Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial

René S Kahn, W Wolfgang Fleischhacker*, Han Boter, Michael Davidson, Yvonne Vergouwe, Ireneus P M Keet, Mihai D Gheorghe, Janusz K Rybakowski, Silvana Galderisi, Jan Libiger, Martina Hummer, Sonia Dollfus, Juan J López-Ibor, Luchezar G Hranov, Wolfgang Gaebel, Joseph Peuskens, Nils Lindefors, Anita Riecher-Rössler, Diederick E Grobbee, for the EUFEST study group†*

Summary

Background **Second-generation antipsychotic drugs were introduced over a decade ago for the treatment of schizophrenia; however, their purported clinical effectiveness compared with first-generation antipsychotic drugs is still debated. We aimed to compare the effectiveness of second-generation antipsychotic drugs with that of a low dose of haloperidol, in first-episode schizophrenia.**

Methods **We did an open randomised controlled trial of haloperidol versus second-generation antipsychotic drugs in 50 sites, in 14 countries. Eligible patients were aged 18–40 years, and met diagnostic criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder. 498 patients were randomly assigned by a web-based online system to haloperidol (1–4 mg per day; n=103), amisulpride (200–800 mg per day; n=104), olanzapine (5–20 mg per day; n=105), quetiapine (200–750 mg per day; n=104), or ziprasidone (40–160 mg per day; n=82); follow-up was at 1 year. The primary outcome measure was all-cause treatment discontinuation. Patients and their treating physicians were not blinded to the assigned treatment. Analysis was by intention to treat. This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN68736636.**

Findings **The number of patients who discontinued treatment for any cause within 12 months was 63 (Kaplan-Meier estimate 72%) for haloperidol, 32 (40%) for amisulpride, 30 (33%) for olanzapine, 51 (53%) for quetiapine, and 31 (45%) for ziprasidone. Comparisons with haloperidol showed lower risks for any-cause discontinuation with amisulpride (hazard ratio [HR] 0·37, [95% CI 0·24–0·57]), olanzapine (HR 0·28 [0·18–0·43]), quetiapine (HR 0·52 [0·35–0·76]), and ziprasidone (HR 0·51 [0·32–0·81]). However, symptom reductions were virtually the same in all the groups, at around 60%.**

Interpretation **This pragmatic trial suggests that clinically meaningful antipsychotic treatment of first-episode of schizophrenia is achievable, for at least 1 year. However, we cannot conclude that second-generation drugs are more efficacious than is haloperidol, since discontinuation rates are not necessarily consistent with symptomatic improvement.**

Funding **AstraZeneca, Pfizer, Sanofi-Aventis.**

Introduction

Second-generation antipsychotic drugs were introduced over a decade ago. They were intended to be more efficacious than were previous drugs for treatment of schizophrenia, and less likely to induce motor side-effects. However, their clinical effectiveness compared with first-generation antipsychotic drugs is still debated.[1–5] Indeed, limited conclusions can be drawn from the studies that have been undertaken so far,[6] since most used restrictive inclusion criteria, leading to over-representation of men and under-representation of patients with comorbidities, such as drug abuse. Moreover, treatment response has almost exclusively been defined by use of scales that measure the extent of psychopathology: in most studies, efficacy has been measured, according to narrowly-defined criteria, but not effectiveness, which is a combination of efficacy and tolerability. Some investigators suggest that trials showing that second-generation antipsychotic drugs are better than haloperidol used doses of haloperidol that were too high.[2] Finally, study durations have typically been less than 2 months, which is imperfect for an illness potentially lasting a lifetime.[6–8]

We[7] and others[6] have suggested that studies that are not restrictive in the inclusion of patients, have long follow-up periods, and use outcome measures which are clinically meaningful, are urgently needed. The time for which patients continue to use a drug is considered a good measure of effectiveness. Even in short-term studies, fewer than 50–60% of patients continue to take their drugs before the study is complete.[9] Pragmatic (open) randomised trials, comparing second-generation drugs with older ones, will arguably provide a better indication of the true value of these drugs in clinical practice than will double-blind trials. Moreover, these trials should include a broad range of patients, so findings have external validity.[6]

Lancet 2008; 371: 1085–97

See **Comment** page 1048

*These authors contributed equally to the study

†Members listed at end of paper

Department of Psychiatry, Rudolf Magnus Institute of Neuroscience (Prof R S Kahn MD, H Boter PhD) **and Julius Center for Health Sciences and Primary Care** (Y Vergouwe PhD, Prof D E Grobbee MD), **University Medical Centre Utrecht, Utrecht, Netherlands; Department of Biological Psychiatry, Medical University Innsbruck, Innsbruck, Austria** (Prof W W Fleischhacker MD, Prof M Hummer MD); **Sheba Medical Center, Tel Hashomer, Israel** (Prof M Davidson MD); **AMC de Meren, Amsterdam, Netherlands** (I P M Keet MD); **Department of Psychiatry, Central Military Hospital, Bucharest, Romania** (Prof M D Gheorghe MD); **Department of Adult Psychiatry, University of Medical Sciences, Poznan, Poland** (Prof J K Rybakowski MD); **Department of Psychiatry, University of Naples SUN, Naples, Italy** (Prof S Galderisi MD); **Department and Clinic of Psychiatry, Charles University Medical School and Faculty Hospital, Hradec Králové, Czech Republic** (Prof J Libiger MD); **Centre Esquirol, Centre Hospitalier Universitaire, Caen, France** (Prof S Dollfus MD); **Institute of Psychiatry and Mental Health, Hospital Clínico San Carlos, Madrid, Spain** (Prof J J López-Ibor MD); **Department and Clinic of Psychiatry, University Hospital of Neurology and Psychiatry St Naum, Sofia, Bulgaria** (L G Hranov MD); **Department of Psychiatry and Psychotherapy, Heinrich-Heine-University, Düsseldorf, Germany** (Prof W Gaebel MD);

University Psychiatric Centre, Campus St Jozef Kortenberg, Katholieke Universiteit Leuven, Leuven, Belgium (Prof J Peuskens MD); **Department of Clinical Neuroscience, Psychiatry Section, Karolinska Institutet, Stockholm, Sweden** (Prof N Lindefors MD); **and Psychiatric Department, University Hospital Basel (CH), Switzerland** (Prof A Riecher-Rössler MD)

Correspondence to: Prof René S Kahn, Department of Psychiatry, Rudolf Magnus Institute of Neuroscience, University Medical Centre Utrecht, PO Box 85500, 3508 GA Utrecht, Netherlands
r.kahn@umcutrecht.nl

Studies examining effectiveness of second-generation antipsychotic drugs in the early stages of schizophrenia are scarce.[7] However, patients in the early stages of schizophrenia might well respond differently to antipsychotic drugs from those who have used them for years or even decades: dopamine-receptor sensitivity is most probably substantially different in patients who have had no previous exposure to the dopamine-antagonistic effects of antipsychotic dugs than in patients who are chronically treated.[10] Moreover, trials of drugs in chronic patients often, by definition, include patients who have responded little, or been non-adherent, to previous treatments.

We undertook a pragmatic open randomised-controlled trial to compare the effectiveness of second-generation antipsychotic drugs, with that of a low dose of haloperidol, in first-episode schizophrenia.

Methods

Setting and participants

A total of 50 centres, of which 36 were university hospitals, participated; the centres were in 13 European countries and Israel. We selected the centres because of their experience of research in schizophrenia. Between Dec 23, 2002, and Jan 14, 2006 we assessed 1047 patients for eligibility. Eligible patients were aged 18–40 years and met criteria of the diagnostic and statistical manual of mental disorders (fourth edition) for schizophrenia, schizophreniform disorder, or schizoaffective disorder; diagnoses were confirmed by the mini international neuropsychiatric interview plus (MINI plus).[11] Patients were excluded if more than 2 years had passed since the onset of positive symptoms; if any antipsychotic drug had been used for more than 2 weeks in the previous year, or for 6 weeks at any time; if patients had a known intolerance to one of the study drugs; or if patients met any of the contraindications for any of the study drugs, as mentioned in the (local) package insert texts.

Study design

The investigators informed eligible patients orally and in writing about the trial, and invited them to participate. Between 4 weeks before and 1 week after randomisation, we obtained baseline data for demographics, diagnoses, present treatment setting, psychopathology (positive and negative syndrome scale [PANSS]),[12] severity of illness (clinical global impression [CGI] scale),[13] overall psychosocial functioning (global assessment of functioning [GAF] scale),[14] depression (Calgary depression scale for schizophrenia [CDSS]),[15] quality of life (Manchester short assessment of quality of life scale [MANSA]),[16] extrapyramidal symptoms (St Hans rating scale [SHRS]),[17] and sexual dysfunction (selected items from the Udvalg for Kliniske Undersøgelser [UKU]).[18] Furthermore, we physically examined all patients; recorded weight, height, and laboratory data (fasting glucose, cholesterol, HDL and LDL, fasting insulin, triglycerides, and prolactin); and obtained an electrocardiogram (ECG).

Patients were randomly assigned by a dedicated web-based online system—which was developed in-house by the Data Management Department of the Julius Center for Health Sciences and Primary Care (version 1.2)—to daily doses of: haloperidol 1–4 mg, amisulpride 200–800 mg, olanzapine 5–20 mg, quetiapine 200–750 mg, or ziprasidone 40–160 mg. The maximum dose of haloperidol was set at 4 mg per day, since studies have suggested that patients with first-episode schizophrenia respond to low doses of antipsychotic drugs.[19,20] Furthermore, higher doses do not increase the antipsychotic effect of haloperidol, but do increase the risk of side-effects, especially in patients with first-episode schizophrenia.[21–26]

All study drugs were given orally, within the above dose ranges, at the treating psychiatrist's discretion. The use of mood stabilisers, benzodiazepines, antidepressants, and anticholinergic drugs was allowed, and documented. Since some study drugs were not registered in all participating countries, we used a minimisation procedure to prevent unequal group sizes at the end of the trial—ie, treatment assignment of new patients depended on the distribution of participants over the treatment groups.[27] Randomisation to ziprasidone was blocked between December, 2003, and October, 2004, because the minimisation procedure used during randomisation assigned ziprasidone to too many patients, in the few countries where ziprasidone was available. Patients and their treating psychiatrists were unmasked for the assigned treatment, since this reflected routine clinical practice, increasing the trial's external validity; it also improved the trial's acceptability for patients and psychiatrists, leading to a more representative group of patients, which further increased the trial's external validity.

