EFFECTIVENESS OF ANTIPSYCHOTIC DRUGS IN FIRST-EPISODE SCHIZOPHRENIA AND SCHIZOPHRENIFORM DISORDER.

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SUMMARY

Background: A new generation of antipsychotics was introduced over a decade ago for the treatment of schizophrenia. However, despite a multitude of studies, their purported clinical superiority is still a matter of debate. This may be partly due to the short duration, restrictive inclusion criteria, and inappropriate outcome measures used in most studies. Pragmatic trials can overcome these limitations.

Methods: This multinational study including 50 sites in 14 countries examined effectiveness, operationalised as continued use of the allotted medication, of the second generation antipsychotics, amisulpride, quetiapine, olanzapine, and ziprasidone in first episode schizophrenia with minimal prior exposure to antipsychotic treatment over a one-year period, in a pragmatic, randomized, open design. The dose of the comparator, haloperidol, was maximized at 4 mg daily. Cox proportional-hazards regression models were used to calculate differences between haloperidol and the four new antipsychotics with adjustments for gender and country.

Findings: 498 patients enrolled, 40% were female and 33% were antipsychotic naive at randomization. The mean daily doses were 2.9 mg for haloperidol, 449 mg for amisulpride, 12.5 mg for olanzapine, 501 mg for quetiapine, 114 mg for ziprasidone. Haloperidol was discontinued prematurely in 61% of patients, while discontinuation was significantly less common on olanzapine (HR 0.27; $p<0.001$), amisulpride (HR 0.36; $p<0.001$), quetiapine (HR 0.49; $p<0.001$), and ziprasidone (HR 0.47; $p=0.002$).

Interpretation: Continuation rates on several of the second generation antipsychotics in this pragmatic trial were high, suggesting that effective and clinically meaningful long-term antipsychotic treatment is achievable in the first stages of schizophrenia.

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INTRODUCTION

A new generation of antipsychotics was introduced over a decade ago with the goal of combining superior efficacy with a diminished propensity to induce (motor) side-effects in the treatment of schizophrenia. However, despite a multitude of studies, their purported clinical superiority is still a matter of debate.[1-5] Indeed, as has been recently argued convincingly, the conclusions that can be drawn from the efficacy studies is limited.[6] Most studies used restrictive inclusion criteria, leading to overrepresentation of males and under-representation of drug-abusing patients and those with co-morbid illness. Moreover, treatment response in these efficacy studies is almost exclusively based on reductions in psychosis rating scales, capturing only one, and arguably not the most relevant, outcome measure in schizophrenia. Finally, studies have generally been shorter than two months which may not be appropriate for an illness potentially lasting a lifetime.[6-8]

It has been suggested by us and others that there is a dire need for studies that are unrestrictive in the inclusion of patients, use long follow-up periods and employ clinically meaningful outcome measures.[6,7] One such outcome is the time patients continue to use their allotted study medication, capturing as it does both efficacy and tolerability, called effectiveness, of the medicines studied. Interestingly, retainment in treatment trials in schizophrenia is very low, usually less than 50-60%, even in short-term studies. Although this may be in part attributable to the presence of a placebo group in some of those studies[9] large drop-out rates are a common feature of all antipsychotic efficacy trials in schizophrenia. It has been argued that the large drop-out rate may in part be due to the double-blind design common to most efficacy studies. Moreover, although double-blind studies carry obvious advantages in reducing bias, a disadvantage is that due to their very nature they do not reflect clinical practice. A solution is the pragmatic trial; this method aims to reflect clinical practice

by including unselected patient samples in a randomized, but open, design. Indeed, it has recently been proposed that it is this kind of studies that need to be conducted to test antipsychotic effectiveness in schizophrenia, particularly in the first stages of the illness.[5,6] Examining effectiveness of the newer antipsychotic drugs is particularly relevant in the early stages of schizophrenia.[7] Evidence is abundant that continued treatment is not only paramount in preventing relapse but that psychotic recurrences lead to poorer subsequent treatment response with rates of response declining and time to response increasing.[4,10] Moreover, it has been shown that antipsychotic treatment may limit the progression in brain loss observed in schizophrenia.[11,12] Thus, whether patients will continue using their medication from the moment of first treatment carries long-term consequences for the subsequent course of their illness. This is particularly relevant in the early stages of the illness, since most of the functional decline takes place during that period of the illness (Häfner et al. 1995, for review Riecher-Rössler et al. 2006).

