

# Short-term treatment with risperidone or haloperidol in first-episode schizophrenia: 8-week results of a randomized controlled trial within the German Research Network on Schizophrenia

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## Abstract

Patients with first-episode schizophrenia appear to respond to lower doses of neuroleptics, and to be more sensitive to developing extrapyramidal side-effects. The authors therefore compared in such patients the efficacy and extrapyramidal tolerability of comparatively low dosages of the atypical neuroleptic risperidone and of the conventional neuroleptic haloperidol. Risperidone was hypothesized to have better extrapyramidal tolerability and efficacy in treating negative symptoms. Patients were randomly assigned under double-blind conditions to receive risperidone ( $n=143$ ) or haloperidol ( $n=146$ ) for 8 wk. The primary efficacy criterion was the estimated difference in the mean change in the Positive and Negative Symptom Scale (PANSS) negative score between treatment groups; secondary efficacy criteria were changes on the PANSS total score and other PANSS subscores, and several other measures of psychopathology and general functioning. The primary tolerability criterion was the difference in baseline-adjusted occurrence rates of extrapyramidal side-effects measured with the Simpson–Angus Scale (SAS) compared between treatment groups. The main hypothesis was that risperidone would be superior in terms of improving negative symptoms and lowering the risk of extrapyramidal symptoms. Secondary tolerability criteria were the other extrapyramidal symptoms, measured with the Hillside Akathisia Scale (HAS) and the Abnormal Involuntary Movement Scale (AIMS). The average mean daily doses were 3.8 mg (s.d. = 1.5) for risperidone and 3.7 mg (s.d. = 1.5) for haloperidol. There were similar, significant improvements in both treatment groups in the primary and secondary efficacy criteria. At week 8 nearly all scores of extrapyramidal side-effects indicated a significantly higher prevalence of extrapyramidal side-effects with haloperidol than with risperidone [SAS: risperidone 36.5% of patients; haloperidol 51.5% of patients; likelihood ratio test,  $\chi^2(1)=7.8$ ,  $p=0.005$ ]. There were significantly fewer drop-outs [risperidone  $n=55$ , drop-out rate = 38.5%; haloperidol  $n=79$ , drop-out rate = 54.1%,  $\chi^2(1)=7.1$ ,  $p=0.009$ ] and a longer non-discontinuation time [risperidone: average of 50.8 d to drop-out; haloperidol: average of 44.0 d to drop-out; log rank test,  $\chi^2(1)=6.4$ ,  $p=0.011$ ] in the risperidone group. Risperidone and haloperidol appear to be equally effective in treating negative and other symptoms of first-episode schizophrenia. Risperidone has better extrapyramidal tolerability and treatment retention rate than the equivalent dose of haloperidol in these patients.

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## Introduction

Neuroleptics are more effective in first-episode schizophrenia (FES) than in patients with multiple episodes (Jäger et al., 2006; Lieberman et al., 1996; Sanger et al., 1999). Lower daily doses are required for adequate improvement, and patients are more sensitive to developing extrapyramidal side-effects (EPS) (Merlo et al., 2002; Sanger et al., 1999; Zhang-Wong et al., 1999).

Only rather limited evidence is available for the efficacy and tolerability of second-generation antipsychotics (SGAs) in FES, especially in comparison to first-generation antipsychotics (FGAs) (Rummel et al., 2003). Earlier short-term trials on acute treatment of FES patients investigated risperidone alone (Kopala et al., 1998; Merlo et al., 2002), risperidone vs. haloperidol (Emsley and the Risperidone Working Group, 1999), and olanzapine vs. haloperidol (Keefe et al., 2004; Lieberman et al., 2003; Sanger et al., 1999). Apart from one study with a dose range of 5–20 mg/d haloperidol (mean dose 10.8 mg/d) (Sanger et al., 1999), the haloperidol dose was kept in the range 2–8 mg/d (Emsley and the Risperidone Working Group, 1999; Lieberman et al., 2003). Besides the short-term studies on FES, long-term studies comparing SGAs with haloperidol or comparing several SGAs with each other have recently been published (Green et al., 2006; Keefe et al., 2007; McEvoy et al., 2007; Schooler et al., 2005). In some of these long-term studies the average dose of study drug was lower than in the short-term studies on acute patients. For example, in the risperidone–haloperidol study by Schooler et al. (2005) the mean modal dose was 3.3 mg for risperidone and 2.9 mg for haloperidol.

All of the studies with haloperidol found the SGA to be significantly superior in terms of extrapyramidal tolerability. The efficacy results are not so consistent. In some studies superior efficacy was found for SGAs either in terms of global outcome, remission rates, relapse rates or scores/subscores of symptom rating scales. The non-discontinuation rate, used as a criterion in recent effectiveness studies such as the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE; Lieberman et al., 2005), was also found in some studies to be more advantageous for SGAs.

Because negative symptoms in general are of great relevance for social functioning, prognosis and course characteristics (Möller et al., 1988, 2000, 2002, Möller, 2004, 2007), as was also described for FES (Haas and Sweeney, 1992; Siegel et al., 2006), and because SGAs have been described to show better efficacy than FGAs

in treating negative symptoms (Möller, 2000b, 2003), special emphasis should be placed on this psychopathological domain in the treatment of FES patients.

Efficacy results from studies on FES are inconsistent for negative symptoms; they have been found to improve similarly and significantly from baseline with risperidone and haloperidol (Emsley and the Risperidone Working Group, 1999), and significantly more with olanzapine than haloperidol (Sanger et al., 1999). One study found no difference between olanzapine and haloperidol in the last observation carried forward (LOCF) analysis (Lieberman et al., 2003), but significantly greater improvement with olanzapine in a mixed-model analysis.

The study was planned in 1999 as part of the German Research Network on Schizophrenia (a nationwide research network funded by the German Ministry of Education and Research; BMBF) (Gaebel et al., 2004; Wolwer et al., 2003). The entire FES study programme consisted of an 8-wk acute study and a subsequent 2-yr, long-term treatment phase, the 1-yr outcome data of which were recently published (Gaebel et al., 2007). The aim was to evaluate whether risperidone shows better efficacy, especially in terms of negative symptoms, and fewer EPS than haloperidol when administered at equivalent dosages in a design aimed at keeping the dose as low as possible.

## Method

### Patients

Subjects were selected from patients admitted to the in-patient departments of the participating centres. Inclusion criteria were: (1) acute manifestation of FES according to ICD-10 F20 criteria; (2) age 18–60 yr; (3) adequate proficiency in German; (4) no involuntary in-patient treatment (at the date of inclusion); (5) written informed consent. Exclusion criteria were: (1) pregnancy; (2) insufficient response to pre-treatment with risperidone or haloperidol; (3) other contraindications for risperidone or haloperidol; (4) mental retardation; (5) organic brain disease; (6) substance abuse; (7) history of suicidal behaviour; (8) severe physical disease; (9) participation in other trials.

### Study design and setting

This was an 8-wk, multicentre, double-blind, parallel-group, randomized, controlled study in in-patients suffering from acute FES. It was conducted in 13

German psychiatric university hospitals according to the principles of good clinical practice and the Declaration of Helsinki. Approval was obtained from the ethics committees of the coordinating centre and the local centres.

