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ORIGINAL PAPER

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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

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Abstract In first-episode schizophrenia the advantage of new atypical neuroleptics compared to low-dose haloperidol as well as the indicated duration of neuroleptic maintenance treatment has still to be based on empirical evidence.

Accordingly, a multi-center study on the optimization of acute and long-term treatment in first-episode schizophrenia is currently being carried out as part of the German Research Network on Schizophrenia. This paper reports on the design, methods and preliminary results of the two-year randomized double-blind study comparing risperidone and low-dose haloperidol within the framework of psychological interventions. In the second treatment year, relapse rates under continued neuroleptic treatment are compared with those under stepwise drug withdrawal substituting instead prodrome-based early intervention (intermittent treatment).

As to the results, by November 2003 142 first episode patients (ICD-10 F20) have been included in the long-term study. One-year relapse rates were very low (3.8 %). On average, symptoms as well as drug side-effects decreased steadily under maintenance treatment. Although compliance on average was high, about 60 % of the patients dropped out during the first study year. More pronounced psychopathology, (neurological) side-effects, lower compliance at study entry and absence of psychological treatment seemed to enhance the risk for drop-out.

In conclusion, treatment in first episode schizophrenia is effective under both (further on blinded) neuroleptics; however these patients are at high risk for treatment drop-out. This emphasizes the need for a special support program.

Key words schizophrenia · first episode · long-term treatment · atypical neuroleptics

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Introduction

Today, a number of efficacious bio-psycho-social treatments for schizophrenia in its various illness phases and stages are available. Accordingly, various treatment guidelines have been developed providing treatment recommendations based on empirical data and expert consensus (e. g. APA 1997, 2002; McEvoy et al. 1999; Kane et al. 2003; Lehman et al. 1998; NICE 2002; Marder et al. 2002). However, many questions are still open and require more research. The German Research Network on Schizophrenia (GRNS), one of 14 nationwide medical research networks funded by the German Ministry of Education and Research (BMBF) in order to improve care in patients with illnesses characterized by high morbidity and/or mortality, has been created with the intent to evaluate new strategies of prevention, treatment, and rehabilitation and to facilitate their practice transfer (Wölwer et al. 2003).

The GRNS is organized with respect to illness development into two main sub-networks (SN I: early recognition and intervention prior to the first episode, SN II: treatment and rehabilitation after illness manifesta-

tion), a special project network on molecular and pharmacogenetic research, and a number of additional overarching projects on more general topics (healthcare economics, public education, postgraduate training and CME, quality assurance, documentation and assessment methodology).

One central issue (of SN II) concerns the optimization of pharmacological long-term treatment in first-episode schizophrenia. The corresponding two-year treatment study described in this paper aims at two as yet unsolved research questions: i) whether the widely claimed superiority of atypical in comparison to low-dose typical neuroleptics can also be confirmed in this population and ii) whether maintenance treatment could be withdrawn and substituted by prodrome-based early intervention after one year in patients recovered from a first episode.

One-year relapse rates in first-episode schizophrenia under conventional neuroleptic treatment range from 0 % to 26 % (Kane et al. 1982; Hogarty and Ulrich 1998; Crow et al. 1986) whereas those under placebo range from 41 % to 55 % (Johnson 1979; Crow et al. 1986). Whereas the lowest relapse rates have been observed under depot medication, relapse rates generally seem to be highest in cases with a longer duration of untreated psychosis (DUP) above one year (drug: 67 %, placebo: 92 %, Crow et al. 1986). Additional psychosocial interventions seem to further reduce relapse rates (Wyatt et al. 1998).

Concerning the usefulness and use of second generation antipsychotic medications (Sartorius et al. 2002) compared to conventional antipsychotics, a number of studies have shown advantages of "atypical" neuroleptics in acute treatment (for review: Leucht et al. 1999) as well as in long-term treatment of schizophrenia (Csernansky et al. 2002; for review: Leucht et al. 2003 a). Novel antipsychotics were often found to be more effective with regard to treatment of negative symptoms, and showed a more favorable profile of extrapyramidal side-effects and beneficial effects on cognitive dysfunctions, depression and compliance (Möller 2000 a, 2000 b, 2003). However, interpretations are restricted as conventional neuroleptics have mostly been administered in rather high dosages. From meta-analyses it has been suggested that atypical and typical neuroleptics are equivalent in symptom reduction and tolerability if the latter are administered in low dosages (Geddes et al. 2000, but see Davis et al. 2003). Low and medium potency neuroleptics might even not induce more extrapyramidal side-effects under a low-dose strategy compared to new generation drugs (Leucht et al. 2003 b). Moreover, recent reports on their side effects profile including weight gain and metabolic effects, i. e. induction of type II diabetes and increased levels of lipids (e. g. Koponen et al. 2002), all of them independent risk factors for cardiovascular disease, have begun to overshadow the positive opinions on atypicals.

Atypical neuroleptics as first choice treatment are recommended for both first and multiple episode schizophrenia (Marder et al. 2002; Kane et al. 2003) or for first episode schizophrenia preferentially (NICE 2002), especially when their subjective effects are considered (Voruganti et al. 2000). The UK National Institute for Clinical Excellence (NICE) recommended recently that "atypical antipsychotics should be considered alongside the existing traditional (typical) drugs as one of the first choice options to treat people with newly diagnosed schizophrenia" (NICE 2002). For these recommendations, however, as yet only acute treatment data seem to be available (Kopala et al. 1998; Emsley 1999; Sanger et al. 1999), whereas independent long-term studies (Hunter et al. 2004) especially in first-episode schizophrenia are still lacking (Geddes 2002; Rummel et al. 2003). In the US, a long-term study on 'Comparative Efficacy and Safety of Atypical and Conventional Antipsychotic Drugs in First-Episode Psychosis' is currently underway, but has as yet reported only results on the 12-weeks acute treatment (Lieberman et al. 2003). In Europe, a multi-national study on first episode patients, the European First Episode Study Trial (EUFEST) comparing long-term treatment with atypical and typical neuroleptics in first episode patients, has started recently (Kahn et al. 2001). Hence, it has to be awaited from further study results, including our own, whether the lower relapse rates of atypicals (15 %) vs typicals (23 %) in multi-episode schizophrenia according to recent meta-analyses (Leucht et al. 2003 a) despite methodological restrictions also apply to first-episode schizophrenia.