A question that can only be addressed in first-episode schizophrenia is antipsychotic effectiveness in patients that have never, or hardly, been exposed to prior treatment with antipsychotics. Indeed, antipsychotic effectiveness in drug-naïve patients may be quite different from that found in patients who have been exposed to (various) antipsychotics for years or even decades. One of the reasons may be biological, i.e. dopamine receptor sensitivity is most likely substantially different in patients who have had no prior exposure to the dopamine antagonistic effects of antipsychotics than in chronically treated patients.[13] Another reason may be methodological: trials in chronic patients often involve patients who are included for the very reason that they failed to respond adequately to, or were non-compliant with, previous treatment(s).

This study examined effectiveness of several second generation antipsychotics (SGA) in first episode schizophrenia with minimal prior exposure to antipsychotic treatment. The dose of the comparator, haloperidol, was maximized at 4 mg daily, since it has been shown that first-episode patients respond to low doses of antipsychotics.[14,15] Furthermore, higher doses do not increase its antipsychotic effect but do enhance the risk of side effects, especially in first-episode patients.[16-21]

METHODS

Setting and participants

The study's design has been described previously in more detail.[7] Before the start of the trial, investigators were trained in the research procedures and the assessments of outcomes, including the use of video tapes. A total of 50 sites participated in 13 European countries and Israel (see Appendix). Eligible patients were 18-40 years of age and met DSM IV criteria for schizophrenia, schizophreniform, or schizoaffective disorder confirmed by the Mini International Neuropsychiatric Interview Plus (MINI+).[22] Patients were excluded if: (1) more than two years had elapsed between onset of positive symptoms and recruitment; (2) any antipsychotic had been used for longer than two weeks in the previous year or for more than a total of six weeks lifetime; (3) patients had a known intolerance to one of the study drugs; (4) patients met any of the contraindications for any of the study drugs as mentioned in the (local) package insert texts. The in- and exclusion criteria were checked by clinical research associates according to guidelines on good clinical practice.

Recruitment and randomization

The treating physicians informed eligible patients orally and in writing on the trial and invited them to participate. Baseline data were obtained between four weeks before and one week after randomization on demographics, diagnoses, current treatment setting, psychopathology (Positive and Negative Syndrome Scale – PANSS)[23]; severity of illness (Clinical Global Impression scale – CGI)[24]; overall psychosocial functioning (Global Assessment of Functioning scale – GAF)[25,26]; extrapyramidal symptoms (EPS; St Hans Rating Scale – SHRS)[27]; and sexual dysfunction (selected items from the Udvalg for Kliniske Undersøgelser

– UKU)[28]. Furthermore, we performed a physical examination including assessments of laboratory data, weight, height, and ECG.

Patients were randomized online to one of the five treatment arms. Since some study drugs were not registered in all participating countries, the minimization procedure was applied to prevent unequal group sizes at the end of the trial, i.e. treatment assignment of new patients depended on the distribution of participants over the treatment arms.[29] However, randomization to ziprasidone was blocked between December 2003 and October 2004 because this procedure assigned ziprasidone to too high numbers of new patients in the few countries where ziprasidone was available. Ziprasidone was randomized again when it became available in more participating countries. This procedure explains the different group sizes (figure 1).

All participants – or their legal representative – gave written informed consent. The trial complied with the Declaration of Helsinki and the ethics committees of the participating centers approved the procedures followed.

Intervention

Patients were randomly assigned to the following drugs: amisulpride 200-800 mg/d, olanzapine 5-20 mg/d, quetiapine 200-750 mg/d, ziprasidone 40-160 mg/d, and haloperidol 1-4 mg/d. All study medication was administered orally within the dose ranges at the treating physician's discretion. Mood stabilizers, benzodiazepines, antidepressants, and anticholinergics were allowed and documented.

Outcome assessment

The primary outcome, Loss of Retention (LOR), was defined by the use – during more than 14 days over a 6-months interval – of: (1) either a dose below the indicated range or complete discontinuation of the study medication, or (2) a dose above the predefined range, or (3) another antipsychotic. The use of any parenteral antipsychotic constituted a LOR-event when it was active for more than 14 days over a 6-months interval; or – in case of multiple parenteral administrations – the active days exceeded 14 days over this interval

Secondary outcomes were: specified reason for a LOR-event (i.e. lack of efficacy, side effects, nonadherence, or other reasons). Data collection of one or more of the following secondary outcomes was targeted at 2 weeks (± 1 week), 4 weeks (idem), 6 weeks (idem), 2 months (idem), 3 months (idem), 6 months (± 1 month), 9 months (idem), and 12 months (idem): psychopathology (PANSS), severity of illness (CGI), treatment setting, psychiatric hospitalization days, serious adverse events, extrapyramidal syndromes (SHRS), sexual dysfunction (selected items of the UKU), weight, local laboratory data, ECG, and concomitant medications. We also assessed psychosocial functioning, depression, quality of life, clinical and social needs, substance abuse, compliance, and some neurocognitive functions. Due to space restrictions results on these measures will be published separately.

