Maintenance Treatment With Risperidone or Low-Dose Haloperidol in First-Episode Schizophrenia: 1-Year Results of a Randomized Controlled Trial Within the German Research Network on Schizophrenia

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Objective: Second-generation antipsychotics (SGAs) have proven superior to first-generation antipsychotics regarding relapse prevention, mainly in multiple-episode patients. Practice guidelines recommend SGAs as first-line treatment particularly in first-episode patients, although evidence for this group is still limited. Accordingly, the hypothesis of whether 1-year relapse rate in first-episode schizophrenia under maintenance treatment with risperidone is lower compared to haloperidol in low dose was tested.

Method: Between November 2000 and May 2004, 1372 patients had been screened for eligibility in the inpatient facilities of 13 German psychiatric university hospitals. 159 remitted patients were enrolled after treatment of an acute first episode of schizophrenia according to ICD-10 F20 criteria. In the randomized controlled trial, double-blind antipsychotic treatment with risperidone or haloperidol was maintained in a targeted dose of 2 to 4 mg/day for 1 year. 151 patients were eligible for analysis. For 127 patients, this was a continuation trial after 8 weeks of randomized, double-blind, acute treatment with the same drugs; 24 patients were additionally randomly assigned after open acute treatment.

Results: With both antipsychotics (risperidone, N = 77; haloperidol, N = 74), no relapse evolved. Additionally, according to 2 post hoc defined measures of "marked clinical deterioration," significant differences occurred neither in the 2 respective deterioration rates (risperidone = 9%/23%; haloperidol = 8%/22%) nor in time until deterioration. Both antipsychotics were equally effective regarding significant symptom reduction and improvement in quality of life. Extrapyramidal symptoms were slightly higher with haloperidol. The overall dropout rate of 68%, however, was not significantly different between the 2 drug groups.

Conclusion: Against the background of an overall favorable outcome, the hypothesized difference between risperidone and low-dose haloperidol regarding relapse prevention could not be supported for this sample of patients with first-episode schizophrenia. Possible design-related reasons for this finding are discussed. With regard to the high dropout rate, special programs are needed to keep schizophrenia patients who are in their early acute and postacute illness course in effective and safe treatment.

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Antipsychotic maintenance treatment has proven effective regarding relapse prevention in patients recovering from a first episode of schizophrenia. One-year relapse rates in first-episode patients on drug treatment compared to placebo vary between 0% versus 41%,[1] 0% versus 57%,[2] 43% versus 64%,[3] and 46% versus 62%,[4] respectively. Assured treatment in this early "critical period" of illness[5] is of great importance, since treatment nonadherence is very common,[6] leading to a nearly 5-fold increase in relapse risk[7] with negative impact on illness course.[8] Therefore, contemporary guidelines recommend maintenance treatment for at least 1 year after a first episode,[9–12] considering also the need for alternative strategies such as intermittent targeted treatment, which seems to be more feasible in first-episode than in multiple-episode patients.[13]

One issue in long-term treatment planning is drug choice, mainly between a first-generation ("typical") antipsychotic (FGA) and a second-generation ("atypical") (SGA) one. In addition to their lower risk of extrapyramidal symptoms,[14,15] SGAs have been proven superior in relapse prevention for multiple-episode schizophrenia.[16] However, weight gain and metabolic effects have recently become a focus of concern regarding SGAs.[17,18] A further matter of debate is whether or not the advantages of SGAs depend on the dosage of FGAs used in comparative trials.[19–21] Hopes that SGAs, with their lower side effect profile, decrease risk for nonadherence have only partly been fulfilled.[22] In addition, results of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study[23] have newly stimulated the typical-atypical controversy, since no differences in drug discontinuation rates between an FGA and several SGAs in multiple-episode patients have been found. Results of the European trial on first-episode schizophrenia are still awaited.[24]

However, SGAs are recommended as first-choice treatment, particularly in first-episode schizophrenia,[9–12,25] although best evidence is still limited for this group of patients.[26] Concerning acute treatment, only 3 randomized controlled trials (RCTs) have been published to our knowledge.[27–29] Regarding long-term treatment, 3 trial reports are also available, all published in the last 3 years. One trial comparing chlorpromazine with clozapine found advantages in symptom remission for clozapine after 12 weeks of acute (inpatient) treatment, which disappeared at the end of the 1-year course.[30] A recent study comparing olanzapine with (low-dose) haloperidol in first-episode psychosis over a 2-year period[31] found no differences in symptom reduction (main outcome measure) and relapse, but demonstrated benefits for olanzapine in treatment adherence and remission rate. The third trial, comparing risperidone with low-dose haloperidol in patients with first-episode psychosis for (at least) 2 years,[32] did not find significant differences between drugs regarding drug

discontinuation, remission rate, and symptom improvement, but relapse rate and time until relapse were in favor of risperidone in the subsample of remitted patients.

To provide empirical data for treatment optimization in first-episode schizophrenia, a comprehensive program for acute and long-term treatment including drug and psychological strategies[33] was initiated in 1999 within the German Research Network on Schizophrenia.[34] Regarding drug treatment, a randomized, double-blind clinical trial with the SGA risperidone or the FGA haloperidol (in low dose) was initiated in the acute phase. In accordance with routine care and as recommended in treatment guidelines,[9,11] acute treatment was continued under randomized, double-blind conditions in the first year of the long-term trial in patients showing responsiveness and tolerability. In the second year of the ongoing long-term trial, drug treatment was randomly either maintained or discontinued, both supplemented by prodrome-based early intervention. The present article reports on 1-year outcome (primary criterion "relapse") of postacute long-term maintenance treatment comparing randomly assigned low-dose haloperidol and risperidone in double-blind fashion.