Beyond this uncertainty regarding the best kind of neuroleptic treatment, for the group of first-episode patients it is furthermore unclear how long treatment should be continued after remission of the first episode (Sheitman et al. 1997; Wyatt et al. 1998). Published guidelines recommend treatment durations of minimum one year (e. g. APA 1997), while the appropriate duration of further treatment in case of symptom remission, however, has not been adequately evaluated. Our own results (Gaebel et al. 2002) indicate no significant relapse differences in first episode patients withdrawn from neuroleptics undergoing prodrome based early intervention vs. those under maintenance treatment, whereas in multiple episode patients maintenance treatment is more effective in preventing relapse compared to early intervention strategies.

Against this background, a comprehensive acute and long-term study in patients with first-episode schizophrenia has been initiated within SN II of the GRNS.

Methods

Study setting and funding

This network study embedded in the GRNS contains several interrelated subprojects conducted in up to 13 German psychiatric university hospitals (Bonn, Düsseldorf, Köln, Munich, Tübingen, Berlin, Essen, Jena, Mannheim, Göttingen, Aachen, Halle, Mainz). The backbone of the study (see Fig. 1) is a prospective double-blind, randomized, parallel-group comparison of risperidone as a standard new generation antipsychotic with haloperidol as a standard conventional antipsychotic in low dosage (for details see below). After an 8-

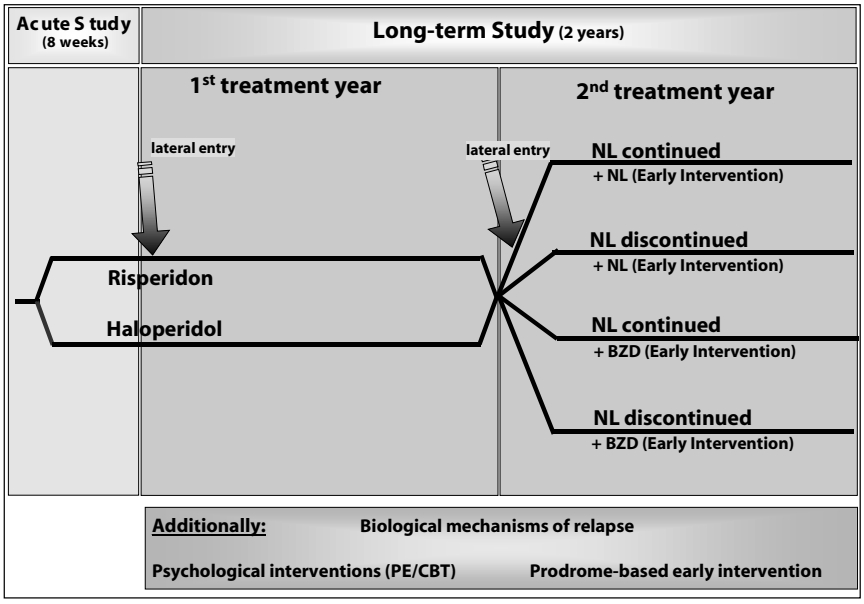

Fig. 1 Study design and cooperating projects (*NL* neuroleptics; *BZD* benzodiazepine; *PE* psychoeducation; *CBT* cognitive-behavioral therapy)

week acute treatment phase ("Optimization of acute treatment in first episode schizophrenia", principal investigator: H.-J. M.) patients are transferred to a subsequent 2-year treatment study ("Pharmacological long-term treatment strategies for relapse prevention in first-episode schizophrenia", principal investigator: W. G.).

In five of the 13 study centers, the pharmacological treatment in the first year of long-term treatment is supplemented by one of two psychological treatment strategies ("Psychological intervention for relapse prevention in first episode schizophrenia", principal investigator: S. K.). Patients are randomly assigned to either a comprehensive cognitive behavioral treatment containing several modules aiming at cognitive remediation, stress reduction and strengthening of coping abilities or to information centered psychoeducation. Neurocognitive and neuromotor vulnerability markers, biochemical indicators of stress reactivity and brain morphological parameters are assessed in a separate subproject at the beginning and after one and two years of long-term treatment ("Biological mechanisms of relapse", principal investigator: W. G.). In addition, neurofunctional correlates of emotional and cognitive impairments are assessed in 8 participating centers by means of fMRI ("Functional brain indicators of relapse", principal investigator: F. Schneider, Düsseldorf).

The two pharmacological acute and long-term core studies are coordinated by the Munich and Düsseldorf center, respectively. They are funded by the BMBF, blinded neuroleptic medication (haloperidol/risperidone) is provided by Janssen Cilag company, and lorazepam bulkware is provided by Wyeth Pharma. All the other associated subprojects are funded solely by the BMBF.

Study design and procedures

The long-term treatment study was designed to test the following two main hypotheses: i) in the first treatment year: relapse rates under risperidone are lower than under low-dose haloperidol maintenance treatment; ii) in the second treatment year: relapse rates in patients under continued maintenance medication are lower than in patients under prodrome-guided early intervention but withdrawn from medication. In addition, in an exploratory manner differences between the two treatment strategies are to be compared with regard to clinical symptoms, side-effects, compliance, cognitive functioning, quality of life, and costs.

As to the study design, the 2-year long-term treatment phase started subsequent to the acute treatment phase (see Fig. 1), in which risperidone or haloperidol were administered in random, double-blind fashion in dosages ranging from 2 mg/day to a maximum of 8 mg/day for 8 weeks. Patients from the acute study were kept on their randomly allocated medication and, if possible, this drug regimen was maintained for one year with a targeted dose between 2 and 4 mg/day. This gives the treating psychiatrist the opportunity to choose an individually appropriate dose despite the as yet unsettled dose correspondence of the two (blinded) study drugs, ranging from 1:1 (Marder et al. 2003) to 1:2.5 (Csernansky et al. 2002; Kane et al. 2003).

