age (years)					
At study admission	31.3	8.8	28.4	9.1	0.29
At first illness	26.1	6.3	25.1	7.3	0.49
Number of prior hospitalisations	1.4	2.1	1.0	1.3	0.73
Illness duration (years)	5.2	5.1	3.3	4.3	0.1
Strauss-Carpenter Scale, total score	51.7	10.1	56.6	9.3	0.12
Global Assessment Scale (GAS)	69.6	14.0	76.5	10.2	0.06
Brief Psychiatric Rating Scale (BPRS)					
Anxious depression	1.8	0.5	1.8	0.8	0.59
Anergia	1.9	1.0	1.8	0.6	0.91
Thought disturbance	1.4	0.7	1.2	0.3	0.66
Activation	1.3	0.5	1.4	0.7	0.84
Hostility	1.4	0.5	1.4	0.7	0.51
Total score	28.2	8.1	27.0	8.3	0.6
Intentionality Scale (InSka), total score	14.8	9.7	12.2	7.3	0.42
Extrapyramidal Symptom Scale (EPS)	1.0	2.1	1.1	2.4	0.7
					Chi^2, p=
Sex (% female)	40.7		37.5		0.81
Marital status (% ever in partnership)	48.1		41.7		0.64
Diagnosis (%)					
Schizophrenia	88.9		91.7		1.0
Paranoid type	66.7		79.2		0.32
Schizoaffective disorder	11.1		8.3		1.0

Expressed Emotion (EE) status

The total sample consisted of 20 (39 %) families low on EE and 31 high on EE, of which 24 (47 %) were high on criticism and 7 (14 %) showed emotional overinvolvement (EOI).

The distribution of EE status across the treatment groups was equally balanced. Fourteen families with high EE (six high criticism, three high EOI, and five high criticism and EOI) and 10 families with low EE were in the targeted, and 17 families with high EE (six high criticism, four high EOI, and seven high criticism and EOI) and 10 families with low EE in the standard group.

Family intervention

On average families received 26 (SD=5.7) sessions of family intervention with no significant difference between the two groups or between high and low EE families (high EE families 27, low EE families 25 sessions).

Relapse rate

Two patients were hospitalised without symptom exacerbation in order to change medication (a change to clozapine).

Four treatment takers dropped out of treatment (two after 6 and two after 12 months). Three of these had been assigned to standard dose and one to targeted intervention. Percentages of relapse were calculated based on the remaining sample (N=47). Nine patients (six male, three female; n. s.) relapsed, eight in targeted and one patient in standard dose treatment. Of these, seven patients had to be hospitalised.

The cumulative relapse rates differed between the two groups throughout the study, but reached significance only after 18 months (χ^2 =7.1, p=.008). Cumulative relapse rates were higher in targeted intervention than in standard treatment: 14 % versus no relapse after 6 months, 18 % versus 4 % after 12 months, and 34 % versus 4 % after 18 months.

Of the nine patients with a relapse, four lived in a low EE and five in a high EE family. Taking only patients from a high EE family into account, the respective relapse rates were 31 % (4 out of 13) in the targeted group and 7 % (1 out of 15) in standard treatment.

Fig. 1 presents the Kaplan-Meier survival curves for time to relapse for the two treatment groups. These display the proportion of patients in both groups who remained free from relapse.

The statistical tests for differences between the two survival curves show significant effects whether relapses are equally weighted (log-rank test χ^2 =7.49, p=.006) or early relapses are more heavily weighted (Wilcoxons Signed Rank test χ^2 =7.43, p=.006). Accordingly, patients in targeted treatment underwent earlier relapses compared to those in a standard regimen. Thus, patients in standard dose treatment not only suffered fewer relapses, but were also kept relapse-free for a longer period of time than patients in a targeted regimen.

