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Efficacy of flupentixol and risperidone in chronic schizophrenia with predominantly negative symptoms

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Abstract

The study investigated the non-inferiority of flupentixol compared to risperidone in the treatment of negative symptoms. In addition, the effects of flupentixol on mood and cognitive symptoms were explored.

In a randomized, double-blind multicenter study, 144 non-acute schizophrenia patients with predominant negative symptoms were treated with a flexible dose of either flupentixol (4–12 mg/d) or risperidone (2–6 mg/d) for up to 25 weeks. In addition to a non-inferiority analysis, a principal component analysis (PCA) of the PANSS was performed post hoc.

Regarding negative symptoms, flupentixol proved to be non-inferior to risperidone. Both drugs improved depressed mood with effect sizes favoring flupentixol. PCA suggested a five-factor structure. Effect sizes for the cognitive factor were up to 0.74 for flupentixol and up to 0.80 for risperidone. EPS scores were rather low and Parkinsonism improved in both groups, but anticholinergic drugs were prescribed significantly more frequently in the flupentixol group, which generally showed significantly more adverse events.

Results indicate that the 1st generation antipsychotic flupentixol improves negative, affective and cognitive symptoms in chronic schizophrenia comparable to risperidone. Further studies should confirm the latter using neuropsychological performance tests and should investigate whether tolerability improves with a markedly lower dose range.

Keywords: Cognitive symptoms; Depression; Flupentixol; Negative symptoms; Risperidone; Schizophrenia

Abbreviations: CC, Cognitive component; CGI, Clinical Global Impression Scale; CPL, Completer sample; D/AC, Depression/anxiety; D-x, Difference score (e.g. D-NC); EC, Excitement component; EPS, Extrapyramidal side effects; ESRS, Extrapyramidal Symptom Rating Scale; FGA, First-generation antipsychotics; FLP, Flupentixol; CI95, 95% confidence interval; ITT, Intent-to-treat; LOCF, Last observation carried forward; LSmeans, Least Squares Means; MADRS, Montgomery Åsberg Depression Rating Scale; NC, Negative component; N.S., Not significant; PANSS, Positive and Negative Syndrome Scale; PC, Positive component; PNS, PANSS Negative Subscale; PPS, PANSS Positive Subscale; RIS, Risperidone; SGA, Second-generation antipsychotics; VfE, Valid for efficacy.

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1. Introduction

The introduction of new antipsychotics which claimed to provide the 'atypical' properties of clozapine led to polarization, with the available neuroleptic drugs divided into two classes. All older antipsychotics were uniformly classified as 'typical' and haloperidol, as the standard comparator in most trials, defined the characteristic profile of the whole class (Davis et al., 2003; Leucht et al., 2003a; Wahlbeck et al., 2001). However, it is well known from research as well as from clinical experience that first-generation antipsychotics (FGA) differ markedly in their biochemical, efficacy and tolerability profiles (Bandelow et al., 1992; Hyttel et al., 1985; Johnson and Malik, 1975; Kong and Yeo, 1985; Parent and Toussaint, 1983; Pinto et al., 1979; Seeman, 2002).

Only a small number of studies compared second-generation antipsychotics (SGAs) to high potency FGAs other than haloperidol (Gattaz et al., 2004; Hoyberg et al., 1993; Huttunen et al., 1995; Jones et al., 2006; Lieberman et al., 2005; Rosenheck et al., 2003; Wetzel et al., 1998). A recent Cochrane review intended to analyze the current data regarding 'risperidone versus typical antipsychotic medication' concluded that– rather than its main objective– the review was essentially a comparison with haloperidol (Hunter et al., 2003). Thus, the relative effectiveness of novel antipsychotics as compared to older drugs is still an open question (Geddes et al., 2000; Leucht et al., 2003b; Lieberman et al., 2005; Wahlbeck et al., 2001).

Negative symptoms are one of the major challenges in the treatment of schizophrenic psychoses as they are particularly important to functional outcome and quality of life (Kirkpatrick et al., 2006). The capability of improving negative symptoms has been described as one of the major advantages of the SGAs (Lublin et al., 2005). Yet, in a recent meta-analysis, haloperidol was inferior to olanzapine and risperidone, but not to sertindole or to quetiapine, which in fact yielded lower effect sizes (Leucht et al., 1999). Another analysis found a significant advantage for risperidone when pooled data were compared (Carman et al., 1995). On a single study level, however, the largest trial by far in the analysis (Peuskens, 1995) found that risperidone did not have a significantly different effect compared to haloperidol, and comparable effects were also demonstrated versus zuclopenthixol. However, none of the trials included in this analysis was designed to test specifically the effects of risperidone on negative symptoms and, across the studies, applied doses may have been markedly higher than those considered appropriate nowadays, particularly for this purpose.

Flupentixol (FLP) is a high potency thioxanthene with D_1/D_2 dopamine receptor antagonism which is much more balanced with regard to its $5HT_{2A}$ receptor blocking properties than is the case with, e.g. haloperidol, fluphenazine or perphenazine (Hyttel et al., 1985; Weiner et al., 2001). Due to the fact that this neurochemical profile is similar to loxapine it has been classified as 'partially atypical' (Ereshefsky, 1995, 1999). As for the thioxanthenes zuclopenthixol and thiothixene (Carman et al., 1995; Serban et al., 1992), beneficial effects of flupentixol on negative symptoms have already been described (Pach et al., 1998). In a recent double-blind six-week trial flupentixol improved negative symptoms markedly and statistically not differently from amisulpride (Müller et al., 2002; Wetzel et al., 1998), a drug said to show the best evidence of efficacy in this area (Leucht, 2004). Also, another double-blind, but small four-week study detected no significant difference between the beneficial effects of flupentixol and olanzapine on negative symptoms (Gattaz et al., 2004).

The aim of the present study was to elucidate further the position of flupentixol among the available antipsychotics in terms of efficacy and tolerability, focusing on negative symptoms. To improve the conclusiveness of the results, only clinically stabilized patients with predominant negative symptoms were included in the study (Leucht et al., 1999).