To investigate the necessary duration of maintenance treatment in first-episode schizophrenia, patients having completed the first treatment year without relapse are randomly allocated to either continuation of maintenance treatment with the study drugs or to stepwise open drug discontinuation (within 3 months) in the second treatment year. In the case of reexacerbation and impending relapse early drug intervention strategies are used in both treatment arms. To this end, patients are assessed at least fortnightly throughout the 2-year study period in order to closely monitor clinical course and possible prodromal symptoms. Within the framework of the vulnerability-stress-coping model, prodromal symptoms are taken as early indicators of impending relapse and, thus, are used as predictors of relapse to guide early intervention.

Despite a number of negative findings in multi-episode schizophrenia (Gaebel 1996), a reanalysis of a previous study on long-term treatment strategies (Pietzcker et al. 1993) suggests that prodrome-guided early intervention strategies may after all be advantageous especially for first-episode patients (Gaebel et al. 2002). Accordingly, an improved instrument for the assessment of prodromal symptoms as well as an empirically based algorithm to trigger the onset of early intervention was developed in a further subproject of the first-episode study ("Prodrome-guided early intervention in first-episode schizophrenia", principal investigator: W. G.) in close cooperation with SN I (Gaebel et al. 2003). In addition to prodromal symptoms, this early intervention algorithm takes into account mild positive symptoms, global clinical deterioration, global functioning, the occurrence of stressful life-events, as well as the clinician's global assessment of the patient's risk for relapse. If the algorithm indicates an impending relapse, patients are randomly treated either by means of resumption or augmentation of neuroleptic treatment in a predefined manner (depending on the basic treatment strategy of either discontinuation or continued maintenance medication) or by means of (additional) treatment with the benzodiazepine lorazepam. This random, double-blind comparison should contribute to the open question whether prodromes are unspecific consequences of stress experience treatable with benzodiazepines or are to be regarded as more specific prepsychotic symptoms requiring neuroleptic treatment (e. g. Carpenter et al. 1999).

In order to increase the recruitment rate the design allowed for lateral entries (see Fig. 1) into the first (patients recovered from a first episode, but not participating in the acute study) and second treatment year (stable first-episode patients after one year of routine maintenance treatment, but not participating in the first study year).

The acute and long-term study were designed and conducted according to the guidelines of ICH-GCP. GCP was assured by involvement of the Düsseldorf Coordinating Center for Clinical Trials (head: C. O.). Blinding of neuroleptic study medication (risperidone/haloperidol) and randomization was provided by Janssen Cilag company. Blinding of neuroleptics/lorazepam and randomization for the second study year (open design: continuation of maintenance treatment/drug withdrawal; blinded design: early intervention with neuroleptics/lorazepam) was carried out by the pharmaceutical department of the University of Mainz. Ethical votes had been obtained from the ethical boards of the coordinating centers and the local centers as well. All data were recorded locally and transmitted via remote data entry to the respective coordinating centers, where they were continuously monitored and stored.

Subjects

Study subjects for the long-term study were selected from patients primarily admitted to the inpatient departments of the participating centers. Inclusion criteria were as follows: 1) having recovered from a first illness episode with a diagnosis according to ICD-10 F20.x, whereas first episode was pragmatically defined as the first inpatient treatment of psychotic symptoms; 2) age between 18 and 55 years; 3) having either participated in the acute treatment study or being suited for lateral entry; 4) being sufficiently able in German language; 5) having given consent after extensive information about the various phases and ramifications of the 2-year study. Exclusion criteria were: 1) pregnancy; 2) contraindication to neuroleptic treatment; 3) mental retardation; 4) organic brain disease; 5) substance abuse/dependence; 6) suicidal behavior in previous history.

Assessments

Patients were seen biweekly at the outpatient departments of the involved centers. Assessments included (see Table 1): 1) psychopathology (e. g. PANSS, CGI); 2) level of functioning (GAF); 3) side effects (EPS, UKU, HAS, AIMS); 4) compliance (CRS), 5) attitude toward drugs (DAI), and 6) stressful life events (MEL).

Further measures concerning coping abilities (SVF, FSKN), familiar atmosphere (FEF) and quality of life (LQLP) are assessed at study entry and after the first and second treatment year. Neurofunctional (EEG, fMRI) and neurocognitive measures (memory, vigilance, visuomotor executive function) are also assessed in a yearly time frame. In addition, biochemical parameters (drug and catecholamine levels in blood; the latter for assessing stress reactivity) were determined every four weeks.

Relapse was predefined as follows: Within two visits increase in PANSS positive score > 10, CGI change score ≥ 6 and decrease in GAF score > 20. Several rater trainings took place. Inter-rater reliability yielded a satisfying to good concordance (e. g. intra-class correlation coefficient of the PANSS positive scale $= 0.74$, $p < 0.001$; Shrout & Fleiss 1979).

Statistical methods

The sample size estimation was conducted in regard to the two main hypotheses resulting in 2 x 70 patients required at entry into the first treatment year and 2 x 36 patients at entry into the second study year yielding an estimated completer sample of 2 x 38 and 2 x 28 patients respectively for testing of the hypotheses each with $\alpha = 0.05$ and $\beta = 0.2$.

Due to the double-blind design, results on drug differences will not be available until the end of the study in June 2005. Therefore, preliminary results presented here refer to the as yet included total sample with respect to sample characteristics, symptom course, level of functioning, side-effects, compliance and attitude toward study drugs. To adjust for drop-out and non-completion rates, treatment course was analyzed by carrying the last observed value forward

