Relapse Prevention in First-Episode Schizophrenia—Maintenance vs Intermittent Drug Treatment With Prodrome-Based Early Intervention: Results of a Randomized Controlled Trial Within the German Research Network on Schizophrenia

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Objective: After acute treatment of the first illness episode in schizophrenia, antipsychotic maintenance treatment is recommended for at least 1 year. Evidence for the optimal subsequent treatment is still scarce. Targeted intermittent treatment was found to be less effective than continuous treatment at preventing relapse in multiple episode patients; however, a post hoc analysis of our own data from a previous study suggested comparable efficacy of the 2 treatment approaches in first-episode patients. The current study was therefore designed to compare prospectively the relapse preventive efficacy of further maintenance treatment and targeted intermittent treatment in patients with *ICD-10*–diagnosed first-episode schizophrenia.

Method: A randomized controlled trial was conducted within the German Research Network on Schizophrenia. Entry screening took place between November 2000 and May 2004. After 1 year of antipsychotic maintenance treatment, stable first-episode patients were randomly assigned to 12 months of further maintenance treatment or stepwise drug discontinuation and targeted intermittent treatment. In case of prodromal symptoms of an impending relapse, patients in both groups received early drug intervention, guided by a decision algorithm. The primary outcome measure was relapse (increase in the Positive and Negative Syndrome Scale positive score > 10, Clinical Global Impressions-Change score ≥ 6, and decrease in Global Assessment of Functioning score > 20 between 2 visits).

Results: Of 96 first-episode patients, only 44 were eligible for the assigned treatment (maintenance treatment, n = 23; intermittent treatment, n = 21). The rates of relapse (19% vs 0%; $P = .04$) and deterioration (up to 57% vs 4%; $P < .001$) were significantly higher in the intermittent treatment group than in the maintenance treatment group, but quality-of-life scores were comparable. Intermittent treatment patients received a significantly lower amount of antipsychotics (in haloperidol equivalents; $P < .001$) and tended to show fewer side effects, particularly extrapyramidal side effects.

Conclusions: Maintenance treatment is more effective than targeted intermittent treatment in preventing relapse, even in stable first-episode patients after 1 year of maintenance treatment, and should be the preferred treatment option. However, about 50% of patients remain stable at a significantly lower drug dose and show fewer side effects, and a substantial proportion refuse maintenance treatment. Alternative long-term treatment strategies, including targeted intermittent treatment, should therefore be provided in individual cases.

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After acute treatment of a first episode in schizophrenia, antipsychotic maintenance treatment is recommended for at least 1 year[1–4] to further improve symptom remission and functioning and to prevent relapse and symptom recurrence. The evidence base for the optimal subsequent treatment strategy is still small, especially for stable patients, and treatment recommendations are limited. Besides further maintenance treatment, another treatment option is targeted intermittent treatment with stepwise drug discontinuation and recommencement of treatment in case of prodromal symptoms or early warning signs of an impending relapse.[2,5] However, several well-controlled trials, most of which were performed in patients with multiple illness episodes, showed higher relapse rates with this regimen than with maintenance treatment (for a summary, see Kane[6]). In addition, there is some evidence that intermittent treatment (with first-generation antipsychotics[2,7]) carries a higher risk of tardive dyskinesia. Treatment guidelines therefore recommend intermittent treatment as an option only for patients for whom maintenance treatment is not suitable or for special groups of patients (eg, patients with reduced treatment adherence or with higher sensitivity to side effects[1]).

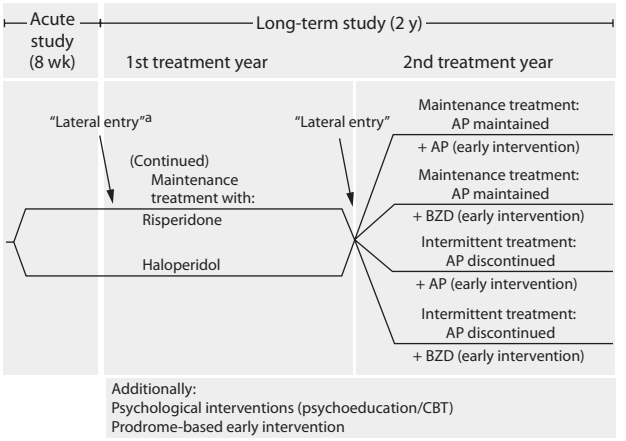
As indicated by a post hoc analysis of data from a previous large multicenter randomized controlled trial (RCT) in Germany, first-episode patients seem to be one of the

special groups for whom targeted intermittent treatment is suitable.[8] Whereas in multiple-episode patients the relapse rate under targeted intermittent treatment was significantly higher than under maintenance treatment, no such difference was found in first-episode patients. At that time (the late 1990s), prospective data from well-controlled (randomized) trials in first-episode schizophrenia were lacking. This was one background against which the entire first-episode study program was planned within the German Research Network on Schizophrenia.[9,10]

In the meantime, a few studies have been published on the effects of drug discontinuation after maintenance treatment in first-episode schizophrenia. A prospective study of a standardized medication algorithm for the long-term treatment of first-episode patients identified, in a post hoc analysis, predictors for relapse.[11] One major predictor was drug discontinuation (which was not provided as a treatment option by the algorithm so that no standardized early intervention procedure took place), which increased the risk for relapse nearly 5-fold. In another prospective study,[12] drug treatment was maintained for at least 12 months and then discontinued in a placebo-controlled crossover phase. Patients remaining sufficiently stable in the discontinuation phase were subsequently followed for 2 years (there was no standardized early intervention procedure after drug discontinuation). The vast majority of patients (78% within the first year, 96% within the whole 2 years) experienced a (low-level) reexacerbation of symptoms, but only 13% had to be rehospitalized.

Recently, the results were published of the only RCT to date that compared maintained antipsychotic treatment with intermittent treatment after drug discontinuation in first-episode patients.[13] After a 6-month stabilization phase with open antipsychotic maintenance treatment, stable patients were randomly assigned to further maintenance treatment or targeted intermittent treatment and followed for 18 months. The treatment regimen (time interval of patient monitoring, recommencement of antipsychotic treatment, or dose increase in case of early warning signs of an impending relapse) was individually determined by the treating physician. Relapse occurred twice as often in the intermittent treatment group as in the maintenance group (43% vs 21%, respectively; $P < .05$), whereas there were no differences in the time spent in hospital or quality of life. These results challenge the efficacy of intermittent treatment in first-episode patients; however, the fact that no standardized early intervention procedure was applied and that drug treatment was discontinued as early as after 6 months may have contributed to the higher relapse rates under intermittent treatment. There is therefore still a great need for a comparison (in particular in RCTs) of the feasibility and relapse-prevention efficacy of targeted intermittent treatment and of maintenance treatment after a first episode in schizophrenia. In addition, studies are needed that investigate the outcome after a longer (1-year) stabilization period with maintenance treatment and when a more standardized early intervention procedure was included.

Figure 1. Design of the First-Episode Study Within the German Research Network on Schizophrenia



[a]Patients included in the respective treatment phase without having participated in the acute study or without having completed the first year of the long-term study.
Abbreviations: AP = antipsychotic, BZD = benzodiazepine, CBT = cognitive-behavioral therapy.

In the late 1990s, it was also discussed whether benzodiazepines—with their sedative effects—are effective at preventing a full exacerbation in schizophrenia in case of prodromal symptoms that indicate an impending relapse.[14] In an explorative RCT, diazepam was shown to be superior to placebo and comparable to fluphenazine in preventing symptom progression. To obtain more empirical data on this topic, the present study compared exploratively early drug intervention—in case of prodromal symptoms—with antipsychotics or the benzodiazepine lorazepam. The primary objective, however, was to compare prospectively differences in relapse rates between continued maintenance treatment and targeted intermittent treatment after stepwise drug discontinuation in patients after a first episode in schizophrenia who were sufficiently stable after 1 year of maintenance treatment.

METHOD

Study Setting

The first-episode study (FES) was part of the German Research Network on Schizophrenia,[9] a nationwide research network funded by the German Ministry of Education and Research (BMBF). The study was conducted as a multicenter clinical trial in 13 German psychiatric university hospitals according to the Declaration of Helsinki and the principles of Good Clinical Practice; Good Clinical Practice was assured by involvement of the Düsseldorf Coordinating Centre for Clinical Trials (head: C.O.). The study was approved by the ethics boards of the coordinating center (Düsseldorf, Germany; principal investigator, W.G.) and the local centers.