The positive–negative distinction of schizophrenic symptoms underlying the usual three-factor solution of the PANSS (Kay et al., 1987) was criticized as being "overly simplistic and too general an approach", and a differentiation of additional discrete psychopathological domains was considered necessary (Lindenmayer et al., 1995a; Remington and Kapur, 2000). A factor analysis of the PANSS was therefore performed post hoc to further clarify treatment effects.

The primary objective of the study was to corroborate the hypothesis that the efficacy of flupentixol on negative symptoms is not inferior to that of risperidone, and the secondary objective was to compare the effects on positive, depressive and extrapyramidal symptoms. Additionally, treatment effects on cognitive symptoms were explored.

2. Methods

2.1. Patient population

Inclusion criteria were: (1) in- and outpatients aged 18–65 years; (2) diagnosis of schizophrenia according to ICD-10 criteria (F20.0–F20.3, F20.5–F20.9) for at least two years; (3) at least three items of the PANSS (Kay et al., 1987) negative syndrome subscale scoring ≥ 4 points; (4) stable clinical state, meaning that maintenance treatment had been started or that consideration of a change in stable medication was not due to any acute exacerbation of positive symptoms. According to the third criterion, a subject belonged either to the 'minus' or to the 'mixed' subtype (Lindenmayer et al., 1984; Opler et al., 1984), assuring a significant level of negative symptoms.

Exclusion criteria were: contraindication to treatment with any of the study drugs or a history of hypersensitivity to one of them; dependence on alcohol or illegal drugs according to ICD-10 criteria; concomitant treatment with lithium, carbamazepine, other mood stabilizers or other psychopharmacological drugs (for exceptions see Section 2.2); treatment with flupentixol or risperidone within the last four weeks preceding the study; history of treatment with clozapine (to avoid inclusion of treatment-resistant cases); concurrent clinically relevant physical conditions; acute suicidal ideation; participation in a clinical study within the last 30 days; in case of females: not using a medically approved method of contraception, pregnancy or breast-feeding.

2.2. Drug administration

Patients were randomly assigned to receive a flexible dose of 4–12 mg of flupentixol (FLP) or 2–6 mg of risperidone (RIS).

Medication was administered in identical capsules containing either 2 mg of flupentixol or 1 mg of risperidone. Drugs were given twice a day (day one 2 × 1, day 2 up to 2 × 2, from day 3 up to 2 × 3 capsules). The first week was defined as a run-in phase, previous medication was washed out and study medication was given at the minimal dosage.

The only permissible concomitant medications were anticholinergic agents (biperiden) and short-term benzodiazepines and non-benzodiazepine hypnotics (for sleep induction), i.e. three periods of up to five days.

2.3. Study design

The study was conducted in accordance with the Guideline for Good Clinical Practice CPMP/768/97, the 1996 World Medical Association Declaration of Helsinki and pertinent German and Austrian legal and regulatory requirements, respectively, and was approved by the local ethics committees. It was a randomized, double-blind, parallel group phase-IV multicenter study with a treatment duration of up to 25 weeks. Visits took place at the beginning of the run-in week, one week later (baseline for assessments), two and four weeks after baseline and then four-weekly until week 24. Twenty-seven centers in Germany and three centers in Austria participated. All patients gave their written informed consent. Patients were explicitly informed that they were free to withdraw from the study at any time for any reason without effect on their medical care. Financial inducement to participate in the study was not offered.

2.4. Assessment instruments

The subscales of the Positive and Negative Syndrome Scale, PANSS, were used to assess positive and negative symptoms and global psychopathology (Kay et al., 1987). Further scales included the Clinical Global Impression Scale, CGI (Guy, 1976), the Montgomery-Asberg Depression Rating Scale, MADRS (Montgomery and Asberg, 1979) and the Extrapyramidal Symptom Rating Scale, ESRS (Chouinard et al., 1980). First assessments were performed at the end of the run-in week when previous medication was tapered out. From this baseline, all scales except the CGI (baseline and weeks 8, 16, 24) were used at every visit. All investigators were specifically trained by using video tapes, and an agreement of at least 80% with the key-ratings was required.

2.5. Data analysis

Since a minimum treatment duration of eight weeks is recommended for trials investigating treatment effects on negative symptoms (Möller et al., 1994), this period was considered as a prerequisite for inclusion in the Valid for efficacy (VfE) sample used for analysis of the primary outcome parameter. The use of a VfE sample is in line with the recommendations of the European Guidelines (ICH E9) and of the European Agency for the Evaluation of Medicinal Products (EMEA; CPMP/EWP/428/99), giving VfE samples priority in case of non-inferiority analyses for statistical reasons. Subjects with at least one observation after randomization were considered eligible for the intent-to-treat (ITT) analysis. Patients with at least one study drug administration after randomization were included in the safety sample.

To make the report of results as transparent as possible and improve comparability to standard procedures in other studies, all analyses of secondary outcome parameters were conducted as exploratory superiority tests. These were performed twice: once for the completer sample (CPL being identical with the per protocol sample) and – as a post hoc extension of the original plan – for a second intent-to-treat sample, where the last observation was carried forward in the case of premature study termination until the final per protocol visit at week 24 (LOCF sample). Also as a post

Table 1a
Demographic and clinical characteristics (intent-to-treat sample, ITT)

	Flupentixol (n=72)	Risperidone (n=72)	Total ITT (n=144)
Age [mean±S.D.]	40.94±12.84	39.83±11.13	40.39±11.98
Males:Females [n (%)]	45 : 27 (62.5 : 37.5)	45 : 27 (62.5 : 37.5)	90 : 54 (62.5 : 37.5)
Working status			
Employed	11 (15.3)	19 (26.49)	30 (20.8)
Unemployed	25 (34.7)	22 (30.6)	47 (32.6)
Retired	26 (36.1)	23 (31.9)	49 (34.0)
In training	7 (9.7)	5 (6.9)	12 (8.3)
Housekeeping	3 (4.2)	3 (4.2)	6 (4.2)
Body mass index [kg/m^2, mean±S.D.]	25.88±5.45	26.73±5.83	26.31±5.64
Diagnosis (ICD-10)			
F20.0 [n (%)]	32 (44.4)	33 (45.8)	65 (45.1)
F20.1 [n (%)]	6 (8.3)	4 (5.6)	10 (6.9)
F20.2 [n (%)]	2 (2.8)	1 (1.4)	3 (2.1)
F20.3 [n (%)]	3 (4.2)	3 (4.2)	6 (4.2)
F20.5 [n (%)]	22 (30.6)	23 (31.9)	45 (31.3)
F20.6 [n (%)]	4 (5.6)	5 (6.9)	9 (6.3)
F20.8 [n (%)]	2 (2.8)	2 (2.8)	4 (2.8)
F20.9 [n (%)]	1 (1.4)	1 (1.4)	2 (1.4)
Years since diagnosis [mean±S.D.]	11.28±9.98	11.50±10.07	11.39±9.99
Number of previous episodes [mean±S.D.]	4.87±4.48	4.73±4.38	4.80±4.42