Sample size determination

On the basis of prior studies we assumed a LOR-event rate at 12 months after enrolment of 70% in patients treated with haloperidol and 40% in patients treated with SGAs. A sample size of 310 patients was needed based on a two-tailed test (α= 5%), a power of 80%, and Bonferroni corrections for each comparison between the SGAs versus haloperidol. However,

since the actual difference may be smaller because of the use of a low dose of haloperidol, we planned to enroll 500 patients, i.e. 100 patients per group.

Data analysis

Following the intention-to-treat principle, all patients randomized were analyzed in the assigned treatment group, including patients who did not take any dose of the assigned study medication. Following our definition of Loss of Retention (LOR) patients were not at risk within the first 2 weeks after randomization. Consequently, these 2 weeks were not included in the 'time-to-event' (time-to-LOR) analysis. We used Kaplan-Meier methods to estimate the time to the LOR event.

After clustering countries with 15 or fewer patients, Cox proportional-hazards regression models were used to estimate differences between haloperidol and the 4 atypicals with adjustments for gender and country. Differences were expressed in hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) and *p* values. For the secondary analyses we calculated these differences between the four newer antipsychotics and, additionally, we assessed these differences per specific reason why patients had a LOR event, for: lack of efficacy, side effects, or nonadherence. Since investigators could indicate more than one reason for the LOR-event, we decided to rank the options as follows - in order of decreasing importance: lack of efficacy according to the investigator, side effects according to the investigator, patient initiated nonadherence, and other reasons.

A multilevel linear mixed-effects model was used to account for the repeated measures of the secondary end points PANSS and CGI score.[30,31] The model was specified in terms of fixed effects for treatment group, time, the PANSS or CGI score at baseline, gender and country. We also studied the interaction between treatment group and time. To assess the linearity of

PANSS and CGI scores across the study measurements, time squared terms were included in the model. The dependent variable was PANSS or CGI score. Random effects within the model were intercept and slope for individual patients. For tests of statistical significance, variability was assessed within treatment groups with the patient being the unit of observation. For the analyses of secondary outcomes (PANSS, CGI, and safety/tolerability data), data were limited to those assessed before a LOR event occurred. Because of high numbers of extreme outliers, we disregarded all prolactin values from three sites (values exceeded 10 U/L) and all insulin values from one site (values exceeded 200 mU/L).
All statistical tests were two-sided and *p* values less than 0.05 were considered significant.

Role of funding sources

This study was funded through the European Group for Research in Schizophrenia (EGRIS) which in turn received funding from three pharmaceutical companies that had no role in the study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit the paper for publication. Representatives of the industries were nonvoting members of the steering committee.[7]

RESULTS

Subjects

Patients were screened between December 2002 and January 2006. The available data show that 1047 patients were screened of whom 406 patients were not eligible, 143 patients were not randomized (121 patients declined informed consent), and 498 patients were randomized to one of the treatment arms (figure 1). Table 1 shows that the groups were well matched. The mean age was 26.0 years. Of the 498 patients enrolled, 200 (40%) were female, 197 (40%) had schizophreniform disorder, and 162 (33%) were antipsychotic naive at randomization. Between randomization and the end of the follow-up some enrolled patients were not eligible: 11 patients (4 on haloperidol, 2 on olanzapine, 2 on quetiapine, and 3 on ziprasidone) turned out to have another cause for the symptoms than schizophrenia; one patient on quetiapine had symptoms for more than two years prior to randomization; and two patients on amisulpride used antipsychotics for more than two weeks in the previous year. Following the intention-to-treat-principle these patients were included in the analysis. The mean daily doses were 2.9 mg for haloperidol, 449 mg for amisulpride, 12.5 mg for olanzapine, 501 mg for quetiapine, 114 mg for ziprasidone (Table 2).