The entire first-episode study program (see Figure 1) consisted of an 8-week acute study[15] and a subsequent 2-year long-term treatment phase.[10,16] Patients with a first

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episode of schizophrenia were included in the acute study and randomly assigned to double-blind treatment with low-dose haloperidol or risperidone. After the 8-week inpatient acute treatment phase, informed consent was renewed and patients were included in the first year of the long-term study, in which they received maintenance treatment with the formerly assigned (still blinded) antipsychotic medication in an outpatient treatment setting. Additionally, "lateral entry" into the maintenance study was made possible: first-episode patients were also included in the first year of the long-term study after up to 8 weeks' (open) acute treatment with haloperidol and randomly assigned to double-blind risperidone or haloperidol. Further study characteristics and the results of both the acute study[15] and the first treatment year[16] are reported elsewhere.

In addition to the pharmacologic treatment in the first study year, a trial of psychological interventions was conducted at 5 study centers (8 weeks of psychoeducation vs 1 year of cognitive-behavioral therapy [CBT] in a random design; S.K. et al, manuscript in preparation).

Design of the Second Treatment Year (maintenance treatment vs intermittent treatment)

The present article reports on the second treatment year of the FES, which compared continued maintenance treatment with intermittent treatment after stepwise drug discontinuation. After 1 year of antipsychotic maintenance treatment, first-episode patients were openly randomly assigned to either continued double-blind maintenance treatment (MT) with the antipsychotic from the previous year (risperidone or haloperidol) or intermittent treatment after stepwise drug discontinuation (IT). In both treatment arms, a prodrome-based early intervention strategy was applied: in case of prodromal symptoms or early warning signs of an impending relapse (as indicated by explicit criteria of a decision algorithm; see below), drug treatment was supplemented (MT) or restarted (IT) to prevent further symptom exacerbation. To investigate exploratively the secondary objective (early drug intervention with an antipsychotic vs with a benzodiazepine), patients in both treatment arms were further randomly assigned to receive—in case of early drug intervention because of prodromal symptoms—double-blind treatment with either the respective antipsychotic or the benzodiazepine lorazepam, resulting in a 2×2 design (see Figure 1; adding an antipsychotic or benzodiazepine in MT patients; starting with an antipsychotic or benzodiazepine in IT patients).

Many patients (about 70%; see Gaebel et al[16]) had dropped out from the study during the first treatment year. To achieve the projected sample size for the second study year, the original design was amended by addition of a lateral entry procedure to allow first-episode patients to enter this study phase after 1 year of maintenance treatment with any antipsychotic. Most of the lateral entry patients were patients who had participated in the first study year but dropped out for various reasons, then been switched (at the doctors' discretion) to another (atypical) second-generation antipsychotic (SGA; open treatment) and continued to attend the biweekly study appointments. The lateral entry patients were also randomly assigned to (1) either continued open maintenance antipsychotic treatment or intermittent treatment and (2) an early intervention drug (the respective antipsychotic or lorazepam), also administered openly for practical reasons. Thus, for patients completing the first study year, applied drugs (for the maintained treatment or for the early intervention with either an antipsychotic [risperidone or haloperidol] or the benzodiazepine lorazepam) were administered double-blind, and for lateral entry patients, drug treatment was open. Treatment procedures for the primary hypothesis (MT vs IT), however, were conducted in open manner for all patients. The randomization and blinding procedures for the second study year were provided by the Johann-Gutenberg University, Mainz, Germany.

Subjects

Patients from 8 German psychiatric university hospitals were included in the second treatment year if they met the following inclusion criteria: (1) had just completed 1 year of antipsychotic maintenance treatment after the first episode (defined as the first inpatient treatment of the respective symptoms and no prior treatment with antipsychotics) of schizophrenia (diagnosed according to *ICD-10* F20); (2) were sufficiently stable (ie, had no relapse in the first postacute year according to the defined criteria [see below] and did not fulfill any criteria of the decision algorithm for early intervention at the beginning of the second year; additional clinical assessment was performed by the treating psychiatrist); (3) had been sufficiently compliant in keeping the biweekly appointments; (4) were aged between 18 and 56 years; (5) were sufficiently proficient in German; and (6) gave written informed consent after receiving detailed information about the study. Exclusion criteria were (1) pregnancy, (2) contraindication for antipsychotic treatment, (3) mental retardation, (4) organic brain disease, (5) substance dependence, (6) suicidal behavior in previous history, (7) serious physical disease, and (8) participation in other incompatible trials.

Assessments

Patient visits were scheduled every 2 weeks. The following assessments were conducted by a study physician at every visit: psychopathology (Positive and Negative Syndrome Scale [PANSS],[17] Clinical Global Impressions scale [CGI],[18] Scale for the Assessment of Negative Symptoms [SANS],[19] Hamilton Depression Rating Scale [HDRS],[20] Calgary Depression Rating Scale for Schizophrenia [CDSS][21,22]); level of functioning (Global Assessment of Functioning [GAF][23]); side effects (Extrapyramidal Side Effects scale [EPS],[24] Udvalg for Kliniske Undersogelser Side Effect Rating Scale [UKU],[25] Hillside Akathisia Scale [HAS],[26] Abnormal Involuntary Movement Scale[27]); compliance (Compliance Rating Scale[28]); drug attitude (Drug Attitude Inventory [DAI][29]); quality of life (Lancashire Quality of Life Profile [LQLP][30]); and subjective well-being (Subjective Well-Being Under Neuroleptics scale [SWN][31]).

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To assess prodromal symptoms, the Early Symptom Questionnaire[32] was modified to a give a list of 22 "nonspecific" symptoms (eg, trouble concentrating, trouble sleeping, restlessness, depressed mood) and 23 "specific" symptoms (eg, ideas of reference, impression of being controlled, perceptual disturbances). Occurrence of the 45 items was rated on a 4-point Likert scale (0 = not at all, 1 = mild, 2 = moderate, 3 = severe) on the basis of a semistructured interview. Overall scores of the respective nonspecific and specific prodromal symptoms were calculated by summing these ratings. In addition, at each visit the treating psychiatrist made an overall clinical assessment of the patient's "risk for relapse" (0 = not at all, 1 = low, 2 = moderate, 3 = high).

In accordance with the vulnerability-stress-coping (VSC) model,[33] the appearance of stressful life events and the respective burden for the patient were recorded (from 1 = none to 5 = very high) at each visit, using a standardized German instrument (Munich Event List [MEL][34]).

ICD-10 diagnostic criteria[35] were reassessed at inclusion in the acute and long-term trials, at the end of the first study year, and in case of study dropout. In addition, patients were assessed according to the Strauss-Carpenter Prognosis Scale[36] at entry in the first and the second treatment years.

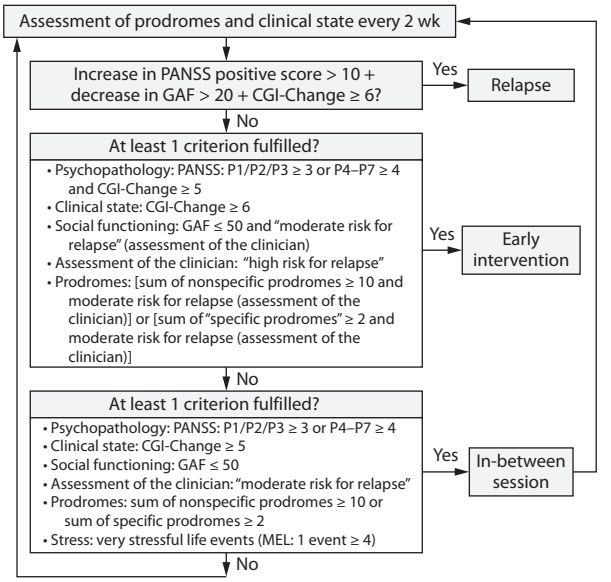
Several rater trainings took place. Interrater reliability was satisfactory to good (intraclass correlation coefficient of the PANSS total score = 0.61, $P < .001$; PANSS positive score = 0.74, $P < .001$).

The primary outcome measure was relapse, which was predefined as fulfillment of all of the following 3 conditions: an increase in the PANSS positive score > 10, a CGI-Change score ≥ 6, and a decrease in GAF score > 20 between 2 visits. A relapse could occur at any time in the study under any treatment condition (and, if it occurred, the treatment "according to protocol" was stopped and changed to drug treatment at the doctors' discretion, and the patient was counted as a "relapse" and also as a "dropout"). Because of the low prevalence of relapse according to these criteria, "marked clinical deterioration"—defined as fulfillment of 1 of the 3 single relapse criteria or increase in PANSS positive score ≥ 7 with a decrease in GAF score > 15 (between 2 visits)—was added post hoc as a further outcome measure. An additional measure of deterioration was adapted from Csernansky et al[37] and defined as an increase (from baseline, ie, the start of the second treatment year) in the sum of the PANSS positive and negative scores ≥ 25% or ≥ 10 points (if baseline value ≤ 40) or a CGI-Change score ≥ 6. Secondary outcome domains were dropout, psychopathology, side effects, quality of life, and social functioning.