Table 1b
Treatment with antipsychotics before inclusion in the study (safety sample)

Antispsychotic	Flupentixol (n=76)	Risperidone (n=77)
Butyrophenone per os	32	24
Phenothiazine per os	11	8
Haloperidol depot/Zuclopentixol depot	3/3	6/2
Olanzapine/Amisulpride/Sertindole	9/3/0	11/3/2
Others	8	9
No current pre-study medication	6	6
Unknown	1	6

hoc extension and in order to enhance comparability, exploratory superiority analyses were performed for the negative scores.

2.5.1. Primary efficacy variable and power calculation

The primary efficacy variable was the difference of adjusted changes from baseline of the PANSS negative subscale at weeks 8, 16, and 24 using a step down procedure. According to a predefined non-inferiority hypothesis it was stated that the difference in change between the two treatment groups was at least −4 points in favor of risperidone. This hypothesis would be rejected if, based on the least squares means, the lower 95% confidence interval of the difference actually found were greater than −4 at any of the tested visits, starting at visit 8 (step down procedure). Under this condition non-inferiority would only be tested at week 24 if the null-hypothesis could also be rejected at all prior visits. Treatment and center were considered as factors and baseline score as covariate.

Using nQuery Advisor 4.0 software, it was calculated that a study with 2×45 patients would have 80% power at a single step of the step down procedure to reject the null-hypothesis when the standard deviation is assumed to be 7.5.

2.5.2. Secondary efficacy and safety variables

Positive symptoms and global psychopathology (PANSS subscales), depression (MADRS), clinical global impression (CGI), extrapyramidal side effects (ESRS) and relapse rates, defined as a decrease of at least 10 points on the PANSS-derived Brief Psychiatric Rating Scale scores, were defined as secondary outcome variables. Repeated measures including baseline, weeks 4, 8, 12, 16, 20 and 24 were analyzed by ANOVA.

Table 2
Reasons for drop-out (safety sample)

Reason	Flupentixol (n=76) [n (%)]	Risperidone (n=77) [n (%)]
Adverse event	9 (11.84)	5 (6.49)
Non-compliance	3 (3.94)	2 (2.60)
Consent withdrawn	7 (9.21)	8 (10.39)
Treatment effect insufficient	5 (6.57)	10 (12.99)
Lost to follow-up	2 (2.63)	4 (5.20)
Death	1 (1.32)	–
Remission	–	1 (1.30)
Subject felt trial drug is inappropriate	7 (9.21)	1 (1.30)
Other reason	–	2 (2.60)
Reason not known	1 (1.31)	1 (1.30)

For vital parameters, ANOVAs were calculated for differences between endpoint and baseline, with the baseline as covariate. Categorical data were calculated with the chi square test or Fisher's exact test, as appropriate; the number of discontinuations over time was compared with the Log Rank test.

Effect sizes (ES) were calculated according to Cohen for changes of scores from baseline to week 24 within groups and between-groups and categorized as small (≥0.20), medium (≥0.50) and large (≥0.80) (Cohen, 1988).

2.5.3. Additional outcome analyses

Response was defined by a 'standard criterion' as a reduction of baseline scores ≥20% (Carman et al., 1995), and by a 'strong criterion' as a reduction ≥50%.

A principal component analysis was performed for baseline PANSS data following Lindenmayer et al. (1995b). Only factors with Eigenvalues ≥1.50 were rotated. After orthogonal equamax rotation, only those items with a minimum load of ≥0.45 were retained for further analysis.

For the suggested differentiation between primary and secondary negative symptoms (Carpenter, 1996; Flaum and Andreasen, 1995; Kirkpatrick et al., 2006), linear regression analyses (stepwise backward) were done to further investigate possible interferences between drug effects on negative symptoms and those on mood, positive symptoms or EPS. An analogue procedure was used to elucidate interferences between effects on the cognitive factor and those on negative, positive and mood-related symptoms.

Association between use of anticholinergic drugs and dose of antipsychotic was analyzed by logistic regression.

Statistical significance was assumed at a two-tailed alpha of ≤0.05. Statistical analyses were performed with SAS Version 9.1.

3. Results

3.1. Subjects' characteristics, study participation, dosage and concomitant medication

A total number of N=153 subjects [safety group] was randomized, n=76 to the flupentixol group and n=77 to the

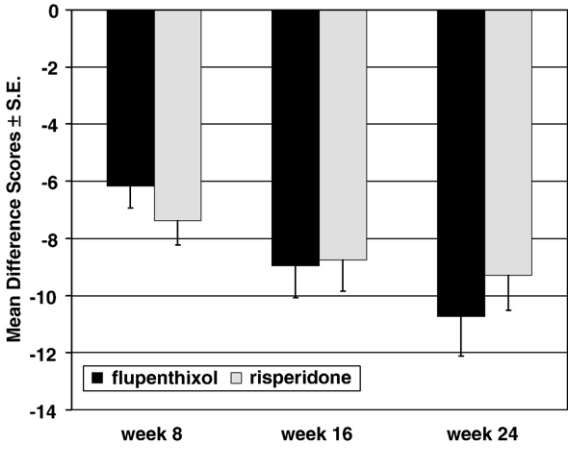

Fig. 1. Change of negative symptoms (valid for efficacy sample). Flupentixol was non-inferior to risperidone at all three times.

risperidone group. No follow-up after randomization was available for $n=9$ patients (FLP=4, RIS=5; N.S.). Thus, $N=144$ patients ($n=72$ in both groups) were considered for the intent-to-treat (ITT) analysis. No statistical difference emerged regarding demographic and clinical variables, including distribution of treatment with antipsychotics during the time preceding inclusion in the study (Table 1a, 1b).