METHOD

Study Setting and Design

The first-episode study is part of the German Research Network on Schizophrenia (GRNS),[34] a nationwide research network, funded by the German Ministry of Education and Research. The study was conducted as a multicenter clinical trial in initially 13 German psychiatric university hospitals, according to the principles of Good Clinical Practice of the International Conference on Harmonization and the declaration of Helsinki. Good clinical practice was assured by involvement of the Düsseldorf Coordinating Centre for Clinical Trials (head: C.O.). Approval votes had been obtained from ethics boards of the coordinating center (Düsseldorf; principal investigator: W.G.) and the local centers. Antipsychotic study medication, blinding, and randomization procedure (block randomization) were provided by Janssen-Cilag.

The entire first-episode study program (for details see Gaebel et al.[33]) consists of an 8-week acute treatment phase (H.-J.M.; M. Riedel, M.D.; M.J.; in preparation, Sept. 2000 to March 2004) and a consecutive 2-year long-term treatment phase. As designed originally, patients with a first-episode of schizophrenia were included in the acute study and randomly assigned to double-blind, low-dose haloperidol or risperidone. After completing the 8-week inpatient acute treatment phase, patients renewed informed consent and were included in the first year of the long-term study, maintaining the formerly assigned (still blinded) antipsychotic medication in an outpatient treatment setting. Additionally, a "lateral entry" procedure was provided as recommended by the scientific advisory board of the GRNS, as compensation for the high dropout rate in the acute study, in order to reach the projected sample size of the long-term study. Thus, first-episode patients after acute treatment with haloperidol for up to 8 weeks were (also) included in the first year of the long-term study (after having given informed consent) and were randomly assigned (for their first time) to double-blind maintenance treatment with either low-dose haloperidol or risperidone.

In 5 study centers, pharmacologic treatment in the first study year was supplemented by a trial of psychological interventions (8-week psychoeducation vs. 1-year cognitive-behavioral therapy; random design; principal investigator: S.K.). The corresponding results as well as those of the (ongoing) second year of the long-term study (continuing maintenance treatment vs. stepwise drug discontinuation, both supplemented by prodrome-based early intervention) and of other cooperating research projects (for details see Gaebel et al.[33]) will be reported elsewhere.

After inclusion in the long-term study, patients were to be seen by study doctors every 2 weeks. Antipsychotic drugs were administered in identically-appearing pills containing 2 mg of either haloperidol or risperidone. Dosing was possible in 1-mg steps up to a targeted total dose of 2 to 4 mg/day by halving the pills. This method gave the treating psychiatrist the opportunity to choose an individually appropriate dose, since dose equivalence ratios for the 2 drugs were still unsettled, ranging from 1:1[35] to 1:2.5.[25,36] Drug dose could be increased (up to 8 mg/day) or lowered (minimum, 1 mg/day) depending on symptoms and side effects as indicated by the respective Clinical Global Impressions (CGI) scales. Concomitant medications were permitted throughout the trial, except for additional antipsychotic agents and mood stabilizers.

Clinical Assessments

Assessments were made at study entry and every visit (fortnightly), including psychopathology (Positive and Negative Syndrome Scale [PANSS],[37] CGI,[38] Scale for the Assessment of Negative Symptoms,[39] Hamilton Rating Scale for Depression,[40] Calgary Depression Rating Scale for Schizophrenia[41,42]); level of functioning (Global Assessment of Functioning [GAF][43]); side effects (Extrapyramidal Side Effects scale,[44] Udvalg for Kliniske Undersogelser Side Effect Rating Scale,[45] Hillside Akathisia Scale,[46] Abnormal Involuntary Movement Scale [AIMS][47]); compliance (Compliance Rating Scale[48]); drug attitude (Drug Attitude Inventory [DAI][49]); quality of life (Lancashire Quality of Life Profile[50]); and subjective well-being (Subjective Well-Being Under Neuroleptics scale[51]). Several rater trainings took place. Interrater reliability yielded a satisfying to good concordance (intra-class correlation coefficient of the PANSS total

score = 0.61, p < .001; PANSS positive score = 0.74, p < .001). ICD-10 diagnostic criteria[52] were reassessed at the end of the first study year or at study dropout.

The primary outcome measure was relapse, which was predefined in accordance with a former research program[13] as an increase in PANSS positive score > 10 and a CGI-Change score ≥ 6 and a decrease in GAF score > 20 between 2 visits. Due to a zero prevalence of relapse according to these criteria, "marked clinical deterioration" was added (post hoc) as a further outcome measure and was defined as fulfillment of one of the single relapse criteria or increase in PANSS positive score ≥ 7 with a decrease in GAF score > 15 (between 2 visits). An additional measure for deterioration was adapted from Csernansky et al.[36] (related to baseline/inclusion in long-term study) as an increase in the sum of 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, social functioning, compliance, and drug attitude.

Statistical Methods

The sample size calculation yielded 2 × 70 patients at entry into the first treatment year (comprising an expected dropout rate of 45%) for testing the hypothesis of a 15% advantage in relapse rate for risperidone (corresponding to Csernansky et al.[36]) with $\alpha = .05$ and $\beta = .2$.

Besides intent-to-treat (ITT) analyses considering all eligible patients, completer analyses (considering patients accomplishing the first treatment year according to protocol) were conducted. For the ITT analyses of continuous (secondary) outcome measures, the last observed value (under regular treatment conditions) was carried forward (last-observation-carried-forward [LOCF] analysis). Due to the explorative character of the latter analyses, mixed-model procedures—although increasingly used—were not applied, since assumptions that have to be made can further restrict interpretability of the results.

The main hypothesis (lower relapse rate with risperidone) was examined by means of χ^2 test and Kaplan-Meier survival analysis (comparing the treatment groups with a log-rank statistic). Due to an inequality of the gender proportion in the drug groups (see Results), additional analyses including gender as a "covariate" were performed (logistic regression or Cox regression with adjustment for gender; Kaplan-Meier analysis stratified for gender). For secondary outcome measures, various statistical test procedures were used (χ^2, Mann-Whitney U test, Wilcoxon test, logistic regression, t test, analysis of variance [ANOVA]) depending on measurement level and fulfillment of preconditions (mainly normal distribution and homogeneity of variances). Likewise, gender was (additionally) included as a "covariate" for adjustment of its disproportion. Data analyses were conducted with SPSS statistical package (V12; SPSS, Inc., Chicago, Ill.) by the biometric section of the coordinating center (Düsseldorf) in cooperation with W.K.