Early Intervention Procedure

On the basis of empirical analyses,[38] explicit criteria for initiation of early drug intervention were defined and integrated into a decision algorithm (see Figure 2). Prodromal symptoms are of limited relapse-predictive validity (for a summary, see Gaebel and Riesbeck[38]), but this validity could be enhanced by considering other parameters of the VSC model as "early warning signs," early recognition and prevention of an exacerbation were based on the following: prodromal symptoms (sum scores of both nonspecific and specific symptoms), attenuated positive symptoms (PANSS positive items), occurrence of stressful events (MEL), decline in social functioning (GAF), clinical global impression (CGI-Change), and the doctors' clinical assessment of the risk for relapse (self-developed rating scale; see Assessments). However, earlier analyses[38] found that the relapse-predictive validity of all these indicators is still limited. Thus, to balance safety (to successfully prevent each reexacerbation) and feasibility (not to intervene continuously and hence suspend intermittent treatment), a 2-level procedure was implemented. In case of very low-intensity "early warning signs" of an impending relapse, the decision algorithm indicated that an "in-between session" (in addition to the regular visits every 2 weeks) should be conducted (see Figure 2). The treating psychiatrist was to initiate the early drug intervention in case of more pronounced early warning signs, indicated by fulfillment of at least 1 of the following criteria (see Figure 2): increased positive symptoms (according to PANSS positive items) equal to or above mild (P1, P2, P3) or moderate (P4, P5, P6, P7), an overall rating of at least "much clinical worsening" (according to CGI), a decline in social functioning to "serious impairment" (according to GAF), an overall assessment by the treating psychiatrist of a "high risk for relapse" (according to a 4-point rating scale), or occurrence of pronounced prodromal symptoms (according to an adapted prodromal symptom assessment; see Figure 2).

Figure 2. Decision Algorithm Guiding Early Intervention in the Event of Prodromal Symptoms or Signs of an Impending Relapse



Abbreviations: CGI-Change = Clinical Global Impressions-Change, GAF = Global Assessment of Functioning, MEL = Munich Event List, PANSS = Positive and Negative Syndrome Scale.

Drug Treatment and Drug Discontinuation Procedure

Study drug treatment in the first year (double-blind risperidone or haloperidol) was continuously administered at

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a target dose of 2 to 4 mg/d (maximally 6 mg/d; for details, see Gaebel et al[16]). If patients dropped out for drug-related reasons, the drug regimen was changed to another SGA administered at a suitable (low) dose; both the SGA and the dose were chosen by the treating physician.

In the second study year, patients randomly assigned to further maintenance treatment (MT) had to maintain the drug regimen from the end of the first year for the whole second year. In patients randomly assigned to drug discontinuation and intermittent treatment (IT), the respective antipsychotic treatment was completely removed in a stepwise fashion over a period of 3 months (at the most). For patients receiving blinded study drug treatment, dose reduction was predefined in 1-mg steps every 1 to 2 weeks. For patients receiving open treatment with an SGA, drug dose was reduced in a stepwise fashion at the doctors' discretion.

If early drug intervention was indicated by the decision algorithm (see Figure 2), it was administered double-blind (risperidone/haloperidol or lorazepam) in identical capsules containing either 1 mg of risperidone or haloperidol or 0.5 mg of lorazepam. Doses up to 2 capsules 3 times per day could be administered (ie, up to 6 mg/d risperidone or haloperidol or 3 mg/d lorazepam) at the physician's discretion. For the lateral entry patients (open SGA treatment at entry into the second study year), early drug intervention was conducted under open treatment conditions: patients were administered either the randomly assigned lorazepam at doses up to 3 mg/d or the previously administered SGA at doses decided on by the treating psychiatrist. Early drug intervention was continued until a stable clinical state was achieved again (ie, the patient achieved scores on the relevant scales below the scores indicating early drug intervention in the decision algorithm; see Figure 2) or for 4 weeks at the most. In case of stabilization or 4 weeks' treatment, the dose of the early intervention drug was reduced in a stepwise fashion over a period of 2 weeks at the most and the patient remained in the study. In case of further symptom progression or if a patient did not return to a stable state within these 6 weeks (at the most), study participation was terminated, and the patient was classified as a dropout.

Additional psychotropic medication was permitted, apart from antipsychotic agents, benzodiazepines, and mood stabilizers.

Statistical Analyses

The sample size calculation found that to test the main hypothesis (lower relapse rate with continued MT than with IT), 28 patients per group would be necessary to detect a 25% advantage in relapse rate for MT with $\alpha = .05$ and $\beta = .2$. To account for the projected dropouts, a total of 71 patients would have to be randomly assigned to enter the second treatment year.

Besides intent-to-treat (ITT) analyses of data from all randomized (and accordingly treated) patients, completer analyses of data from patients who completed the second treatment year according to protocol were performed. For the ITT analyses of continuous (secondary) outcome measures, the last observed value (under according-to-protocol conditions) was carried forward (last-observation-carried-forward [LOCF] analysis). In addition, mixed-model regression analyses were conducted that included estimates for missing values based on the preceding treatment course.

The main hypothesis (lower relapse rate with MT) was examined by means of a χ^2 test; in addition, a Kaplan-Meier survival analysis (comparing the treatment groups with a log rank statistic) was performed. Because the degree of negative symptoms at entry into the second study year differed between the treatment groups, additional analyses were performed that included negative symptoms as a covariate (logistic regression or Cox regression with adjustment for negative symptoms). Secondary outcome measures were compared at study endpoint (including and adjusting for baseline scores as a covariate) and regarding group differences in changes from baseline to endpoint based on various statistical test procedures (χ^2, Mann-Whitney *U* test, Wilcoxon test, logistic regression, *t* test, analysis of variance, analysis of covariance), depending on the measurement level and fulfillment of preconditions (mainly normal distribution and homogeneity of variances). Negative symptoms were additionally included as a covariate to adjust for initial group differences.

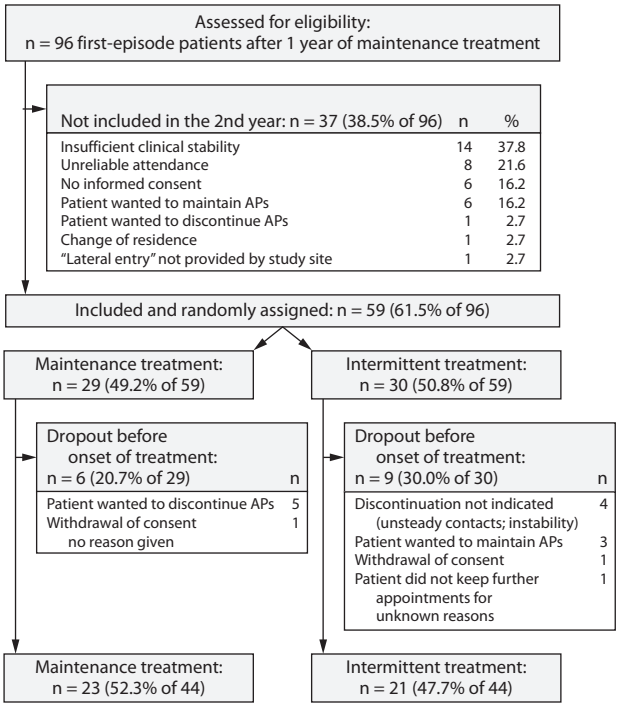
To compare treatment groups with regard to differences in antipsychotic drugs, especially in the administered doses, daily doses were transformed into haloperidol equivalents. SGA doses were converted to haloperidol equivalents according to Kane et al[39(p25)] (1 mg of haloperidol corresponds to 5 mg of aripiprazole, 75 mg of clozapine, 2.5 mg of olanzapine, 100 mg of quetiapine, 1 mg of risperidone, and 40 mg of ziprasidone).

Data analyses were performed with the SPSS statistical package (V15) by the biometric section of the coordinating center (Düsseldorf, Germany), in cooperation with W.K.