A statistically equal portion of $n=41/76$ (53.9%) in the FLP group and $n=43/77$ (55.8%) in the RIS group completed the whole study [completer group, CPL]. The type or number of reasons for drop-out (Table 2) did not differ significantly between the groups and the Log Rank test revealed no significant difference regarding number of drop-outs per visit. The duration of trial participation in the ITT sample did not differ either (FLP: [mean±S.D.]: 19.30±8.41; RIS: 19.36±8.63 weeks, N.S.).

Mean dose±S.D. of trial medication in mg per day was 6.68±2.99 for FLP–ITT, 6.23±2.86 for FLP–CPL, 3.51±1.21 for RIS–ITT and 3.56±1.20 for RIS–CPL.

Twenty-one patients in the FLP–ITT group (FLP–CPL: $n=11$) and twenty-five patients in the RIS–ITT group (RIS–CPL: $n=18$) received benzodiazepines as concomitant medication, the proportions not being statistically different. The number of periods of benzodiazepine use was significantly higher in FLP–ITT, but not in the FLP–CPL group (FLP–ITT: $n=1.5\pm1.0$, RIS–ITT: 1.0±0.2, $p<0.05$; FLP–CPL: 1.5±1.2, RIS–CPL: 1.1±0.2, N.S.). The mean daily doses±S.D., calculated as diazepam equivalents (Laux et al., 2000), were: FLP–ITT 11.7±11.7 mg vs. RIS–ITT 8.2±4.8 mg (N.S.); FLP–CPL 9.4±6.8 mg vs. RIS–CPL 8.3±5.4 mg (N.S.).

3.2. Effectiveness

3.2.1. PANSS negative subscale — primary outcome analysis

After eight weeks of treatment, $n=107$ patients (FLP=51, RIS=56) were eligible for VfE analysis. PANSS negative scale (PNS) scores improved in both treatment arms (Fig. 1). Based on the LS_{means}, the difference between the baseline-related score changes within the two conditions was −1.11 (CI_{95}−3.30; 1.07) at week 8 (LS_{means} FLP=21.54, RIS=20.43), 0.10 (CI_{95}−2.69; 2.90) at week 16 (LS_{means} FLP=19.20, RIS=19.30) and 1.60 (CI_{95}−1.63; 4.83) at week 24 (LS_{means} FLP=17.37, RIS=18.97). As the lower limit of the confidence interval was above the critical threshold of −4 points at all three time points (step down procedure), the alternative hypothesis could be accepted that the efficacy of flupentixol on negative symptoms is non-inferior to risperidone.

3.2.1.1. Additional analyses. Corresponding results were observed for the LOCF sample and for the completer sample, when data were calculated by repeated measures ANOVAs (Table 3). A large effect size (Table 4) on negative symptoms was observed for both drugs in the completer sample; in the LOCF sample both conditions achieved effect sizes just below the 0.8 criterion. The between-group ES at week 24 was near zero in both samples, supporting the result of the non-inferiority analysis.

Table 3
PANSS scores during course of treatment: three-factor and five-factor solution for LOCF[a] and completer groups

		Drug	ITT groups (flupentixol [FLP] $n=72$; risperidone [RIS] $n=72$)				Completer groups (flupentixol [FLP] $n=41$; risperidone [RIS] $n=43$)			
			Week 0	Week 24	Time [F, p]	Treatment [F, p]	Treatment × Time [F, p]	Week 0	Week 24	Time [F, p]	Treatment [F, p]	Treatment × Time [F, p]
3-factor solution	Negative	FLP	27.67±5.44[b]	21.06±8.85	50.7	0.2	0.5	27.20±5.51	17.78±7.78	63.9	0.1	0.4
		RIS	27.65±5.40	21.03±8.86	<0.0001	N.S.	N.S.	27.42±5.48	18.09±7.52	<0.0001	N.S.	N.S.
	Positive	FLP	14.72±4.47	13.96±6.35	5.3	0.5	0.3	13.93±4.22	10.78±4.88	19.8	0.41	0.41
		RIS	14.65±5.45	13.13±6.45	<0.0001	N.S.	N.S.	13.91±4.72	10.47±3.94	<0.0001	N.S.	N.S.
	General psychopathology	FLP	40.90±10.77	34.90±14.48	15.9	0.7	1.1	39.71±10.76	28.29±11.20	33.8	0.3	1.5
		RIS	39.47±9.93	35.07±15.09	<0.0001	N.S.	N.S.	38.42±10.22	29.91±12.87	<0.0001	N.S.	N.S.
5-factor solution	Negative component	FLP	20.79±4.77	15.31±6.62	52.2	0.2	0.7	20.88±4.89	12.78±5.89	62.3	0.1	0.8
		RIS	20.54±4.93	15.40±6.89	<0.0001	N.S.	N.S.	20.53±5.17	13.28±5.84	<0.0001	N.S.	N.S.
	Excitement component	FLP	8.83±3.67	8.60±4.24	1.1	1.0	0.8	8.05±3.21	6.66±3.25	6.7	0.7	1.44
		RIS	8.35±3.13	8.26±4.16	N.S.	N.S.	N.S.	7.84±2.78	6.70±2.48	<0.0001	N.S.	N.S.
	Cognitive component	FLP	15.03±4.58	12.63±5.82	15.28	0.08	0.32	14.71±4.58	10.71±5.25	25.3	0.2	0.3
		RIS	14.57±4.03	12.64±5.68	<0.0001	N.S.	N.S.	14.16±4.24	10.67±4.89	<0.0001	N.S.	N.S.
	Positive component	FLP	9.67±3.75	8.72±4.69	19.37	0.6	0.54	9.34±3.63	6.63±3.71	19.4	0.6	0.5
		RIS	9.57±4.27	8.46±5.07	<0.0001	N.S.	N.S.	9.07±4.11	6.63±3.61	<0.0001	N.S.	N.S.
	Depression/anxiety component	FLP	16.50±5.64	13.71±5.62	16.9	0.21	0.48	16.20±5.83	11.05±4.36	28.8	0.0	0.6
		RIS	16.36±4.95	13.76±6.06	<0.0001	N.S.	N.S.	16.28±5.56	11.86±5.43	<0.0001	N.S.	N.S.