Subjects

Study subjects were selected from patients admitted to the inpatient departments of the participating centers. Inclusion criteria were (1) having successfully (CGI-Change score ≤ 3, i.e., "very much"/"much"/"minimally" improved) completed acute treatment (within the 8-week acute trial or with haloperidol in standard routine inpatient care) for schizophrenia (according to ICD-10 F20) in the first illness episode (defined as the first inpatient treatment of the respective symptoms and no former treatment with antipsychotic medication); (2) being aged from 18 to 55 years; (3) being sufficiently proficient in German language; (4) having no involuntary inpatient treatment (at the date of inclusion); and (5) providing written informed consent after explicit 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.

Between November 2000 and May 2004, 1372 patients had been screened for eligibility in the inpatient facilities of the 13 hospitals (Figure 1). Thereof, 159 first-episode patients were included in the long-term study, 132 (83%) after participation in the acute-study and 27 (17%) by lateral entry (for reasons of noninclusion and dropout, see Figure 1).

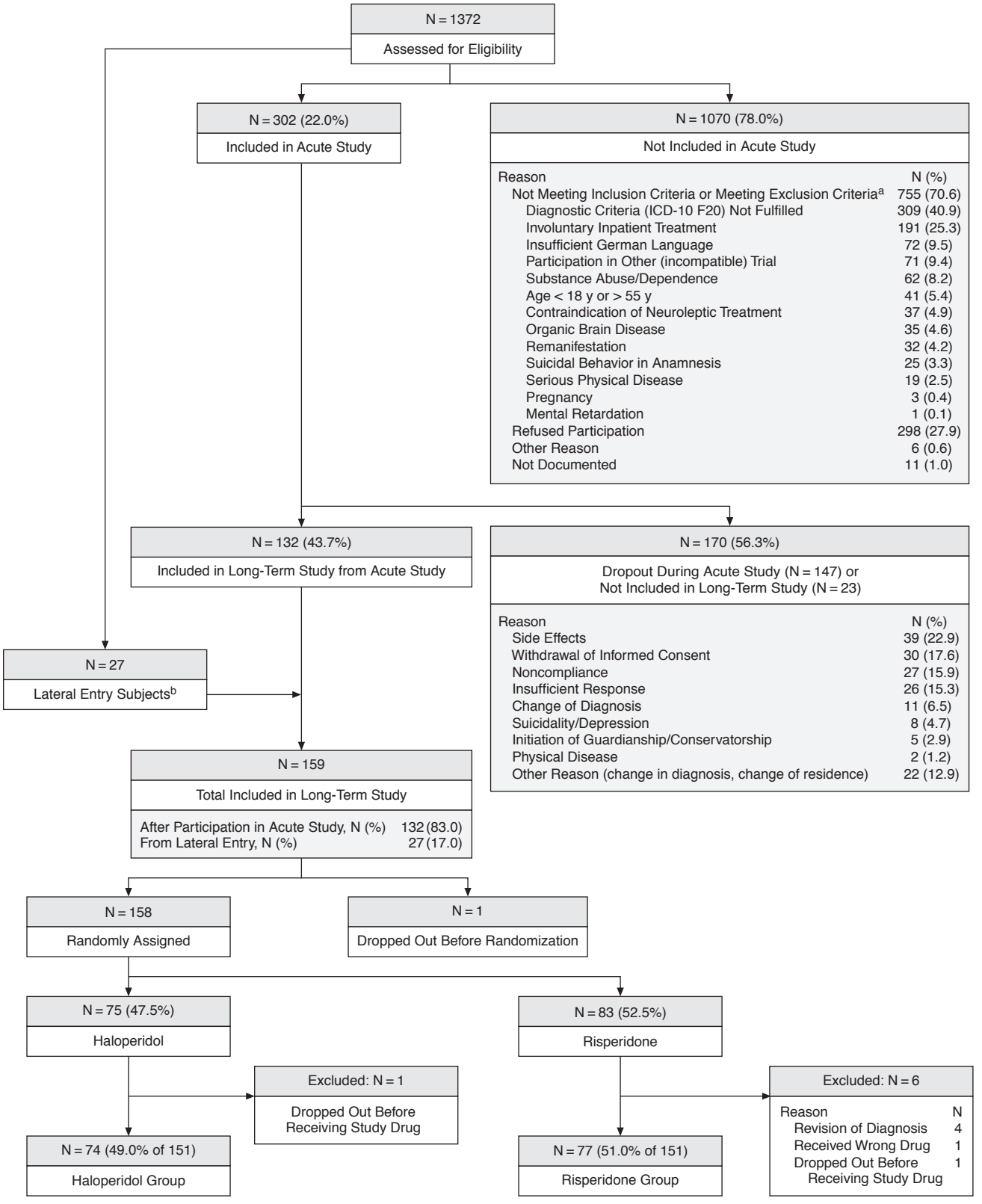
Thereof, 158 patients were randomly assigned to either haloperidol (N = 75, 47.5%) or risperidone (N = 83, 52.5%; $\chi^2 = 0.4$, df = 1, p = .5). Of the randomly assigned patients included in the long-term study, 7 patients had to be excluded post hoc from the analyses (for reasons, see Figure 1). Hence, ITT analyses were run on 74 patients in the haloperidol group and 77 patients in the risperidone group.

RESULTS

Sample Characteristics

Mean age of the 151 patients considered for ITT analysis was 31.6 (SD = 10.0) years; 58.3% (N = 88) were male (Table 1). Main access to the long-term study was via the acute study (84.1%, N = 127). After acute treatment, at baseline, positive symptoms were almost fully remitted (mean PANSS positive score = 10.8, SD = 5.4), and negative and general symptoms were mild on average. The mean drug dose was still at the upper limit of the targeted dose range (mean = 4.1, SD = 2.2), but side effects (assessed by different scales) were low. Compliance ratings were high, corresponding to a positive attitude concerning (antipsychotic) drugs, as measured by the DAI.