All participants—or their legal representatives—provided written informed consent. The trial complied with the Declaration of Helsinki, and was approved by the ethics committees of the participating centres. The Julius Centre for Health Sciences and Primary Care monitored the trial according to Good Clinical Practice and International Conference on Harmonisation guidelines.

Procedures

Before the start of the trial, site coordinators were trained to use the MINI plus and to assess outcomes—eg, video tapes were used to train assessments of the PANSS. The site coordinators could delegate assessments to competent co-investigators—eg, a psychiatrist (including a trainee in psychiatry), research nurse, or psychologist. The primary outcome was all-cause discontinuation of haloperidol, compared with discontinuation of the various second-generation antipsychotic drugs. Treatment discontinuation was defined as: (1) the use of a dose below the predefined range including complete discontinuation;

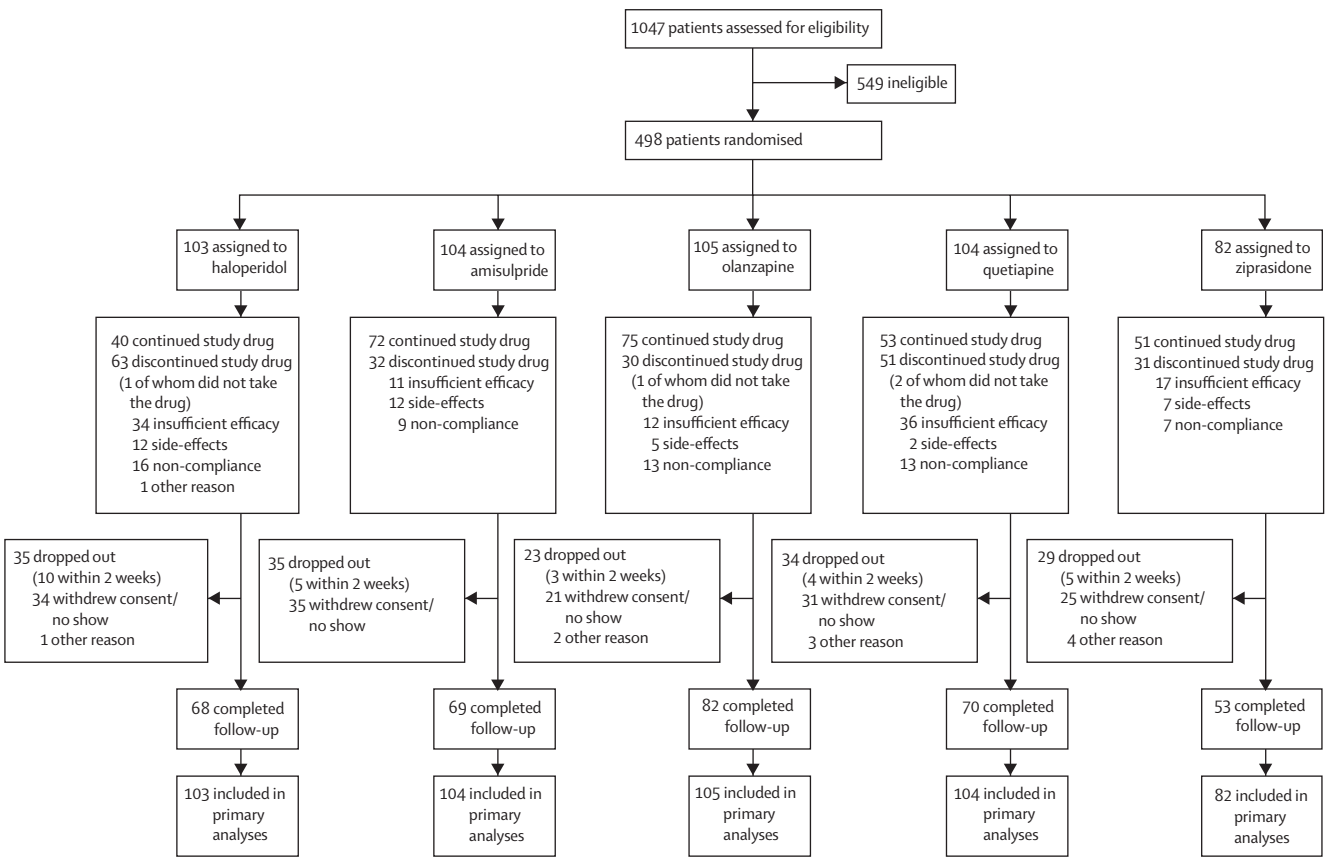

Figure 1: **Trial profile**

	Haloperidol (N=103)	Amisulpride (N=104)	Olanzapine (N=105)	Quetiapine (N=104)	Ziprasidone (N=82)	Total (N=498)
Sociodemographic characteristics						
Age (years)	25·4 (5·6)	25·2 (4·9)	26·3 (5·9)	26·4 (5·7)	26·7 (5·7)	26·0 (5·6)
Women	39/103 (38%)	46/104 (44%)	38/105 (36%)	36/104 (35%)	41/82 (50%)	200/498 (40%)
White	93/103 (90%)	102/104 (98%)	100/105 (95%)	97/104 (93%)	77/82 (94%)	469/498 (94%)
Years of education*	12·4 (2·5)	12·8 (2·9)	12·7 (3·4)	12·0 (2·9)	12·4 (2·6)	12·5 (2·9)
Living alone	14/100 (14%)	12/104 (12%)	12/104 (12%)	20/104 (19%)	8/81 (10%)	66/493 (13%)
Employed or student	42/101 (42%)	55/104 (53%)	46/105 (44%)	46/104 (44%)	42/82 (51%)	231/496 (47%)
Diagnosis†						
Schizophreniform	36/103 (35%)	42/104 (40%)	35/105 (33%)	38/104 (36%)	47/82 (57%)	198/498 (40%)
Schizoaffective	8/103 (8%)	5/104 (5%)	9/105 (9%)	8/104 (8%)	5/82 (6%)	35/498 (7%)
Schizophrenia	59/103 (57%)	57/104 (55%)	61/105 (58%)	58/104 (56%)	30/82 (37%)	265/498 (53%)
Depression (at present)†	9/97 (9%)	5/103 (5%)	9/103 (9%)	17/103 (17%)	6/81 (7%)	46/487 (9%)
Suicidality (at present)†	12/98 (12%)	10/104 (10%)	13/103 (13%)	15/103 (15%)	8/81 (10%)	58/489 (12%)
Substance dependence/abuse (at present)†	23/98 (23%)	16/104 (15%)	24/103 (23%)	29/103 (28%)	20/81 (25%)	112/489 (23%)
Inpatient	87/103 (84%)	97/104 (93%)	101/105 (96%)	89/104 (86%)	71/82 (87%)	445/498 (89%)
Antipsychotic naive	36/103 (35%)	44/104 (42%)	25/105 (24%)	40/104 (38%)	17/82 (21%)	162/498 (33%)
Psychopathology score (PANSS)‡						
Total	88·9 (19·8)	86·4 (19·2)	87·5 (21·1)	91·5 (22·6)	88·3 (20·1)	88·5 (20·6)
Positive scale	22·8 (5·6)	23·0 (6·1)	23·1 (6·3)	23·7 (6·7)	23·0 (6·3)	23·1 (6·2)

(Continues on next page)