Table 1 List of used assessment instruments

Instrument (abbrevation)	Instrument (full text)	Reference
AIMS	Abnormal Involuntary Movement Scale	Guy (1976a)
CGI	Clinical Global Impression	Guy (1976b)
CRS	Compliance Rating Scale	Kemp and David (1996)
DAI	Drug Attitude Inventory	Hogan et al. (1983)
EPS	Rating Scale for Extrapyramidal Side Effects	Simpson and Angus (1970)
FEF	Fragebogen zur Erfassung der emotionalen Familienatmosphäre (Family expressed emotion questionnaire)	Feldmann et al. (1995)
FSKN	Frankfurter Selbstkonzeptskalen (Frankfurt Self-Concept Scales)	Deusinger (1986)
GAF	The Global Assessment of Functioning Scale	Frances et al. (1994)
HAS	Hillside Akathisia Scale	Fleischhacker et al. (1989)
ICD-10	International statistical classification of diseases and related-health problems (10th Revision)	WHO (1992)
LQLP	Lancashire Quality of Life Profile	Oliver (1991)
MEL	Münchner Ereignisliste (Munich Event List)	Maier-Diewald et al. (1983):
PANSS	Positive and Negative Symptom Scale	Kay et al. (1986)
SCPS	Strauss-Carpenter Prognosis Scale	Strauss and Carpenter (1978)
SVF	Stressverarbeitungsfragebogen (Coping with stress questionnaire)	Janke et al. (1985)
UKU	Udvalg for Kliniske Undersogelser Side Effect Rating Scale	Scandinavian Society of Psychopharmacology Committee of Clinical Investigations (1987)

(LOCF analysis). Because for most of the variables neither normal distribution nor homogeneity of variances is given, nonparametric tests were conducted. In addition, to identify relevant drop-out predictors (at study entry), a Cox regression analysis was performed including significant predictors from univariate analysis.

Preliminary results

Patient recruitment and sample characteristics

From November 2000 to November 2003, 1334 patients were screened, of whom 20.3 % (271 patients) could be included in the acute study (see Fig. 2); 139 patients have completed the acute study up to now, 12 are still participating.

The majority of the acute study completers (84.9 %, n = 118) were eligible for the long-term study. Reasons for non-inclusion (n = 21) were persisting side effects (n = 8), refusal to continue study (n = 8), non-response (n = 2) and change of residence outside the catchment area of the study centers (n = 3).

If possible, screened patients not included in the acute study were contacted further on leading to another 24 patients to be included in the long-term study by lateral entry, resulting in a total of 142 patients included in the long-term study (83.1 % after having completed the acute study and 16.9 % by lateral entry, see Fig. 3). Eighty-two of the total 142 patients are male (57.7 %) and 60 are female (42.3 %). The average age at study entry is 31.0 years (SD = 9.8).

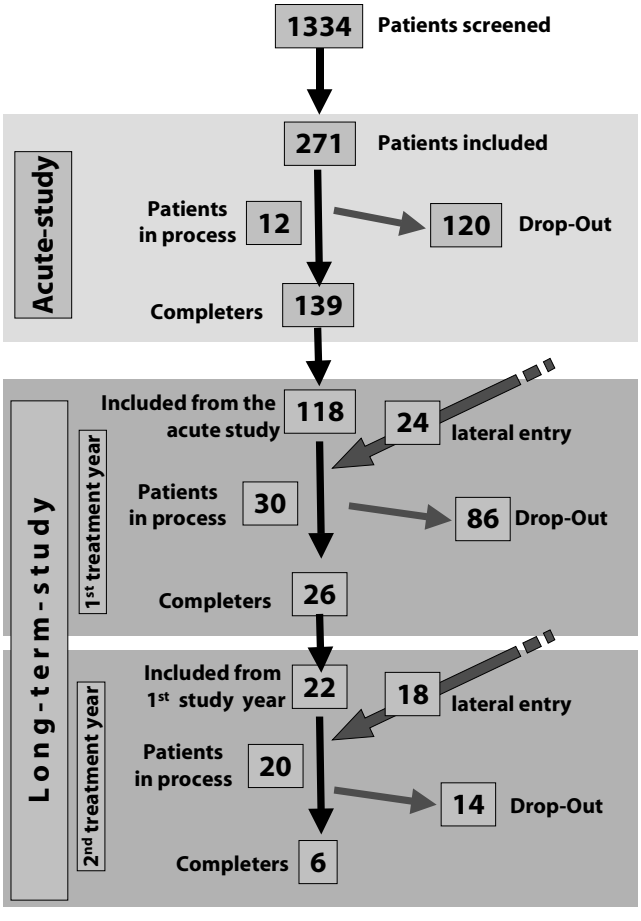

Fig. 2 Patient recruitment in the acute and long-term study (first and second treatment year; November 2000 to November 2003)

Comparing characteristics of patients included in the long-term study and those not included (n = 1034) yielded no significant difference for gender (screened male patients not included in the long-term study 57 %; Chi-square = 0.031; p = 0.93) and borderline significance for age (mean = 32.6, SD = 11.9; t = 1.6; p = 0.06). The latter finding results from patients not fitting the age criterion for inclusion (14 patients above 65 years; max = 84), as Table 2 illustrates.

Lack of consent to participate is by far the most frequent reason to be excluded from the study. In almost 30 % the diagnostic inclusion criteria were not fulfilled, and in about 18 % patients involuntarily hospitalized had to be excluded.

First study year

As can be seen from Table 3 for the sub-sample of n = 115 patients with entered data of treatment course, symptoms (PANSS positive, negative and general scale score) and illness severity (CGI) were (on average) of mild extent at study entry and further decreased significantly during the course of treatment (LOCF analysis). The level of functioning (GAF) likewise reflects (on average) mild impairments at study entry and also improved significantly throughout the first treatment year.

Side effects as well were (very) moderate at study entry and tended to decrease towards the end of the first study year. Patients' compliance and attitudes toward neuroleptics were already high at study entry, and drug attitudes further improved during the first treatment year.

As intended, drug dosage for both drugs could be kept at a low level; at the beginning of the long-term study the average dose was 3.6 mg/day (SD = 2.4) and varied only slightly throughout the further course between 4.4 mg/day and 2.0 mg/day on average (range: 1 to 10 mg/day).