Figure 1. Flow Diagram of Subject Progress Through the Phases of the Randomized Trial



[a]Multiple reasons possible.
[b]A "lateral entry" procedure was provided as recommended by the scientific advisory board of the German Research Network on Schizophrenia, as compensation for the high dropout rate in the acute study, in order to reach the projected sample size of the long-term study.

Table 1. Sample Characteristics and Drug Group Differences at Entry in the Long-Term Study (intent-to-treat sample)

Characteristic	Total (N = 151)[a]	Risperidone Group (N = 77)[a]	Haloperidol Group (N = 74)[a]	p[b]
Age, mean (SD), y	31.6 (10.0)	30.9 (9.6)	32.3 (10.5)	NS
Gender, male, N (%)	88 (58.3)	53 (68.8)	35 (47.3)	.007
Time since onset of first psychotic symptoms, N (%)				NS
≤ 6 mo	86 (57.0)	47 (61.0)	39 (52.7)	
> 6 mo	57 (37.7)	26 (33.8)	31 (41.9)	
Not documented	8 (5.3)	4 (5.2)	4 (5.4)	
Mode of study entry, N (%)				NS
From acute study	127 (84.1)	67 (87.0)	60 (81.1)	
By lateral entry	24 (15.9)	10 (13.0)	14 (18.9)	
Medical attendance, mean (SD)				
Frequency of visits	13.3 (10.0)	13.4 (9.9)	13.1 (10.2)	NS
Time between consecutive visits, d	14.5 (3.3)	14.4 (2.7)	14.5 (3.8)	NS
Study drug dose, mean (SD), mg/d	4.1 (2.2)	4.2 (2.1)	4.1 (2.2)	NS
Participation in "psychological trial," N (%)				
Total	91 (60.3)	46 (59.7)	45 (60.8)	NS
CBT group	42 (46.2)	18 (39.1)	24 (53.3)	(.17)
Strauss-Carpenter Prognostic Scale[53] score, mean (SD)	57.3 (9.3)	57.7 (8.9)	57.0 (9.7)	NS
CGI-Severity of Illness score, mean (SD)	3.5 (1.1)	3.6 (1.0)	3.5 (1.3)	NS
PANSS score, mean (SD)				
Positive	10.8 (5.4)	11.0 (5.2)	10.6 (5.6)	NS
Negative	14.9 (6.1)	15.3 (6.2)	14.5 (6.0)	NS
General	26.7 (9.9)	27.7 (10.0)	25.6 (9.7)	(.08)
SANS total composite score, mean (SD)	22.0 (17.0)	22.7 (17.1)	21.2 (17.0)	NS
CDSS total score, mean (SD)	2.5 (3.4)	2.6 (3.6)	2.4 (3.3)	NS
HAM-D total score, mean (SD)	6.4 (6.4)	6.6 (6.2)	6.2 (6.6)	NS
Side effects, mean (SD)				
Extrapyramidal Side Effects scale total score	1.4 (3.1)	1.5 (3.0)	1.4 (3.2)	NS
AIMS total score	0.3 (1.2)	0.2 (1.0)	0.3 (1.4)	NS
UKU total score	4.1 (5.2)	4.2 (4.6)	3.9 (5.8)	NS
Hillside Akathisia Scale total score	2.6 (6.7)	2.5 (6.3)	2.7 (7.0)	NS
Social functioning, mean (SD)				
GAF score	63.9 (14.0)	65.2 (13.1)	62.6 (14.8)	NS
Lowest GAF score in the foregoing year	41.3 (15.1)	42.3 (15.0)	40.2 (15.1)	NS
Compliance Rating Scale score, mean (SD)[c]	6.1 (1.1)	6.0 (1.1)	6.2 (1.0)	(.09)
Attitude regarding drugs (DAI score), mean (SD)[d]	20.9 (5.4)	20.4 (5.1)	21.3 (5.6)	NS
Quality of life, mean (SD)				
Lancashire Quality of Life Profile total score	4.1 (1.1)	4.0 (1.0)	4.1 (1.1)	NS
SWN total score	88.9 (17.5)	90.2 (16.2)	87.6 (18.7)	NS

[a]Reduced N in single scales due to missing values.
[b]For comparison of risperidone with haloperidol; χ^2 for frequencies/proportions; t test or Mann-Whitney U Test for continuous data. Values in parentheses indicate values $.05 < p < .2$.
[c]Compliance Rating Scale score: 1 = very low; 7 = very high.
[d]Range, 0–30; high means (very) positive attitude.
Abbreviations: AIMS = Abnormal Involuntary Movement Scale, CBT = cognitive-behavioral therapy, CDSS = Calgary Depression Rating Scale for Schizophrenia, CGI = Clinical Global Impressions, DAI = Drug Attitude Inventory, GAF = Global Assessment of Functioning, HAM-D = Hamilton Rating Scale for Depression, NS = not significant, PANSS = Positive and Negative Syndrome Scale, SANS = Scale for the Assessment of Negative Symptoms, SWN = Subjective Well-Being under Neuroleptics, UKU = Udvalg for Kliniske Undersogelser Side Effect Rating Scale.