Repeated measures ANOVA.
[a] ITT = intent-to-treat sample (with last observation arried forward).
[b] Mean (S.D.).

Table 4
Effect size for within and between-group comparisons

	Component	Flupentixol		Risperidone		flupentixol vs. risperidone	
		ITT[a]	CPL[b]	ITT	CPL	ITT	CPL
PANSS 3-factor solution	Negative	0.76	1.27	0.79	1.23	0.00	0.08
	Positive	0.13	0.62	0.26	0.63	0.13	0.06
	General psychopathology	0.45	0.96	0.39	0.89	0.12	0.27
PANSS 5-factor solution	Negative	0.85	1.33	0.79	1.18	0.05	0.14
	Excitement	0.06	0.34	0.02	0.44	0.04	0.08
	Cognitive	0.43	0.74	0.41	0.80	0.09	0.10
	Positive	0.22	0.69	0.23	0.54	0.04	0.06
	Depression/anxiety	0.48	1.05	0.46	0.90	0.03	0.15
MADRS	Total score	0.40	0.99	0.22	0.51	0.18	0.38
CGI	Total score	0.71	0.56	0.93	0.51	0.05	0.14

Effect sizes were calculated according to Cohen (1988).
[a] ITT = intent-to-treat sample (with last observation carried forward).
[b] CPL = completer sample.

Regression analysis was calculated with change in the PNS score from baseline to week 24 as dependent variable and the respective difference scores of the PANSS positive subscale (PPS), the MADRS and the ESRS as independent variable for each treatment condition and each sample (LOCF, CPL). ESRS scores did not contribute significantly in any calculation, and were thus removed from the model. MADRS and primarily PPS difference scores significantly predicted the improvement of PNS scores in all analyses. Based on the respective adjusted r^2 coefficients, the amount of variance explained by the two variables was FLP–LOCF: 52.7%; RIS–LOCF: 50.2%; FLP–CPL: 47.2%; RIS–CPL: 37.6%. Thus, 47.3 to 72.4% of variance of the PNS difference scores was not explained by the assumed confounders.

3.2.2. Secondary psychopathological variables

The positive and global psychopathology PANSS subscales improved significantly from baseline to endpoint, and no significant differences were found between the treatment groups in the CPL or LOCF sample (Table 3). Respective ES are shown in Table 4.

Both drugs decreased MADRS scores significantly (Fig. 2) (LOCF: treatment N.S.; time $F=11.2$, $p<0.001$; treatment × time N.S.; CPL: treatment N.S.; time $F=21.8$, $p<0.001$; treatment × time N.S.). For effect sizes see Table 4. Completion of treatment led to a large ES for flupentixol and a medium ES for risperidone, which was also reflected by at least small ES derived from group comparisons.

The CGI improved significantly with both treatments, in the LOCF sample (FLP [mean±S.D.]: 4.82±0.79 to 3.97±1.22; RIS: 4.76±0.81 to 3.93±1.38; treatment N.S.; time $F=38.5$, $p<0.0001$; treatment × time N.S.) as well as in the CPL sample (FLP: 4.85±0.65 to 3.76±1.20; RIS: baseline 4.67±0.81, endpoint 3.77±1.44; treatment N.S.; time $F=38.1$, $p<0.0001$; treatment × time N.S.). For ES see Table 4.

3.2.3. Relapse rates

With 13/72 (18.1%) in the flupentixol group and 10/72 (13.9%) in the risperidone group, relapse rates were clinically comparable and did not differ statistically.

3.2.4. Additional outcome analyses

3.2.4.1. PANSS factor analysis. The principal component analysis suggested five factors: *negative* (NC), *excitement* (EC), *cognitive* (CC), *positive* (PC), and *depression/anxiety* (D/AC) (Table 5). They accounted for 53.4% of total variance (NC=12.6%, EC=11.1%, CC=10.37%, PC=9.8%, and D/AC=9.6%).

All five factors, except EC in the LOCF sample, improved significantly during the trial (Table 3). The respective effect sizes are shown in Table 4. Regression analysis with change of NC scores as dependent variable and difference scores of PC (D-PC), D/AC (D-D/AC) and ESRS (D-ESRS) as independent variables yielded different results, depending on group and sample. D-D/AC and, to a much lesser extent, D-ESRS scores explained 42.2% of variance in the FLP–LOCF group (numbers based on adjusted r^2). For RIS–LOCF, D-PC and D-D/AC explained 47.7% of variance. In the FLP–CPL group, D-D/AC explained 15.0%, and in the RIS–CPL group, D–ESRS

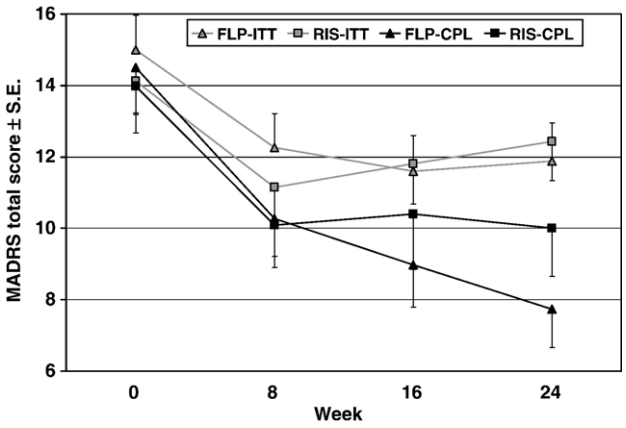

Fig. 2. MADRS and CGI effect sizes. MADRS = Montgomery Asberg Depression Rating Scale; CGI = Clinical Global Impression Scale; FLP = flupentixol, RIS = risperidone; ITT = intent-to-treat sample (with last observation carried forward), CPL = completer sample; ≥0.20: small effect size; ≥0.50: medium ES; ≥0.80: large ES.