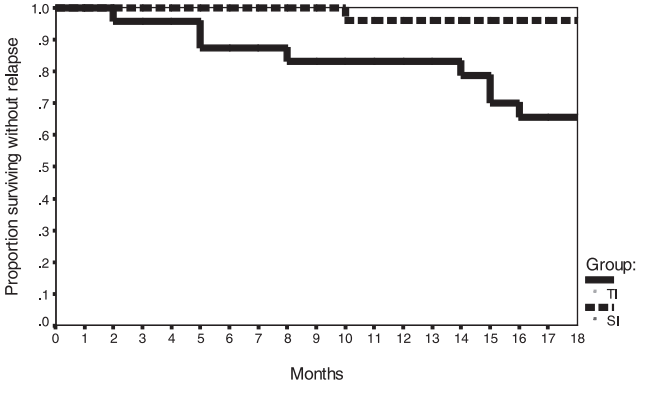

Fig. 1 Survival times to relapse for standard (SI) and targeted (TI) intervention.

Medication

The average daily dose levels per month for the two groups are depicted in Fig. 2.

From the second month on, dose levels for the targeted group were significantly lower than for the standard intervention group. The mean daily dosage during the first year after discharge amounted to 312 mg CPZ equivalents (SD=152) in the standard and 161 mg CPZ equivalents (SD=144) in the targeted treatment group. This difference was highly significant (U=123.0, $p < .001$). Standard-dose patients were subjected to double the dosage over time than those in targeted intervention.

Daily mean dosages calculated on the basis of medicated periods only, i. e. not including time without neuroleptic medication, were still significantly different between the two groups during the first year (314 mg CPZ equivalents (SD=150) in the standard and 201 mg CPZ equivalents (SD=134) in the targeted treatment group, U=154.0, p=.006). Thus, targeted patients were exposed

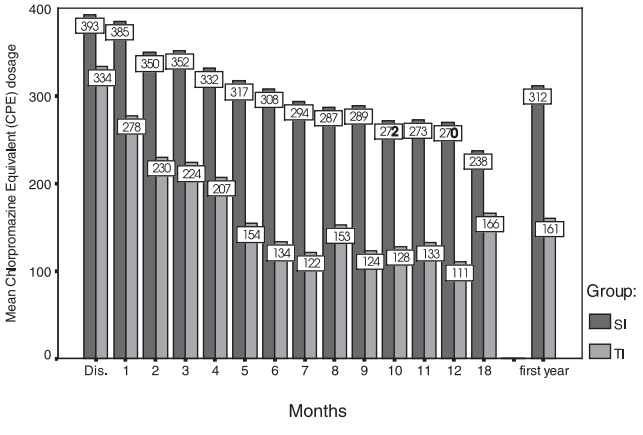

Fig. 2 Mean daily neuroleptic drug dosages per month for standard (SI) and targed (TI) intervention.

to lower and briefer (see below) neuroleptic dosages by any criterion.

Medication-free time period

In the targeted group the number of neuroleptic-free months during the first year varied considerably. Two patients could reduce their dosage to zero after two, one after three and another one after four months without having to reinstate medication at a later point in time (18 % with a minimum of eight months without medication during the first year). Three patients (14 %) were neuroleptic-free for seven months. Another three patients (14 %) remained withdrawn from neuroleptics for three to five months. Five patients (23 %) were without medication for only one to two months. The medication dosage of a substantial percentage of patients in targeted intervention could not be reduced to zero during the first year (N=7, 32 %).

If the definition of a strict targeted strategy is that neuroleptics have to be withdrawn within five months, then one third of the patients fulfilled this criterion (at least seven months without medication). This corresponds to the criterion used by Pietzcker et al. (1993) for their principal treatment-related reason for dropout, i. e. the impossibility of withdrawing the neuroleptics within six months or maintaining withdrawn patients for at least four weeks in the targeted strategies.

Those patients who could not be withdrawn from medication during the first five months differed significantly in their neuroleptic dosage at discharge from the remaining patients in the targeted group (399 mg CPZ equivalents (SD=233) versus 194 mg CPZ equivalents (SD=79), U=19.0, p=.018). Additionally, they revealed significantly more side-effects at discharge and worse social adjustment (SAS, global score: 2.85 versus 2.41, U=16.5, p=.03, lower values indicate better social adjustment). However, they did not differ with respect to further pre-treatment characteristics such as sex, age, particular diagnosis, illness duration, number of prior hospitalisations, type of administered neuroleptic (clozapine versus others), psychopathology, EE as assessed by the CFI, or overall prognosis given by the Strauss-Carpenter Scale.