Table 2. Frequencies and Reasons for Study Dropout and Discontinuation of Randomized Antipsychotic Treatment

Frequencies and Reasons	Total (N = 151)	Risperidone Group (N = 77)	Haloperidol Group (N = 74)	p[a]
Total dropout/study drug discontinuation, N (%)	103 (68.2)	53 (68.8)	50 (67.6)	NS
Kaplan-Meier estimated time until dropout, mean, wk	26.5	26.8	26.2	NS
Study-related reasons for dropout, N (%)	96 (63.6)	49 (63.6)	47 (63.5)	NS
Lack of acceptance	43 (28.5)	20 (26.0)	23 (31.1)	NS
Withdrawal of informed consent	19 (12.6)	8 (10.4)	11 (14.9)	
Noncompliance	17 (11.3)	9 (11.7)	8 (10.8)	
Absence without any reason	7 (4.6)	3 (3.9)	4 (5.4)	
Insufficient response[b]	15 (9.9)	12 (15.6)	3 (4.1)	.02[b]
Side effects	31 (20.5)	14 (18.2)	17 (23.0)	NS
Not specified	10 (6.6)	5 (6.5)	5 (6.8)	
Extrapyramidal	11 (7.3)	4 (5.2)	7 (9.5)	
Non-extrapyramidal	10 (6.6)	5 (6.5)	5 (6.8)	
Other[c]	7 (4.6)	3 (3.9)	4 (5.4)	NS
Non–study-related reasons for dropout, N (%)[d]	7 (4.6)	4 (5.2)	3 (4.1)	NS

[a]For comparison of risperidone with haloperidol; χ^2 for frequencies/proportions; log-rank test for survival analysis.
[b]Clinical judgment, no formal criteria; no significant differences in Positive and Negative Syndrome Scale ratings.
[c]Suicidality, contraindication of respective antipsychotic treatment, violation of protocol.
[d]Non–study-related/organizational reasons, such as change of residence.

Table 3. Intent-to-Treat Sample: Drug Treatment, Symptoms, Side Effects, Compliance, Level of Functioning, and Quality of Life at Entry Into the Long-Term Study (L0) and at the End of the First Treatment Year (L1)

		Risperidone Group (N = 77)[b]		Haloperidol Group (N = 74)[b]				
Measurement	Time[a]	Mean	SD	Mean	SD	Significant Effect[c]	p[c]	Adjusted p Value[d]
Study drug dose, mg/d	L0	4.2	2.1	4.1	2.2	time	< .001	
	L1	3.6	2.3	3.3	2.0			
CGI-Severity of Illness score	L0	3.6	1.0	3.5	1.3			
	L1	3.4	1.3	3.3	1.3			
PANSS scores								
Positive	L0	11.0	5.2	10.6	5.6	time	< .001	
	L1	10.4	5.1	9.0	3.1	end	.03	.048
Negative	L0	15.3	6.2	14.5	6.0			
	L1	15.1	6.6	13.5	6.3			
General	L0	27.7	10.0	25.6	9.7	(group)	(.09)	(.06)
	L1	27.0	10.6	24.1	8.8			
PANSS 5-factor solution								
Positive symptoms	L0	13.7	6.1	12.6	6.0	time	.003	
						end	.03	.05
	L1	12.9	6.0	11.0	3.8	(group)	(.06)	(.13)
Negative symptoms	L0	15.6	6.3	14.6	6.2			
	L1	15.3	6.5	13.9	6.8			
Disorganized thought	L0	12.0	5.0	11.4	4.7	time	.002	
						end	.02	.01
	L1	11.5	5.0	9.9	3.4	(time × group)	(.08)	(.06)
Uncontrolled hostility/excitement	L0	5.4	2.3	5.0	2.5	end	.05	(.07)
	L1	5.4	2.7	4.7	1.2	(group)	(.09)	(.19)
Anxiety/depression	L0	7.4	3.1	6.9	3.2			
	L1	7.2	3.4	7.0	3.4			
SANS total composite score	L0	22.7	17.1	21.2	17.0			
	L1	20.6	16.4	19.7	18.0			
SANS attentional impairment score	L0	1.2	1.2	1.4	1.3	time	.001	
						end	.05	.049
	L1	1.1	1.2	0.9	1.1	time × group	(.055)	.046
CDSS total score	L0	2.6	3.6	2.4	3.3			
	L1	2.9	4.1	2.8	3.7			
HAM-D total score	L0	6.6	6.2	6.2	6.6			
	L1	6.1	6.2	5.7	6.4			

(continued)

As scheduled, the (mean) time interval between consecutive visits was about 14 days.

Drug group characteristics were (almost) similar at entry in the long-term study (see Table 1) except for a statistically significant difference regarding gender resulting in a higher rate of male patients in the risperidone group (68.8%) than in the haloperidol group (47.3%, p = .007; the proportion of male patients at entry in the acute trial was 65.1% for risperidone and 54.7% for haloperidol, p = .13; see H.-J.M.; M. Riedel, M.D.; M.J.; in preparation, Sept. 2000 to March 2004). Therefore, all subsequent analyses were additionally controlled for gender. Drug groups did not differ significantly (p = .86) regarding proportion of patients included by centers/study sites.

Relapse and Marked Clinical Deterioration

Regarding the predefined criteria, no relapse occurred. Regarding "marked clinical deterioration," rates were 9.1% (7/77) for risperidone and 8.1% (6/74) for haloperidol ($\chi^2 = 0.046$, df = 1, p > .05). Kaplan-Meier survival analysis yielded no significant group difference (mean survival time: risperidone = 47.1 weeks, haloperidol = 47.8 weeks; log-rank = 0.03, df = 1, p > .05). Deteriorations adapted from Csernansky et al.[36] amounted to 23.4% (18/77) for risperidone and 21.6% (16/74) for haloperidol ($\chi^2 = 0.067$, df = 1, p > .05). Kaplan-Meier survival analysis yielded no significant group difference (mean survival time: risperidone = 38.8 weeks, haloperidol = 40.5 weeks; log-rank = 0.1, df = 1, p > .05). Controlling for gender or center/study site also yielded no significant group differences.

Dropout

Table 2 gives frequencies and reasons for study dropout. Overall, dropout rate amounted to 68.2% (patients by lateral entry: 83.2%, 20/24). However, there was no significant difference in dropout rate between the 2 drug groups or in time until dropout, also when controlling for gender or center/study site. Further details are given in Table 2.