Table 5
Component loadings: 5-factor model of schizophrenic symptoms

Components		Equamax-rotated component loadings				
		1	2	3	4	5
Negative component						
N4[a]	Passive/apathetic social withdrawal	**0.85**	◊	◊	◊	◊
N2	Emotional withdrawal	**0.84**	◊	◊	◊	◊
G16	Active social avoidance	**0.73**	◊	◊	◊	◊
N1	Blunted affect	**0.72**	◊	0.28	◊	◊
N3	Poor rapport	**0.70**	0.24	0.22	◊	◊
Excitement component						
G14	Poor impulse control	◊	**0.73**	◊	◊	0.24
P4	Excitement	◊	**0.66**	◊	0.38	◊
P7	Hostility	◊	**0.66**	0.23	◊	◊
G5	Mannerisms and posturing	◊	**0.53**	0.33	◊	◊
G8	Uncooperativeness	0.30	**0.48**	0.31	◊	0.21
Cognitive component						
P2	Conceptual disorganization	◊	◊	**0.70**	0.42	◊
N5	Difficulty in abstract thinking	◊	◊	**0.66**	◊	◊
G10	Lack of judgement and insight	◊	0.28	**0.62**	◊	◊
G13	Disturbance of volition	◊	0.31	**0.48**	◊	0.30
G11	Poor attention	◊	◊	**0.61**	◊	0.28
Positive component						
P1	Delusions	◊	◊	◊	**0.76**	◊
P3	Hallucinations	◊	◊	◊	**0.75**	◊
G9	Unusual thought content	◊	0.39	0.26	**0.65**	◊
P6	Suspiciousness/persecution	◊	0.43	◊	**0.45**	◊
Depression/anxiety component						
G6	Depression	◊	◊	◊	◊	**0.80**
G3	Guilt feelings	◊	◊	◊	◊	**0.69**
G2	Anxiety	◊	0.30	◊	0.30	**0.69**
G4	Tension	◊	0.47	◊	0.37	**0.49**
N6	Lack of spontaneity	0.37	◊	0.31	◊	**0.48**
G7	Motor retardation	0.29	◊	0.27	−0.30	**0.48**
Other PANSS items						
G1	Somatic concern	0.31	◊	◊	0.37	0.29
P5	Grandiosity	◊	0.42	◊	0.25	−0.32
N7	Stereotyped thinking	0.37	◊	0.44	◊	◊
G10	Disorientation	◊	◊	0.40	◊	◊
G15	Preoccupation	0.25	0.25	0.28	0.41	◊

◊ = component loading ≤ 0.20.
[a] Original PANSS item numbers.

explained 30.7% of variance. Thus, across groups the amount of variance of NC difference scores not explained by the assumed confounders was between 52.3% and 85%.

To further elucidate improvement of cognitive symptoms, changes of positive, negative (D-NC) or depression/anxiety symptoms were considered as independent variables. Regarding the LOCF sample, in both treatment groups D-NC and, to a markedly lower extent, D-PC explained 45.6% (FLP) and 38.8% (RIS) of variance, respectively. In the FLP–CPL group D-NC and D-D/A explained 35.5%, in the RIS–CPL group D-PC explained 24.6% of variance. In summary, 54.4% to 75.4% of variance of the CC difference scores was not explained by the assumed confounders.

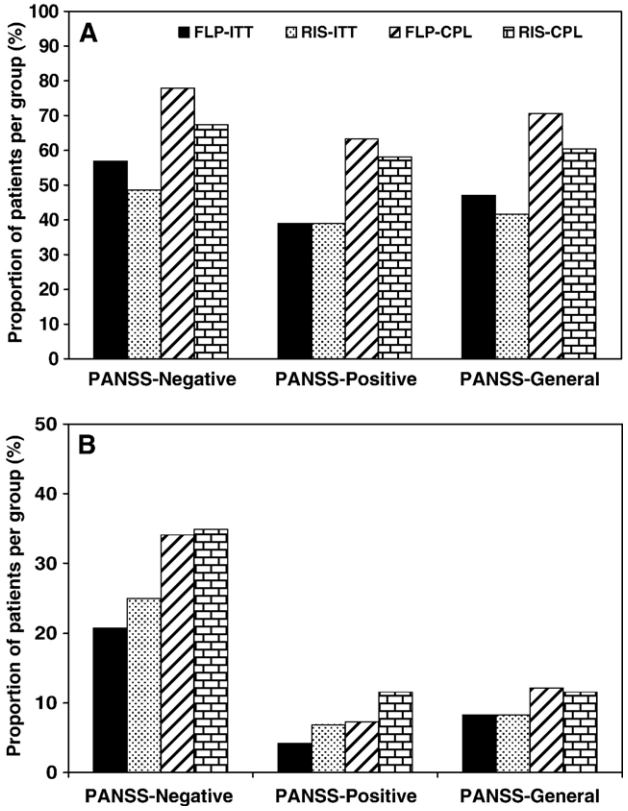

Fig. 3. Response rates. A: baseline reduction <20% (standard criterion; B: baseline reduction <50% (strong criterion). FLP = flupentixol, RIS = risperidone; ITT = intent-to-treat sample (with last observation carried forward), CPL = completer sample. No group comparison revealed any significant difference.

3.2.4.2. Categorical response criteria. As Fig. 3 demonstrates, both treatments produced a considerable number of responders in terms of negative symptoms. Due to the inclusion criteria, the proportions of responders with respect to the PANSS positive scores or PANSS general psychopathology scores were smaller, especially when the strong criterion was used. None of the comparisons between treatment groups in either sample revealed a statistically significant difference. The same applied to any factor derived from the principal component analysis.