Primary outcome

Table 2 and figure 2a show that time to the LOR event for any cause was significantly shorter in patients on haloperidol than on any of the four SGAs: olanzapine (HR 0.27; $p<0.001$), amisulpride (HR 0.36; $p<0.001$), quetiapine (HR 0.49; $p<0.001$), and ziprasidone (HR 0.47; $p=0.002$). Also, as a group the SGAs showed a longer time to the LOR event compared to haloperidol (HR 0.39; 95% CI 0.29-0.53; $p<0.001$; results not presented in a table or figure).

Secondary outcomes

Loss of Retention

The SGAs did not differ from each other on time to LOR for any cause, except that patients on olanzapine stayed longer on their assigned study drug than those on quetiapine (HR 0.50; $p<0.01$).

Comparing time to LOR because of lack of efficacy (figure 2b and table 2) showed that patients on haloperidol dropped out sooner than those on olanzapine (HR 0.17; $p<0.001$), amisulpride (HR 0.22; $p<0.001$), and ziprasidone (HR 0.51; $p=0.04$) but not quetiapine ($p=0.13$). Also, analyzing the time to treatment discontinuation between the SGAs revealed that patients stayed longer on olanzapine (HR 0.26; $p<0.001$) and on amisulpride (HR 0.36; $p<0.01$) than on quetiapine.

The time to a LOR event because of side effects (figure 2c and table 2) in the haloperidol group was shorter than in the quetiapine group (HR 0.12; $p<0.01$) and the olanzapine group (HR 0.23; $p<0.01$).

Finally, table 2 and figure 2d show that patients on haloperidol did not differ in time to the LOR event due to antipsychotic non-adherence.

PANSS

The decrease of the total PANSS score was statistically significant in all treatment groups (p<0.001; Figure 3). After circa six months the change in PANSS total scores compared with baseline leveled off. Compared with haloperidol, the other four medications showed a lower PANSS score after 12 months of treatment (56.0, 54.2, 53.8, 51.4, and 53.7 for haloperidol, olanzapine, quetiapine, amisulpride and ziprasidone, respectively).

CGI

All treatment groups showed statistically significant reductions on the CGI compared to baseline (p<0.001).

Safety and tolerability

Table 3 shows the outcomes of safety and tolerability. Two patients died during the follow up (suicide). About 20% of the patients were admitted to hospital after randomization, but the proportions did not differ significantly for the five groups.

Differences were found on the prevalence of neurological side effects: higher proportions of patients on haloperidol or ziprasidone experienced akathisia as compared with patients on the other antipsychotics (26-28% vs. 10-16%; p<0.01) and more patients on haloperidol showed signs of Parkinsonism than patients assigned to any of the SGAs (34% vs. 6-17%; p<0.001). Though the proportions of patients being overweight were high (34-54%) and did not differ between treatment arms, weigh gain (>7% from baseline) and weight change (overall and per month) were highest for patients on olanzapine and lowest for patients on haloperidol or ziprasidone (e.g. 86% on olanzapine showed >7% weight gain vs. 39-53% for the other drugs

[p<0.001]; +1.7 kg/month on olanzapine vs. +0.8-1.0 kg/month for the other drugs [p<0.001]).

We found no differences between treatment arms on fasting glucose, cholesterol, high- and low-density lipoprotein, fasting insulin, and triglycerides, except for 89% of patients on amisulpride having hyperprolactinemia, versus 41-50% in patients on other antipsychotics (p<0.001), and amisulpride showing greater increases in prolactin values per month (p<0.001; data not shown in table).

High proportions of patients used concomitant medication with more patients on haloperidol or olanzapine taking antidepressants (15-18% vs. 6-7%; p<0.01). Additionally, higher proportions of patients on haloperidol or amisulpride received anticholinergics (28-36% vs. 17-21%; p<0.01) than the other patients.

Post-hoc analyses

Comparing males and females revealed no differences in time to the LOR event.

Additionally, analyses excluding patients who did not take the assigned antipsychotic or who - after all - did not meet the inclusion criteria did not change the results.