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

Differences in secondary outcome measures between treatment groups were compared in 2 types: first regarding

Table 3 (continued). Intent-to-Treat Sample: Drug Treatment, Symptoms, Side Effects, Compliance, Level of Functioning, and Quality of Life at Entry Into the Long-Term Study (L0) and at the End of the First Treatment Year (L1)

		Risperidone Group (N = 77)[b]		Haloperidol Group (N = 74)[b]				
Measurement	Time[a]	Mean	SD	Mean	SD	Significant Effect[c]	p[c]	Adjusted p Value[d]
Side effects								
Extrapyramidal Side Effects scale total score	L0	1.5	3.0	1.4	3.2	time	.046	
						(end)	(.07)	(.1)
	L1	1.6	3.2	2.3	3.3	(time × group)	(.095)	(.13)
AIMS total score	L0	0.2	1.0	0.3	1.4			
	L1	0.2	0.9	0.4	1.6			
AIMS incapacitation	L0	0.0	0.1	0.1	0.3	end	(.06)	.04
	L1	0.0	0.0	0.1	0.2	group	.04	.02
UKU total score	L0	4.3	4.6	3.9	5.8			
	L1	4.1	5.0	4.5	5.8			
UKU neurological side effects	L0	0.7	1.1	0.6	1.2	(end)	(.1)	(.16)
	L1	0.8	1.2	1.0	1.5			
Hillside Akathisia Scale total score	L0	2.5	6.4	2.7	7.0			
	L1	4.4	10.6	3.1	10.1			
Compliance[e]	L0	6.0	1.1	6.2	1.0	time	.02	
	L1	5.6	1.7	6.1	1.4	(group)	(.051)	(.12)
Attitude regarding drugs[f]	L0	20.3	5.1	21.3	5.6	(end)	(.1)	(.15)
	L1	21.4	5.1	20.6	6.3	(time × group)	(.08)	(.09)
Social functioning[g]	L0	65.2	13.1	62.6	14.8			
	L1	65.9	15.1	64.8	13.9			
Quality of life								
LQLP total score	L0	4.0	1.0	4.1	1.1			
	L1	4.1	1.4	4.2	1.2			
LQLP (general) health	L0	4.3	1.5	4.5	1.5	time	.046	
	L1	4.7	1.5	4.6	1.4	(time × group)	(.09)	(.10)
SWN total score[h]	L0	90.2	16.2	87.6	18.7	(time × group)	(.13)	(.054)
	L1	85.7	17.6	87.5	18.7			

[a]L0 = entry into long-term study; L1 = at the end of the first treatment year (last-observation-carried-forward analysis for dropout patients).
[b]Reduced N in single scales due to missing values.
[c]"End" = drug group differences at L1 after adjusting for baseline scores (1-way ANCOVA); 2-way ANOVA: "time" = main effect change from L0 to L1; "group" = persisting main-effect risperidone vs. haloperidol; "time × group" = interaction (change from L0 to L1 differs between risperidone and haloperidol). Values in parentheses indicate values $.05 < p < .2$.
[d]p Value adjusted for gender; significance level for "end," "group," and "time × group" after including and controlling for gender as a covariate. Values in parentheses indicate values $.05 < p < .2$.
[e]Compliance Rating Scale score; 1 = very low, 7 = very high.
[f]DAI score; 0 = low/negative, 30 = high/positive.
[g]GAF score.
[h]Higher means better.
Abbreviations: AIMS = Abnormal Involuntary Movement Scale, ANCOVA = analysis of covariance, ANOVA = analysis of variance, CDSS = Calgary Depression Rating Scale for Schizophrenia, CGI = Clinical Global Impressions scale, DAI = Drug Attitude Inventory, GAF = Global Assessment of Functioning scale, HAM-D = Hamilton Rating Scale for Depression, LQLP = Lancashire Quality of Life Profile, 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.

differences at the end of the first treatment year (i.e., "L1"; LOCF for dropout patients) by conducting 1-way analyses of covariance (ANCOVAs; testing for drug group differences and controlling for the respective baseline score as covariate) and second by comparing the changes from baseline ("L0," i.e., at inclusion in the long-term study) to endpoint (2-way ANOVAs; particularly focusing on the interaction term "time × group"). Likewise, additional ANCOVAs were conducted including gender as a covariate. Table 3 gives the respective explorative results.

Regarding endpoint comparisons (see "end" effect in Table 3), significant differences were found for some psychopathological scales in favor of haloperidol, and some borderline significant differences in side effect scales (higher Extrapyramidal Side Effects scale scores with haloperidol) were found. There was no significant difference between the 2 drug groups concerning patients receiving anti-Parkinsonian drugs (only if indicated).

Regarding changes from baseline to endpoint, some borderline values (< 10%) were obtained for "time × group" interaction; however, none reached the 5% significance level (see Table 3). Instead, several (highly) significant "time" effects were obtained (both groups showing reduction in study drug dose, improvement in positive symptoms, negative symptoms, and quality of life; overall increase in extrapyramidal side effects and decline in compliance) as well as 2 significant group differences over both time points (with haloperidol: greater "incapacitation," as measured by the AIMS, somewhat better compliance).

Controlling for gender, none of the mentioned effects was notably modified, except for a significant group

difference in compliance, which disappeared. Additional analyses regarding side effects for the subgroup of patients already included in the acute study yielded similar results compared to the total sample.

Tardive Dyskinesia

Tardive dyskinesia (TD) was defined according to a meta-analysis[15] using the Schooler-Kane criteria (any AIMS item score ≥ 3 or at least 2 AIMS item scores ≥ 2) in addition to the Glazer-Morgenstern criteria (total AIMS score ≥ 3 and at least 1 AIMS item score ≥ 2).[15] Respective prevalence (at any visit of the 1-year course) and incidence rates (no TD in visits 1 and 2; occurrence in the remaining visits) were identified, each with presence over 1 or 2 consecutive visits. All calculated TD rates were higher in the haloperidol group compared to risperidone; however, none reached the 5% significance level (e.g., new emergent TD for at least 2 visits according to Schooler-Kane: risperidone = 0% (0/68), haloperidol = 4.5% (3/67); p = .12). Some differences yielded borderline significance levels (e.g., incidence, at least at 1 visit, according to Glazer-Morgenstern: risperidone = 4.4% (3/68), haloperidol = 12.3% (8/65); p = .1). This tendency also prevails in the respective time to occurrence of (first) TD (survival analyses; mean time haloperidol = 45.2 weeks; risperidone = 49.5 weeks; log-rank = 2.84, df = 1, p = .09). Adjusting for gender did not influence statistical significance. Additional analyses for the subgroup of patients already included in the acute study (i.e., without the lateral entries under open haloperidol acute treatment) resulted in greater differences in favor of risperidone only for prevalence rates (including the first 2 visits of the long-term trial; e.g., according to Schooler-Kane: risperidone = 0% (0/67), haloperidol = 6.8% (4/59); p < .05).