Relapse/clinical deterioration

Up to November 2003, only one patient (i. e. 3.8 % of all 26 patients completing the first treatment year) has fulfilled the predefined criteria for relapse. Hence, additional analyses were performed to identify clinical deterioration below the relapse criteria, for the completer and the total sample separately (see Table 4). During the first treatment year overall 6 patients (5.2 % of all 115 patients with data entry) have been rated in the study process as 'severely ill' or beyond (CGI severity ≥ 6; none of the patients in the completer sample), 12 patients (10.4 %) have been given a value of 5 ('moderately severe') or higher in at least one PANSS positive item

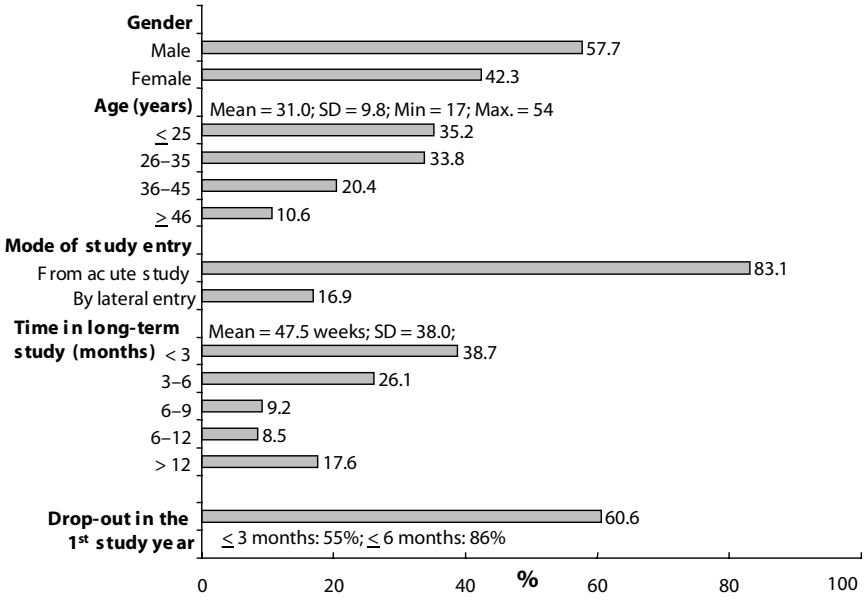

Fig. 3 Patient characteristics (percentage; n = 142 patients included in the long-term study)

Table 2 Reasons for non-inclusion of screened patients (n = 1037; multiple responses possible)

	N	Percent
Lack of consent to participation	775	74.7
Diagnostic criteria for F20 not fulfilled or diagnosis other than F20	304	29.3
Involuntary inpatient treatment (according to German law)	188	18.1
Insufficient German language	71	6.8
Participation in another (incompatible) study	69	6.7
Substance abuse/dependence	62	6.0
Younger than 18 or older than 55 years	38	3.7
Organic brain deficits	35	3.4
Previous multiple admission/multiple episode patients	32	3.1
Contraindication to neuroleptic treatment	24	2.3
Suicidal behavior in previous history	24	2.3
Serious physical disease	19	1.8
Technical/administrative reasons (change of hospital, residence outside catchment area)	11	1.1
Pregnancy	3	0.3
Mental retardation	1	0.1

(none of the patients in the completer sample), and in 10 patients (8.7 %) an increase in the PANSS positive score of 7 points or more was observed (2 patients in the completer sample). For social functioning, in 18 patients (15.7 %) a GAF score of 40 or below was recorded ('Some impairment in reality testing or communication OR major impairment in several areas'; 1 patient in the completer sample). Combining the single measures, in overall 7 patients (6.1 % of all 115 patients) the clinical condition was rated as 'marked clinical deterioration' (defined as 'severe' in one single scale or 'markedly' in two or more scales).

Drop-out

During the course of the first treatment year, 86 patients (60.6 %) dropped out, most of them within the first 6 months (86 %; see Fig. 4). Eight patients had to be excluded due to predefined criteria (change of residence; change of diagnosis to acute or transient psychotic disorders of two lateral entries and change to schizo-affective and organic delusional disorder of patients included from the acute study respectively, see Fig. 5). Most patients dropped out due to lack of acceptance/non-compliance, followed by intolerable side effects (n = 20; thereof 10 due to EPMS), persisting (positive) symptoms or even clinical deterioration despite of maintenance treatment (n = 13), and affective instability or suicidality (n = 6). Termination was rarely caused by protocol violation (n = 2) and contraindication of neuroleptic treatment (marked side effects even at a very low dose; n = 1).

In order to control for the representativeness of the remaining sample and to identify potential drop-out predictors at study entry, those patients remaining in the

Table 3 Psychopathology, level of functioning, side-effects and compliance at entry into the long-term study and at the end of the first treatment year (n = 115 patients with data entry; LOCF-analysis for patients who dropped out or did not yet finish the first treatment year)

	Possible range	Study entry Mean (SD)	End of 1st treatment year Mean (SD)	Z (Wilcoxon)	p
PANSS: positive score	7–49	10.2 (4.6)	8.7 (3.4)	–5.42	**< 0.001**
PANSS: negative score	7–49	14.8 (5.9)	13.5 (5.9)	–2.92	**0.003**
PANSS: general score	16–112	26.8 (9.6)	23.9 (8.9)	–4.72	**< 0.001**
CGI: severity	1–7	3.5 (1.1)	3.0 (1.3)	–4.03	**< 0.001**
Level of functioning (GAF)	0–100	62.7 (12.5)	67.1 (15.5)	–3.48	**< 0.001**
Side-effects (UKU; total score)	0–156	4.6 (5.2)	3.9 (5.5)	–1.86	0.063
Psychological side effects (UKU)	0–30	2.9 (3.8)	2.4 (3.8)	–2.15	**0.031**
Neurological side effects (UKU)	0–24	0.8 (1.1)	0.6 (1.2)	–1.57	n. s.
– Dystonia (UKU)	0–3	0 (0.1)	0 (0.1)	0.00	n. s.
– Rigidity (UKU)	0–3	0.2 (0.5)	0.3 (0.6)	–0.44	n. s.
– Hypokinesia (UKU)	0–3	0.2 (0.5)	0.2 (0.5)	–1.51	n. s.
– Hyperkinesia (UKU)	0–3	0 (0.2)	0 (0.2)	–0.38	n. s.
– Tremor (UKU)	0–3	0.15 (0.5)	0.08 (0.4)	–2.27	**0.023**
– Akathisia (UKU)	0–3	0.1 (0.3)	0.1 (0.3)	–0.89	n. s.
Autonomic side effects (UKU)	0–33	0.6 (1.1)	0.3 (0.9)	–2.92	**0.004**
Other side effects (UKU)	0–75	0.6 (1.2)	0.9 (2)	–1.05	n. s.
Adverse effect assessed by patient (UKU)	0–3	0.7 (0.7)	0.7 (0.8)	–0.87	n. s.
Adverse effect assessed by psychiatrist (UKU)	0–3	0.8 (0.7)	0.7 (0.8)	–0.92	n. s.
Akathisia (HAS)	1–7	1.2 (0.6)	1.1 (0.2)	–2.38	**0.017**
Tardive Dyskinesia (AIMS)	1–4	0.1 (0.3)	0.1 (0.4)	–0.28	n. s.
Extrapyramidal side effects (EPS)	0–40	1.8 (2.7)	1.6 (3.1)	–1.82	0.068
Compliance Rating Scale (CRS)	1–7	6.1 (1.1)	5.9 (1.5)	–0.53	n. s.
Attitude toward study drugs (DAI)	0–30	20.9 (4.9)	21.8 (5.3)	–2.57	**0.010**