Side-effects

No significant differences between the two groups emerged at any time point in any of the side-effect measures. Although ratings were generally low in all of the instruments used, the extrapyramidal symptoms still decreased significantly from discharge to any one of the three principal assessment points in both groups. Over the 18-month period no incidence of tardive dyskinesia was reported.

Psychopathological findings and social integration

The patterns of results were similar for various measures and assessment points: Patients in both groups improved significantly with regard to overall psychopathology (observer ratings: BPRS total score, InSka total score; self-rating scales: SCL–90-R general symptomatic index) and global social adjustment (GAS, SAS total score) (Table 2). The GAS measures symptom-related social integration and may therefore be regarded as a psychopathological as well as a social measure. In a number of ratings, significant improvement was first shown in the standard group in the six months following discharge, whereas any significant improvement in the targeted group did not appear until the one-year time point (BPRS total score, GAS, SAS total score). Additionally, in these measures the level of significant improvement was higher for the standard group than for the targeted group, at least at the 12-month time point. The self-rating scale SCL–90-R failed to show a significant improvement to 18 months in the standard treatment group. The difference between the two groups approached significance at this time point with the targeted group having fewer self-rated symptoms.

However, there were no significant differences in any of the global variables between the two groups (Table 2) including occupational functioning, household role, frequency of social contact, social and leisure activities, and personal well-being. Thus, any differences that might be due to the higher relapse rate of the targeted group appear to be balanced at the principal assessment time points.

Burden

The family burden rated by the individual patient improved significantly in the standard treatment group, whereas there was no significant improvement in the targeted group (Table 2). Nonetheless, the cross-sectional differences in family burden did not reach significance level at any time point.

Relatives

In general, similar patterns of results were obtained for the relatives (Table 3). They showed no significant differences between the two groups with regard to self-rated psychopathology (SCL–90-R), bodily complaints (BEB), or the general functioning of the family (FAM = Family Assessment Measure) at any time point. Family burden was significantly higher in the targeted-treatment group at six months and marginally significant at one year, but did not differ at the eighteen-month time point.

Significant improvements were obtained in self-rated symptomatology and bodily complaints in the period from hospital discharge to the one-year and eighteen-

Table 2 Psychopatholgy observer and self-rating, social integration and family burden of the patients in the standard (SI) versus the targeted intervention (TI) group for the various assessment points

	SI (N=27)		TI (N=24)		U[1]
	mean	SD	mean	SD	p
BPRS[2] total score, discharge	28.22	8.14	27.00	8.27	0.60
BPRS[2] total score, 6 months	23.41**	6.93	25.26	10.31	0.56
BPRS[2] total score, 12 months	23.60**	7.37	23.68*	6.38	0.79
BPRS[2] total score, 18 months	22.30**	5.91	22.10**	4.77	0.57
InSka[3] total score, discharge	14.81	8.93	11.54	7.18	0.24
InSka[3] total score, 6 months	9.40**	9.31	8.72*	8.32	0.91
InSka[3] total score, 12 months	6.95**	4.83	6.75**	7.73	0.45
InSka[3] total score, 18 months	6.43**	5.02	7.14*	5.46	0.68
GAS[4], discharge	69.59	13.99	76.46	10.19	0.06
GAS[4], 6 months	79.37**	11.60	77.83	19.30	0.93
GAS[4], 12 months	78.00**	15.75	82.95*	14.45	0.29
GAS[4], 18 months	82.17**	13.38	84.00*	10.21	0.89
SCL–90-R GSI[5], discharge	0.66	0.64	0.52	0.46	0.60
SCL–90-R GSI[5], 6 months	0.25**	0.22	0.29**	0.36	0.55
SCL–90-R GSI[5], 12 months	0.30**	0.29	0.39**	0.58	0.50
SCL–90-R GSI[5], 18 months	0.33	0.26	0.27**	0.41	0.08
SAS[6] total score, discharge	2.67	0.28	2.70	0.41	0.84
SAS[6] total score, 6 months	2.31**	0.25	2.37	0.31	0.60
SAS[6] total score, 12 months	2.30**	0.27	2.39*	0.29	0.38
SAS[6] total score, 18 months	2.27**	0.25	2.32**	0.23	0.30
Family burden global rating, discharge	52.22	25.2	51.25	26.26	0.83
Family burden global rating, 6 months	38.15*	24.8	39.09	20.22	0.67
Family burden global rating, 12 months	33.75**	21.0	45.50	26.65	0.13
Family burden global rating, 18 months	31.36*	23.0	41.90	27.86	0.31