Rehospitalization and Serious Adverse Events

In both drug groups, 7 patients were readmitted to a psychiatric hospital (risperidone = 9.1%, haloperidol = 9.4%; p > .05; in 5 patients due to persisting or progressing symptoms [risperidone, N = 3; haloperidol, N = 2]). Seven serious adverse events were documented (3 in the risperidone group, 3.9%; 4 in the haloperidol group, 5.4%; p > .05), i.e., 2 suicide attempts and 2 deteriorations with rehospitalization (1 each in both drug groups), 2 serious side effects (agitated depression, tremor; both under haloperidol), and 1 drug overdose by patient (risperidone).

Completer Analysis

In each drug group, 24 patients completed the first study year (risperidone = 31.2% of 77; haloperidol = 32.4% of 74). Mean age was approximately 34 years; 64.6% were male. All the above analyses were conducted for the completer sample. Due to the highly significant disproportion in gender between the drug groups (risperidone = 83.3% male, haloperidol = 45.8%; $\chi^2 = 7.4$, df = 1, p = .007), gender was (additionally) included in the respective analyses. Altogether, results correspond to the ITT analyses and are available from the authors.

DISCUSSION

Since evidence regarding differential efficacy of FGAs and SGAs in the long-term treatment of first-episode schizophrenia was limited in the late 1990s, a double-blind randomized controlled trial was designed comparing relapse rate and other outcome criteria under maintenance treatment with risperidone versus low-dose haloperidol. As practiced in routine care and as recommended by treatment guidelines, drug treatment was expanded from the acute into the stable phase and continued for 1 year. This design accumulates a sample of patients with greater responsiveness and tolerability, and, hence, results have to be interpreted against this background.

Of the 159 patients included between 2000 and 2004, 151 were eligible for the ITT analysis. At entry into the long-term study, on average, positive symptoms were almost fully remitted, side effects were low, social functioning was still mildly impaired, and compliance was high. During the 1-year maintenance treatment, positive symptoms continued to decrease significantly under both drugs, side effects in general did not change, the mild deficit in social functioning persisted, but compliance worsened slightly and significantly. Dosage of both drugs could be kept low (mean dose for the first year: risperidone = 3.9, SD = 2.0 mg/day; haloperidol = 3.6, SD = 1.8 mg/day) and could even be reduced significantly over time.

Based on predefined criteria, no relapse emerged in the first postacute year under study drugs, corresponding to trials with (assured) maintenance treatment, also under FGAs.[1,2] Accordingly, the main hypothesis of an advantage of risperidone (N = 77) compared to low-dose haloperidol (N = 74) was not supported. In addition, no differences were obtained for rehospitalization rates, 2 additional measures of deterioration, and time until deterioration.

These results are at variance with those of Schooler et al.[32] of first-episode psychosis, showing a significant advantage in relapse prevention for risperidone compared to haloperidol over at least 2 years in the subsample of remitted patients (N = 400; risperidone = 42.1%, haloperidol = 54.7%; average doses: risperidone = 3.3 mg/day, haloperidol = 2.9 mg/day). However, additional analyses on our sample for patients fulfilling a 3-month remission criterion adapted from Andreasen et al.[54] did not result in significant differences in relapse and deterioration rates (total remission rate for the 6-month criterion: risperidone = 61.1%, haloperidol = 53.3% of 36 and 30 patients, respectively, having been at least 6 months in study; not

significant). The comparability of our results with the Schooler et al.[32] data is limited, as about 50% of their sample was diagnosed as having schizoaffective or schizophreniform disorder, 70% were not drug naive, and up to 2 inpatient pretreatments were permitted. Similar to our findings, however, Schooler et al.[32] obtained no significant differences in remission and discontinuation rate and symptom improvement. Another recently published long-term trial on first-episode psychosis comparing olanzapine and haloperidol did not find any differences in relapse and response rate, whereas remission rate was in favor of olanzapine.[31]

Other trials comparing maintenance treatment with risperidone or haloperidol include multiple-episode schizophrenia, and report either significant (N = 365, 2 years, risperidone = 25.4%, haloperidol = 39.9%; average doses: risperidone = 4.9 mg/day, haloperidol = 11.7 mg/day)[36] or nonsignificant (N = 62, 2 years, risperidone = 12%, haloperidol = 27%; average doses: risperidone = 6.1 mg/day, haloperidol = 4.6 mg/day)[35] relapse differences.

The results of the other outcome measures of the present trial should be treated reservedly due to the multiple significance tests and the resulting higher α error level, which was accepted here for not missing possible drug group differences. Considering this, patients treated with haloperidol showed (slightly) lower positive symptom scores at the end of the first treatment year. No differences emerged regarding negative symptoms and depression, social functioning, and quality of life. No differences[31,32] or only marginal[35] differences were also reported by other authors, contrary to Csernansky et al.,[36] who found advantages for risperidone regarding positive and negative symptoms.

Considering (motor) side effects, patients treated with (low-dose) haloperidol showed an increase in extrapyramidal symptoms during treatment course, whereas no increase or a smaller increase in the risperidone group was observed ($.05 \leq p \leq .1$). The rate of patients with antiparkinsonian drugs (administered only if indicated) was also nonsignificantly lower with risperidone. Tardive dyskinesia rates, although higher with haloperidol, did not differ significantly either in our total sample or in the subgroup of patients included already in the acute trial. The 4 reference trials reported more distinct differences in extrapyramidal side effects with haloperidol, with significant, more "emergent" TD with haloperidol evolving in 1 trial only,[32] corresponding to meta-analytic results reporting higher TD rates in FGAs compared to SGAs.[15] Similar to other findings,[55] the highest TD rates of 10% to 15% (based on very low criteria) were observed under haloperidol treatment, even in low dose.