Table 6
Adverse events (>%5)

Adverse event	Flupentixol [*n* (%)]	Risperidone [*n* (%)]
Total number	76 (100)	77 (100)
Worsening of mental state	8 (10.5)	6 (7.8)
Akathisia	6 (7.9)	4 (5.2)
Leukocytosis	4 (5.3)	5 (6.5)
Extrapyramidal symptoms	5 (6.6)	4 (5.2)
Insomnia	5 (6.6)	4 (5.2)
Irritability	4 (5.3)	4 (5.2)
Headache	5 (6.6)	3 (3.9)
Albuminuria	3 (3.9)	4 (5.2)
Rhinitis	4 (5.3)	0 (0.0)
Tremor	4 (5.3)	0 (0.0)

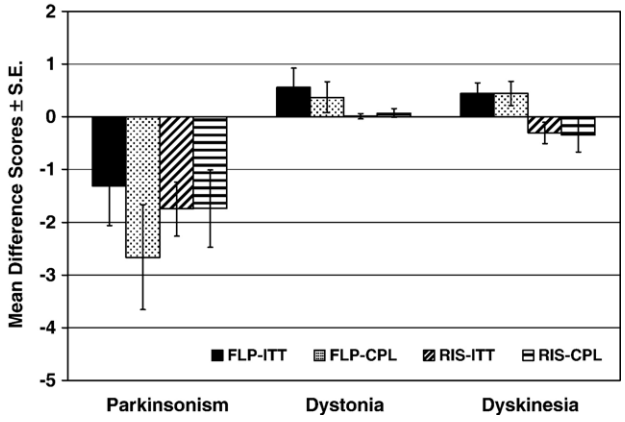

Fig. 4. Change of ESRS scores from baseline to week 24. FLP = flupentixol, RIS = risperidone; ITT = intent-to-treat sample (with last observation carried forward), CPL = completer sample. For statistics see text.

3.2.5. Tolerability

3.2.5.1. Adverse events. With regard to the safety sample ($n=153$), 57 (75.0%) patients in the flupentixol group and 46 (59.7%) patients in the risperidone group reported adverse events ($p=0.038$, Fisher's Exact Test). Table 6 lists the most frequent adverse events (>5%); group comparisons of individual events revealed no statistical difference. The same statistical result was obtained for the number of drop-outs due to adverse events (Table 2).

3.2.5.2. Extrapyramidal side effects. Changes of EPS indices are displayed in Fig. 4. Parkinsonism scores improved significantly with no statistically significant treatment × time interaction (LOCF: treatment $F=6.66$, $p=0.011$; time $F=5.32$, $p<0.0001$; treatment × time $F=0.3$, N.S.; CPL: treatment $F=0.48$, N.S.; time $F=4.8$, $p<0.0001$; treatment × time $F=0.4$, N.S.).

Dystonia scores as well as dyskinesia scores did not change significantly in any group or sample and no significant group differences emerged.

At baseline, 22.2% of FLP–LOCF and 18.1% of RIS–LOCF patients received biperiden (N.S.) (CPL: FLP = 26.8%, RIS = 20.0%; N.S.). After baseline, biperiden was newly prescribed for 26.4% of FLP–LOCF patients and for 6.9% of RIS–LOCF patients ($p<0.005$) (CPL: FLP = 26.8%, RIS = 11.1%; N.S.). The resulting total numbers of patients receiving biperiden during the study differed either significantly or on a trend level (FLP vs. RIS: LOCF = 48.6%:25.0%, $p<0.01$; CPL = 53.7%:32.6%, $p<0.10$). Explorative logistic regressions with 'use of biperiden' as the categorical dependent variable and the cumulative dose of either FLP or RIS as independent variable showed a trend ($p<0.10$) for higher FLP, but not for higher risperidone doses to be associated with an increased use of the anticholinergic drug.

3.2.5.3. Vital parameters. In the LOCF groups, body mass index (BMI) changed by [mean ± S.D.] 0.03 ± 2.18 (0.6 ± 7.72%) with FLP, and by 0.52 ± 1.68 (2.73 ± 6.79%) with RIS (N.S.); the numbers for the CPL groups were 0.32 ± 1.86 (1.67 ± 6.74%) for FLP and 0.88 ± 1.91 (4.02 ± 7.69%) for RIS (N.S.).

Diastolic blood pressure decreased in the FLP–LOCF group by −0.76 ± 10.44 mmHg and increased in the RIS–LOCF group by 2.98 ± 9.40 mmHg (N.S.); the corresponding numbers in the CPL groups were −0.69 ± 10.22 for FLP and 2.49 ± 9.58 for RIS (N.S.).

Heart rate (beats per minute) increased from baseline by 0.29 ± 10.36 in the FLP–LOCF group and decreased by −3.27 ± 12.61 in the RIS–LOCF group (N.S.); for CPL the difference was 0.87 ± 11.26 in the FLP group and −1.97 ± 12.85 in the RIS group (N.S.).

4. Discussion

The study confirmed the main hypothesis that the efficacy of flupentixol on negative symptoms is not inferior to that of risperidone.

This result was further supported by additional outcome parameters, i.e. comparable effect sizes and a considerable and statistically not different number of responders for both treatments with either criterion, i.e. ≥20% or ≥50% improvement. From a clinical point of view, it is most noteworthy that patients who were compliant with the respective treatments achieved an average score reduction of more than 9 points or over 34%, and even with the more conservative LOCF approach a reduction of almost 24% with each treatment was still seen.

Improvement of negative symptoms by risperidone has been observed in several studies (Carman et al., 1995; Chouinard et al., 1993; Leucht et al., 1999; Marder et al., 1997). In a recent long-term study, risperidone was significantly superior to haloperidol. (Csernansky et al., 2002). The results for flupentixol are also in line with earlier findings (Gattaz et al., 2004; Pach et al., 1998; Wetzel et al., 1998). However, for both drugs this is the first study investigating their ability to improve negative symptoms in a dedicated, clinically stabilized sample selected a priori for predominant negative symptoms according to the criteria given by Kay et al. (1987). Also, its six-month duration was in accordance with the minimum treatment period demanded in this area (Laughren and Levin, 2006).