[1] Between group comparison, Mann-Whitney U-Test
[2] *BPRS* Brief Psychiatric Rating Scale
[3] *InSka* Intentionality Scale
[4] *GAS* Global Assessment Scale
[5] *SCL-90-R* Symptom Check-List 90-R, *GSI* General Symptomatic Index
[6] *SAS* Social Adjustment Scale II, lower values indicate better social adjustment
* significant ($p < .05$) within group comparison from discharge to the respective timepoint (linear rank statistic)
** significant ($p < .01$) within group comparison from discharge to the respective timepoint (linear rank statistic)

month time points. Only the relatives of targeted-intervention patients had already improved in symptomatology at the six-month time point. In contrast, the relatives of standard-treatment patients experienced significantly less family burden earlier than the relatives of the targeted-intervention patients (Table 3).

Typical versus atypical neuroleptic medication (clozapine)

An overview of how many patients in each study group were treated with typical or atypical neuroleptic medication, i. e. clozapine, may be of interest because of different side-effects. Therefore a thorough examination of a possible differential effect of clozapine was performed. Of the 51 patients in the study, half received clozapine (N=25, 49 %). The relative distribution of patients on clozapine versus those on typical neuroleptics in the two study groups did not differ significantly (p=.12). In the standard dose group 16 patients were on clozapine (59 %) versus 11 on typical neuroleptics (41 %), and in the targeted group 9 patients were on clozapine (38 %) versus 15 on typical neuroleptics (62 %).

As eight of the nine relapses occurred in the targeted group, we examined how the relapses were distributed across the patients on clozapine in this group only. Of the nine patients on clozapine in this group, one half suffered a relapse (N=4, 50 %). Of the 15 patients on typical neuroleptics, about a quarter (N=4, 27 %) suffered a relapse. This distribution within the patients on targeted medication was not statistically significant (χ^2 =1.25, p=.26).

Thus, the distribution of patients on clozapine across

Table 3 Psychopatholgy and family burden self-rating of the relatives of the standard (SI) versus the targeted intervention (TI) group for the various assessment points

	SI (N=37)		TI (N=36)		U[1]
	mean	SD	mean	SD	p
SCL–90-R GSI[2], discharge	0.35	0.26	0.43	0.35	0.48
SCL–90-R GSI[2], 6 months	0.30	0.25	0.30*	0.28	0.79
SCL–90-R GSI[2], 12 months	0.28*	0.24	0.30*	0.32	0.94
SCL–90-R GSI[2], 18 months	0.27*	0.21	0.27**	0.33	0.60
Family burden global rating, discharge	60.00	30.55	65.00	27.93	0.49
Family burden global rating, 6 months	41.89**	23.07	56.06	28.06	0.03
Family burden global rating, 12 months	38.53**	29.45	50.94*	29.44	0.08
Family burden global rating, 18 months	36.88**	26.81	44.72**	29.03	0.27

[1] Between group comparison, Mann-Whitney U-Test
[2] *SCL-90-R* Symptom Check-List 90-R, *GSI* General Symptomatic Index
* significant ($p < .05$) within group comparison from discharge to the respective timepoint (linear rank statistic)
** significant ($p < .01$) within group comparison from discharge to the respective timepoint (linear rank statistic)

the two study groups did not affect the results differently. As the rate and degree of side-effects in this study with comparatively low doses of neuroleptics were generally low, the possible disadvantage of more or more severe side-effects, or both, for patients on typical neuroleptics was hardly seen.