### Treatment

Patients were assessed for suitability at screening and baseline. Patients pretreated with psychotropic drugs underwent a washout period of 4–7 d, if clinically justified. After random assignment to treatment groups in a 1:1 ratio, patients received 2 mg/d of the study medication (once daily). Investigators, hospital staff and patients were blinded to treatment assignment. Patients at each centre were consecutively allocated a labelled container of medication, supplied by the Coordinating Centre. The identification consisted of a letter representing the centre, a three-digit patient number, a three-letter abbreviation of the study name and a number representing the investigation period.

Dose could be increased by 1–2 mg/d between day 3 and week 1, if required, and then at each weekly assessment up to a maximum of 8 mg/d, whereby the total dose should not exceed 4 mg/d by week 2. The criterion for a dose increase (apart from between day 3 and the week 1) was the non-achievement of symptom improvement of at least one level on the Clinical Global Impression (CGI; Guy, 1976b). If EPS appeared, dosage reductions were permitted in steps of 1–2 mg/d at the weekly evaluations.

Co-medication with psychotropic substances was generally not allowed, with the exception of the following:

- Short-acting benzodiazepines for insomnia.
- Lorazepam was permitted at the lowest possible dose for the shortest possible time to arrest agitation, psychotic anxiety, etc.; after week 4, the dose was not allowed to exceed 4 mg/d over 4 d/wk. Continuous administration of benzodiazepines was not allowed.
- If dose reduction of the study drug did not achieve the desired effect, the anticholinergic biperiden (up to 6 mg/d) was prescribed to treat EPS, and the beta-blocker propranolol (up to 80 mg/d) to treat akathisia, usually for a maximum of 14 d at a time.

### Assessments

The negative scale of the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) was assessed as the primary efficacy criterion. Secondary

efficacy criteria were: PANSS total, positive and general subscale, Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1982), Hamilton Rating Scale for Depression (HAMD; Hamilton, 1960), Calgary Depression Scale for Schizophrenia (CDSS; Addington et al., 1990; Muller et al., 1999), CGI, Young Mania Rating Scale (YMRS; Young et al., 1978). Compliance was monitored at every visit with a questionnaire. Prognosis was assessed at baseline with the Strauss–Carpenter Prognosis Scale (SCPS; Strauss and Carpenter, 1978). At both baseline and week 8, functioning was measured with the Global Assessment of Functioning Scale (GAF; Frances et al., 1994) and the Social and Occupational Functioning Assessment Scale (SOFAS; APA, 1994). Several rater trainings took place. Inter-rater reliability yielded a satisfactory to good concordance which fitted to values in other publications (e.g. intra-class correlation coefficient of the PANSS positive scale = 0.74,  $p < 0.001$ ; Shrout and Fleiss, 1979).

Adverse events were assessed at every visit and EPS recorded using the Simpson–Angus Scale (SAS; Simpson and Angus, 1970), Hillside Akathisia Scale (HAS; Fleischhacker et al., 1989) and Abnormal Involuntary Movement Scale (AIMS; Guy, 1976a).

A broad range of safety laboratory assessments [differential blood count, clinical chemistry (sodium, potassium, calcium, glucose, total bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma-glutamyltransferase, creatinine, urea, uric acid, creatinine kinase, lactate dehydrogenase, total protein), thyroid-stimulating hormone, blood sedimentation rate, urine status] were performed at selection and repeated at baseline and at weeks 2, 4, 6, and 8. An ECG was conducted at selection and week 8.

### Statistical methods

A sample size of 176 patients/group was estimated to test the hypothesis of an advantage for risperidone (two-sided test) at week 8 in the primary efficacy parameter PANSS negative score and the primary tolerability criterion SAS on the basis of the following assumptions:  $\alpha = 0.05$ ; power  $1 - \beta = 0.8$ , expected group difference of  $d = 0.3$  standard deviations.

The intent-to-treat (ITT) sample comprised all randomized patients except those whose initial diagnosis had been revised, and the per protocol sample of all patients who completed the 8-wk trial as in-patients or who were discharged prior to week 8. Drop-outs were patients who discontinued for any reason. Differences in time to drop-out between treatment groups were

evaluated using Kaplan–Meier analysis. Continuous outcome measures are presented as means and standard deviations, categorical variables as absolute frequencies ( $n$ ) and percentages. Treatment group differences at baseline were evaluated using two-sample  $t$  tests and Pearson's  $\chi^2$  tests. Two alternative analytical strategies were applied to the ITT data: (1) last observation (under regular treatment conditions) carried forward (LOCF analysis); (2) the observed cases were analysed using methods for longitudinal data.

Based on the special importance of negative symptoms and some positive findings for SGAs in this respect, the estimated difference in the mean change in the PANSS negative score between the two treatment groups [analysis of covariance (ANCOVA) and mixed-model analysis] was chosen as the primary efficacy criterion. The LOCF was analysed using ANCOVA including terms for baseline value and treatment in the model (Vickers and Altman, 2001). Baseline-to-endpoint differences were tested for with paired  $t$  tests. Observed cases (scores at each week) were analysed using mixed-effects models (Hedeker and Gibbons, 2006; Singer, 1998), including a common intercept, treatment-specific linear slopes, and a common quadratic slope as fixed effects for treatment and week. Subject-specific intercepts and slopes were included as random effects. A first-order autoregressive covariance structure was chosen in order to account for observations within a subject to be autocorrelated over time. This model was determined by starting from a preliminary model allowing for treatment-specific intercepts, linear and quadratic slopes, and subsequently eliminating non-significant terms according to likelihood ratio tests. Patients were classified as treatment responders if they had (1) a rating  $\leq 3$  in PANSS items 1–3, 5, 6, (2) a  $\geq 30\%$  reduction from baseline in PANSS total score, and (3) a CGI severity score  $\leq 4$  (cf. Lieberman et al., 2003). Time to response was estimated using Kaplan–Meier analysis.

The primary tolerability criterion in terms of EPS was the SAS score. AIMS and HAS were secondary tolerability criteria. Scores of these tolerability criteria were dichotomized (0,  $>0$ ) because  $>50\%$  of the sample showed total scores of zero throughout the study (presumably due to the low dosages of medication applied). Therefore, since the continuous total scores markedly deviated from normal, methods for categorical data analysis were applied to the dichotomized values; average continuous total scores of the tolerability criteria are not reported because they are strongly influenced by outlying values. Instead, prevalence of EPS was estimated by the proportion of

patients having a total score  $>0$ . LOCF analyses were performed using logistic regression including terms for baseline value and treatment. Observed cases (weekly prevalence rates) were evaluated by generalized estimation equation (GEE) models (Agresti, 2002; Liang and Zeger, 1986) including a common intercept, treatment-specific linear and quadratic slopes as effects for treatment and week. The correlation in the responses over time was accounted for by specifying an autoregressive working correlation structure. This model was determined by starting from a preliminary model allowing for treatment-specific intercepts, linear and quadratic slopes, and subsequently eliminating non-significant terms according to Wald tests. In addition, incidence of EPS was estimated as the proportion of patients with a change in side-effects total score from 0 at baseline to  $>0$  at endpoint. Incidence rates were compared using Pearson's  $\chi^2$  tests.

Supplementary analyses were performed on the per protocol sample in order to confirm the results obtained by the ITT analyses (results are not reported). Statistical hypotheses were tested on a two-sided  $\alpha$ -level of 5%.