	Haloperidol (N=103)	Amisulpride (N=104)	Olanzapine (N=105)	Quetiapine (N=104)	Ziprasidone (N=82)	Total (N=498)
(Continued from previous page)						
Negative scale	21·5 (7·9)	20·3 (7·2)	21·1 (6·9)	22·0 (7·4)	21·3 (8·8)	21·2 (7·6)
General psychopathology scale	44·5 (9·7)	43·1 (10·1)	43·4 (11·4)	45·8 (12·3)	43·9 (9·9)	44·1 (10·8)
Severity of illness score (CGI)§	4·9 (0·7)	4·8 (0·8)	4·8 (0·8)	4·9 (0·8)	4·8 (0·8)	4·8 (0·8)
Overall functioning score (GAF)¶	38·6 (12·2)	40·3 (12·5)	43·0 (15·1)	38·8 (14·2)	39·3 (12·9)	40·0 (13·5)
Depression score (CDSS)‖	5·0 (5·1)	4·7 (5·0)	5·5 (4·9)	5·7 (5·2)	4·3 (3·8)	5·1 (4·9)
Quality of life score (MANSA)**	3·9 (0·8)	4·1 (0·9)	4·0 (1·0)	4·0 (1·0)	4·2 (0·9)	4·0 (0·9)
Extrapyramidal symptoms score (SHRS)						
Akathisia	15/99 (15%)	8/104 (8%)	8/104 (8%)	10/102 (10%)	8/81 (10%)	49/490 (10%)
Dystonia	2/99 (2%)	3/104 (3%)	0/104 (0%)	1/102 (1%)	3/81 (4%)	9/490 (2%)
Parkinsonism	13/99 (13%)	11/104 (11%)	6/104 (6%)	8/102 (8%)	15/81 (19%)	53/490 (11%)
Dyskinesia	1/99 (1%)	1/104 (1%)	0/104 (0%)	0/102 (0%)	1/81 (1%)	3/490 (1%)
Sexual dysfunction score (UKU)††						
Men	15/61 (25%)	14/57 (25%)	15/65 (23%)	15/67 (22%)	13/41 (32%)	72/291 (25%)
Women	10/36 (28%)	11/46 (24%)	9/38 (24%)	11/33 (33%)	7/38 (18%)	48/191 (25%)
Weight						
Overweight (BMI ≥25 kg/m^2)	20/96 (21%)	11/101 (11%)	17/104 (16%)	20/102 (20%)	16/81 (20%)	84/484 (17%)
BMI (kg/m^2)	22·3 (3·5)	21·7 (3·6)	22·0 (3·0)	22·7 (3·3)	22·5 (3·8)	22·2 (3·4)
Prolactin (U/L)						
Hyperprolactinaemia‡‡	67/89 (75%)	63/88 (72%)	69/88 (78%)	53/90 (59%)	49/67 (73%)	301/422 (71%)
Mean (SD)	1·0 (1·1)	1·4 (1·3)	0·8 (0·7)	0·7 (0·7)	1·4 (1·4)	1·0 (1·1)
Median (IQR)	0·8 (0·4–1·1)	1·0 (0·3–2·0)	0·7 (0·4–1·1)	0·5 (0·2–0·9)	0·8 (0·5–1·6)	0·7 (0·4–1·3)
Fasting glucose (mmol/L)						
Hyperglycaemia§§	8/99 (8%)	4/103 (4%)	6/101 (6%)	8/97 (8%)	9/81 (11%)	35/481 (7%)
Mean (SD)	4·6 (0·7)	4·6 (0·6)	4·7 (0·8)	4·6 (0·6)	4·8 (0·7)	4·7 (0·7)
Median (IQR)	4·6 (4·2–4·9)	4·6 (4·3–4·9)	4·7 (4·3–5·1)	4·6 (4·3–5·0)	4·8 (4·4–5·2)	4·6 (4·3–5·0)
Cholesterol (mmol/L)						
Hypercholesterolaemia¶¶	24/99 (24%)	23/103 (22%)	24/102 (24%)	17/95 (18%)	23/80 (29%)	111/479 (23%)
Mean (SD)	4·6 (1·1)	4·3 (1·0)	4·4 (1·1)	4·3 (1·0)	4·6 (1·2)	4·4 (1·1)
Median (IQR)	4·5 (3·8–5·1)	4·4 (3·7–5·1)	4·4 (3·6–5·1)	4·1 (3·6–4·6)	4·4 (3·9–5·3)	4·4 (3·7–5·1)
HDL (mmol/L)						
Low concentration of HDL‖‖	21/98 (21%)	12/101 (12%)	17/102 (17%)	17/95 (18%)	12/78 (15%)	79/474 (17%)
Mean (SD)	1·3 (0·4)	1·4 (0·4)	1·4 (0·4)	1·3 (0·4)	1·4 (0·3)	1·4 (0·4)
Median (IQR)	1·3 (1·1–1·5)	1·3 (1·1–1·6)	1·3 (1·1–1·6)	1·3 (1·1–1·5)	1·3 (1·1–1·5)	1·3 (1·1–1·5)
LDL (mmol/L)						
High concentration of LDL***	19/96 (20%)	16/99 (16%)	21/100 (21%)	11/89 (12%)	19/78 (24%)	86/462 (19%)
Mean (SD)	2·6 (1·1)	2·6 (0·8)	2·7 (1·1)	2·4 (0·8)	2·8 (1·2)	2·6 (1·0)
Median (IQR)	2·6 (2·0–3·2)	2·5 (2·0–3·2)	2·6 (1·9–3·3)	2·3 (1·9–2·9)	2·6 (2·2–3·2)	2·5 (1·9–3·2)
Fasting insulin (mU/L)						
Mean (SD)	10·9 (8·1)	9·3 (7·8)	11·6 (21·6)	8·6 (11·3)	10·5 (8·2)	10·1 (12·3)
Median (IQR)	7·5 (5·0–16·0)	7·0 (4·0–11·0)	7·0 (5·0–9·0)	6·0 (4·0–8·0)	8·0 (5·0–13·5)	5·0 (7·0–11·0)

(Continues on next page)

(2) the use of a dose greater than the predefined range; (3) the use of another antipsychotic drug—each for more than 14 days over 6 months; or (4) the use of any parenteral antipsychotic drug when the drug was active for more than 14 days over 6 months. Treatment discontinuation was defined as occurring on the 15th day as soon as one of the four criteria for discontinuation was met. The reason for treatment discontinuation was noted. When investigators recorded more than one reason for discontinuation, we ranked the reasons in order of decreasing importance: insufficient efficacy according to the treating psychiatrist, side-effects according to the treating psychiatrist, patient reported non-adherence, and other reasons. Subsequently, we selected the most important reason for the statistical analyses.

Efficacy outcomes consisted of PANSS, CGI, GAF, CDSS, MANSA, and adherence to antipsychotic drugs (one-item 7-points rating scale; higher scores suggest

	Haloperidol (N=103)	Amisulpride (N=104)	Olanzapine (N=105)	Quetiapine (N=104)	Ziprasidone (N=82)	Total (N=498)
(Continued from previous page)						
Triglycerides (mmol/L)						
Hypertriglyceridaemia†††	25/99 (25%)	10/102 (10%)	21/103 (20%)	13/95 (14%)	17/80 (21%)	86/479 (18%)
Mean (SD)	1·4 (1·0)	1·1 (0·6)	1·4 (1·1)	1·2 (0·7)	1·3 (0·8)	1·3 (0·8)
Median (IQR)	1·1 (0·8–1·7)	1·0 (0·7–1·2)	1·0 (0·7–1·6)	1·1 (0·8–1·4)	1·1 (0·7–1·6)	1·1 (0·7–1·5)
Prolonged QTc interval‡‡‡	2/95 (2%)	5/97 (5%)	4/97 (4%)	2/94 (2%)	1/73 (1%)	14/456 (3%)

Data are n/N (%) or mean (SD), unless otherwise indicated. Denominators change because of incomplete data. PANSS=positive and negative syndrome scale. CGI=clinical global impression. GAF=global assessment of functioning. CDSS=Calgary depression scale for schizophrenia. MANSA=Manchester short assessment of quality of life scale. SHRS=St Hans rating scale. UKU=udvalg for kliniske undersøgelser. *Years in school from 6 years of age onwards. †According to the mini international neuropsychiatric interview plus (MINI plus). Depression includes major depressive episode (with or without melancholic features) and dysthymia. Suicidality includes medium to high suicide risk. Substance dependence/abuse includes alcohol dependence/abuse. ‡Theoretical scores range from 30–210 (total scale), 7–49 (positive scale), 7–49 (negative scale), 16–112 (general psychopathology scale). Higher scores indicate more severe psychopathology. §Theoretical scores range from 1–7; higher scores indicate greater severity of illness. ¶Theoretical scores range from 1–100; higher scores indicate better functioning. ||Theoretical scores range from 0–27; higher scores indicate more depression. **Theoretical scores range from 1–7; higher scores indicate better quality of life. ††Cases scored moderate/severe on selected items of the UKU. For men: increased/decreased libido, orgastic dysfunction, gynaecomastia, or erectile/ejaculatory dysfunction (six items); for women: increased/decreased libido, orgastic dysfunction, menorrhagia, amenorrhoea, galactorrhoea, or dry vagina (seven items). ‡‡Hyperprolactinaemia: men >0·38 U/L; women >0·53 U/L (men >18 ng/ml; women >25 ng/mL; to convert values in ng/mL to U/L we arbitrarily used a conversion factor of 0·0212).[20] §§Hyperglycaemia: fasting glucose level ≥5·55 mmol/L. ¶¶Hypercholesterolaemia: cholesterol concentration ≥5·17 mmol/L. ||||Low concentration of HDL <1·03 mmol/L. ***High concentration of LDL ≥3·36 mmol/L. †††Hypertriglyceridaemia: triglyceride level ≥1·69 mmol/L. ‡‡‡QTc prolongation: men >450 mseconds, women >470 mseconds.

Table 1: **Baseline characteristics of patients**

better adherence).[28] The safety and tolerability outcomes were admission to psychiatric hospital, serious adverse events, SHRS, selected items of the UKU, weight, laboratory data, ECG, and use of concomitant drugs. Data was collected at 0·5, 1, 1·5, 2, 3, 6, 9, and 12 months for one or more of the efficacy, safety, and tolerability outcomes. In practice, more than 90% of the PANSS and CGI ratings were completed by the investigator who assessed treatment discontinuation.

Statistical analysis

We assumed a treatment discontinuation rate, at 12-month follow-up, of 70% in patients receiving haloperidol, and 40% in patients receiving second-generation antipsychotic drugs (hazard ratio [HR] 0·42). We needed 45 patients per treatment group, on the basis of a two-tailed test with α=5% and 1-β=80%. However, we suspected that the discontinuation rate of haloperidol might be smaller than was inferred from previous studies, since we intended to use low doses of haloperidol. Therefore we planned to enrol 100 patients per group—ie, 500 patients in total.

Analysis was by intention to treat. Given the definition of treatment discontinuation, patients were not at risk for the outcome within the first 2 weeks after randomisation. Therefore, these 2 weeks were not considered for analysis of treatment discontinuation.