RESULTS

A total of 1,372 patients were screened for eligibility for the entire FES program (acute and long-term phase) at the inpatient facilities of 13 German university hospitals between November 2000 and May 2004. Of these 1,372 patients, 302 first-episode patients were included in the acute trial and 159 in the first year of the long-term trial. For the second year of the long-term study, 96 first-episode patients who had received 1 year of maintenance treatment were assessed for eligibility (see Figure 3), 48 (50%) of them as lateral entry patients. Nearly 40% (n = 37) were not eligible to be included in the trial (for reasons, see Figure 3; 26 [70%] were lateral entry patients), but 59 (22 [37.3%] by lateral entry) were included and randomly allocated to further maintenance treatment (MT, n = 29) or intermittent treatment (IT, n = 30). A further 15 patients dropped out immediately after random assignment (9 [60%] of them were lateral entry patients): in the MT group, 6 patients (20.7%) withdrew their consent

Figure 3. Participant Flow and Random Assignment to Maintenance Antipsychotic Treatment or Intermittent Treatment



Abbreviation: AP = antipsychotic.

(5 wanted to discontinue taking drugs, 1 did not give a reason), and in the IT group, 9 patients (30.0%) were not treated according to the random allocation (in 4 patients, this was at the discretion of the treating psychiatrist, who did not consider drug discontinuation indicated because of insufficient stability or problems in attending appointments; 3 patients wanted to maintain antipsychotics; 1 patient withdrew consent; and 1 patient did not keep any further appointments, without giving a reason). Since these 15 patients never received the randomly allocated treatment, they were excluded from the analyses. This attrition rate before onset of treatment did not significantly differ between treatment groups ($\chi^2 = 0.67$; $P = .4$). Overall, 44 patients were treated according to randomization and included in the ITT analyses: 23 in the MT group (52.3%) and 21 in the IT group (47.7%).

Sample Characteristics

The mean age of the 44 patients was 33.1 years (SD = 9.5; Table 1), and 25 (56.8%) were male. Nearly all patients (42; 95.5%) had participated in the preceding first year of the long-term study, and most of them (n = 31; 70.5%) completed the first year receiving double-blind treatment (which continued to be administered double-blind in the second year). Thirteen patients were lateral entries; 11 of them had participated in the first study year but had dropped out from randomized drug treatment and changed to open SGA treatment (5 patients with olanzapine, 3 with quetiapine, and 1 patient each with amisulpride, risperidone, and clozapine). Two patients were new and had not participated in the foregoing long-term study phase (1 was receiving olanzapine and the other both ziprasidone and aripiprazole).

There were some pronounced baseline differences between the treatment groups. Compared to the IT group, the MT group had a 10% lower proportion of male subjects, about 20% more participants from the CBT group of the preceding psychological trial, and a higher (ie, better) mean SWN score; however, these differences were not statistically significant. There were significant differences in the PANSS negative and SANS scores, in attitude toward drugs (DAI), and in quality of life. Differences in compliance rating and side effects according to UKU (mainly psychological symptoms) reached borderline significance. This indicates a somewhat better clinical state of the patients in the MT group, mainly because of fewer negative symptoms. To control for these a priori treatment group differences, additional statistical analyses were performed that included the PANSS negative score as a covariate. There were no significant differences in stressful life events during the second treatment year, and random assignment of the early intervention drug (the respective antipsychotic or lorazepam) was very well balanced between treatment groups. The proportion of first-year completers to "lateral entries" also did not differ significantly between treatment groups, and the type and dose of antipsychotics administered in both groups were comparable.

Relapse, Deterioration, and Rehospitalization

No relapse (according to the predefined criteria) occurred in the MT group (0/23), whereas 19% (4/21) of the IT group relapsed ($\chi^2 = 4.8$; $P = .04$ [Fisher exact test]). The respective Kaplan-Meier survival analysis yielded an estimated mean survival time from the beginning of the second study year of 52.0 weeks for the MT group and 46.1 weeks for the IT group (log rank = 6.3; $P = .01$). Rates for marked clinical deterioration were 0% for MT and 42.9% for IT (9/21; $\chi^2 = 12.4$; $P < .001$ [Fisher exact test]). Kaplan-Meier survival analysis yielded a mean survival time of 52.0 weeks for the MT group and 41.1 weeks for the IT group (log rank = 15.1; $P < .001$). Deteriorations, defined according to Csernansky et al,[37] occurred in 4.3% of the MT group (1/23) and 57.1% of the IT group (12/21; $\chi^2 = 12.8$; $P < .001$ [Fisher exact test]). The respective survival analysis also yielded a significant difference (Figure 4). Controlling for PANSS negative scores did not affect the statistical significance of any of these results. Likewise, controlling for assignment to the early intervention drugs (antipsychotic vs benzodiazepine) did not affect any of these or the following results. In particular, in the IT group there was no difference in relapse or deterioration rate between the 2 early intervention drugs (antipsychotic vs benzodiazepine; the details of this comparison will be described in a separate publication). In addition, there was no significant effect of lateral entry (yes/no) on relapse or deterioration. No patient in the MT group but 4 patients in the IT group had to be readmitted to hospital (3 because of relapse and 1 after marked clinical deterioration; $P < .05$).

Table 1. Sample Characteristics and Treatment Group Differences at Entry Into the Second Year of the Long-Term Study (ITT sample)

Characteristic	Total (n = 44)[a]	Maintenance Antipsychotic Treatment (n = 23)[a]	Intermittent Treatment (n = 21)[a]	P[b]
Age, mean (SD), y	33.1 (9.5)	32.3 (8.9)	34.0 (10.3)	NS
Gender, n (%) male	25 (56.8)	12 (52.2)	13 (61.9)	NS
Formerly included in acute trial, n (%)	35 (79.5)	17 (73.9)	18 (85.7)	NS
Study drug assigned in 1st year				NS
Risperidone				
n (%)	21 (47.7)	12 (52.2)	9 (42.9)	
Dose, mean (SD), mg/d	3.5 (1.4)	3.4 (1.5)	3.6 (1.4)	
Haloperidol				
n (%)	21 (47.7)	11 (47.8)	10 (47.6)	
Dose, mean (SD), mg/d	2.8 (1.0)	2.7 (0.8)	2.9 (1.3)	
Did not participate in the 1st year, n (%)	2 (4.5)	0 (0.0)	2 (9.5)	
Completer 1st year, n (%)	31 (70.5)	17 (73.9)	14 (66.7)	NS
Time receiving study drugs in 1st year, mean (SD), wk	40.3 (20.2)	40.6 (20.0)	39.9 (20.9)	NS
Formerly included in the psychological intervention trial, n (%)	32 (72.7)	18 (78.3)	14 (66.7)	NS
CBT group in the psychological intervention trial, n (%)	15 (46.9)	10 (55.6)	5 (35.7)	NS
Early drug intervention assignment, n (%)				NS
Antipsychotic	20 (45.5)	10 (43.5)	10 (47.6)	
Benzodiazepine (lorazepam)	24 (54.5)	13 (56.5)	11 (52.4)	
Strauss-Carpenter prognosis score, mean (SD)	59.7 (8.2)	61.2 (7.4)	56.9 (9.1)	NS
CGI-S score, mean (SD)	2.3 (1.0)	2.3 (1.0)	2.4 (1.0)	NS
PANSS score, mean (SD)				
Positive	7.7 (2.0)	7.9 (2.6)	7.5 (0.9)	NS
Negative	11.6 (5.5)	10.3 (5.0)	13.0 (5.8)	**.04**
General	20.4 (6.4)	19.8 (6.2)	21.0 (6.6)	NS
SANS total composite score, mean (SD)	13.5 (14.5)	10.2 (12.9)	17.1 (15.7)	**.049**
CDSS total score, mean (SD)	0.9 (1.6)	1.0 (1.8)	0.7 (1.3)	NS
HDRS total score, mean (SD)	2.2 (3.3)	2.2 (3.9)	2.2 (2.4)	NS
Prodromal symptoms, sum score, mean (SD)				
Nonspecific	2.8 (4.6)	3.1 (5.6)	2.5 (3.3)	NS
Specific	0.4 (1.5)	0.6 (1.9)	0.2 (0.6)	NS
Risk for relapse assessment, mean (SD)	0 (0.0)	0 (0.0)	0 (0.0)	NS
Side effects				
EPS total score, mean (SD)	0.7 (1.8)	0.4 (1.1)	1.1 (2.4)	NS
AIMS total score, mean (SD)	0.2 (0.6)	0.2 (0.7)	0.1 (0.7)	NS
UKU total score, mean (SD)	1.5 (2.3)	1.0 (1.6)	2.2 (2.8)	(.08)
HAS total score, mean (SD)	1.3 (5.5)	0.3 (1.3)	2.4 (7.9)	NS
Subjective well-being (SWN total score; higher = better), mean (SD)	91.3 (20.8)	94.9 (23.2)	87.4 (17.5)	NS
Social functioning (GAF score), mean (SD)	75.0 (12.2)	77.7 (13.6)	72.0 (9.9)	NS
GAF, lowest score in the preceding year, mean (SD)	61.5 (13.9)	63.6 (17.1)	59.8 (10.9)	NS
Compliance (1 = very low; 7 = very high), mean (SD)	6.6 (0.9)	6.7 (1.1)	6.5 (0.7)	(.07)
Attitude toward drugs (DAI score; 0 = low/negative; 30 = high/positive), mean (SD)	22.3 (4.5)	24.1 (3.9)	20.1 (4.4)	**.01**
Quality of life: LQLP total score, mean (SD)	4.9 (1.0)	5.3 (1.0)	4.6 (0.8)	**.04**
Total 2nd treatment year: stressful life events (MEL; sum of patients' burden), mean (SD)	1.5 (2.1)	1.0 1.6	2.0 2.5	NS