## Results

### Sample characteristics

Between November 2000 and May 2004, 1372 patients were screened. The unexpectedly slow recruitment rate meant that recruitment had to be discontinued for pragmatic reasons before reaching the planned sample size. There were 1070 patients (78.0%) unsuitable for the study: 755/1070 (70.6%) patients did not fulfil inclusion or fulfilled exclusion criteria, 298 (27.9%) patients refused to participate, and 17 were not included for other reasons. Of the remaining 302 patients included (total sample), 105 completed the 8-wk trial as in-patients, 50 were discharged before completion (per protocol sample 155; risperidone 88, haloperidol 67), and 134 discontinued prematurely (risperidone 55, haloperidol 79). Besides fulfilling the criteria for schizophrenia according to ICD-10 F20, 289/302 (95.70%) patients also fulfilled the respective DSM-IV criteria.

The ITT sample consisted of 289 patients (risperidone 143, haloperidol 146) as 13 patients were not eligible for inclusion in the analysis. Details of the numbers selected and the number of drop-outs are presented in Figure 1.

With the actual sample size of  $n=143$  (risperidone) and  $n=146$  (haloperidol) only a slightly larger effect size of  $d=0.33$  standard deviations was detectable at  $\alpha=0.05$  and  $1-\beta=0.8$ .

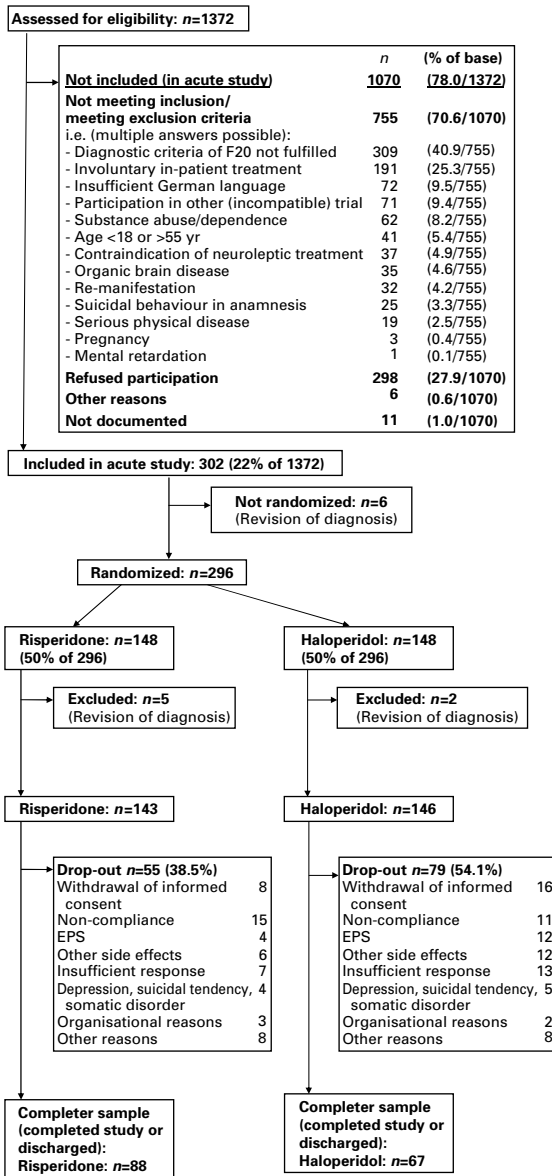


Figure 1. Flow of subjects through the study.

**Drop-outs**

There were significantly fewer drop-outs with risperidone (n=55, drop-out rate=38.5%) than haloperidol [n=79, drop-out rate=54.1%,  $\chi^2(1)=7.1, p=0.009$ ] (Figure 1). The Kaplan–Meier analysis of the discontinuation rates mirrors these results [log rank test,  $\chi^2(1)=6.4, p=0.011$ ] (Figure 2): average of 50.8 d to drop-out for a risperidone patient, and 44.0 d for a haloperidol patient. Side-effects were the most frequent reason for drop-out in both groups, but more often the reason in the haloperidol group [risperidone 10/143 (7%), haloperidol 24/146 (16.4%); Fisher’s exact test,  $p=0.017$ ]. A higher proportion of patients

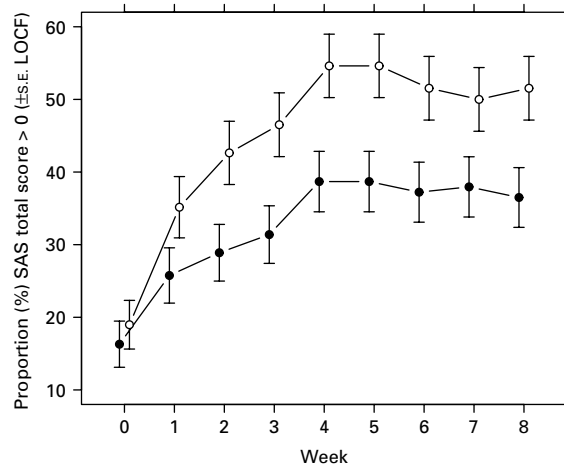


Figure 2. Prevalence of movement disorders over the 8-wk study, defined by the proportion of patients having Simpson–Angus Scale (SAS) total score >0. Differences between risperidone (●) and haloperidol (○) are significant based on last observation carried forward (LOCF) analysis [logistic regression, likelihood ratio test,  $\chi^2(1)=7.8, p=0.005$ ] and generalized estimation equation analysis [Wald test,  $\chi^2(2)=6.6, p=0.036$ ].

dropped out due to EPS with haloperidol [8.2% (12/46)] than with risperidone [4/143 (2.8%), Fisher’s exact test,  $p=0.069$ ]. Further reasons for drop-out were non-compliance [risperidone 15/143 (10.5%), haloperidol 11/146 (7.5%)], withdrawal of informed consent [risperidone 8/143 (5.6%), haloperidol 16/146 (11%)], insufficient response [risperidone 7/143 (4.9%), haloperidol 13/146 (8.9%)] and others [risperidone 15/143 (10.5%), haloperidol 15/146 (10.3%)]; the frequency of drop-outs in each of these categories did not differ significantly between groups.

**Baseline characteristics**

The ITT sample consisted of 117/289 (40.5%) women and 172/289 (59.5%) men, mean age 30.1±9.8 yr. The mean PANSS total score at baseline was 79.1, indicating a severity level typical for an acute episode sample (see Table 1).