	Haloperidol (N=103)	Amisulpride (N=104)	Olanzapine (N=105)	Quetiapine (N=104)	Ziprasidone (N=82)	p value
Mean dose before discontinuation of treatment (mg/day [SD])	3·0 (1·2)	450·8 (171·9)	12·6 (4·7)	498·6 (201·4)	107·2 (35·0)	
Maximum (or higher) dose received*	56/92 (61%)	26/100 (26%)	54/103 (52%)	39/104 (38%)	37/79 (47%)	<0·0001
Discontinuation for any cause†	63/103 (72%)	32/104 (40%)	30/105 (33%)	51/104 (53%)	31/82 (45%)	
Months to discontinuation (95% CI)‡	0·5 (0·5–0·9)	5·3 (3·0–12+)	6·3 (3·7–12+)	1·2 (0·7–2·0)	1·1 (0·8–8·2)	
Cox-model treatment comparisons (HR [95% CI])§						
Haloperidol		0·37(0·24–0·57)	0·28 (0·18–0·43)	0·52 (0·35–0·76)	0·51 (0·32–0·81)	<0·0001
Amisulpride			0·74 (0·45–1·23)	1·39 (0·86–2·25)	1·35 (0·79–2·32)	
Olanzapine				1·60(0·99–2·59)	1·62 (0·92–2·86)	
Quetiapine					1·05 (0·61–1·81)	
Discontinuation because of insuffient efficacy†	34/103 (48%)	11/104 (14%)	12/105 (14%)	36/104 (40%)	17/82 (26%)	
Cox-model treatment comparisons (HR [95% CI])§						
Haloperidol		0·22(0·11–0·43)	0·20 (0·10–0·38)	0·68 (0·41–1·13)	0·51 (0·27–0·95)	<0·0001
Amisulpride			0·92 (0·40–2·11)	3·04 (1·47–6·32)	2·47 (1·08–5·66)	
Olanzapine				2·95 (1·46–5·95)	2·54 (1·09–5·93)	
Quetiapine					0·89 (0·44–1·79)	

(Continues on next page)

	Haloperidol (N=103)	Amisulpride (N=104)	Olanzapine (N=105)	Quetiapine (N=104)	Ziprasidone (N=82)	p value
(Continued from previous page)						
Discontinuation because of side-effects†	12/103 (20%)	12/104 (20%)	5/105 (6%)	2/104 (3%)	7/82 (14%)	
Cox-model treatment comparisons (HR [95% CI])§						
Haloperidol		0·71(0·32–1·61)	0·26 (0·09–0·75)	0·13 (0·03–0·59)	0·55 (0·20–1·51)	0·023
Amisulpride			0·35 (0·12–1·02)	0·19(0·04–0·89)	0·84 (0·29–2·47)	
Olanzapine				0·38 (0·07–2·10)	1·56 (0·43–5·66)	
Quetiapine					3·13(0·57–17·11)	
Discontinuation because of non-adherence†	16/103 (30%)	9/104 (13%)	13/105 (17%)	13/104 (19%)	7/82 (14%)	
Cox-model treatment comparisons (HR [95% CI])§						
Haloperidol		0·50(0·22–1·15)	0·49 (0·23–1·04)	0·48 (0·22–1·04)	0·50 (0·19–1·32)	0·241
Amisulpride			1·01 (0·42–2·42)	1·04(0·42–2·60)	0·86 (0·30–2·45)	
Olanzapine				0·90 (0·40–2·02)	0·84 (0·31–2·32)	
Quetiapine					0·92 (0·31–2·74)	
Discontinuation because of other reasons†	1/103 (4%)	0/104	0/105	0/104	0/82	

HR=hazard ratio. *Proportion of patients who have received the maximum or even a higher dose for at least 1 day. †The percentages are Kaplan-Meier estimates of treatment discontinuation within 12 months. ‡Kaplan-Meier estimates. Months at risk for treatment discontinuation, excluding the first 14 days after randomisation. For amisulpride and olanzapine no upper limit for the CI could be estimated because the upper limit is above the maximum follow-up time. The 95% CI includes the true population 25th percentile with probability 0·95. §Cox proportional-hazards regression models, with adjustments for country.

Table 2: **Treatment doses and treatment discontinuation by allocated treatment**

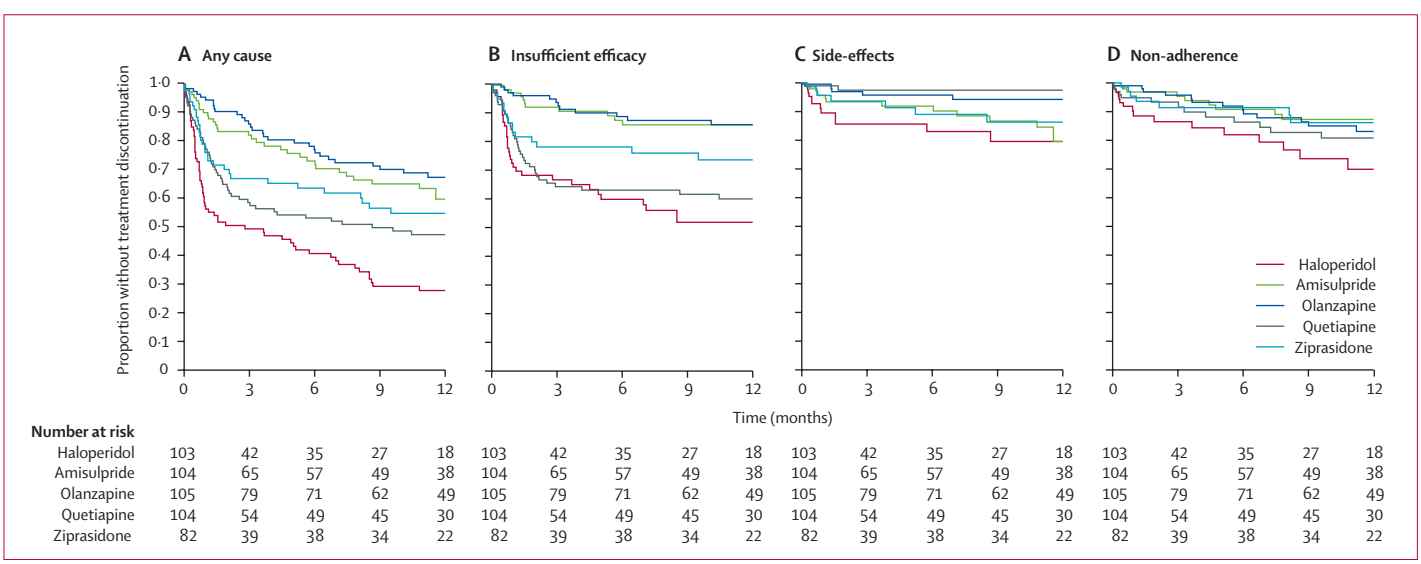

Figure 2: **Time to treatment discontinuation because of any cause (A), insufficient efficacy (B), side-effects (C), and non-adherence (D)**

We used Kaplan-Meier curves to estimate the probability of treatment discontinuation at 12 months. Cox proportional-hazards regression analysis was used to estimate differences of discontinuation probabilities between haloperidol and the four second-generation antipsychotic drugs, adjusted for country, since in some countries not all study drugs were included in the randomisation process. Differences were expressed in HRs, with corresponding 95% CIs. Countries with 15 or fewer patients were clustered to prevent unstable estimates.

We used data obtained before treatment discontinuation for analysis of secondary outcomes. We compared continuous efficacy outcomes, that were repeatedly measured after baseline, between treatment groups, with longitudinal multilevel linear mixed-effects regression models.[29] We studied whether the association of the continuous variable time from baseline with the secondary outcomes was linear, and we transformed the variable when appropriate. The multilevel model included random effects for the intercepts of the regression model and time coefficient of individual patients. The models

included fixed effects for treatment group, baseline score, and country. We tested the interaction between treatment group and time, and included it in the model when statistically significant. Comparisons between treatment groups of continuous safety and tolerability outcomes were assessed with linear regression, accounting for the time at risk and adjusting for country. Dichotomous safety and tolerability outcomes were studied with Poisson regression analysis, accounting for the time at risk for an adverse event and adjusting for country. We analysed weight change in a manner similar to that used for the efficacy outcomes. Subgroup analyses devised post-hoc were: sex, suicidality at baseline (suicidal *vs* non-suicidal patients), and substance dependence or abuse at baseline (patients with substance dependence or abuse *vs* patients without substance dependence or abuse).

We analysed all secondary outcomes with S-Plus (version 6.1), and the other data with SPSS (12.0). All statistical tests were two-sided. This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN68736636.

Role of the funding sources

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. 498 patients were randomly assigned to five treatment groups (figure 1). During follow-up, some enrolled patients appeared not to be eligible: 11 patients (four on haloperidol, two on olanzapine, two on quetiapine, and three on ziprasidone) had another cause for the symptoms than schizophrenia, another patient on quetiapine had positive symptoms exceeding 2 years before randomisation, and two patients on amisulpride had used antipsychotic drugs for more than 2 weeks in the previous year. These patients, and those who did not take any dose of the assigned study medication, were included in the analysis. Baseline characteristics of randomised patients were much the same between the groups (table 1). Table 2 shows the mean antipsychotic doses given every day, and the proportions of patients who discontinued treatment for any cause.

Treatment discontinuation for any cause differed between treatment groups ($p<0·0001$; table 2), and was substantially lower in patients on all of the second-generation antipsychotic drugs than in those taking haloperidol (figure 2). Additionally, treatment discontinuation because of insufficient efficacy differed between treatment groups ($p<0·0001$; table 2), with the risk of discontinuation lower in patients on second-generation antipsychotic drugs than in those on haloperidol (figure 2), although the difference between haloperidol and quetiapine was not significant (table 2). Treatment discontinuation because of side-effects also differed between treatment groups ($p=0·023$; table 2), which was mostly attributable to better tolerability of olanzapine and quetiapine than that of haloperidol (figure 2). Discontinuation of treatment for non-adherence did not differ significantly between treatment groups ($p=0·241$; table 2 and figure 2).