The most intriguing finding was the overall dropout rate of 68.2%, corresponding to findings recently reported by Lieberman et al.[56] In our study, however, about 50% of the dropouts kept further appointments with their psychiatrists after medication change (open treatment), 30% until the end of the first year. Hence, a "complete" discontinuation rate of 40% to 50%, although in the range of other studies,[6,31,32,57,58] is still high and contributes to a high risk for relapse.[7] Dropout was mainly caused by patient withdrawal/noncompliance, side effects, or nonresponse.

In our sample, dropout rates did not differ between drugs, corresponding to other long-term trials comparing risperidone and low-dose haloperidol[32,35] as well as other SGAs and (lower-dose) FGAs.[20,22,23] In contrast, Csernansky et al.[36] reported a higher dropout rate for (higher-dosed) haloperidol, suggesting disadvantages for FGAs depending on dose. In contrast, Green et al.[31] found lower dropout rates for olanzapine compared to haloperidol even in low dose.

A number of methodological limitations have to be considered. Since gender was not evenly distributed between the 2 drug groups (higher rate of male patients in the risperidone group), and male gender is known to be a predictor of poor illness course, the risperidone group may have been biased toward poorer outcome. However, controlling for gender did not noticeably affect any results.

Sample size was considerably reduced by dropout, which may have affected study results. This is an increasing problem in general, particularly in RCTs on antipsychotic treatment.[59] Recent long-term trials (e.g., CATIE[23]) deal with this "problem" by focusing on dropout as the primary outcome criterion. Our primary outcome measure was a priori–defined relapse, supplemented post hoc by different measures of "deterioration." Accordingly, treatment discontinuation limits interpretation by reduction of sample size (power) and shortened observation period. However, several issues minimize probability of misinterpretation: (1) dropout rates were nearly identical in both drug groups and hence ITT analysis was balanced, (2) the completer analysis yielded nearly identical results, and (3) the follow-up of discontinued patients also yielded nearly identical results (1 relapse according to the predefined criteria in a patient formerly receiving risperidone). Nevertheless, the high dropout rate, although a result on its own, restricts data interpretation and study conclusions.

In addition, the limited trial length of 1 year may have contributed to lack of relapse. However, from the other 2-year trials, only Marder et al.[35] reported a noticeable additional relapse rate after the first year (from 8% to 19%), whereas almost no additional relapses after the first year were reported by Csernansky et al.[36] and Schooler et al.,[32] with significant differences in relapse rates already emerging in the middle of the first postacute year.[32]

Despite these arguments, results may still have been biased by the selection procedure of study subjects, partly due to the (continuation) design chosen. Initially the exclusion criteria excluded (among others) nonconsenting or (predominantly younger) patients with a comorbid

substance dependence (the latter also contributing to the relatively high mean age of 31.6 years, which is in accordance with reports on other first-episode samples[60]). Subsequently, the acute study worked as a kind of "filter" for the long-term study, keeping mainly those patients in the trial who did not drop out due to side effects, insufficient response, or lack of compliance. Correspondingly, dropout rate in the long-term study of patients participating in the acute trial was about 66%, compared to 85% of the patients included by lateral entry. Therefore, the long-term sample represented a positive selection of those individuals, who seemed to benefit from the acute drug treatment to which they had been randomly assigned, possibly blurring drug differences. In patients with a less favorable prognosis, advantages of SGAs may preferentially emerge, as demonstrated for multiple-episode patients[15] or treatment-resistant schizophrenia (see Chakos et al.,[61] mainly for clozapine) but not in a recent trial.[62] Subgroup analyses for the 127 patients who participated in the acute study yielded no significant drug group differences, and considering inclusion characteristics (after acute study vs. lateral entry) as a covariate in the respective analyses of the total sample did not affect any of the results.

Finally, patients received intense support from study doctors (fortnightly visits) or from psychological interventions (75% of the patients were included in the clinical trial comparing psychoeducation and cognitive-behavioral therapy). It could be assumed that this also contributed to the generally positive outcome in patients' adherent to treatment. However, results do not support this interpretation, since significant differences between study centers with versus without participation in the psychological trial did not occur regarding deterioration rates and changes in PANSS scores. Only dropout rates differed significantly (61% vs. 83%; $\chi^2 = 7.4$, df = 1, p = .006), but none of these effects varied between drugs, e.g., similar dropout rates for both drug groups in the subgroup of patients from centers with psychotherapy (p = .7) as well as in the subgroup of patients from centers without psychotherapy (p = .7).

CONCLUSION

Maintenance drug treatment in first-episode schizophrenia is effective with atypical (risperidone) and low-dose typical (haloperidol) antipsychotic medication regarding relapse prevention and symptom reduction. Side effects on average are mild under both drug conditions, but extrapyramidal side effects and TD are slightly higher under haloperidol. Despite a positive sample selection (with respect to general prognosis for first-episode cases, acute drug response, tolerability, and compliance), long-term dropout (due to lack of acceptance, clinically rated insufficient response, and side effects) is still noticeable. Based on these observations, it may be concluded that (1) equal drug efficacy in long-term treatment can be assumed for first-episode patients who have attained remission due to compliance, responsiveness, and tolerability already in acute treatment; (2) haloperidol even in low dose bears a higher risk for extrapyramidal side effects and TD; (3) due to a high dropout rate, the development of institutional programs is mandatory to keep first-episode patients in an effective treatment during the "critical" period of an otherwise chronic illness, starting already in the prepsychotic illness phase.[63] The first-episode schizophrenia study group within the GRNS is currently developing concepts and materials to implement such an integrative program in Germany.

Drug names: chlorpromazine (Thorazine, Sonazine, and others), clozapine (Clozaril, FazaClo, and others), haloperidol (Haldol and others), olanzapine (Zyprexa), risperidone (Risperdal).

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