The only significant difference in baseline characteristics between the two groups was the proportion of patients with an AIMS total score >0 [ $\chi^2(1)=4.2, p=0.041$ , see Table 1]. The baseline SANS total score showed a numerical difference of about 4 points between the two treatment groups (risperidone 36.1±28.5, haloperidol 40.3±25.7; n.s.), but this was not reflected in the PANSS negative score (risperidone 19.0±8.3, haloperidol 19.6±8.1; n.s.). Values of the mean PANSS total score, an indicator of the severity of

**Table 1.** Sample characteristics and drug-group differences at entry in the study (ITT sample; two-sample *t* test for continuous variables, Pearson's  $\chi^2$  test for categorical variables)

	Total ( <i>n</i> = 289) <sup>a</sup>		Ris ( <i>n</i> = 143) <sup>a</sup>		Hal ( <i>n</i> = 146) <sup>a</sup>		<i>t</i>	d.f.	<i>p</i>
	Mean	s.d.	Mean	s.d.	Mean	s.d.			
Age (yr)	30.1	9.8	29.5	9.5	30.7	10.0	-1.00	287	0.319
PANSS total score	79.1	24.0	77.3	23.0	80.8	24.8	-1.20	273	0.233
Positive score	21.3	6.2	20.9	6.1	21.8	6.3	-1.27	273	0.206
Negative score	19.3	8.2	19.0	8.3	19.6	8.1	-0.60	273	0.550
General score	38.5	12.8	37.5	11.9	39.4	13.6	-1.24	273	0.216
SANS total 'composite' score	38.2	27.1	36.1	28.5	40.3	25.7	-1.28	273	0.203
HAMD total score	14.9	8.1	14.4	8.0	15.4	8.2	-1.03	273	0.304
CDSS Total score	4.2	4.3	4.2	4.5	4.3	4.1	-0.07	275	0.947
CGI: Severity	5.2	0.8	5.1	0.9	5.2	0.8	-0.73	271	0.466
YMRS	5.3	5.4	5.0	5.2	5.5	5.5	-0.78	276	0.438
SCPS	55.1	11.5	55.2	11.1	55.0	12.0	0.11	232	0.913
GAF: current level (GAF <sub>1</sub> )	45.6	13.8	46.7	14.3	44.5	13.3	1.34	274	0.180
GAF: lowest level in the foregoing year (GAF <sub>2</sub> )	44.4	16.0	44.8	16.2	44.0	15.8	0.41	264	0.682
SOFAS: current level (SOFAS <sub>1</sub> )	46.6	13.2	47.2	13.9	45.9	12.5	0.87	272	0.384
SOFAS: lowest level in the foregoing year (SOFAS <sub>2</sub> )	46.0	15.5	46.3	16.7	45.7	14.3	0.32	261	0.752
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	$\chi^2$	d.f.	<i>p</i>
Gender, <i>n</i> (% male)	172	59.5	92	64.3	80	54.8	2.73	1	0.099
Time since onset of first psychotic symptoms < 6 months	150	56.2	73	54.9	77	57.5	0.18	1	0.672
SAS total score > 0	48	17.6	22	16.3	26	19.0	0.34	1	0.562
AIMS total score > 0	16	5.8	4	2.9	12	8.7	4.19	1	0.041
HAS total score > 0	38	13.9	15	11.0	23	16.7	1.82	1	0.177

ITT, Intent to treat; PANSS, Positive and Negative Syndrome Scale; SANS, Scale for the Assessment of Negative Symptoms; HAMD, Hamilton Depression Rating Scale; CDSS, Calgary Depression Scale for Schizophrenia; CGI, Clinical Global Impression; YMRS, Young Mania Rating Scale; SCPS, Strauss-Carpenter Prognosis Scale; GAF, Global Assessment of Functioning; SOFAS, Social and Occupational Functioning Assessment Scale; SAS, Simpson-Angus Scale; AIMS, Abnormal Involuntary Movement Scale; HAS, Hillside Akathisia Scale.

<sup>a</sup> Reduced *n* in single scales due to missing values.

the psychopathological symptoms, as well as mean SCPS score, an indicator of the global prognosis, were similar.

### Dosing

The aim to keep the average neuroleptic dose as low as possible was achieved and was ~4 mg/d for both drugs (risperidone 3.8 ± 1.5 mg/d, haloperidol 3.7 ± 1.5 mg/d).

### Concomitant medications

There was no significant difference between groups in the prescription rates of lorazepam [risperidone 54.8% of patients, haloperidol 62.9% of patients;  $\chi^2(1) = 1.67$ ,

$p = 0.197$ ] or propranolol [risperidone 4.0% of patients, haloperidol 6.5% of patients;  $\chi^2(1) = 0.73$ ,  $p = 0.393$ ]. The prescription rate (risperidone 38.7% of patients, haloperidol 34.7% of patients; n.s.) and average dose (risperidone 4.1 ± 1.6 mg/d, haloperidol 4.0 ± 1.6 mg/d; n.s.) of biperiden was similar in both groups.

### Efficacy

The results of the ITT sample are presented.

Both treatment groups showed marked, statistically significant improvements from baseline to week 8 in the primary efficacy criterion (PANSS negative score; paired *t* test,  $p < 0.001$ ) and in the secondary efficacy

criteria (paired *t* test,  $p < 0.001$  for all parameters except CDSS, for which  $p < 0.01$ ) (Table 2), indicating efficacy in various symptom domains. Efficacy did not differ significantly in either the LOCF or mixed-model analysis (Table 2); the same was true for global functioning (GAF and SOFAS) (Table 2).

Both drugs were effective with respect to treatment response defined after Lieberman et al. (2003) [i.e. (1) a rating  $\leq 3$  in PANSS items 1–3, 5, 6, (2) a  $\geq 30\%$  reduction from baseline in PANSS total score, and (3) a CGI severity score  $\leq 4$ ]. At week 8, 66/134 (49.3%) of patients showed a response with risperidone and 63/127 (49.6%) with haloperidol. The Kaplan–Meier estimated average time to response was 41.0 d with risperidone and 38.6 d with haloperidol [log rank test,  $\chi^2(1) = 0.1$ ,  $p = 0.753$ ].

### Safety and tolerability

#### Safety

Both compounds were safe, i.e. no serious adverse events occurred.

#### EPS

After 8 wk, all three EPS-related scores indicated a higher prevalence of EPS, defined by the number of patients having a total parameter score  $> 0$  with haloperidol than with risperidone. LOCF analysis found a significant difference in baseline-adjusted prevalence rates after 8 wk in favour of risperidone for both the primary tolerability criterion, the SAS [risperidone 36.5% of patients, haloperidol 51.5% of patients; likelihood ratio test,  $\chi^2(1) = 7.8$ ,  $p = 0.005$ ] (Figure 3), and the AIMS [risperidone 8.8% of patients, haloperidol 21.7% of patients; likelihood ratio test,  $\chi^2(1) = 6.4$ ,  $p = 0.011$ ] (Table 3a). The resulting odds ratios suggest that the risk of EPS is more than doubled in the haloperidol group at endpoint. The prevalence rates of the HAS showed no significant difference. GEE analyses confirmed the results of LOCF analyses, indicating a higher weekly increase in risk of EPS for haloperidol; this effect was again significant for SAS and AIMS, but not for HAS (Table 3a).

Another categorical analysis (Lieberman et al., 2003), evaluated the incidence of EPS defined by a change in total parameter score from 0 at baseline to  $> 0$  at endpoint; only the AIMS score showed a significant difference between the two treatment groups [risperidone 5.9% of patients, haloperidol 14.7% of patients;  $\chi^2(1) = 5.7$ ,  $p = 0.017$ ] (Table 3b). In a supportive analysis, incidence was re-defined by a change in EPS total score from  $< 1$  at baseline to  $\geq 1$  at

endpoint (note that Fisher's exact test was used because of the small number of cases per cell). The results were similar, and the results for SAS and HAS also reached statistical significance (SAS  $p = 0.008$ , AIMS  $p = 0.017$ , HAS  $p = 0.001$ ) (Table 3c).