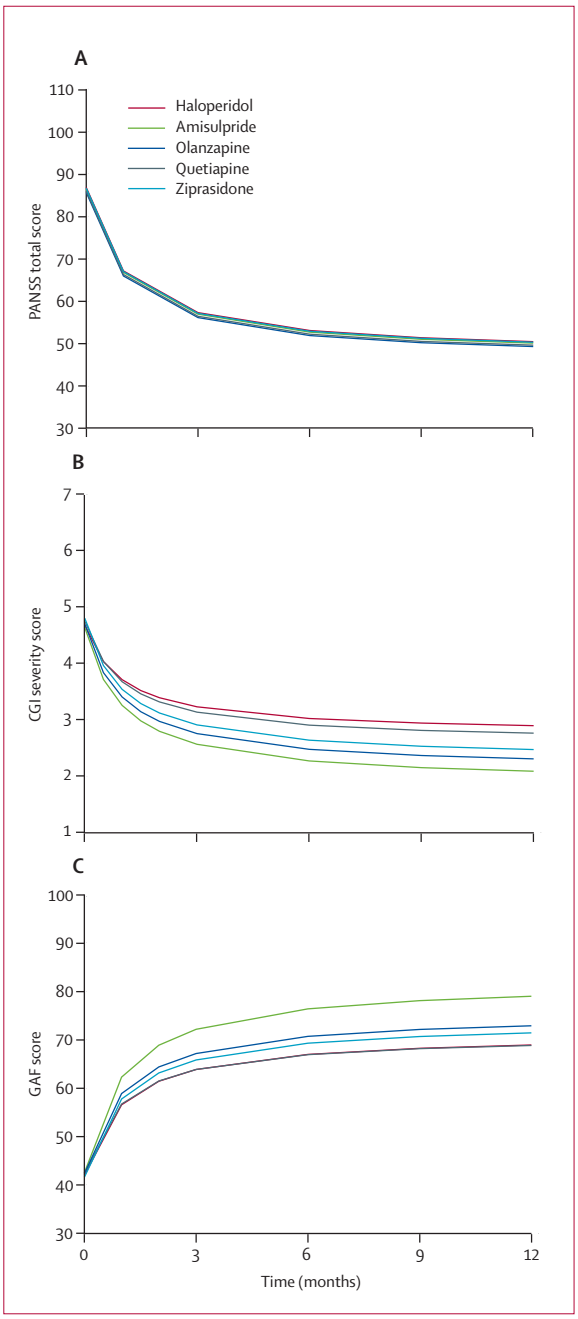

***Figure 3*: PANSS total score (A), CGI severity score (B), and GAF score (C) during 12 months of follow-up**

PANSS=positive and negative syndrome scale. CGI=clinical global impression. GAF=global assessment of functioning. The lowest curve for GAF scores consists of the haloperidol and quetiapine curves, which are almost identical.

Figure 3 shows the decrease of the total scores for psychopathology (PANSS) and severity of illness (CGI), and the increase of the overall functioning scores (GAF) of the five treatment groups during the 12 months follow-up. The differences between the treatment groups and the interaction between treatment and time were not significant for the PANSS (p=0·70 and p=0·15, respectively), but were significant for the CGI scale (p=0·0006 and p=0·003) and the GAF scale (p=0·006 and p=0·016). We recorded no significant differences between treatment effects for the depression score (CDSS), quality-of-life score (MANSA), and adherence with antipsychotic drugs (data not shown). Table 3 shows the mean scores for the efficacy outcomes at 12 months.

	Haloperidol	Amisulpride	Olanzapine	Quetiapine	Ziprasidone	p value
Psychopathology score (PANSS)	53·3 (1·7)	52·1 (1·8)	52·4 (1·7)	52·9 (1·7)	53·1 (2·0)	0·70
Severity of illness score (CGI)	3·0 (0·3)	2·3 (0·3)	2·4 (0·3)	2·9 (0·3)	2·5 (0·3)	0·0006
Overall functioning score (GAF)	64·3 (3·5)	74·4 (3·6)	68·3 (3·5)	64·2 (3·5)	66·8 (3·8)	0·006
Depression score (CDSS)	1·9 (0·2)	1·8 (0·2)	1·8 (0·2)	1·9 (0·2)	1·9 (0·3)	0·94
Quality–of-life score (MANSA)	4·7 (0·7)	4·7 (0·07)	4·7 (0·07)	4·7 (0·07)	4·8 (0·08)	0·12
Adherence with antipsychotic drugs	5·8 (0·11)	6·0 (0·11)	6·0 (0·11)	5·8 (0·11)	5·9 (0·13)	0·15

Data are mean (SE) after 12 months follow-up adjusted for baseline values and country. Adherence with antipsychotic drugs was only adjusted for country, since adherence could not be assessed at baseline. PANSS=positive and negative syndrome scale. CGI=clinical global impression. GAF=global assessment of functioning. CDSS=Calgary depression scale for schizophrenia. MANSA=Manchester short assessment of quality of life scale.

Table 3: **Outcomes of efficacy**

	Haloperidol	Amisulpride	Olanzapine	Quetiapine	Ziprasidone	p value
Admission to psychiatric hospital						
Admitted to hospital after randomisation/at risk for admission	14/64 (22%)	14/88 (16%)	18/89 (20%)	14/60 (23%)	4/60 (7%)	0·094
Admissions to hospital after randomisation/total patient–years at risk for admission (rate)	16/31·5 (0·51)	18/52·4 (0·34)	29/60·0 (0·48)	18/36·0 (0·50)	6/34·0 (0·18)	0·055
Adverse events						
Any serious adverse event	5/103 (5%)	3/104 (3%)	5/105 (5%)	3/104 (3%)	0/82 (0%)	*
Extrapyramidal symptoms (SHRS)†						
Akathisia	19/73 (26%)	15/94 (16%)	10/97 (10%)	11/85 (13%)	19/68 (28%)	0·007
Dystonia	1/73 (1%)	3/94 (3%)	0/97 (0%)	1/85 (1%)	2/68 (3%)	*
Parkinsonism	25/73 (34%)	16/94 (17%)	6/97 (6%)	9/85 (11%)	11/68 (16%)	<0·0001
Dyskinesia	2/73 (3%)	1/94 (1%)	0/97 (0%)	0/85 (0%)	0/68 (0%)	*
Sexual dysfunction (UKU)†						
Men	15/48 (31%)	14/48 (29%)	15/60 (25%)	16/57 (28%)	19/35 (54%)	0·101
Women	11/24 (46%)	21/45 (47%)	18/38 (47%)	10/28 (36%)	11/33 (33%)	0·774
Weight‡						
Overweight (BMI ≥25 kg/m^2)	16/43 (37%)	31/72 (43%)	45/83 (54%)	25/55 (45%)	14/43 (33%)	0·585
Weight gain >7% from baseline	23/43 (53%)	45/72 (63%)	71/83 (86%)	36/55 (65%)	16/43 (37%)	0·053
Weight change from baseline (kg)	7·3 (1·8)	9·7 (1·7)	13·9 (1·7)	10·5 (1·8)	4·8 (1·9)	<0·0001
Prolactin (U/L)§						
Hyperprolactinaemia¶	12/27 (44%)	42/47 (89%)	29/58 (50%)	15/37 (41%)	12/24 (46%)	0·017
Change from baseline						
Mean (SE)	–0·4 (0·3)	0·5 (0·2)	–0·2 (0·1)	–0·2 (0·1)	–1·2 (0·4)	
Median (IQR)	0·0 (–0·3 to 0·1)	0·5 (0·1 to 1·4)	–0·2 (–0·6 to 0·1)	–0·1 (–0·4 to 0·1)	–0·4 (–2·7 to 0·1)	
Per month in study	–0·04 (0·03)	0·12 (0·04)	–0·03 (0·02)	–0·04 (0·02)	–0·16 (0·05)	<0·0001
Fasting glucose (mmol/L)§						
Hyperglycaemia‖	6/33 (18%)	11/53 (21%)	19/63 (30%)	9/41 (22%)	7/32 (22%)	0·794
Change from baseline						
Mean (SE)	0·4 (0·2)	0·5 (0·1)	0·5 (0·1)	0·5 (0·1)	0·2 (0·2)	
Median (IQR)	0·3 (0·0 to 0·9)	0·5 (0·0 to 1·0)	0·5 (0·1 to 1·0)	0·4 (0·0 to 0·9)	0·3 (–0·2 to 0·9)	
Per month in study	0·04 (0·03)	0·07 (0·02)	0·07 (0·02)	0·06 (0·02)	0·04 (0·02)	0·699

(Continues on next page)

Table 4 shows the outcomes of safety and tolerability. One patient died (suicide) during the follow-up period. Rates of admission to hospital were 7–23%, and did not differ significantly between groups (table 4). Higher proportions of patients on haloperidol or ziprasidone had akathisia than did those on other antipsychotic drugs