[a]Reduced n in single scales due to missing values.
[b]For comparison of maintenance treatment with intermittent treatment; χ^2 for frequencies/proportions; *t* test or Mann-Whitney test for continuous data. Boldface indicates statistical significance.
Abbreviations: AIMS = Abnormal Involuntary Movement Scale, CBT = cognitive-behavioral therapy, CDSS = Calgary Depression Rating Scale for Schizophrenia, CGI-S = Clinical Global Impressions-Severity of Illness scale, DAI = Drug Attitude Inventory, EPS = Extrapyramidal Side Effects scale, GAF = Global Assessment of Functioning, HAS = Hillside Akathisia Scale, HDRS = Hamilton Depression Rating Scale, ITT = intent to treat, LQLP = Lancashire Quality of Life Profile, MEL = Munich Event List, NS = nonsignificant, PANSS = Positive and Negative Syndrome Scale, SANS = Scale for the Assessment of Negative Symptoms, SWN = Subjective Well-Being Under Neuroleptics scale, UKU = Udvalg for Kliniske Undersogelser Side Effect Rating Scale.

Dropout

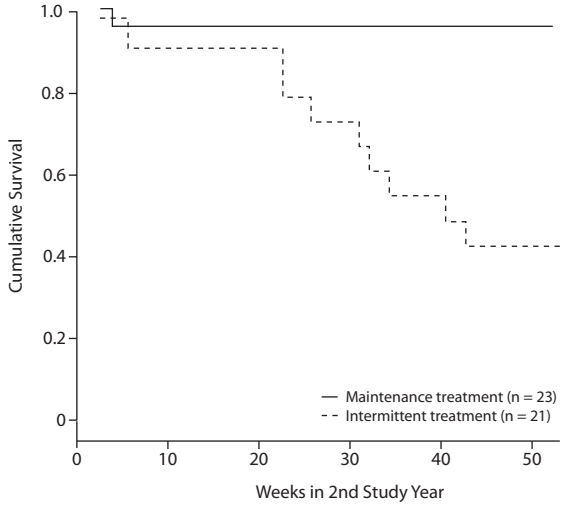
In the MT group, 17.4% of the patients dropped out (4/23: 2 patients because they wanted to discontinue antipsychotic treatment; 1 patient because of side effects; and 1 patient because of deterioration) and in the IT group 61.9% (13/21: 10 patients because of relapse or deterioration; 1 patient because of not showing up, without giving any reason; 1 patient because of insufficient compliance in attending the appointments; and 1 patient because of death [by car accident]). This difference was highly significant ($\chi^2 = 9.2$; $P = .002$), as was the (mean) time to dropout in the Kaplan-Meier survival analysis (MT = 48.6 weeks; IT = 36.9; log rank = 10.0; $P = .002$).

Symptoms, Side Effects, Compliance, Social Functioning, and Quality of Life

Several differences in secondary outcome measures became apparent in the ITT sample (LOCF analysis of dropout or relapsing patients; see Table 2): patients in the MT group (on average) scored significantly better (at study endpoint [adjusted for the respective baseline scores] and in change from study entry to endpoint) on the CGI-Severity of Illness scale, the PANSS positive and general scores, the sum of nonspecific and specific prodromal symptoms, the HDRS, and social functioning (according to GAF). In addition, MT patients (on average) showed a significantly better attitude toward drugs (DAI). For the PANSS negative score and the SANS, the significantly better scores for MT persisted throughout the trial. There were no group differences in quality of life or subjective well-being (after adjusting for baseline differences), and the latter improved significantly over time in both groups. In addition, a mixed-model regression analysis of quality-of-life scores, controlling for baseline differences, found no significant group differences. Side effects in general also showed a significant decrease over time in both groups (UKU total score), with a trend toward more improvement in the IT group (EPS, UKU).

In the subsample of patients completing the second study year according to protocol (ie, not including dropout patients, particularly due to relapse or deterioration), there were no such significant group differences between MT (n = 19) and IT (n = 8; see Table 3). There was a trend for patients in the MT group to have fewer depressive symptoms (HDRS, CDSS; $P < .15$) and (nonspecific and specific) prodromal

Figure 4. Survival Analysis for Clinical Deterioration[a] for Patients Receiving Maintenance Antipsychotic Treatment Versus Intermittent Treatment[b]



[a]According to the definition of Csernansky et al.[37]
[b]Mean survival time (Kaplan-Meier estimates): intermittent treatment = 41.0 weeks; maintenance treatment = 50.0 weeks; log rank = 13.4; $P < .001$.

symptoms ($P < .15$), to have better social functioning (GAF: $P = .1$), and to show a more positive attitude toward drugs ($P = .09$). On the other hand, in the IT patients, side effects decreased more (EPS: $P = .02$; UKU, HAS: $P < .15$) and quality of life tended to improve more (IT: from 4.3 to 4.7; MT: from 5.3 to 5.2; $P = .12$). However, in both groups, subjective well-being improved significantly ($P = .02$).

Antipsychotic Drug Treatment

At entry into the second study year, drug treatment (drug class and dose) was comparable in both treatment groups (Table 4). Seventeen patients in the MT group continued to receive double-blind treatment with the study drug from the first treatment year (mean daily dose = 2.9 mg, SD = 1.5; 9 patients received risperidone: mean daily dose = 2.8 mg, SD = 1.5; 8 received haloperidol: mean daily dose = 3.0 mg, SD = 1.5). Six patients in the MT group received open treatment with an SGA (3 patients received olanzapine: mean daily dose = 13.3 mg, SD = 7.6; 3 received quetiapine: mean daily dose = 550.0 mg, SD = 132.3).

In the IT group, 14 patients initially received blinded study drugs (mean daily dose = 2.5 mg, SD = 1.2; 7 patients received risperidone: mean daily dose = 3.1 mg, SD = 1.5; 7 received haloperidol: mean daily dose = 1.9 mg, SD = 0.6) and 6 patients received open treatment (3 received olanzapine: mean daily dose = 8.5 mg, SD = 3.1; and 1 patient each received monotherapy with risperidone [mean daily dose = 2.0 mg], ziprasidone [80 mg/d], and clozapine [200 mg/d]). One patient in the IT group was initially treated with both aripiprazole (30 mg/d) and ziprasidone (80 mg/d). The initial drug dose, transformed into haloperidol equivalents, did not (significantly) differ between treatment groups (MT: mean daily dose = 3.6 mg, SD = 2.0; IT: mean daily dose = 2.9 mg/d, SD = 1.6; $P = .2$).

Drug treatment in the further course of the second study year was as follows (see Table 5). In the MT group, all patients, except for the 2 dropouts, maintained treatment with their initially administered drug for the second year. Antipsychotic drugs were maintained for an average of 347 days (SD = 79 days) at an average mean daily dose (haloperidol equivalents) of 3.1 mg/d (SD = 1.7). After entry into the second treatment year, antipsychotic treatment in the IT group was initially maintained for an average of 24 days (SD = 25 days) at a mean daily dose (haloperidol equivalents) of 2.9 mg/d (SD = 1.6 mg/d). Drugs were afterward tapered off over an average of 70 days (SD = 51 days), ie, 10 weeks, which corresponded well with the planned time frame of a maximum of 12 weeks. The mean daily dose during this tapering-off period was 1.7 mg/d (haloperidol equivalents; SD = 1.2 mg/d). Antipsychotic drugs were completely discontinued for a mean period of 160 days (about 5 months; SD = 112 days); this calculation includes a discontinuation of "0" days for 2 patients for whom complete discontinuation was not feasible. Accordingly, the mean daily dose (during the withdrawal period) was 0 mg/d (SD = 0 mg/d). In 8 patients, antipsychotic treatment had to be restarted; however, this did not lead to sufficient symptom improvement, and the patients had to drop out of the study because of further deterioration. After restarting treatment, the treatment period lasted (on average) for about 17 days (SD = 9).

In total, patients in the IT group received a significantly lower amount of antipsychotics (mean daily dose = 1 mg/d haloperidol equivalents, SD = 0.8) than patients in the MT group (3.1 mg/d, SD = 1.7; $P < .001$).