The incidence of EPS was also calculated in relation to average dose per day, with a cut-off point at 4 mg ( $< 4$  mg vs.  $\geq 4$  mg). The differences between the two treatment groups were again in favour of risperidone, and for SAS and HAS were more pronounced between the higher-dose groups (Table 3d).

#### Clinical laboratory test values

Only one of the 146 patients receiving haloperidol showed clinically significant laboratory test abnormalities. There were no abnormal laboratory values in the risperidone group in the safety parameters mentioned above.

### Discussion

The dose of both neuroleptics was kept as low as possible in this study (average dose  $\sim 4$  mg/d). The dose equivalence for risperidone and haloperidol has not been finally clarified. In this fixed flexible dosing study, a relationship of 1:1 was observed, which is similar to some other studies (Marder et al., 2003; Schooler et al., 2005), while others, for example, reported a 1:2.5 ratio (Csernansky et al., 2002).

The results in the outcome parameters show that risperidone and haloperidol are similarly efficacious in treating FES. Contrary to the hypothesis, risperidone was not superior in treating negative symptoms. Other short-term FES studies that compared an SGA with haloperidol found inconsistent results in negative symptoms. Emsley and the Risperidone Working Group (1999) found that negative symptoms significantly improved with both risperidone and haloperidol. Lieberman et al. (2003) found similar reductions in symptom severity with olanzapine and haloperidol in the LOCF analysis, but olanzapine had significantly greater decreases in the PANSS negative scale, among others, in a mixed-model analysis.

However, the second part of the hypothesis, the lower risk of risperidone in terms of EPS, could be substantiated. Both the LOCF and the longitudinal data analysis confirmed the superiority of risperidone in terms of extrapyramidal tolerability, especially at dose levels  $> 4$  mg. EPS were more prevalent in the haloperidol group, as shown by a significantly greater proportion of scores  $> 0$  in the SAS and AIMS scales,

**Table 2.** Treatment response: psychopathological parameters at baseline and end of study (ITT sample), LOCF (ANCOVA to adjust for possible imbalance at baseline) and mixed-model analysis

	Mean scores $\pm$ S.D. at baseline and end of study				Difference in baseline-to-endpoint improvement			
					LOCF analysis		Difference in weekly improvement	
	Risperidone ( $n = 143$ ) <sup>a</sup>		Haloperidol ( $n = 146$ ) <sup>a</sup>		Mixed-model analysis			
	Baseline	Week 8	Baseline	Week 8	Estimated difference	$p$	Estimated difference	$p$
PANSS scores								
PANSS total score	77.3 $\pm$ 23.0	56.6 $\pm$ 19.7	80.8 $\pm$ 24.8	57.5 $\pm$ 22.2	-0.21	0.920	-0.041	0.899
Positive score	20.9 $\pm$ 6.1	12.0 $\pm$ 5.3	21.8 $\pm$ 6.3	12.7 $\pm$ 5.8	0.45	0.494	0.059	0.510
Negative score	19.0 $\pm$ 8.3	16.0 $\pm$ 6.6	19.6 $\pm$ 8.1	15.8 $\pm$ 7.1	-0.13	0.850	-0.031	0.770
General score	37.5 $\pm$ 11.9	28.6 $\pm$ 10.3	39.4 $\pm$ 13.6	28.9 $\pm$ 11.4	-0.34	0.759	-0.049	0.767
SANS total 'composite' score	36.1 $\pm$ 28.5	30.5 $\pm$ 24.2	40.3 $\pm$ 25.7	31.3 $\pm$ 25.1	-2.25	0.353	-0.238	0.552
HAMD total score	14.4 $\pm$ 8.0	8.0 $\pm$ 7.2	15.4 $\pm$ 8.2	8.5 $\pm$ 7.9	0.12	0.891	0.061	0.658
CDSS total score	4.2 $\pm$ 4.5	3.1 $\pm$ 4.3	4.3 $\pm$ 4.1	3.1 $\pm$ 4.2	-0.08	0.868	0.018	0.807
CGI: Severity	5.1 $\pm$ 0.9	3.9 $\pm$ 1.2	5.2 $\pm$ 0.8	3.9 $\pm$ 1.3	-0.05	0.749	-0.002	0.948
YMRS	5.0 $\pm$ 5.2	2.0 $\pm$ 3.4	5.5 $\pm$ 5.5	2.0 $\pm$ 3.4	0.02	0.964	0.026	0.618
GAF: current level (GAF <sub>1</sub> )	46.7 $\pm$ 14.3	60.3 $\pm$ 14.4	44.5 $\pm$ 13.3	58.1 $\pm$ 15.4	-1.30	0.440	-0.215	0.905
SOFAS: current level (SOFAS <sub>1</sub> )	47.2 $\pm$ 13.9	58.5 $\pm$ 14.4	45.9 $\pm$ 12.5	56.7 $\pm$ 14.6	-1.09	0.500	-0.242	0.892

ITT, Intent to treat; LOCF, last observation carried forward; PANSS, Positive and Negative Syndrome Scale; SANS, Scale for the Assessment of Negative Symptoms; HAMD, Hamilton Depression Rating Scale; CDSS, Calgary Depression Scale for Schizophrenia; CGI, Clinical Global Impression; GAF, Global Assessment of Functioning; SOFAS, Social and Occupational Functioning Assessment Scale.

<sup>a</sup> Reduced  $n$  in single scales due to missing values.

**Table 3a.** Prevalence of movement disorder side effects estimated by the proportion of patients having a total parameter score >0. Drug-group differences at end of study (ITT sample), LOCF (logistic regression to adjust for possible imbalance at baseline) and GEE analysis

	Total		Risperidone		Haloperidol		LOCF analysis		GEE analysis	
	(n=289) <sup>a</sup>	(%)	(n=143) <sup>a</sup>	(%)	(n=146) <sup>a</sup>	(%)	OR	p	OR	p
SAS total score >0 at week 8	117	(43.8)	50	(36.5)	67	(51.5)	2.09	0.005	1.32	0.036
AIMS total score >0 at week 8	40	(15.0)	12	(8.8)	28	(21.7)	2.74	0.011	1.42	0.004
HAS total score >0 at week 8	87	(32.6)	39	(28.5)	48	(36.9)	1.49	0.149	1.28	0.103

ITT, Intent to treat; LOCF, last observation carried forward; GEE, generalized estimation equation; SAS, Simpson–Angus Scale; AIMS, Abnormal Involuntary Movement Scale; HAS, Hillside Akathisia Scale.

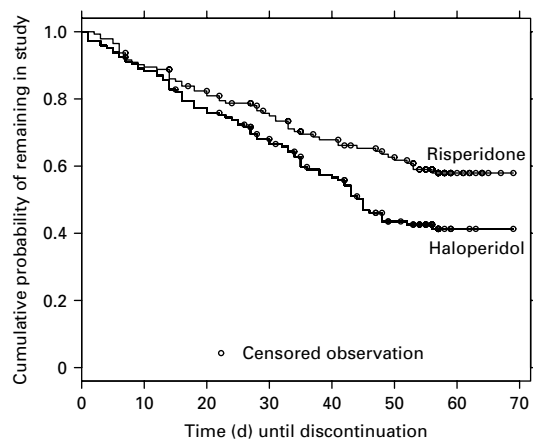
<sup>a</sup> Reduced n in single scales due to missing values.