	Haloperidol	Amisulpride	Olanzapine	Quetiapine	Ziprasidone	p value
(Continued from previous page)						
Cholesterol (mmol/L)§						
Hypercholesterolemia**	15/33 (45%)	24/53 (45%)	37/66 (56%)	12/43 (28%)	17/32 (53%)	0·276
Change from baseline						
Mean (SE)	0·5 (0·3)	0·7 (0·2)	0·8 (0·1)	0·6 (0·1)	0·4 (0·2)	
Median (IQR)	0·7 (–0·2 to 1·3)	0·5 (0·1 to 1·4)	0·7 (0·2 to 1·3)	0·6 (0·1 to 1·1)	0·3 (–0·2 to 1·0)	
Per month in study	0·04 (0·05)	0·11 (0·02)	0·11 (0·02)	0·07 (0·02)	0·04 (0·02)	0·144
HDL (mmol/L)§						
Low concentration of HDL††	6/32 (19%)	15/53 (28%)	16/65 (25%)	8/43 (19%)	5/32 (16%)	0·894
Change from baseline						
Mean (SE)	–0·1 (0·1)	–0·2 (0·0)	–0·1 (0·0)	–0·1 (0·1)	–0·1 (0·0)	
Median (IQR)	–0·1 (–0·2 to 0·1)	–0·1 (–0·3 to 0·1)	–0·1 (–0·4 to 0·0)	0·0 (–0·2 to 0·1)	–0·1 (–0·2 to 0·1)	
Per month in study	–0·02 (0·01)	–0·02 (0·01)	–0·02 (0·01)	–0·01 (0·01)	–0·01 (0·01)	0·894
LDL (mmol/L)§						
High concentration of LDL‡‡	16/31 (52%)	23/52 (44%)	35/66 (53%)	13/42 (31%)	13/32 (41%)	0·602
Change from baseline						
Mean (SE)	0·5 (0·2)	0·7 (0·2)	0·7 (0·1)	0·7 (0·1)	0·3 (0·1)	
Median (IQR)	0·4 (0·0 to 1·5)	0·5 (–0·1 to 1·2)	0·6 (0·1 to 1·3)	0·7 (0·1 to 1·0)	0·1 (–0·2 to 0·9)	
Per month in study	0·05 (0·04)	0·11 (0·03)	0·09 (0·02)	0·09 (0·02)	0·03 (0·02)	0·303
Fasting insulin (mU/L)§						
Change from baseline						
Mean (SE)	2·0 (1·4)	8·6 (3·1)	2·5 (3·9)	2·1 (1·2)	0·1 (2·0)	
Median (IQR)	3·0 (–2·3 to 6·0)	2·5 (–0·3 to 11·5)	4·0 (0·3 to 11·0)	1·0 (–1·0 to 3·5)	0·0 (–3·0 to 4·0)	
Per month in study	0·31 (0·24)	1·04 (0·36)	0·58 (0·35)	0·11 (0·14)	–0·13 (0·25)	0·080
Triglycerides (mmol/L)§						
Hypertriglyceridaemia§§	13/33 (39%)	19/53 (36%)	26/66 (39%)	11/42 (26%)	10/32 (31%)	0·908
Change from baseline						
Mean (SE)	0·2 (0·1)	0·5 (0·1)	0·3 (0·1)	0·3 (0·1)	0·1 (0·2)	
Median (IQR)	0·1 (–0·2 to 0·8)	0·4 (0·1 to 0·9)	0·3 (–0·1 to 0·7)	0·2 (–0·2 to 0·7)	0·1 (–0·3 to 0·4)	
Per month in study	0·02 (0·02)	0·07 (0·02)	0·04 (0·02)	0·04 (0·02)	0·02 (0·02)	0·439
Electrocardiographical findings						
Prolonged QTc interval¶¶	1/19 (5%)	1/42 (2%)	3/43 (7%)	2/22 (9%)	0/21 (0%)	0·459
Concomitant drug						
Lithium	0/103 (0%)	0/104 (0%)	3/105 (3%)	3/104 (3%)	0/82 (0%)	*
Mood stabilisers/anticonvulsants	26/103 (25%)	19/104 (18%)	25/105 (24%)	26/104 (25%)	17/82 (21%)	0·096
Antidepressants	19/103 (18%)	13/104 (13%)	30/105 (29%)	6/104 (6%)	8/82 (10%)	<0·0001
Hypnotics or sedatives	17/103 (17%)	17/104 (16%)	24/105 (23%)	24/104 (23%)	15/82 (18%)	0·366
Anxiolytic drugs	53/103 (51%)	56/104 (54%)	58/105 (55%)	50/104 (48%)	36/82 (44%)	0·170
Anticholinergic drugs	46/103 (45%)	35/104 (34%)	23/105 (22%)	20/104 (19%)	18/82 (22%)	<0·0001

Data are n/N (%) or mean (SE), unless otherwise indicated. SHRS=St Hans rating scale. UKU=udvalg for kliniske undersøgelser. Denominators fluctuate because of incomplete data. p values are based on tests that compare all treatment groups (four degrees of freedom), accounting for time at risk and adjusting for country. *p values could not be estimated because of low numbers of events. †Percentages are based on the number of patients with at least one follow-up assessment (SHRS and UKU: 1, 3, 6, 9, 12 months)—patients scored positive on at least one evaluation. The analyses on extrapyramidal symptoms were also adjusted for the use of anticholinergic drugs before extrapyramidal symptoms. UKU: cases scored moderate/severe on severity of sexual dysfunction. ‡Percentages and change scores are based on the patients with at least one follow-up assessment (3, 6, 9, 12 months). The maximum weight measured during follow-up was analysed for overweight and weight gain; mean weight change scores were estimated at 12 months. §Percentages are based on the number of patients with at least one assessment after baseline (6 and 12 months). The highest lab value measured during follow-up and the corresponding blood collection date were selected for the analyses. For HDL we selected the lowest lab value. ¶Hyperprolactinaemia: men >0·38 U/L; women >0·53 U/L (men >18 ng/mL; women >25 ng/mL; to convert values in ng/mL to U/L we arbitrarily used a conversion factor of 0·0212).[20] ||Hyperglycaemia: fasting glucose concentration ≥5·55 mmol/L. **Hypercholesterolaemia: cholesterol concentration ≥5·17 mmol/L. ††Low concentration of HDL <1·03 mmol/L. ‡‡High concentration of LDL ≥3·36 mmol/L. §§Hypertriglyceridaemia: triglyceride concentration ≥1·69 mmol/L.¶¶QTc prolongation at 12 months: men >450 mseconds, women >470 mseconds.

Table 4: **Outcomes of safety and tolerability**

(overall p=0·007; table 4), and more patients on haloperidol showed signs of parkinsonism than did those assigned to a second-generation antipsychotic drug (overall p<0·0001; table 4). Higher proportions of patients on haloperidol or amisulpride used anticholinergic drugs (overall p<0·0001; table 4), and higher proportions of patients on olanzapine used antidepressants (overall p<0·0001; table 4). The proportion of patients who were overweight or who had more than 7% weight gain from baseline was high, but did not differ significantly between treatment groups (table 4). Weight change from baseline was highest for patients on olanzapine, and lowest for patients on haloperidol or ziprasidone (overall p<0·0001; table 4). More patients on amisulpride had hyperprolactinaemia than did those on the other antipsychotic drugs (overall p=0·017; table 4), and taking amisulpride resulted in greater increases in prolactin values per month (overall p<0·0001; table 4). We recorded no other significant differences in laboratory values between treatment groups (table 4).

Subgroup analyses for sex, suicidality, and substance abuse did not show statistically significant differences on all-cause treatment discontinuation between patients on haloperidol and those taking second-generation antipsychotic drugs (data not shown). Our results did not change after exclusion of patients who did not take the assigned antipsychotic drug, or did not meet the inclusion criteria (data not shown).

Discussion

Our study has shown that in patients with first-episode schizophrenia and schizophreniform disorder, treatment discontinuation over 12 months was significantly greater in patients given a low dose of haloperidol than in those assigned to treatment with second-generation antipsychotic drugs, with the lowest discontinuation with olanzapine. However, symptomatic improvement (measured by PANSS) and rates of admission to hospital did not differ significantly between groups. Global improvement as measured with the CGI or GAF scales differed between treatments, with most improvement recorded with amisulpride and least with quetiapine and haloperidol.

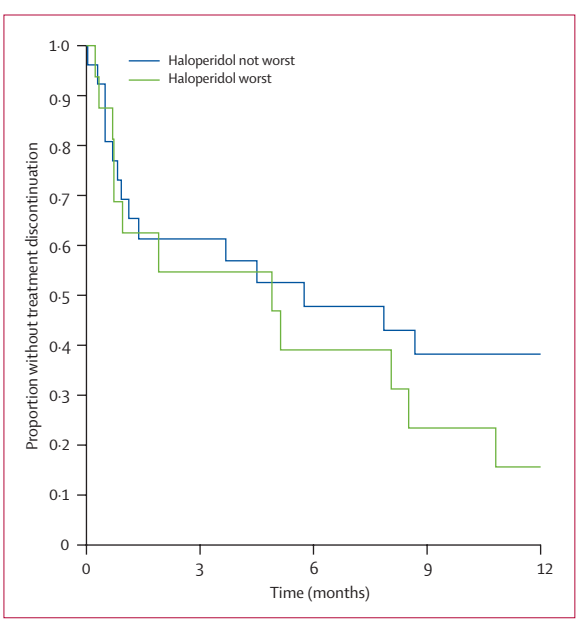

Figure 4: **Time to treatment discontinuation for any cause in patients assigned to haloperidol at sites at which the coordinator thought that haloperidol was the worst option, versus sites at which the coordinator believed that it was not**

Side-effects varied—signs of parkinsonism were more frequent with haloperidol than with second-generation antipsychotic drugs, whereas weight change was most pronounced in patients on olanzapine, and lowest in those on haloperidol and ziprasidone. Patients on haloperidol and amisulpride were most likely to be prescribed anticholinergic drugs, and patients on olanzapine were prescribed antidepressants most often. We noted few patients with dystonia, even in the haloperidol group, suggesting that the low dose used in this study is well tolerated in this respect. Overall, the side-effects that we recorded are generally consistent with those from other studies, although the findings on antidepressant prescription were different from those of a previous study, in which olanzapine decreased depressive symptoms in patients with schizophrenia.[19] Schooler and colleagues[20] undertook a large (n=555), double-blind, randomised trial comparing the effects of risperidone (mean dose 3·3 mg)—a second-generation antipsychotic drug—with a low dose of haloperidol (2·9 mg), in patients with recent onset schizophrenia, over 1 year. The primary outcome was the number of relapses, but discontinuation rates were also reported, and did not significantly differ between the two groups—around 36·5% for haloperidol, and 42% for risperidone. Patients with drug abuse and concomitant drugs were excluded, and previous antipsychotic treatment was allowed for up to 12 weeks. In another double-blind study of 263 patients with first-episode schizophrenia,[30] haloperidol (mean dose 4·8 mg) was compared with olanzapine (10·2 mg) over a 2-year follow-up. This sample was predominantly male (82%), and previous treatment was kept to a maximum of 16 weeks. Patients who abused drugs were excluded. Estimated discontinuation rates at 1 year (data extrapolated by us) were much higher than in our study—about 75% for the haloperidol group and around 65% for olanzapine, with a significantly larger group continuing treatment with olanzapine than with haloperidol at 2 years.[30] Although the discontinuation rate for haloperidol in that double-blind study was similar to that in our trial, the rate with olanzapine was substantially higher than it was in our sample. A 1-year double-blind study comparing effectiveness, defined as completion rates on the assigned drug, between olanzapine, quetiapine, and risperidone (n=400), in patients with recent onset schizophrenia reported low completion rates, of

about 30%.[31] Discontinuation rates did not differ between the drugs tested.