Both drugs improved mood significantly with effect sizes indicating an advantage for FLP. Beneficial effects of both drugs on depressive symptoms have been described earlier (Kong and Yeo, 1985; Marder et al., 1997; Myers and Thase, 2001; Pach et al., 1998; Peuskens et al., 2000; Pinto et al., 1979; Wetzel et al., 1998), but only rarely based on a dedicated depression rating scale (Dollfus et al., 2005; Goto et al., 2006). For other FGAs only slight improvements or even worsening effects have been reported (Csernansky et al., 2002; Marder et al., 1997; Pinto et al., 1979). However, there are only a few data in this respect.

Acting on the assumption that positive symptoms, mood and EPS (Tollefson and Sanger, 1997) are the most important contributors to secondary negative symptoms, the variance of changes in PNS scores not explained by these variables can be interpreted as strongly associated with changes of primary negative symptoms. Thus it could be inferred that a considerable amount of the improvement of negative scores observed in the present study can be assigned to direct treatment effects. Of course, other factors may also interfere, and the described procedure may have eliminated common variance, thus

obscuring the true and perhaps greater direct effects on primary negative symptoms. However, all statistical approaches to discriminate between primary and secondary negative symptoms should only be taken as an approximation: "If two phenomena are truly confounded, statistical strategies will not necessarily succeed in disentangling them" (Kane, 2006). Yet, as discussed elsewhere (Flaum and Andreasen, 1995), a distinction between primary and secondary negative symptoms merely by clinical assessment has its pitfalls, too. Nevertheless, this distinction should not be ignored as it may be important for treatment decisions (Flaum and Andreasen, 1995).

The five-factor solution of the symptoms assessed by the PANSS confirms earlier results (Bell et al., 1994a; Davies et al., 1998; Lancon et al., 1998; Lindenmayer et al., 1995a,b; Lykouras et al., 2000; Marder et al., 1997). The amount of variance explained by the present solution was also in line with these earlier reports. However, despite the fact that the number and general content of the components are consistent across the different studies, there are psychopathologically important differences regarding the item composition, which may be due to clinically different samples and methodological differences. It does not appear justified at present simply to transfer a factor solution calculated for a certain sample to another one. In the present study, explorative post hoc analysis revealed significant improvements of the negative, cognitive, positive and depression/anxiety components for both antipsychotics with no significant difference between them. Cognitive impairment has been defined as a central target for treatment, relatively independent of other symptom dimensions (Bell and Mishara, 2006; Gold, 2004) and is another domain claimed to be a special treatment option of SGAs. Improving effects of risperidone have been shown in several studies using neuropsychological performance tests (Bilder et al., 2002; Harvey et al., 2003; Keefe et al., 2006; Meltzer and McGurk, 1999). In our study, flupentixol and risperidone yielded comparable effect sizes with regard to the PANSS cognitive factor. Two other studies using a five-factorial model also described a significant improvement in this component with risperidone (Csernansky et al., 2002; Marder et al., 1997). Twenty mg/d of haloperidol for eight weeks yielded a significant but inferior improvement (Marder et al., 1997), but in the long-term study, no effect of haloperidol was observed (Csernansky et al., 2002). A recent long-term study comparing risperidone to low-dose haloperidol found no general difference between the effects of both drugs on neuropsychological performance, though the dosage of risperidone may have been too high (Green et al., 2002).

In the current study, drug effects on positive, negative and affective symptoms were considered as possibly associated with an improvement in cognitive scores. In the LOCF sample, changes of negative symptoms in particular predicted the course of the cognitive factor. However, more than half of the variance was not explained by any of the three variables. Of course, analogue limitations should be considered as discussed above for negative symptoms.

The PANSS cognitive component cannot replace neuropsychological testing, though modest to good correlations with different performance-based cognitive test results have been reported (Bell et al., 1994b; Ehmann et al., 2004; Good et al., 2004; Hofer et al., 2005). Hence, the cognitive factor can be assumed to be a limited, but clinically useful indicator of neuropsychological performance. It can also be considered that, from a clinical point of view, the cognitive factor provides a more general assessment of the cognitive state, particularly since formal thought disorder has been shown to be specifically related to functional outcome (Racenstein et al., 1999). The beneficial effects of flupentixol as well as risperidone on different psychopathological dimensions are consistent with a recent analysis of their effects on quality of life assessed during the same study, showing a significant improvement with no significant difference between the groups (Hertling et al., 2003).

Although the treatment effects of flupentixol were comparable to risperidone, its overall tolerability as measured by the cumulative number of adverse events was significantly lower, mainly due to neurological side effects. The number of drop-outs related to adverse events was numerically but not statistically higher in the FLP group. With respect to the growing understanding of the clinical importance of weight gain and associated health problems, it is noteworthy that the BMI changed only slightly with both drugs, numerically slightly in favor of flupentixol. It should be pointed out that during the six-month study period, only a relatively small number of patients dropped out due to adverse events.

The mean dosage of risperidone was already lower than in the long-term studies of Csernansky et al. (2002) or Green et al. (2002). It should also be possible to further decrease the maintenance dosage of flupentixol considerably, as a dosage of 6 mg/d leads to a D2 receptor occupancy of 70%, which has been described as the threshold for a sufficient clinical response (Farde et al., 1992). The assumption that lower doses would lead to better tolerability is supported by the association between the flupentixol dose and use of anticholinergic drugs observed in the present study. As anticholinergic drugs have been associated with disturbed cognitive performance (Zachariah et al., 2002), it can be speculated that a lower dose of flupentixol may even be associated with an improved efficacy on cognition via a lower need for such drugs, a hypothesis which should be investigated in a further study dedicated to cognitive effects.

5. Conclusion

In summary, based on a sample of schizophrenia patients with predominant negative symptoms, this study confirmed that the efficacy of flupentixol on these symptoms is comparable to that of risperidone. Moreover, analyses of secondary and additional variables revealed that flupentixol also had comparable beneficial effects on depressed mood and on cognitive symptoms as measured by PANSS. The greater use of biperiden and the higher number of adverse events indicates that tolerability was in favor of risperidone, at least in the given dose range. A low-dose study is necessary to further investigate both tolerability and – as a decreased need for anticholinergic drugs is expected – efficacy on cognition, thereby completing the clinical assessment by appropriate neuropsychological performance tasks.

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