Discussion

This study was designed to assess the relative effectiveness of standard-dose pharmacotherapy versus targeted neuroleptic treatment in conjunction with behavioural family intervention in preventing relapses in schizophrenic patients living in high or low EE families.

The patients in this study were not preselected according to their stability during an initial drug-withdrawal period as is often performed in comparable studies of alternative neuroleptic dosage strategies. They were sampled from a broad range of prognostically heterogeneous cases. Thus, these patients were not restricted to those who were good candidates for a medication reduction strategy.

Targeted intervention

Differences in relapse rates were seen despite monitoring for prodromal signs. Comparing the present study to other studies of targeted medication strategies the relapse rate under standard treatment was very low, whereas under targeted intervention it was in the low to medium range, e. g. Pietzcker et al. (1993) 15 % vs 35 % over one and 23 % vs 49 % over two years. Although these studies differ with regard to patient selection, methodology, and criteria for relapse, all but one (Herz et al., 1991) reported a significantly higher relapse rate two years after discharge for targeted-treatment patients in contrast to standard-dose patients.

Apart from the significant differences with regard to relapse between the two groups, most of the other global variables used did not show significant differences. This pattern of results was – with a few exceptions – also reported by Carpenter et al. (1990), Herz et al. (1991), Jolley et al. (1990), and Pietzcker et al. (1993).

There may be a number of reasons for this. First, we have to take into consideration that only the cumulative relapse rates and the time to relapse represent truly longitudinal assessments across the whole course of the study without any interruption. All other data including the psychopathological data represent cross-sectional assessments (albeit often done) especially at the 6-, 12- and 18-month time points. Assessment instruments usually cover a certain time period in retrospect (for instance, a month).

Second, several studies (Pietzcker et al., 1993; Schooler et al., 1997) found that treatment differences were smaller in the rehospitalisation rate compared to the relapse rate. This could indicate that relapses under intermittent treatment were less severe. Thus, they could have been treated more often in a shorter time period or even on an outpatient basis, or both. The adjunct of family management in the current study might have facilitated this tendency. Thus, the few relapses that there were, could only have had minor effects on the cross-sectional assessments.

Third, according to a multidimensional concept of outcome, various measures are sensitive to the expected treatment effects in different target areas. As has been shown (Gaebel, 1993), cross-sectionally these different areas are at best moderately intercorrelated. Outcome is not a single process, but consists of several "semi-independent" processes, conceptualised by Strauss and Carpenter (1974) as "open linked systems". This suggests that multiple aetiologies need to be considered for psychiatric disability. The cause of poor social functioning may be quite different from the cause of symptomatology or relapse. Thus, one system, especially the outcome criteria relapse and need for hospitalisation, are not necessarily dependent on other outcome criteria such as social contacts.

Among the few additional differences in other studies were a significantly better extent and quality of employment among continuously treated patients for the reduced sample still in treatment after two years in the Carpenter et al. study (1990), and significantly lower extrapyramidal side-effects in the targeted group after two years in the study by Jolley et al. (1989, 1990).

Contrary to expectation the two groups in our study did not differ significantly with regard to side-effects. This may be due to the generally low dosage in the continuous treatment group. Side-effects were generally very mild and tardive dyskinesia was not reported at all.

Additionally, we had a rather high proportion of patients with clozapine who generally showed a favourable pattern of side-effects in our dosage range, usually with no extrapyramidal symptoms.

Additionally, in the ANI study there were no differences in side-effects, neither according to extrapyramidal symptoms, nor according to the global rating of all side-effects or tardive dyskinesia, and the average scores of side-effects were also very low. This may demonstrate the advantage of treatment strategies whose medications are in the lower dosage range.

Almost none of the studies involved any family variable. Only Herz et al. (1991) reported scores on a "Significant Other Scale". Objective burden at one year, 18 months, and two years, and subjective burden at two years only were significantly higher for the intermittent treatment group. This parallels our six-month finding of a higher family burden, but this difference had disappeared by the 18-month time point.