For abbrevations of the used instruments see Table 1

Table 4 Rates of relapse (according to the predefined criteria) and signs of 'marked clinical deterioration' in completer and total sample

	% in completer sample (n = 26)	% in total sample** (n = 115)
Relapse	3.8	0.9
CGI*-severity ≥ 6 ('severely ill')	0.0	5.2
'moderately severe' or higher (≥ 5) in at least one PANSS*-positive item	0.0	10.4
Increase of ≥ 7 points in PANSS*-positive score	7.7	8.7
GAF*-score ≤ 40	3.8	15.7
'marked clinical deterioration' ('severe' in one single scale or 'markedly' in two or more scales)	3.8	6.1

* For abbrevations of the used instruments see Table 1; ** Patients with data entry in November 2003

study (until November 2003, n = 56) were compared with those who dropped out (n = 78; the 8 patients excluded due to administrative reasons were not included in this analysis). In univariate analyses no significant differences were found for sex and age, whereas received psychotherapy (drop-out-rate of patients with/without psychotherapy: 52.5 % respectively 76.1 %; p = 0.007), mode of study-entry (drop-out-rate of patients taken over from the acute study: 55.8 %; drop-out-rate of patients included by lateral entry: 84.6 %; p = 0.006; whereby mode of study entry was significantly related to psychotherapy in that way that patients included from the acute study more often received psychotherapy) and several clinical measures at entrance into long-term treatment reached a significance level (see Table 5).

Patients who dropped out demonstrated at study entry (on average) significantly more pronounced positive, negative and general symptoms, higher illness severity and (slightly) poorer compliance. Although the mean dosage of study drugs of patients who dropped out and those who remain in the study was similar (3.7 mg/day and 3.5 mg/day respectively), few differ-

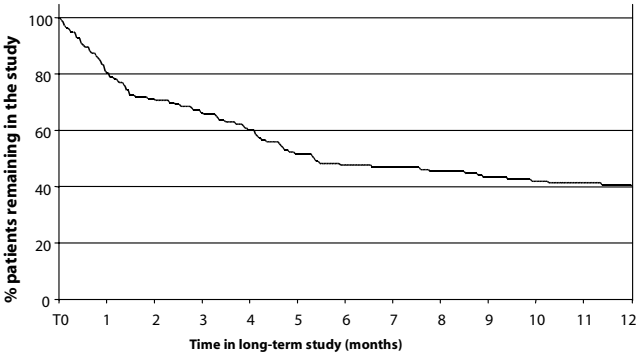

Fig. 4 Survival plot of drop-out patients (n = 142)

ences were obtained in neurological side effects (measured by UKU) favoring those who did not drop out (hypokinesia, tremor, and dystonia).

The multivariate analysis conducted (Cox regression analysis; dependent variable: time to drop-out; covariates: psychotherapy (yes/no), mode of study entry (direct/lateral), PANSS scores, UKU neurological side-effects) yielded the PANSS positive score ($p = 0.023$) and the UKU score ($p = 0.019$) at study entry as significant predictors; mode of study entry just missed the significance level ($p = 0.087$).

Second study year

Meanwhile, 40 first episode patients could be included into the second study year. From the 19 patients randomized to 'maintenance treatment' two patients refused and wanted to discontinue treatment. In contrast, from the 19 patients randomized to 'drug discontinuation', 6 patients refused and wanted to continue neuroleptic treatment ($p = 0.059$). Whereas until now no patient relapsed under maintenance treatment, 3 patients relapsed (according to the predefined criteria) after discontinuation of neuroleptic medication and had to be rehospitalized (i. e. 33 % of the patients in whom drug discontinuation was conducted). Due to the small database results on the relapse predictive validity of the prodromal symptoms as well as of the decision algorithm guiding early intervention have to be awaited.

Discussion

At present the study can only answer questions related to the neuroleptic long-term treatment of first-episode schizophrenia in general. Hence, the main hypotheses cannot be proven until the medication code is broken. However, the illness course for up to one year under assured maintenance medication seems to be favorable for cases with recovery from the first illness manifestation. The relapse rate observed – irrespective of the kind of neuroleptic drug – was extremely low. This was also true even if less strict criteria for exacerbation were applied. In fact the figure reported so far is in the range of empirical findings reported for the application of depot neuroleptics. According to Hogarty & Ulrich (1998) one would expect a higher relapse rate for oral treatment, whereas Kane et al. (1982) and Hogarty and Ulrich (1998) found a similar or even lower relapse rate for depot treatment. The relapse rate of 3.9 % for the one-year completers is also lower than the average rate of 15 % reported for maintenance treatment under various atypical neuroleptics in patients with first and multiple episodes in schizophrenia reported by Leucht et al. (2003 a). The provision of psychological interventions for part of the sample may have had an additional influence on outcome, at least in other domains of outcome besides relapse. However, this will be the focus of future analyses.