In a double-blind study, the CATIE trial compared the effectiveness of second-generation antipsychotic drugs with that of the low-potency first-generation drug perphenazine:[8] 1493 patients with chronic schizophrenia were randomly assigned to olanzapine, quetiapine, risperidone, ziprasidone, and perphenazine. Consistent with our results, when insufficient efficacy was the reason for discontinuation, time to discontinuation was longer in the olanzapine group than in the perphenazine and quetiapine groups. However, we noted that olanzapine also showed a longer time to discontinuation than did ziprasidone, which was different from what was reported in CATIE. Furthermore, discontinuation rates with second-generation antipsychotic drugs were substantially lower in our study.

Just as discontinuation rates were lower in our study than in other trials, symptomatic improvement was more pronounced than in other long-term studies of first-episode schizophrenia. Although symptom severity at baseline was comparable with that in other studies[20,30,31] (ie, PANSS scores of around 75–90), we recorded a symptom reduction of around 35 points, whereas in most other studies it varied from 18 to 21. The minimum score on the PANSS is 30, meaning that the symptom reduction in this study was more than 60%, which is regarded as a clinically meaningful response.[32] By contrast, other studies recorded symptom reductions of 40%.[20,31] At 12 months of treatment, mean global functioning was good: borderline mentally ill to mildly ill on the severity of illness scale (CGI), with mean overall functioning (GAF) scores of more than 65 (ie, moderate to mild symptoms, or moderate to some difficulty in social, occupational, or educational functioning).

How can we account for the differences between our results and those of previous studies? Patients with first-episode schizophrenia are likely to do better than are those with chronic schizophrenia—partly because they might be more sensitive to drugs, and partly because they are a much more heterogeneous group. Notably, two-fifths of our patients met the diagnostic criteria for schizophreniform disorder, but not for schizophrenia or schizoaffective disorder, so might have been especially likely to respond to treatment. Our trial was an open trial, in which patients may respond better to treatment than in double-blind trials. We did not include a placebo group: indeed, long-term placebo studies are very rare in schizophrenia. However, a study that followed up chronic patients for at least 1 year reported symptomatic worsening of around 30% in patients on placebo,[33] increasing the likelihood that the improvement reported in our patients was clinically meaningful. We used broad inclusion criteria, aiming to make our findings as externally valid as possible. 40% of our patients were women, a proportion similar to that in the population with schizophrenia.[34]

We did not use the same selection of drugs as did other trials. Notably, we used the high-potency first-generation drug haloperidol, whereas CATIE used perphenazine—which, like chlorpromazine, is a low-potency drug. Low-potency first-generation antipsychotic drugs, especially in low doses, might not be more likely than second-generation drugs to cause extrapyramidal symptoms.[4]

Patients are not treated in a vacuum, and systems of health care and social care differ between the USA and Europe. The extent to which this might affect outcomes remains a matter of speculation.

How do we explain the discrepancy between PANSS scores and readmission rates, on the one hand, and discontinuation rates, on the other? Patients were not significantly more likely to be non-adherent to haloperidol than to be non-adherent to other drugs. Moreover, the discontinuation rates of haloperidol were much closer to those of risperidone and olanzapine in two earlier double-blind long-term studies.[19,20] We therefore wondered whether expectations of psychiatrists could have led to haloperidol being discontinued more often, in our open study. Such an occurence would have important implications for the interpretation of trials in psychiatry, since even in double-blind studies, blindness can often not be fully maintained, because different drugs tend to have different side-effects—so the results of effectiveness trials could reflect provider bias.

We assessed provider expectations at the end of the study, but before any of the analyses were undertaken. We obtained data from 32 (64%) of the 50 site coordinators. 11 (34%) site coordinators expected haloperidol to lead to the worst outcome, and 21 (66%) of them thought that it be no worse than the second-generation drugs. We tested whether discontinuation rates for haloperidol were different for patients from the sites at which haloperidol was expected to do worse than in the other sites, and noted a non-significant difference (HR 1·39 [95% CI 0·28–6·97], p=0·69; figure 4).

We conclude that although the high continuation rates for several of the second-generation antipsychotic drugs suggest that clinically meaningful long-term antipsychotic treatment is achievable in the first-episode of schizophrenia, it cannot be concluded that second-generation antipsychotic drugs are more efficacious than is haloperidol in the treatment of these patients.

Contributors

RSK, WWF, MD, IPMK, and SG designed the study. RSK and WWF obtained funding and supervised the study. HB and YV analysed the data. RSK, WWF, HB, YV, and DEG interpreted the data and RSK, HB, and YV drafted the report. MD, IPMK, MDG, JKR, SG, JL, MH, SD, JJL-I, LGH, WG, JP, NL, AR-R participated in the collection of data. All authors participated in the critical revision of the report and approved the final report.

EUFEST (European First-Episode Schizophrenia Trial) Study Group

Principal investigators: R S Kahn, W W Fleischhacker.
Executive committee: R S Kahn, I P M Keet (trial coordinator until July 2004), H Boter (trial coordinator since July 2004).

Management group: R S Kahn, W W Fleischhacker, H Boter, C Brugman, H Burger, D E Grobbee, M C Hafkamp, I P M Keet, K Nijssen.
Steering Committee: R S Kahn, W W Fleischhacker, H Boter, I P M Keet, C Brugman, M Davidson, S Dollfus, W Gaebel, S Galderisi, M Gheorghe, I Gonen, D E Grobbee, L G Hranov, M Hummer, J Libiger, N Lindefors, J J López-Ibor, K Nijssen, J Peuskens, A Riecher-Rössler, J K Rybakowski, G Sedvall, M v Wilmsdorff.
Office manager: P C Ywema.
Julius Centre Study Team: data management—N Boekema, H den Breeijen, M van den Haak, P Huizinga, R Veen; project managers—C Brugman, M C Hafkamp, K M Nijssen; site monitoring—P Berackova, A Blizanowska, C Brugman, M C Hafkamp, T Huizinga, H van Gelderen, M Gordat, S Lorteau, G Makhanlal, H Moqadar.
Tangent Data Study Team (co-monitoring Romania): I Gonen, A Mihailescu, R Radici, C Zus.
Participating investigators (CC=country coordinator; SC=site coordinator), centres, and countries: Austria—M Hummer (CC and SC Innsbruck), M Muhlbacher (SC Salzburg), H Widmoser (SC Hall in Tirol); *Belgium*—J Peuskens (CC), J Hulselmans (SC Antwerpen), C Mertens (SC Gent), E Thijs (SC Kortenberg); *Bulgaria*—L G Hranov (CC and SC Sofia), S Georgiev (SC Plovdiv), L Sayan (SC Bourgas); *Czech Republic*—J Libiger (CC and SC Hradec Králové), E Češková (SC Brno), D Seifertová (SC Praha-Bohnice); *France*: S Dollfus (CC and SC Caen I), G Allio (SC Rouen), B Chabot (SC Caen II), A Navarre Coulaud (SC Dieppe), P Thomas (SC Lille); *Germany*—W Gaebel (CC), M Krebs (SC Berlin), R Lencer (SC Lübeck), K Leopold (SC Berlin), T Wobrock (SC Homburg); *Israel*—M Davidson (CC), Y Abramovitch (SC Beer-Yaakov), D Amital (SC Ness Ziona), A Caspi (SC Ramat Gan), A Kaplan (SC Beer Sheva), I Treves (SC Shalvata), P Zipris (SC Pardessiya); *Italy*—S Galderisi (CC), M Casacchia (SC L' Aquila), G Invernizzi (SC Milano II), A Mucci (SC Naples), S Scarone (SC Milano I), A Vita (SC Melzo); *Netherlands*—H Boter (CC and SC Utrecht), I P M Keet (CC and SC Utrecht); *Poland*—J K Rybakowski (CC and SC Poznan), M Jarema (SC Warsaw), M Masiak (SC Lublin), J Rabe-Jablonska (SC Lodz); *Romania*—M Gheorghe (CC), V Burtea (SC Brasov), P Boisteanu (SC Iasi), C Friedman (SC Constanta), M Ienciu (SC Timisoara), A Ionescu (SC Buzau), I Miclutia (SC Cluj), T Mihai (SC Tulcea), D Prelipceanu (SC Bucuresti II), T Udistroiu (SC Craiova), D Vasile (SC Bucuresti I); *Spain*—J J López Ibor (CC), J L Carrasco (SC Madrid); *Sweden*—N Lindefors (CC and SC Stockholm), G Sedvall (CC), F A Wiesel (SC Uppsala); *Switzerland*—A Riecher-Rössler (CC), U Gschwandtner (SC Basel)