Over the 18-month period targeted patients received significantly less medication than patients in continuous treatment. Nonetheless, a substantial number of patients could not be withdrawn from medication in the targeted group. This parallels the findings by Carpenter et al. (1990) that targeted patients were drug-free for

only 48 % of the study time, or by Pietzcker et al. (1993) who reported that patients in intermittent treatments were off drugs for about 40 % of the observation period.

Patients who could not be withdrawn from medication in the targeted group in time had been maintained at higher dosage levels than the remainder at discharge from the hospital and had shown more side-effects and worse social integration. Consequently, in accordance with Pietzcker et al. (1993), it may be assumed that those patients who could not be withdrawn from medication function by suppressing symptoms rather than by preventing or delaying a further relapse. This may be the reason why they do not appear to be good candidates for a strict form of targeted intervention.

Our results indicate that targeted medication, even in combination with family therapy, is not a viable alternative as a routine out-patient treatment for all patients with schizophrenia. However, it may be an alternative treatment for patients unwilling to be on medication for an extended period of time or for whom other contraindications to maintenance treatment, such as a unbearable side-effects, exist (Carpenter and Tamminga, 1995). The results of the ANI study showing that targeted intervention is superior to resuming antipsychotic medication only once full symptoms have emerged, supports this recommendation.

Summing up, one might conclude that our study was not so much a maintenance study of family intervention in the context of standard versus targeted neuroleptic treatment, but rather a contrast between low dose versus targeted dose in conjunction with family intervention. All in all, we succeeded in providing a gradual and carefully monitored effort to reduce dosage over time and to deliver the lowest possible effective dose.

The mean dosage we reached during the first year (312 mg CPZ equivalents) in the continuous treatment group corresponds exactly to the lower level of the recommended range of maintenance dosage in general (300–600 mg CPZ equivalents; Dixon and Lehman, 1995; Lehman and Steinwachs, 1998). In addition, this dosage, as well as our average daily dose in targeted treatment (161 mg CPZ equivalents), was similar to those used in the other studies of targeted intervention (for instance, 290 mg for maintenance and 150 mg for intermittent treatment in the Herz et al. study, 1991). Dixon et al. (1995) even conclude in their review that a substantial percentage of patients (up to 50 %) may also be successfully maintained at dosages below 300 mg CPZ equivalents. However, their statement that "daily dosages below 150 to 165 mg CPZ equivalents carry a particularly high risk of relapse" is substantiated by our findings, even with the addition of family intervention. Thus, our results support the value of constant low dose strategies among drug-responsive patients.

Family intervention

Treatment was not provided by behavioural family therapy originators. Generally, there are two stages of generalisation for psychosocial treatments. The first is from the originators to other investigators doing carefully controlled trials, but not carrying out studies under routine clinical conditions (e. g. the TSS study by Schooler et al., 1997). Only if treatments prove to be effective during this stage, are they applied in routine clinical settings (second step). Our study represents the step to implementing therapy in more routine treatment venues.

Family treatments were delivered with full fidelity to the specified treatment approach. Ongoing competency was monitored through review of video- or audiotaped sessions and supervision. Adherence to specific components and skills of behavioural family intervention was assessed by behavioural family therapy competency scales comprising global and specific therapeutic competency (Hahlweg et al., 1990; Lober and Winkler, 1989). The family therapists maintained a competence that ranged from adequate to outstanding (Dürr and Hahlweg, 1996). Experience and clinical credentials of SI family therapists were the same as TI family therapists. No loss of competency occurred over the course of the study. There was consistent exposure to regular meetings, and no difference in the amount of family intervention received by the two medication regimens. These findings suggest that the family intervention was adequately taught, learnt and practised.

In contrast to many other studies (e. g. Schooler et al., 1997) we did not only include patients in contact with the families of origin, thus not precluding older and married patients.

Apart from the low relapse rate, within analysis showed that patients and relatives improved on a number of other variables, e. g. psychopathology, social adjustment, family burden and family communication (see Rieg et al., 1991).