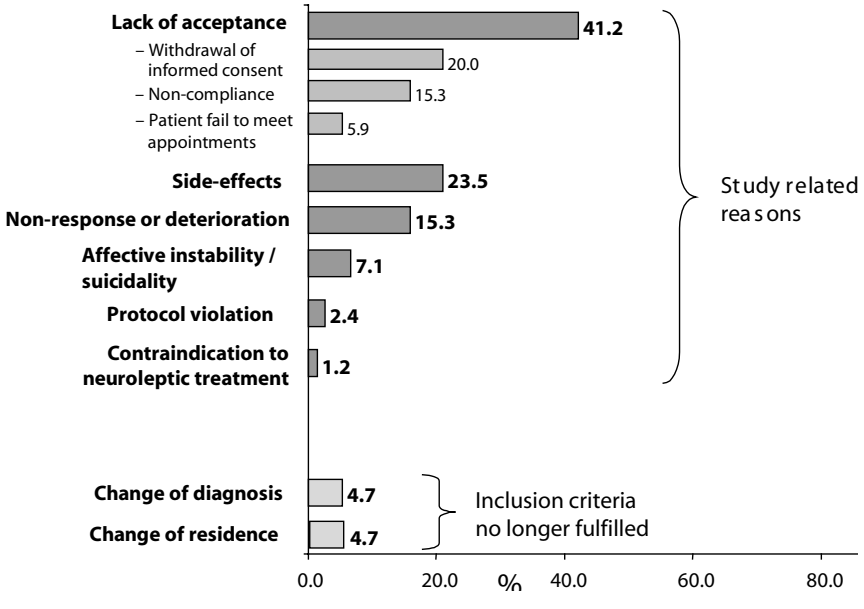

Fig. 5 Reasons for study drop-out (n = 86)

Table 5 Differences at study entry between patients remaining in the study vs. those who dropped out (not due to administrative reasons)

	Drop-out: No (n = 43) Mean (SD)	Drop-out: Yes (n = 64) Mean (SD)	Z (Mann-Whitney)	p
PANSS: positive score	9.0 (3.0)	12.1 (6.3)	–3.6	**0.000**
PANSS: negative score	13.0 (5.2)	16.7 (6.4)	–2.9	**0.004**
PANSS: general score	23.8 (8.7)	28.9 (11.3)	–2.9	**0.004**
CGI: severity	3.2 (1.2)	3.8 (1.1)	–2.2	**0.027**
Level of functioning (GAF)	64.9 (12.3)	59.5 (13.5)	–1.4	n. s.
Lowest GAF-score last year	43.6 (16.1)	38.5 (14.8)	–1.8	0.070
Strauss-Carpenter prognosis score	57.3 (10.5)	56.8 (9.5)	–0.3	n. s.
Side-effects (UKU; total score)	3.7 (4.0)	5.0 (6.6)	–0.7	n. s.
Psychological side effects (UKU)	2.2 (3.1)	3.1 (4.6)	–0.9	n. s.
Neurological side effects (UKU)	0.4 (0.9)	1.0 (1.4)	–2.7	**0.007**
– Dystonia (UKU)	0.1 (0.3)	0 (0)	–1.7	0.089
– Rigidity (UKU)	0.1 (0.4)	0.3 (0.7)	–1.6	n. s.
– Hypokinesia (UKU)	0.0 (0.2)	0.3 (0.6)	–2.5	**0.012**
– Hyperkinesia (UKU)	0 (0.2)	0 (0.2)	–0.3	n. s.
– Tremor (UKU)	0.0 (0.2)	0.2 (0.6)	–1.7	0.097
– Akathisia (UKU)	0.1 (0.3)	0.2 (0.4)	–1.3	n. s.
Autonomic side effects (UKU)	0.4 (0.9)	0.7 (1.3)	–0.9	n. s.
Other side effects (UKU)	0.8 (1.6)	0.6 (1.3)	–0.7	n. s.
Adverse effect assessed by patient (UKU)	0.6 (0.6)	0.9 (0.9)	–1.4	n. s.
Adverse effect assessed by psychiatrist (UKU)	0.7 (0.7)	0.9 (0.9)	–1.0	n. s.
Akathisia (HAS)	1.2 (0.6)	1.3 (0.6)	–1.3	n. s.
Tardive Dyskinesia (AIMS)	0.1 (0.4)	0.1 (0.3)	–0.3	n. s.
Extrapyramidal side effects (EPS)	0.8 (1.3)	2.1 (3.7)	–1.6	n. s.
Compliance Rating Scale (CRS)	6.3 (1.0)	5.8 (1.3)	–2.2	**0.028**
Attitude toward study drugs (DAI)	21.5 (5.3)	20.1 (4.9)	–1.4	n. s.

For abbrevations of the used instruments see Table 1

The results demonstrate that during long-term treatment recovery continues beyond remission from a first illness manifestation. This is true for positive, negative and general symptoms as well as for level of functioning. At the same time side-effects – although low after acute treatment – decrease steadily over time. This may in part be related to dose reduction. On average, attitudes toward study drugs slightly improve. This may be in accordance with findings on non-significant differences in adherence rate between risperidone and haloperidol after six months of treatment (Dolder et al. 2002). It remains to be shown, however, whether this beneficial course is different for the two types of drug and dependent on the kind of psychological intervention.

Obviously the most intriguing finding is the high drop-out rate of about 60 % during the first year of maintenance treatment, about 40 % being related to patients' lack of treatment acceptance. Wahlbeck et al. (2001) have recently reported on drop-out rates in randomized antipsychotic drug trials. From their database they concluded that drop-out rates significantly increased over the years since the mid-1950 s reaching about 60 % at the beginning of the 21st century. Significant contributors were length of trial, whereas type of drug (typical vs atypical) had no influence after clozapine trials had been excluded. Although similar drop-out rates under routine treatment conditions cannot generally be inferred from drug trials, the findings might be indicative for a special risk of first-episode patients to early withdraw from treatment. Hence, even the positive illness course of those who remain in treatment for up to one year may not be representative for first-episode cases in general and their further relapse proneness. As Linszen et al. (1998) demonstrated, the illness course of early schizophrenia remains at risk for multiple relapse even after intensive intervention and hence calls for ongoing support to continue disease management, medication compliance and stress management beyond the first years. Similarly, Robinson et al. (1999) were able to show that there is a high rate of relapse within 5 years of recovery from a first episode of schizophrenia and schizoaffective disorder. Five years after initial recovery, the cumulative first relapse rate was 81.9 %. Analyses controlling for antipsychotic drug use showed that patients with poor premorbid adaptation to school and premorbid social withdrawal relapsed earlier, whereas a number of other variables, including DUP, time to response of the initial episode, and adverse effects during treatment were not significantly related to time to relapse.