Benzodiazepine Treatment

At entry into the second treatment year, no patient in either group was receiving (open or blinded) benzodiazepine drug treatment. In the further course of the second treatment year, the mean daily dose for all patients in the IT group (0.041 mg/d) was slightly higher than in the MT group (0.008 mg/d); however, this difference was not significant ($P = .13$).

DISCUSSION

A multicenter RCT was conducted within the German Research Network on Schizophrenia to investigate the indicated duration of antipsychotic maintenance treatment after a first episode in schizophrenia and the feasibility of targeted intermittent treatment in first-episode patients. After acute treatment of their first illness episode in schizophrenia and after sufficient stabilization during 1 year of maintenance treatment, patients with no relapse were randomly assigned to further maintenance treatment (MT) or to intermittent treatment after stepwise drug discontinuation (IT). A standardized early intervention procedure was supplemented in both groups, and, in case of prodromal symptoms or early warning signs of an impending relapse, drug treatment (with either antipsychotics or the benzodiazepine lorazepam) was added (MT) or restarted (IT).

Table 2. ITT Sample: Symptoms, Side Effects, Compliance, Level of Functioning, and Quality of Life at Entry (L1) and at End (L2) of the Second Year of the Long-Term Study (LOCF analysis for patients who dropped out)

		Maintenance Antipsychotic Treatment (n = 23)[a]		Intermittent Treatment (n = 21)[a]			
Measure	Time	Mean	SD	Mean	SD	Significant Effect[b]	*P*[b]
CGI-S score	L1	2.3	1.0	2.4	1.0	Time × group[c]	**.03**
	L2	2.2	1.0	3.3	1.5	End	**.008**
PANSS score							
Positive	L1	7.9	2.6	7.5	0.9	Time × group[c]	**.001**
	L2	7.8	2.6	13.3	8.0	End	**.002**
Negative	L1	10.3	5.0	13.0	5.8		
	L2	9.8	4.3	13.8	8.0		NS[d]
General	L1	19.8	6.2	21.0	6.6	Time × group[c]	**.03**
	L2	19.1	5.9	26.7	11.0	End	**< .001**
SANS total composite score	L1	10.2	12.9	17.1	15.7		
	L2	6.3	10.8	16.0	17.8		NS[d]
Nonspecific prodromes (sum score)	L1	3.1	5.6	2.5	3.3	Time × group[c]	**.002**
	L2	1.8	3.5	8.7	9.9	End	**.002**
Specific prodromes (sum score)	L1	0.6	1.9	0.2	0.6	Time × group[c]	**.009**
	L2	0.5	1.8	5.0	8.9	End	**.009**
CDSS total score	L1	1.0	1.8	0.7	1.3		
	L2	0.3	1.0	1.0	2.0		NS
HDRS total score	L1	2.2	3.9	2.2	2.4	Time × group[c]	**.005**
	L2	1.5	3.1	7.4	8.7	End	**.003**
Social functioning (GAF)	L1	77.7	13.6	72.0	9.9	Time × group	**.02**
	L2	79.4	10.1	62.1	16.7	End	**< .001**
Side effects							
EPS total score	L1	0.4	1.1	1.1	2.4	Time × group[c]	(.09)
	L2	0.3	0.8	0.0	0.2	End	(.1)
AIMS total score	L1	0.2	0.7	0.1	0.7		
	L2	0.2	0.7	0.0	0.0		NS
UKU total score	L1	1.0	1.6	2.2	2.8	Time	**.009**
	L2	0.6	1.6	0.8	2.4	Time × group	(.10)
HAS total score	L1	0.3	1.3	2.4	7.9		
	L2	0.1	0.4	2.2	10.3		NS
Subjective well-being (SWN total score; higher = better)	L1	94.9	23.2	87.4	17.5	Time	**.03**
	L2	99.3	22.1	92.1	18.0		
Compliance (1 = very low; 7 = very high)	L1	6.7	1.1	6.5	0.7		
	L2	6.2	1.7	6.3	1.4		NS
Attitude toward drugs (DAI score; 0 = low/negative; 30 = high/positive)	L1	24.1	3.9	20.1	4.4	Time × group	**< .05**
	L2	24.7	4.0	18.5	5.6	End	**.04**
Quality of life: LQLP total score	L1	5.3	1.0	4.6	0.8		
	L2	5.3	1.2	4.8	0.9		NS

[a]Reduced n in single scales due to missing values.
[b]"End" = drug group differences at L2 after adjusting for L1 scores (1-way analysis of covariance); 2-way analysis of variance: "time" = main effect change L1 to L2; "group" = persisting main effect maintenance treatment vs intermittent treatment; "time × group" = interaction (change from L1 to L2 differs between maintenance treatment and intermittent treatment). Boldface indicates statistical significance.
[c]A significant time effect exists but was not reported because of a significant time × group interaction.
[d]A significant group difference persisted throughout the trial.
Abbreviations: AIMS = Abnormal Involuntary Movement Scale, CDSS = Calgary Depression Rating Scale for Schizophrenia, CGI-S = Clinical Global Impressions-Severity of Illness scale, DAI = Drug Attitude Inventory, EPS = Extrapyramidal Side Effects scale, GAF = Global Assessment of Functioning, HAS = Hillside Akathisia Scale, HDRS = Hamilton Depression Rating Scale, ITT = intent to treat, LOCF = last observation carried forward, LQLP = Lancashire Quality of Life Profile, NS = nonsignificant, PANSS = Positive and Negative Syndrome Scale, SANS = Scale for the Assessment of Negative Symptoms, SWN = Subjective Well-Being Under Neuroleptics scale, UKU = Udvalg for Kliniske Undersogelser Side Effect Rating Scale.

Of the 96 first-episode patients available after 1 year of maintenance treatment, 37 (38.5%) could not be included in this phase of the trial, and another 15 (15.6%) dropped out immediately after random assignment to treatment. Accordingly, of the first-episode patients after a 1-year stabilization phase under maintained treatment, about 50% were not eligible for targeted intermittent treatment because of instability, insufficient compliance (mainly concerning keeping close and timely contact with the treating physician), or the patient's decision to continue taking antipsychotics. The eligibility rate of about 50% is somewhat higher than that in a study assessing the eligibility of multiple-episode patients for targeted intermittent treatment in an outpatient facility[40] but in the range of the prospective study by Gitlin et al[12] in first-episode patients, suggesting that targeted intermittent treatment is feasible after 1 year in only about 50% of first-episode patients. On the other hand, of all of the patients who refused to participate in the second-year study phase, about 10%–20% preferred to discontinue antipsychotic maintenance treatment after 1 year, indicating the need for alternative treatment strategies.

Relapse was defined as the major outcome criterion, and the analyses yielded a significantly higher relapse rate with the targeted intermittent treatment strategy (19%) than with maintenance treatment (0%; $P < .05$). Additionally defined measures of (marked) clinical deterioration resulted in higher prevalence rates, indicating the sensitivity of results to the underlying outcome criteria. However, the same or even greater statistically and clinically significant group differences (IT: deterioration in up to 57% of patients; MT: in less than 5%) emerged. Furthermore, 19% of the IT patients but none of the MT patients had to be readmitted to hospital. On the basis of our own previous reanalysis of first-episode schizophrenia,[8] we would have expected no (significant) differences. However, these results are comparable with those in multiple-episode patients[6] and with those from the only prospective RCT published so far in first-episode patients after a 6-month stabilization phase with a less standardized early intervention procedure.[13] These results indicate that even after 1 year of maintenance treatment and in patients highly selected for stability and compliance the risk for relapse or deterioration is noticeably (in our sample about 10-fold) higher after stepwise drug discontinuation and intermittent treatment—including an

Table 3. Completer Sample: Symptoms, Side Effects, Compliance, Level of Functioning, and Quality of Life at Entry (L1) and at End (L2) of the Second Year of the Long-Term Study (LOCF analysis for patients who dropped out)