The exploratory comparison of the relapse rates in our study with those from other studies of family intervention, as well as those using drug therapy alone or with supportive, individual therapy (i. e., the comparison groups in the Falloon, Leff, Hogarty and Anderson, Köttgen, Tarrier, Randolph, Xiong, and Zhang studies) indicates that both of our study groups did better than the comparison groups in these other studies where there was no family intervention. This suggests that engaging families may have contributed to the improved outcome.

These data on the impact of behavioural family management are exclusively exploratory, as confirmative testing was restricted to the comparison of standard dose versus targeted maintenance pharmacotherapy in preventing relapses in schizophrenia.

Limitations

Obviously more control groups would be needed in order to definitely attribute these changes to the family intervention. The problems in allocating patients to the control groups without family intervention forced us to change the original design of the study. Patients objected to being allocated to these control groups because the out-patient treatment without family intervention on offer was basically the therapy the patients routinely received from their psychiatrists in private practice. Therefore, the patients felt no further advantage by taking part in the study and withdrew.

This is a well-known problem especially in psychotherapy studies (Holle and Pritsch, 1995). If the experimental and the control treatments are seen as qualitatively very different by the patients, recruitment problems often arise (Holle, 1995). The greater the difference between two treatment alternatives appears to be to the patient, the more likely is their rejection of randomisation or their postrandomisation withdrawal. Randomisation into two different drug therapies or into two kinds of psychotherapies is not as difficult as randomisation into drug *or* psychotherapeutic treatments (Hartmann-Lange, 1995).

In psychotherapy studies a considerable number of patients is a priori biased. Either (a certain kind of) psychotherapy is demanded or strictly rejected. Few patients are actually indifferent to the treatment alternatives.

The other German study on alternative treatment strategies in schizophrenia (Pietzcker et al., 1993) did not run into these difficulties and was able to recruit patients into the neuroleptic treatment conditions. This may have been due to several reasons. First, their experimental and control treatments did not differ so much from a patient's point of view. Second, patients were not as biased to certain treatments as to those in psychotherapy studies. Third, neuroleptic out-patient treatment was not given by psychiatrists in private practice, but by the staff of the same institution that conducted the whole study. Thus, there was no break after hospital discharge and patients remained affiliated to the research facility.

A further limitation might be that the chosen timeframe for the observation of prodromal symptoms may have been too broad. Therefore, at the last contact preceding a relapse, prodromal signs present but not yet fully developed may have been overlooked. Although the more intensive inclusion of the family compared to other studies such as the ANI study may have compensated for this possible disadvantage in our study, we cannot rule out this possibility. Although the most often reported time between the first sign of impending relapse and hospitalisation was greater than one month in the study by Herz and Melville (1980), other authors (Pietzcker et al., 1993; Gaebel et al., 1993) now recommend a time-frame of two weeks for the whole study period.

Thus, future studies should apply an even tighter time-frame as well as even more standardised measures in assessing the transition period between prodromal symptoms and full-blown relapse.

New neuroleptic agents are now available in the treatment of schizophrenia, which are not restricted in use as is the case with clozapine. Up to now we have had little information regarding their efficacy in maintenance treatment. Therefore, new medications in conjunction with psychosocial treatments will prompt a new generation of studies to investigate their additive and interactive effects. However, our study shows that even with atypical neuroleptics such as clozapine a minimum dose level for relapse prevention has to be maintained. This statement may also apply to studies with patients receiving other atypical neuroleptics or a greater share of patients receiving atypical drugs, or both. Therefore, we do not think that the launch of other atypical neuroleptics would alter our results or lead to other conclusions, although new neuroleptics with better effects on negative symptoms are highly desirable.

All in all, there is no clear-cut advantage in using the targeted approach in the general population of schizophrenics irrespective of the accompanying psychosocial intervention. The clinical conclusion to be drawn is that continuous low-dose maintenance pharmacotherapy represents the most favourable neuroleptic treatment for relapse prevention even under continuous psychoeducational family intervention.

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