Conflict of interest statement

RSK has received grants, honoraria for education programmes, or served as consultant for Astellas, AstraZeneca, BMS, Eli Lilly, Janssen-Cilag, Pfizer, Roche, and Sanofi-Aventis. WWF has received research grants from BMS/Otsuka, Eli Lilly, Janssen-Cilag, and Servier; honoraria for educational programmes from AstraZeneca and Pfizer; speaking fees from AstraZeneca, BMS/Otsuka, Janssen-Cilag, and Pfizer; and advisory board honoraria from AstraZeneca, BMS/Otsuka, Janssen-Cilag, Servier, and Wyeth. MD has received research grant support, travel support, speaker fees, or consultancy fees from JNJ, Pfizer, Lundbeck, Teva, BioLineRx, Eli Lilly, Sanofi-Aventis, Roche, Servier, and Tangent Data. JKR has acted as a consultant or as a speaker for Adamed-Poland, Bristol-Myers Squibb, Eli Lilly, Janssen-Cilag, Lundbeck, Organon, Pfizer, Sanofi-Aventis, and Servier. JL has received speaker's honoraria, travel grants, or consultancy fees from Eli Lilly, Bristol-Myers Squibb, Lundbeck, and Servier. JL was a member of the advisory boards of Eli Lilly and Bristol-Myers Squibb and he is a faculty member of the Lundbeck Institute (Lundbeck Neuroscience Foundation). MH has received speaking fees and financial support for visiting congresses from Janssen-Cilag, Sanofi-Aventis, Pfizer, and Bristol-Myers Squibb. JJL-I is member of the scientific committee of Fundación Lilly (Spain), Wyeth member of the global strategy consultant board, and board member of the Lundbeck Neuroscience Foundation (LINF). JJL-I has attended several meetings financed by Eli Lilly, Bristol-Myers Squibb, GlaxoSmithKline, and Lundbeck. LGH has received speaker's honoraria, sponsorship for congresses, or investigator's fees from Bristol-Myers Squibb, Corcept Therapeutics, GlaxoSmithKline, Eli Lilly, Sanofi-Aventis, and Lundbeck. WG is or has been a member of the speaker bureau for AstraZeneca GmbH, Bristol-Myers Squibb GmbH and Co KG, GlaxoSmithKline, Janssen-Cilag GmbH, Lilly Deutschland GmbH, Lundbeck GmbH, and Sanofi-Synthelabo GmbH/Aventis. WG is member of the advisory board for Lilly Deutschland GmbH, Lundbeck GmbH, Novartis Pharma GmbH, and Wyeth Pharma GmbH. WG has received or is currently receiving research grants from Bristol-Myers Squibb GmbH and Co KG, Lilly Deutschland GmbH, Wyeth Pharma GmbH, Janssen-Cilag GmbH, and Lundbeck GmbH. JP has received consultancy fees and research grants from and participated in clinical trials sponsored by AstraZeneca, Sanofi-Aventis, Eli Lilly, Pfizer, and Janssen-Cilag. AR-R has received unconditional grants from Eli Lilly, Janssen-Cilag, AstraZeneca, Bristol-Myers Squibb, and Lundbeck. AR-R is a member of advisory boards of Janssen-Cilag and Eli Lilly. HB, YV, IPMK, MDG, SG, SD, NL, and DEG declare that they have no conflict of interest.

Acknowledgments

We thank all patients who participated in the study and M Edlinger from the Julius Center for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht, Netherlands (currently at Department of General and Transplant Surgery, University Hospital Innsbruck, Austria), who advised on the statistical analyses. EUFEST was funded by the European Group for Research in Schizophrenia (EGRIS) with grants from AstraZeneca, Pfizer, and Sanofi-Aventis. The representatives of these companies were allowed to comment on the report, but the final approval of content was exclusively retained by the investigators.

References

1 Davis JM, Chen N, Glick ID. A meta-analysis of the efficacy of second-generation antipsychotics. *Arch Gen Psychiatry* 2003; **60:** 553–64.
2 Geddes J, Freemantle N, Harrison P, Bebbington P. Atypical antipsychotics in the treatment of schizophrenia: systematic overview and meta-regression analysis. *BMJ* 2000; **321:** 1371–76.
3 Leucht S, Pitschel-Walz G, Abraham D, Kissling W. 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. *Schizophr Res* 1999; **35:** 51–68.
4 Leucht S, Wahlbeck K, Hamann J, Kissling W. New generation antipsychotics versus low-potency conventional antipsychotics: a systematic review and meta-analysis. *Lancet* 2003; **361:** 1581–89.
5 Rummel C, Hamann J, Kissling W, Leucht S. New generation antipsychotics for first episode schizophrenia. *Cochrane Database Syst Rev* 2003; **4**: CD004410.
6 Stroup TS, Alves WM, Hamer RM, Lieberman JA. Clinical trials for antipsychotic drugs: design conventions, dilemmas and innovations. *Nat Rev Drug Discov* 2006; **5:** 133–46.
7 Fleischhacker WW, Keet IP, Kahn RS. The European First Episode Schizophrenia Trial (EUFEST): Rationale and design of the trial. *Schizophr Res* 2005; **78:** 147–56.
8 Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med* 2005; **353:** 1209–23.
9 Kemmler G, Hummer M, Widschwendter C, Fleischhacker WW. Dropout rates in placebo-controlled and active-control clinical trials of antipsychotic drugs: a meta-analysis. *Arch Gen Psychiatry* 2005; **62:** 1305–12.
10 Suhara T, Okubo Y, Yasuno F, et al. Decreased dopamine D2 receptor binding in the anterior cingulate cortex in schizophrenia. *Arch Gen Psychiatry* 2002; **59:** 25–30.
11 Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998; **59** (suppl 20)**:** 22–33.
12 Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 1987; **13:** 261–76.
13 Guy W. Clinical Global Impressions (CGI) Scale. In: Rush AJ Jr, Pincus HA, First MB, et al (eds). Handbook of Psychiatric Measures. Washington, DC: American Psychiatric Association, 2000: 100–02.
14 Jones SH, Thornicroft G, Coffey M, Dunn G. A brief mental health outcome scale-reliability and validity of the Global Assessment of Functioning (GAF). *Br J Psychiatry* 1995; **166:** 654–59.

15 Addington D, Addington J, Maticka-Tyndale E, Joyce J. Reliability and validity of a depression rating scale for schizophrenics. *Schizophr Res* 1992; **6:** 201–08.

16 Priebe S, Huxley P, Knight S, Evans S. Application and results of the Manchester Short Assessment of Quality of Life (MANSA). *Int J Soc Psychiatry* 1999; **45:** 7–12.

17 Gerlach J, Korsgaard S, Clemmesen P, et al. The St Hans Rating Scale for extrapyramidal syndromes: reliability and validity. *Acta Psychiatr Scand* 1993; **87:** 244–52.

18 Lingjaerde O, Ahlfors UG, Bech P, Dencker SJ, Elgen K. The UKU side effect rating scale. A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. *Acta Psychiatr Scand Suppl* 1987; **334:** 1–100.

19 Lieberman JA, Tollefson G, Tohen M, et al, for the HGDH Study Group. Comparative efficacy and safety of atypical and conventional antipsychotic drugs in first-episode psychosis: a randomized, double-blind trial of olanzapine versus haloperidol. *Am J Psychiatry* 2003; **160:** 1396–404.

20 Schooler N, Rabinowitz J, Davidson M, et al. Risperidone and haloperidol in first-episode psychosis: a long-term randomized trial. *Am J Psychiatry* 2005; **162:** 947–53.

21 McEvoy JP, Hogarty GE, Steingard S. Optimal dose of neuroleptic in acute schizophrenia. A controlled study of the neuroleptic threshold and higher haloperidol dose. *Arch Gen Psychiatry* 1991; **48:** 739–45.

22 Remington G, Kapur S, Zipursky RB. Pharmacotherapy of first-episode schizophrenia. *Br J Psychiatry Suppl* 1998; **172:** 66–70.

23 Stone CK, Garve DL, Griffith J, Hirschowitz J, Bennett J. Further evidence of a dose-response threshold for haloperidol in psychosis. *Am J Psychiatry* 1995; **152:** 1210–12.

24 Kapur S, Remington G, Jones C, et al. High levels of dopamine D2 receptor occupancy with low-dose haloperidol treatment: a PET study. *Am J Psychiatry* 1996; **153:** 948–50.

25 Kapur S, Zipursky R, Roy P, et al. The relationship between D2 receptor occupancy and plasma levels on low dose oral haloperidol: a PET study. *Psychopharmacology (Berl)* 1997; **131:** 148–52.

26 Kapur S, Zipursky R, Jones C, Remington G, Houle S. Relationship between dopamine D(2) occupancy, clinical response, and side effects: a double-blind PET study of first-episode schizophrenia. *Am J Psychiatry* 2000; **157:** 514–20.

27 Pocock SJ. Clinical trials: a practical approach. Chichester: Wiley, 1993.

28 Kemp R, Hayward P, Applewhaite G, Everitt B, David A. Compliance therapy in psychotic patients: randomised controlled trial. *BMJ* 1996; **312:** 345–49.

29 Goldstein H, Healy MJR, Rasbash J. Multi-level time series models with applications to repeated measure data. *Stat Med* 1994; **13:** 1643–55.

30 Green AI, Lieberman JA, Hamer RM, et al. Olanzapine and haloperidol in first episode psychosis: two-year data. *Schizophr Res* 2006; **86:** 234–43.

31 McEvoy JP, Lieberman JA, Perkins DO, et al. Efficacy and tolerability of olanzapine, quetiapine, and risperidone in the treatment of early psychosis: a randomized, double-blind 52-week comparison. *Am J Psychiatry* 2007; **164:** 1050–60.

32 Leucht S, Kane JM, Etschel E, Kissling W, Hamann J, Engel RR. Linking the PANSS, BPRS, and CGI: clinical implications. *Neuropsychopharmacol* 2006; **31:** 2318–25.

33 Arato M, O'Connor R, Meltzer HY. A 1-year, double-blind, placebo-controlled trial of ziprasidone 40, 80 and 160 mg/day in chronic schizophrenia: the Ziprasidone Extended Use in Schizophrenia (ZEUS) study. *Int Clin Psychopharmacol* 2002; **17:** 207–15.

34 Aleman A, Kahn RS, Selten JP. Sex differences in the risk of schizophrenia: evidence from meta-analysis. *Arch Gen Psychiatry* 2003; **60:** 565–71.