**Table 3b.** Incidence of movement disorder side effects defined (after Lieberman et al., 2003) by a change in total parameter score from 0 at baseline to >0 at endpoint (week 8, LOCF, Pearson’s  $\chi^2$  test)

	Total		Risperidone		Haloperidol		$\chi^2(1)$	p
	(n=289) <sup>a</sup>	(%)	(n=143) <sup>a</sup>	(%)	(n=146) <sup>a</sup>	(%)		
SAS total score 0 at baseline, >0 at week 8	80	(30.1)	33	(24.6)	47	(35.6)	3.81	0.051
AIMS total score 0 at baseline, >0 at week 8	27	(10.2)	8	(5.9)	19	(14.7)	5.66	0.017
HAS total score 0 at baseline, >0 at week 8	62	(23.4)	25	(18.7)	37	(28.2)	3.40	0.065

LOCF, Last observation carried forward; SAS, Simpson–Angus Scale; AIMS, Abnormal Involuntary Movement Scale; HAS, Hillside Akathisia Scale.

<sup>a</sup> Reduced n in single scales due to missing values.



**Figure 3.** Kaplan–Meier analysis of discontinuation rates. The difference in time to discontinuation between treatment groups is significant [log rank test,  $\chi^2(1) = 6.4$ ,  $p = 0.011$ ].

and a numerically greater frequency of scores >0 in the HAS scale. Surprisingly, this difference was not mirrored by the prescription rates of the anticholinergic biperiden. In general risperidone, like other SGAs, has better extrapyramidal tolerability than haloperidol (Leucht et al., 1999; Möller, 2000a), an advantage which was found consistently in FES studies (Emsley and the Risperidone Working Group, 1999; Lieberman et al., 2003; Sanger et al., 1999; Schooler et al., 2005). The differences favouring risperidone in terms of EPS were especially convincing in the sub-analysis of the FUTURIS study (Kopala et al., 2003), which compared in an ex-post analysis patients with equivalent doses of risperidone and haloperidol in FES, i.e. 1 mg vs. 1 mg, 2 mg vs. 2 mg, etc. On the other side, based on a double-blind RCT in a small sample (n=40) of FES patients comparing 2 mg and 8 mg of haloperidol, it was suggested that even a dose around

**Table 3c.** Incidence of movement disorder side effects defined (after Lieberman et al., 2003) by a change in total parameter score from <1 at baseline to  $\geq 1$  at endpoint (week 8, LOCF, Fisher's exact test)

	Total		Risperidone		Haloperidol		OR	<i>p</i>
	( <i>n</i> =289) <sup>a</sup>	(%)	( <i>n</i> =143) <sup>a</sup>	(%)	( <i>n</i> =146) <sup>a</sup>	(%)		
SAS total score <1 at baseline, $\geq 1$ at week 8	19	(7.1)	4	(2.9)	15	(11.5)	4.32	0.008
AIMS total score <1 at baseline, $\geq 1$ at week 8	9	(3.4)	1	(0.7)	8	(6.2)	8.93	0.017
HAS total score <1 at baseline, $\geq 1$ at week 8	22	(8.3)	4	(2.9)	18	(13.8)	5.27	0.001

LOCF, Last observation carried forward; SAS, Simpson–Angus Scale; AIMS, Abnormal Involuntary Movement Scale; HAS, Hillside Akathisia Scale.

<sup>a</sup> Reduced *n* in single scales due to missing values.

**Table 3d.** Incidence of movement disorder side effects (cf. Lieberman et al., 2003) by average dose per day, and difference in incidence between treatment groups

	Risperidone		Haloperidol		Difference (%)							
	<4 mg		$\geq 4$ mg		<4 mg		$\geq 4$ mg					
	<i>n</i>	(%)	<i>n</i>	(%)	<i>n</i>	(%)	Estimate	(95% CI)	Estimate	(95% CI)		
SAS total score 0 at baseline, >0 at week 8	21	(29.6)	10	(20.4)	25	(32.9)	21	(47.7)	−3.3	(−18.3 to 11.7)	−27.3	(−42.3 to −12.3)
AIMS total score 0 at baseline, >0 at week 8	5	(6.9)	3	(6.1)	12	(16.2)	5	(11.4)	−9.3	(−19.5 to 1.0)	−5.2	(−15.5 to 5.0)
HAS total score 0 at baseline, >0 at week 8	12	(16.9)	11	(22.4)	18	(23.4)	17	(38.6)	−6.5	(−19.3 to 6.4)	−16.2	(−29.0 to −3.3)

SAS, Simpson–Angus Scale; AIMS, Abnormal Involuntary Movement Scale; HAS, Hillside Akathisia Scale.

4 mg might be too high in FES and that 2 mg might be a more suitable dosage (Oosthuizen et al., 2004). However, the results of the study by Oosthuizen et al. (2004) seem to be somewhat in contrast to the results of the 7-arm sertindole–haloperidol study by Zimbroff et al. (1997) which compared in a double-blind, randomized design three dosages of sertindole, three dosages of haloperidol and placebo in a sample of 497 patients. This non-FES study found no significant difference between 4, 8 and 16 mg haloperidol.

One of the central, clinically relevant findings of this study is that the overall rate of discontinuation is significantly lower in the risperidone group (38.5% vs. 54.1% with haloperidol;  $p < 0.01$ ). Other FES studies also found higher drop-out rates with haloperidol than the SGA comparator, although these did not always reach statistical significance. For example, the 6-wk study of risperidone vs. haloperidol found

drop-out rates of 20% and 31%, respectively (Emsley and the Risperidone Working Group, 1999), and the 12-wk comparison of olanzapine vs. haloperidol of 32% and 46%, respectively (Lieberman et al., 2003). The relevance of the lower drop-out rate becomes apparent when considering that the non-discontinuation estimation by a survival analysis approach was recently used as the primary outcome measure in so-called 'effectiveness' studies (Lieberman et al., 2005).

Although the sample size was smaller than originally planned, the difference in power between the planned and actual sample was very small (0.08), i.e. there was no relevant effect on the power of the study. Thus, the study would not have reached different conclusions if a larger number of patients had been included. Although a proportion of patients was not drug naive, in contrast to some of the other FES studies

(Emsley and the Risperidone Working Group, 1999; Kopala et al., 1998), it is presumed that pre-treatment with neuroleptics did not confound the main results of the study. Another limitation is that the inclusion of in-patients only means that the results can only be generalized to outpatients with caution.

The efficacy and tolerability results of this study, together with the findings in the literature in first- and multi-episode patients, seem to indicate that it is much easier to demonstrate the advantage of SGAs in the dimension of EPS, where the indications are quite robust and consistent across the studies. In contrast, differences concerning the hypothesized broader efficacy spectrum, especially in terms of negative or depressive symptoms, are not so pronounced and the results are quite varied (Möller, 2003, 2005). Although FES patients show negative symptoms, they might not be as good a target population to show differences between SGAs and FGAs as multi-episode patients, and especially patients with enduring and predominant negative symptoms (Möller et al., 1994).