		Maintenance Antipsychotic Treatment (n = 19)[a]		Intermittent Treatment (n = 8)[a]			
Measure	Time	Mean	SD	Mean	SD	Significant Effect[b]	P[b]
CGI-S	L1	2.0	0.9	2.8	0.9		
	L2	2.1	0.9	2.4	0.7		NS
PANSS score							
Positive	L1	7.3	0.8	7.8	1.2		
	L2	7.2	0.5	8.1	3.2		NS
Negative	L1	9.6	4.3	15.4	5.3		
	L2	9.1	2.8	13.4	9.1		NS[c]
General	L1	18.6	3.8	25.3	8.6		
	L2	18.1	3.0	21.9	6.8		NS[c]
SANS total composite score	L1	8.7	12.8	21.4	15.4		
	L2	5.7	9.7	17.6	18.0		NS[c]
Nonspecific prodromes (sum score)	L1	2.1	4.6	4.1	4.3		
	L2	1.2	2.1	4.1	5.7	End	(.12)
Specific prodromes (sum score)	L1	0.1	0.2	0.0	0.0	Time × group	(.10)
	L2	0.0	0.0	0.6	1.8		
CDSS total score	L1	0.7	1.6	1.3	1.5		
	L2	0.1	0.2	0.8	1.8	End	(.08)
HDRS total score	L1	1.2	2.9	2.9	2.2		
	L2	0.7	1.8	3.8	6.8	End	(.11)
Social functioning (GAF)	L1	79.5	13.2	70.5	9.5		
	L2	80.9	9.2	71.8	8.0	End[c]	(.10)
Side effects							
EPS total score	L1	0.3	0.8	1.6	2.7	Time × group[d]	**.02**
	L2	0.2	0.7	0.0	0.0		
AIMS total score	L1	0.1	0.2	0.4	1.1		
	L2	0.1	0.5	0.0	0.0		NS
UKU total score	L1	0.6	1.1	1.9	2.3	Time × group[d]	(.14)
	L2	0.2	0.4	0.4	1.1		
HAS total score	L1	0.0	0.0	1.3	3.5	Time × group	(.10)
	L2	0.1	0.5	0.0	0.0		
Subjective well-being	L1	93.7	23.5	92.2	15.2	Time	**.02**
(SWN total score; higher = better)	L2	98.8	22.7	101.5	13.6		
Compliance (1 = very low;	L1	6.8	0.5	6.6	0.5		
7 = very high)	L2	6.5	1.4	6.9	0.4		NS
Attitude toward drugs	L1	23.8	3.9	20.4	4.5	Time × group[c]	(.09)
(DAI score; "0 = low/negative;	L2	24.5	4.0	19.3	7.0		
30 = high/positive)							
Quality of life: LQLP total score	L1	5.3	1.0	4.3	0.8	Time × group	(.12)
	L2	5.2	1.2	4.7	1.0		

[a]Reduced n in single scales due to missing values.
[b]"End" = drug group differences at L2 after adjusting for L1 scores (1-way analysis of covariance); 2-way analysis of variance: "time" = main effect change L1 to L2; "group" = persisting main effect maintenance treatment vs intermittent treatment; "time × group" = interaction (change from L1 to L2 differs between maintenance treatment and intermittent treatment). Boldface indicates statistical significance.
[c]A significant group difference persisted throughout the trial.
[d]A significant time effect exists but was not reported because of a significant time × group interaction.
Abbreviations: AIMS = Abnormal Involuntary Movement Scale, CDSS = Calgary Depression Rating Scale for Schizophrenia, CGI-S = Clinical Global Impressions-Severity of Illness scale, DAI = Drug Attitude Inventory, EPS = Extrapyramidal Side Effects scale, GAF = Global Assessment of Functioning, HAS = Hillside Akathisia Scale, HDRS = Hamilton Depression Rating Scale, LOCF = last observation carried forward, LQLP = Lancashire Quality of Life Profile, NS = nonsignificant, PANSS = Positive and Negative Syndrome Scale, SANS = Scale for the Assessment of Negative Symptoms, SWN = Subjective Well-Being Under Neuroleptics scale, UKU = Udvalg for Kliniske Undersogelser Side Effect Rating Scale.

elaborated early intervention procedure based on prodromal symptoms and other early warning signs integrated in a decision algorithm—than with continued maintenance treatment. On the other hand, about 50% of the patients in the IT group remained stable; predictors for and characteristics of these patients are required and will be provided in a companion article.

As with the relapse and deterioration rates, large differences were found between the treatment groups in several secondary outcome measures in the ITT analysis. Patients in the MT group had significantly better scores at the end of the 1-year observation phase on nearly all psychopathologic measures (CGI, PANSS positive and general, HDRS, nonspecific and specific prodromes) and on social functioning (GAF). There were no significant group differences in quality of life (LQLP) or subjective well-being (SWN), and the latter improved significantly in both groups.

Although the 2 treatment groups received a comparable amount and similar kinds of antipsychotics at entry into this trial phase, the cumulative antipsychotic dose administered in the 2 groups differed significantly in the second treatment year. The mean daily dose of antipsychotics in the MT group was rather low at about 3 mg/d, as measured in a haloperidol-equivalent dose, whereas patients in the IT group received (on average) about 1 mg/d ($P < .001$); the mean dose in the IT group covers an initial maintenance phase of about 3 to 4 weeks (with an average mean daily dose of about 3 mg/d), a phase of about 10 weeks in which antipsychotics were tapered off (mean daily dose = 1.7 mg/d), a phase of about 6 months in which antipsychotics were withdrawn completely (0 mg/d), and (in 8 patients) a 2-week phase in which drug treatment was restarted.

Side effects in the IT group—with their overall lower amount of antipsychotics—tended to be lower than in the MT group or decreased to a greater extent (in some scales to zero); however, the differences between the groups were not or only marginally significant ($P \leq .1$). The significance level was not reached mainly because (very) few or only mild side effects emerged in the patients receiving low-dose maintenance antipsychotic treatment and because drug treatment had already been adjusted, in some cases because of side effects.[10]

Results were different when the comparison of outcome measures between treatment groups included only those patients who had successfully completed the second treatment year. There were no significant differences in psychopathologic symptoms, except for slightly higher depression scores

Table 4. Antipsychotic Treatment (daily doses) at Entry Into the Second Treatment Year

	Maintenance Antipsychotic Treatment					Intermittent Treatment				
		Dose (mg/d)		Haloperidol Equivalents			Dose (mg/d)		Haloperidol Equivalents	
Drug	n	Mean	SD	Mean	SD	n	Mean	SD	Mean	SD
Study drug, first year (blinded)	17	2.9	1.5	2.9	1.5	14	2.5	1.2	2.5	1.2
Risperidone	9	2.8	1.5	2.8	1.5	7	3.1	1.5	3.1	1.5
Haloperidol	8	3.0	1.5	3.0	1.5	7	1.9	0.6	1.9	0.6
Aripiprazole	0	…	…	…	…	1[a]	30.0	…	6.0	…
Clozapine	0	…	…	…	…	1	200.0	…	2.7	…
Olanzapine	3	13.3	7.6	5.3	3.1	3	8.5	3.1	3.4	1.2
Quetiapine	3	550.0	132.3	5.5	1.3	0	…	…	…	…
Risperidone (open)	0	…	…	…	…	1	2.0	…	2.0	…
Ziprasidone	0	…	…	…	…	2[a]	80.0	0.0	2.0	0.0
Overall[b]	23			3.6	2.0	21[a]			2.9	1.6

[a]One patient received both aripiprazole and ziprasidone.
[b]$P = .22$ for differences in mean daily dose between maintenance and intermittent treatment.

(CDSS, HDRS) or more pronounced "prodromal" symptoms and a somewhat lower functional state (GAF; whereby differences at study entry persisted throughout the second year) in the IT group, which reached borderline significance ($P \leq .1$). On the other hand, quality-of-life scores (LQLP) tended to increase more ($P = .12$) and side effect ratings tended to decrease more in the IT group. Again, these results indicate that there is a (small) group of patients in whom targeted intermittent treatment seems feasible and who might profit from this treatment strategy.

All of these results must be discussed in the light of some limitations of the trial. First, the sample size of randomized patients was rather low; although the projected number of patients required to detect a 25% difference in relapse rate was initially reached, it was just missed in the end because some patients dropped out directly after random allocation. Nevertheless, the difference of 19% in the primary outcome measure, relapse, reached the significance level (since a smaller sample size is required to reveal significant results at the margins of the percent distribution), and there are no reasons to expect that a larger sample size would have (noticeably) changed results in central tendency. In addition, the difference corresponds nearly exactly to the reported results of the other RCT[13] that compared maintenance and intermittent treatment in first-episode patients (21% relapse with MT vs 43% with IT). On the other hand, other differences in secondary outcome measures would not have been able to reach statistical significance because of the small sample size; this is especially true for the analyses of the (very small) completer sample. Thus, restrictions regarding statistical power and generalizability of results have to be considered, in particular for the secondary outcome measures and the very small completer sample (IT: 8 patients!).