Who is at increased risk for drop-out? More pronounced psychopathology at study entry, i. e. poorer outcome from acute treatment seem to be single main predictors. In addition, more pronounced neurological (i. e. motor) side-effects, possibly due to acute treatment with haloperidol, are another set of predictors. Possibly in the same context, candidates for drop-out tend to be less compliant – independent of drug attitudes – already at study entry. Interestingly, in our sample the Strauss-Carpenter prognosis score did not differentiate between the two groups. Lateral entry because of non-fulfillment of inclusion criteria for the acute treatment study, seems to be another risk factor. Those patients who cannot be included in an acute study treatment regimen may be a risk population for non-compliance and hence treatment drop-out. Psychological intervention on the contrary may have the potential to keep patients in treatment, independent of its more specific effects on components of the vulnerability-stress-coping model. Accordingly, psychoeducation or more specific cognitive behavioral treatment may have the same effect on retainment. Multivariate analysis, however, only confirmed the predictive validity of the pattern of symptom status and side-effect profile. In any case, planned catamnestic assessments will clarify the further illness course of those who left treatment early.

Concerning results from the second study year no definite conclusions can presently be drawn from the small sample. However, up to now it turned out that those patients randomized to drug withdrawal more often refused this strategy. Moreover, relapse more often occurred in those cases randomized to drug withdrawal. According to the findings of Robinson et al. (1999), discontinuing antipsychotic drug therapy in first-episode schizophrenia increased the risk of relapse by almost five times. However, as the authors point out, many of their patients refused drug therapy – even after experiencing one or more relapses and despite vigorous patient and family educational efforts. Together with the high drop-out rates we observed in the first study year – despite a well-structured treatment program including psychoeducation –, these facts highlight the pressing need for developing strategies more acceptable to this particular group of patients, who often do not realize or accept the diagnosis of schizophrenia and its treatment options as yet available (Lacro et al. 2002). Compliance enhancing strategies such as psychoeducation, compliance therapy or the application of depot neuroleptics – a topic, which has recently reentered discussion as a new "paradigm" with the availability of a first atypical depot formulation (risperidone) (Kane and Malhotra 2003) – should be further developed or refined (Dolder et al. 2003). In our sample, it cannot be ruled out that some patients' refusal to withdraw medication according to randomization was due to the effect of psychoeducation to be further analyzed. However, it is often the illness and treatment concepts of the patients which render these strategies unsuccessful. Accordingly, it is not only side-effects which make patients refuse their medication, as recent reports on the non-significant difference of quite considerable non-adherence rates around 50 % for typical and atypical neuroleptics demonstrate (Dolder et al. 2002). That early intervention strategies seem to be more successful in first-episode than in multiple-episode patients may refer to better acceptance and compliance of the former with an intermittent treatment strategy, giving them a feeling of greater self-determination and independence. At the same time, first-episode patients on average seem to have a better illness prognosis, seem to tolerate free medication periods longer and seem to respond to targeted medication faster (Gaebel et al. 2002). On the other hand, in first-episode schizophrenia with each recurring episode time to acute treatment response seems to increase (Lieberman et al. 1997). Gitlin et al. (2001) could demonstrate that symptom exacerbation after neuroleptic discontinuation in remitted recent-onset schizophrenia, although frequent, is responsive to early reinstatement of medication so that hospitalization can be avoided in most of the cases. From their findings they conclude that at least some recent-onset patients should be considered for a trial of drug discontinuation, but only if careful clinical monitoring is available for rapid resumption of medication in case psychotic symptoms reemerge.

Treatment of schizophrenia in the 21st century has to integrate models of shared decision-making, offering the patient all the options available, but also accepting patient decisions at variance with these options (Gaebel 2004). For the question, whether and when to withdraw medication in stable patients after their first illness breakdown, an experimentally set standard is still not available – only recommendations from consensus guidelines to keep medication for a year or two and then to gradually withdraw it (Wyatt et al. 1998). Hence, the major motive of the present study is to scientifically improve and evaluate treatment options, which are often practiced by the patients themselves, though in an unsystematic and unsuccessful manner. Of course, this endeavor has to be balanced with potential dangers – which also have to be conveyed to the patients – resulting from harm to self (or others) either directly or indirectly via the putative neurobiological mechanisms associated with DUP and relapse leading to illness progression (Lieberman et al. 2001; Bottlender et al. 2002).

Conclusions

Although the present 2-year study is not yet finished, a number of conclusions can already be drawn from its preliminary results of the first treatment year. Oral neuroleptic long-term treatment with randomly applied low-dose haloperidol or risperidone for up to one year in first-episode schizophrenia is highly effective and on average well tolerated. Relapse rate or deterioration are extremely low and side-effects can be kept to a minimum. However, the risk to drop out from treatment is

rather high. This comes particularly true for patients with higher positive symptom scores and more pronounced motor side-effects at study entry after acute treatment. Whether this mainly refers to treatment with haloperidol cannot be decided until the unblinding of the medication code. Retainability in long-term treatment seems to be more easily guaranteed in cases of assured participation in the acute study phase and better compliance at study entry. Adjunctive psychological intervention also seems to increase retainability. Patients successfully maintained for one year tend to keep their medication beyond the first year despite randomization to drug withdrawal.

In conclusion, the group of first-episode schizophrenia patients seems to be at high risk for drop out from long-term treatment. As a consequence, first-episode patients should be timely given the most effective and best tolerated medication, they should be kept on 'their' medication, should be regularly monitored for side-effects, drug attitude and compliance, and should be offered psychological interventions as early as possible. In case of impending loss of retainment special treatment programs should be offered in addition to keep patients in the service system.

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