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#### Statement of Interest

H.-J. Möller has received/is receiving research grants/support from, serves as a consultant or is on the advisory board for, or is a member of the speaker bureau for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Eisai, GlaxoSmithKline, Janssen-Cilag, Lundbeck, Merck, Novartis, Organon, Pfizer, Sanofi Aventis, Sepracor, Servier, Wyeth. M. Gastpar is a consultant or member of the advisory board for AstraZeneca, Lundbeck, Pfizer, Servier, Wyeth. F. Schneider has received/is receiving research grants/support from, serves as a consultant or is on the advisory board for AstraZeneca, Janssen-Cilag, Lundbeck Neuroscience, Wyeth. W. Gaebel has received/is receiving research grants/support from, serves as a consultant or is on the advisory board for, or is a member of the speakers'

bureau for AstraZeneca GmbH, Bristol-Myers Squibb GmbH & Co. KG, GlaxoSmithKline, Janssen-Cilag GmbH, Lilly Deutschland GmbH, Lundbeck GmbH, Novartis Pharma GmbH, Sanofi-Synthelabo GmbH/Aventis, Wyeth Pharma GmbH.

#### References

- Addington D, Addington J, Schissel B** (1990). A depression rating scale for schizophrenics. *Schizophrenia Research* 3, 247–251.
- Agresti A** (2002). *Categorical Data Analysis*. New York: Wiley.
- Andreasen NC** (1982). Negative symptoms in schizophrenia. Definition and reliability. *Archives of General Psychiatry* 39, 784–788.
- APA** (1994). *Diagnostic and Statistical Manual of Mental Disorders* (4th edn). Washington DC: American Psychiatric Association.
- Coldham EL, Addington J, Addington D** (2002). Medication adherence of individuals with a first episode of psychosis. *Acta Psychiatrica Scandinavica* 106, 286–290.
- Csernansky JG, Mahmoud R, Brenner R** (2002). A comparison of risperidone and haloperidol for the prevention of relapse in patients with schizophrenia. *New England Journal of Medicine* 346, 16–22.
- Emsley RA, the Risperidone Working Group** (1999). Risperidone in the treatment of first-episode psychotic patients: a double-blind multicenter study. Risperidone Working Group. *Schizophrenia Bulletin* 25, 721–729.
- Fleischhacker WW, Bergmann KJ, Perovich R, Pestreich LK, Borenstein M, Lieberman JA, Kane JM** (1989). The Hillside Akathisia Scale: a new rating instrument for neuroleptic-induced akathisia. *Psychopharmacology Bulletin* 25, 222–226.
- Frances A, Pincus HA, First MB** (1994). The Global Assessment of Functioning Scale (GAF). *Diagnostic and Statistical Manual of Mental Disorders – IV*. Washington DC: American Psychiatric Association.
- Gaebel W, Moller HJ, Buchkremer G, Ohmann C, Riesbeck M, Wolwer W, Von Wilmsdorff M, Bottlender R, Klingberg S** (2004). Pharmacological long-term treatment strategies in first episode schizophrenia – study design and preliminary results of an ongoing RCT within the German Research Network on Schizophrenia. *European Archives of Psychiatry and Clinical Neuroscience* 254, 129–140.
- Gaebel W, Riesbeck M, Wölwer W, Klimke A, Eickhoff M, Von Wilmsdorff M, Jockers-Scherübl MC, Kühn K, Lemke M, Bechdolf A, et al.** (2007). Maintenance treatment with risperidone or low-dose haloperidol in first-episode schizophrenia: one-year results of a randomized controlled trial within the German Research Network on Schizophrenia. *Journal of Clinical Psychiatry* 68, 1763–1774.
- Green AI, Lieberman JA, Hamer RM, Glick ID, Gur RE, Kahn RS, McEvoy JP, Perkins DO, Rothschild AJ, Sharma T, et al.** (2006). Olanzapine and haloperidol in first

- episode psychosis: two-year data. *Schizophrenia Research* 86, 234–243.
- Guy W** (1976a). Abnormal Involuntary Movement Scale (AIMS). In: *ECDEU Assessment Manual for Psychopharmacology* (revised edn). Washington DC: US Department of Health, Education and Welfare.
- Guy W** (1976b). Clinical Global Impression (CGI). In: *ECDEU Assessment Manual for Psychopharmacology* (revised edn). Washington DC: US Department of Health, Education and Welfare.
- Haas GL, Sweeney JA** (1992). Premorbid and onset features of first-episode schizophrenia. *Schizophrenia Bulletin* 18, 373–386.
- Hamilton M** (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery and Psychiatry* 23, 56–62.
- Hedeker DR, Gibbons RD** (2006). *Longitudinal Data Analysis*. Hoboken: John Wiley.
- Jäger M, Riedel M, Messer T, Pfeiffer H, Laux G, Naber D, Gaebel W, Huff W, Schmidt LG, Heuser I, et al.** (2006). Psychopathological characteristics and treatment outcome of first episode compared with multiple episode schizophrenic disorders. *European Archives of Psychiatry and Clinical Neuroscience* Published online: 10 October 2006. doi: 10.1007/s00406-006-0683-1.
- Kay SR, Fiszbein A, Opler LA** (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin* 13, 261–276.
- Keefe RS, Seidman LJ, Christensen BK, Hamer RM, Sharma T, Sitskoorn MM, Lewine RR, Yurgelun-Todd DA, Gur RC, Tohen M, et al.** (2004). Comparative effect of atypical and conventional antipsychotic drugs on neurocognition in first-episode psychosis: a randomized, double-blind trial of olanzapine versus low doses of haloperidol. *American Journal of Psychiatry* 161, 985–995.
- Keefe RS, Sweeney JA, Gu H, Hamer RM, Perkins DO, McEvoy JP, Lieberman JA** (2007). Effects of olanzapine, quetiapine, and risperidone on neurocognitive function in early psychosis: a randomized, double-blind 52-week comparison. *American Journal of Psychiatry* 164, 1061–1071.
- Kopala L, Rabinowitz J, Davidson M** (2003). Extrapyramidal signs and symptoms (EPS) in recent onset schizophrenia: a comparison of risperidone and haloperidol. *European Neuropsychopharmacology* 13 (Suppl. 4), S338.
- Kopala LC, Good KP, Fredrikson D, Whitehorn D, Lazier L, Honer WG** (1998). Risperidone in first-episode schizophrenia: improvement in symptoms and pre-existing extrapyramidal signs. *International Journal of Psychiatry in Clinical Practice* 2, 19–25.
- Leucht S, Pitschel-Walz G, Abraham D, Kissling W** (1999). Efficacy and extrapyramidal side-effects of the new antipsychotics olanzapine, quetiapine, risperidone, and sertindole compared to conventional antipsychotics and placebo. A meta-analysis of randomized controlled trials. *Schizophrenia Research* 35, 51–68.
- Liang K-Y, Zeger SL** (1986). Longitudinal data analysis using generalized linear models. *Biometrika* 73, 13–22.
- Lieberman JA, Koreen AR, Chakos M, Sheitman B, Woerner M, Alvir JM, Bilder R** (1996). Factors influencing treatment response and outcome of first-episode schizophrenia: implications for understanding the pathophysiology of schizophrenia. *Journal of Clinical Psychiatry* 57 (Suppl. 9), 5–9.
- Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Keefe RS, Davis SM, Davis CE, Lebowitz BD, Severe J, Hsiao JK** (2005). Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *New England Journal of Medicine* 353, 1209–1223.
- Lieberman JA, Tollefson G, Tohen M, Green AI, Gur RE, Kahn R, McEvoy J, Perkins D, Sharma T, Zipursky R, Wei H, Hamer RM** (2003). Comparative efficacy and safety of atypical and conventional antipsychotic drugs in first-episode psychosis: a randomized, double-blind trial of olanzapine versus haloperidol. *American Journal of Psychiatry* 160, 1396–1404.
- Marder SR, Glynn SM, Wirshing WC, Wirshing DA, Ross D, Widmark C, Mintz J, Liberman RP, Blair KE** (2003). Maintenance treatment of schizophrenia with risperidone or haloperidol: 2-year outcomes. *American Journal of Psychiatry* 160, 1405–1412.
- McEvoy JP, Lieberman JA, Perkins DO, Hamer RM, Gu H, Lazarus A, Sweitzer D, Olexy C, Weiden P, Strakowski SD** (2007). Efficacy and tolerability of olanzapine, quetiapine, and risperidone in the treatment of early psychosis: a randomized, double-blind 52-week comparison. *American Journal of Psychiatry* 164, 1050–1060.
- Merlo MC, Hofer H, Gekle W, Berger G, Ventura J, Panhuber I, Latour G, Marder SR** (2002). Risperidone, 2 mg/day vs. 4 mg/day, in first-episode, acutely psychotic patients: treatment efficacy and effects on fine motor functioning. *Journal of Clinical Psychiatry* 63, 885–891.
- Möller HJ** (2000a). Definition, psychopharmacological basis and clinical evaluation of novel/atypical neuroleptics: methodological issues and clinical consequences. *World Journal of Biological Psychiatry* 1, 75–91.
- Möller HJ** (2000b). State of the art of drug treatment of schizophrenia and the future position of the novel/atypical antipsychotics. *World Journal of Biological Psychiatry* 1, 204–214.
- Möller HJ** (2003). Management of the negative symptoms of schizophrenia. New treatment options. *CNS Drugs* 17, 793–823.
- Möller HJ** (2004). Course and long-term treatment of schizophrenic psychoses. *Pharmacopsychiatry* 37 (Suppl. 2), 126–135.
- Möller HJ** (2005). Antidepressive effects of traditional and second generation antipsychotics: a review of the clinical data. *European Archives of Psychiatry and Clinical Neuroscience* 255, 83–93.
- Möller HJ** (2007). Clinical evaluation of negative symptoms in schizophrenia. *European Psychiatry* 22, 380–386.
- Möller HJ, Bottlender R, Groß A, Hoff P, Wittmann J, Wegner U, Strauss A** (2002). The Kraepelinian dichotomy:

- preliminary results of a 15-year follow-up study on functional psychoses: focus on negative symptoms. *Schizophrenia Research* 56, 87–94.
- Möller HJ, Bottlender R, Wegner U, Wittmann J, Strauß A** (2000). Long-term course of schizophrenic, affective and schizoaffective psychosis: focus on negative symptoms and their impact on global indicators of outcome. *Acta Psychiatrica Scandinavica* 102 (Suppl. 407), 54–57.
- Möller HJ, Schmid Bode W, Cording-Tömmel C, Wittchen HU, Zaudig M, von Zerssen D** (1988). Psychopathological and social outcome in schizophrenia versus affective/schizoaffective psychoses and prediction of poor outcome in schizophrenia. Results from a 5–8 year follow-up. *Acta Psychiatrica Scandinavica* 77, 379–389.
- Möller HJ, van Praag HM, Aufdembrinke B, Bailey P, Barnes TR, Beck J, Bentsen H, Eich FX, Farrow L, Fleischhacker WW, et al.** (1994). Negative symptoms in schizophrenia: considerations for clinical trials. Working group on negative symptoms in schizophrenia. *Psychopharmacology (Berlin)* 115, 221–228.
- Muller MJ, Marx-Dannigkeit P, Schlosser R, Wetzel H, Addington D, Benkert O** (1999). The Calgary Depression Rating Scale for Schizophrenia: development and interrater reliability of a German version (CDSS-G). *Journal of Psychiatric Research* 33, 433–443.
- Oosthuizen P, Emsley R, Jadri TH, Keyter N** (2004). A randomized, controlled comparison of the efficacy and tolerability of low and high doses of haloperidol in the treatment of first-episode psychosis. *International Journal of Neuropsychopharmacology* 7, 125–131.
- Rummel C, Hamann J, Kissling W, Leucht S** (2003). New generation antipsychotics for first episode schizophrenia. *Cochrane Database of Systematic Reviews*. Issue 4. Art. no.: CD004410.
- Sanger TM, Lieberman JA, Tohen M, Grundy S, Beasley Jr. C, Tollefson GD** (1999). Olanzapine versus haloperidol treatment in first-episode psychosis. *American Journal of Psychiatry* 156, 79–87.
- Schooler N, Rabinowitz J, Davidson M, Emsley R, Harvey PD, Kopala L, McGorry PD, Van HI, Eerdeken M, Swyzen W, De Smedt G** (2005). Risperidone and haloperidol in first-episode psychosis: a long-term randomized trial. *American Journal of Psychiatry* 162, 947–953.
- Shrout PE, Fleiss JL** (1979). Intraclass correlations: uses in assessing rater reliability. *Psychological Bulletin* 86, 420–428.
- Siegel SJ, Irani F, Brensinger CM, Kohler CG, Bilker WB, Ragland JD, Kaner SJ, Gur RC, Gur RE** (2006). Prognostic variables at intake and long-term level of function in schizophrenia. *American Journal of Psychiatry* 163, 433–441.
- Simpson GN, Angus JWS** (1970). A rating scale for extrapyramidal side effects (EPS). *Acta Psychiatrica Scandinavica* 212 (Suppl. 44), 11–19.
- Singer JD** (1998). Using SAS PROC MIXED to fit multilevel models, hierarchical models, and individual growth models. *Journal of Educational and Behavioral Statistics* 24, 323–334.
- Strauss JS, Carpenter Jr. WT** (1978). The prognosis of schizophrenia: rationale for a multidimensional concept. *Schizophrenia Bulletin* 4, 56–67.
- Vickers AJ, Altman DG** (2001). Analysing controlled trials with baseline and follow up measurements. *British Medical Journal* 323, 1123–1124.
- Wolwer W, Buchkremer G, Hafner H, Klosterkötter J, Maier W, Moller HJ, Gaebel W** (2003). German research network on schizophrenia-bridging the gap between research and care. *European Archives of Psychiatry and Clinical Neuroscience* 253, 321–329.
- Young RC, Biggs JT, Ziegler VE, Meyer DA** (1978). A rating scale for mania: reliability, validity and sensitivity. *British Journal of Psychiatry* 133, 429–435.
- Zhang-Wong J, Zipursky RB, Beiser M, Bean G** (1999). Optimal haloperidol dosage in first-episode psychosis. *Canadian Journal of Psychiatry* 44, 164–167.
- Zimbroff DL, Kane JM, Tamminga CA, Daniel DG, Mack RJ, Wozniak PJ, Sebree TB, Wallin BA, Kashkin KB, and the Sertindole Study Group** (1997). Controlled, dose-response study of sertindole and haloperidol in the treatment of schizophrenia. *American Journal of Psychiatry* 154, 782–791.