Another limitation results from the highly selected sample, which was due to the inclusion and exclusion criteria, among other things. For example, the exclusion of (predominantly younger) patients with comorbid substance dependence contributed to a relatively high mean age of 33 years; however, this mean age is similar to that of other (similarly selected) first-episode samples.[41] Further selection resulted from dropout during the foregoing acute study and the first year of the long-term study, which was substantial (45% and 68%, respectively) and led to a high (positive) selection of patients who tolerated and responded to drug treatment very well and who were highly compliant with the study and treatment regimen. This may have contributed to an overall very low relapse rate after 2 years of about 10% (0% with 2 years of maintenance treatment!). On the other hand, it seems reasonable that this may also have contributed to the higher relapse rate in the drug withdrawal/IT group, because antipsychotic drugs seem to have played a major role in stabilizing these patients. According to the VSC model,[33] other protective factors (in particular, psychological issues like coping abilities or stress management) contribute to the stabilization of a distorted psychobiological "system." Although psychological interventions took place within the foregoing treatment phase in nearly all patients, the "protective power" of antipsychotic treatment (ie, neuropharmacologic prevention of symptom re-exacerbation even under the occurrence of stress) may have resulted in less development or exercise of other cognitive-behavioral (coping) competences. Thus, after suspending this major stabilizing factor (ie, antipsychotic treatment), "system breakdown" (ie, relapse or deterioration) seems more likely than in patients in whom multiple factors contribute more evenly to their stabilization.

Besides the antipsychotic "verum" effect of the administered drugs, a "placebo effect" (see Diederich and Goetz,[42] for example) must be considered; a placebo effect might have contributed to a better outcome of the MT group because the patients knew they were receiving drug treatment, whereas those in the IT group knew that they were not. However, relapse preventive efficacy of antipsychotics has also been proven in placebo-controlled trials,[43] suggesting that differences between MT and IT were—at least in part—due to a "true" verum effect of MT antipsychotic medication.

Another limitation results from a (slight but) significant difference in the amount of negative symptoms present in the treatment groups before the intervention. The more pronounced negative symptoms in the IT group might indicate a higher vulnerability, resulting in a higher risk for relapse. However, all analyses were additionally performed with the PANSS negative score as a covariate, and none of the results was noticeably affected after controlling for these pretreatment differences.

In addition, the kind of drug used in the early intervention strategy (the respective antipsychotic or the benzodiazepine lorazepam) could have influenced the results. Whereas benzodiazepine may have been sufficiently effective

Table 5. Antipsychotic Treatment (daily doses) in the Course of the Second Treatment Year

Treatment Phase	n	Dose (mg/d) Mean	Dose (mg/d) SD	Haloperidol Equivalents Mean	Haloperidol Equivalents SD
Group: Maintenance Treatment					
Treatment phase: maintained treatment					
Duration, d	23	346.5	79.0		
Study drug, first year (blinded)	17	2.4	1.0	2.4	1.0
Risperidone	9	2.2	1.0	2.2	1.0
Haloperidol	8	2.7	1.0	2.7	1.0
Aripiprazole	0	…	…	…	…
Clozapine	0	…	…	…	…
Olanzapine	3	11.8	7.6	4.7	3.0
Quetiapine	3	495.1	82.4	5.0	0.8
Risperidone (open)	0	…	…	…	…
Ziprasidone	0	…	…	…	…
Overall antipsychotic treatment[a]	23			3.1	1.7
Group: Intermittent Treatment					
Treatment phase: initial maintenance treatment					
Duration, d	21	24.2	25.2		
Study drug, first year (blinded)	14	2.5	1.2	2.5	1.2
Risperidone	7	3.1	1.5	3.1	1.5
Haloperidol	7	1.9	0.6	1.9	0.6
Aripiprazole	1	30.0	…	6.0	…
Clozapine	1	200.0	…	2.7	…
Olanzapine	3	8.5	3.1	3.4	1.2
Quetiapine	0	…	…	…	…
Risperidone (open)	1	2.0	…	2.0	…
Ziprasidone	2	80.0	0.0	2.0	0.0
Overall antipsychotic treatment	21			2.9	1.6
Treatment phase: tapering off					
Duration, d	21	70.1	50.5		
Study drug, first year (blinded)	14	1.4	0.6	1.4	0.6
Risperidone	7	1.5	0.8	1.5	0.8
Haloperidol	7	1.3	0.4	1.3	0.4
Aripiprazole	1	30.0	…	6.0	…
Clozapine	1	84.3	…	1.1	…
Olanzapine	3	4.5	1.5	1.8	0.6
Quetiapine	0	…	…	…	…
Risperidone (open)	1	1.0	…	1.0	…
Ziprasidone	2	38.7	28.2	1.0	0.7
Overall antipsychotic treatment	21			1.7	1.2
Treatment phase: discontinued					
Duration, d	21[b]	159.5	111.8		
Study drug, first year (blinded)	14	0.0	0.0	0.0	0.0
Risperidone	7	0.0	0.0	0.0	0.0
Haloperidol	7	0.0	0.0	0.0	0.0
Aripiprazole	1	0.0	…	0.0	…
Clozapine	1	0.0	…	0.0	…
Olanzapine	1	0.0	…	0.0	…
Quetiapine	0	…	…	…	…
Risperidone (open)	1	0.0	…	0.0	…
Ziprasidone	2	0.0	0.0	0.0	0.0
Overall antipsychotic treatment	21			0.0	0.0
Treatment phase: restart (until dropout)					
Duration, d	8	16.5	9.4		
Study drug, first year (blinded)	3	3.8	0.9	3.8	0.9
Risperidone	2	4.1	0.9	4.1	0.9
Haloperidol	1	3.0	…	3.0	…
Aripiprazole	0	…	…	…	…
Clozapine	0	…	…	…	…
Olanzapine	1	9.6	…	3.9	…
Quetiapine[c]	1	800.0	…	8.0	…
Risperidone (open)[c]	3	2.8	1.6	2.8	1.6
Ziprasidone[c]	2	82.9	24.1	2.1	0.6
Overall antipsychotic treatment	8			4.5	3.7
Overall second treatment year (only visits "according to protocol")					
Duration, d	21	259.9	105.4		
Overall antipsychotic treatment[a]	21			1.0	0.8

[a] $P < .001$ for differences in overall mean daily dose between maintenance and intermittent treatment.
[b] In 2 patients, drug discontinuation was not realizable so that the duration of discontinuation was considered to be 0 days.
[c] One patient received (open) risperidone and ziprasidone and 1 received (open) risperidone and quetiapine as the early drug intervention.

when added to maintained antipsychotic treatment in the MT group, its sedative effect may have been insufficient to prevent symptom recurrence or relapse in the IT group. This was tested separately (the results regarding differences in early intervention with antipsychotic or benzodiazepine will be reported elsewhere), and no significant difference was found between antipsychotic and benzodiazepine regarding prevention of relapse (or deterioration) in the IT group.

Besides these limitations, what may have contributed to the differences between treatment groups? Each single step of the "prodrome-based early intervention" procedure may have affected the results. First, the relapse-predictive validity of prodromal symptoms is limited (the sensitivity is at the most about 80%). Hence, it is likely that not every symptom re-exacerbation or impending relapse was detected in its preliminary stages, resulting in a higher relapse rate in the IT group. Second, the treating psychiatrist may not have reacted quickly enough to the early warning signs as indicated by the decision algorithm. Finally, even if detected at early stages and treated quickly enough by drugs at adequate doses, further symptom progression and a full reexacerbation may not have been avertable. The respective analyses of all these questions are ongoing and will be presented elsewhere. In addition, besides biologic treatment strategies, psychosocial interventions also have shown efficacy in relapse prevention[44] and must be considered.

CONCLUSIONS

Even if first-episode patients are stabilized after 1 year of antipsychotic maintenance treatment, when antipsychotics are discontinued in a stepwise fashion and a standardized prodrome-based early drug intervention is supplemented, these patients are at a significant and noticeably higher risk for relapse or symptom recurrence than patients who continue to receive maintenance treatment. Thus, maintenance treatment should be the preferred option for the second postacute year, even in stable first-episode patients. On the other hand, with intermittent treatment, quality of life scores were comparable, cumulative drug dose and side effects were lower, and about 50% of patients remained stable. In addition, some patients insisted on discontinuing drug treatment (sooner or later), indicating a need for alternative treatment strategies to maintenance treatment, including targeted intermittent treatment. Additional studies and analyses should therefore be performed to provide further data on the recommended duration of maintenance treatment, effective alternatives, and characteristics of patients for whom alternative treatment would be indicated. The results of these studies will hopefully allow preparing guidelines that will help psychiatrists determine the optimal individualized long-term treatment strategy for their (first-episode) patients.

Drug names: aripiprazole (Abilify), clozapine (Clozaril, FazaClo, and others), diazepam (Diastat, Valium, and others), haloperidol (Haldol), lorazepam (Ativan and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal and others), ziprasidone (Geodon).

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