DISCUSSION

The main finding is that effectiveness, expressed as continued use of the assigned study medication, of SGAs was significantly greater than that of a low dose of haloperidol in first-episode schizophrenia and schizophreniform patients. This superior effectiveness could be attributed to both the improved therapeutic efficacy and better tolerability of olanzapine; larger therapeutic efficacy of amisulpride and ziprasidone; and superior tolerability of quetiapine as compared to haloperidol. The overall discontinuation rate varied widely, from 61% for haloperidol to 28% for olanzapine. Patients who completed the entire study on their allotted medication did equally well symptomatically at the end of the 12 months follow-up. About 20% of all patients were (re)admitted to hospital during the follow-up period, but this percentage was not different for the study drugs. Side-effects varied: haloperidol showed more Parkinsonism than the SGAs, while weight gain was most pronounced in patients on olanzapine, and lowest on those on haloperidol and ziprasidone. A higher proportion of patients on haloperidol and amisulpride was prescribed anticholinergic medication.

This is the first study comparing long-term effectiveness of various SGAs with that of a first-generation antipsychotic in a large group of unselected first-episode schizophrenia patients. Indeed, 40% of the patients at baseline were diagnosed as schizophreniform, and a third had never been exposed to prior antipsychotic treatment. Exceptionally for most antipsychotic treatment trials, 40% of the sample was female, reflecting as it does the male to female distribution of this illness in the population.[32] Finally, consistent with the unrestrictive inclusion criteria, a quarter of the patients exhibited suicidal thoughts, 9% suffered from co-morbid depression and almost one in five met criteria for current substance dependence or abuse. Therefore, it is difficult to compare its results to those of earlier studies.

One large study (n=555) compared the effects of risperidone (modal dose 3.3 mg), a SGA, to a low dose of haloperidol (2.9 mg) in a double blind randomized design. Primary outcome was number of relapses, but discontinuation rates were also reported, and were not significantly different for the two groups, i.e. around 36.5% for haloperidol, and 42% for the risperidone group. However, patients with drug (ab)use and concomitant medications were excluded and prior antipsychotic treatment was allowed for up to 12 weeks. Nevertheless these results may suggest that under double-blind conditions dropout rates on haloperidol may be lower than in our study. Similar to our results, akathisia and parkinsonism were more pronounced on haloperidol than on the SGAs.[15]

In another double-blind study in 263 first-episode schizophrenia patients haloperidol (modal dose 4.8 mg) was compared to olanzapine (10.2 mg) over a two year follow-up period. This sample was predominantly male (82%) and prior treatment was maximized at 16 weeks. Drug abuse was excluded. In this study, estimated discontinuation rates at one year (data extrapolated) were considerably higher than in our study: approximately 75% for the haloperidol group and around 65% for olanzapine, with a significantly larger group continuing treatment on olanzapine than on haloperidol at two years.[33]

Low completion rates of around 30% were also found in a one-year study comparing effectiveness, defined as completion rates on the assigned drug, between three SGAs (olanzapine, quetiapine and risperidone, n=400) in patients in the early course of schizophrenia. In contrast to our findings, discontinuation rates did not differ among the compounds tested.[34] Whether the large difference in discontinuation rates between studies can solely be explained by the difference in open versus double blind design remains open to debate.

In chronic schizophrenia, effectiveness of SGAs has been compared to that of the low potency first-generation antipsychotic, perphenazine. In that study, 1493 chronic schizophrenia patients were randomized to olanzapine, quetiapine, risperidone, ziprasidone and perphenazine.[8] Similar to the results in our study, olanzapine was found superior in effectiveness as compared to quetiapine (and versus risperidone, which was not tested in this study). Also consistent with our results, when lack of efficacy was the reason for discontinuation, time to discontinuation was longer in the olanzapine group than in the patients on perphenazine and quetiapine but, as we found, similar to that of ziprasidone. In contrast to that study, overall discontinuation rates in our study were considerably lower, even when groups are compared with the lowest discontinuation rates in both studies: in our study 28% of patients on olanzapine discontinued treatment within a year versus 64% in the other study. It could be argued that this difference may be due to the patient groups studied, since first-episode patients respond better and faster than chronic patients. Also, patients in our study were unlikely to have failed prior treatments (since their prior exposure in the year prior to enrolment was maximized at two weeks), whereas in the study in chronic patients this may have been a reason for inclusion.

It could be argued that results of our study are biased by the open nature of the design. Physicians could have been motivated to discontinue patients on haloperidol earlier than when the study would have been double-blind. However, such a bias contrasts with the high rates of first-generation antipsychotics still being prescribed in Europe. The discontinuation on the patients on haloperidol and quetiapine due to lack of efficacy occurred mostly within the first two months of the study. Whether this is attributable to investigator bias or to a lack of efficacy early in the treatment, or dosing issues, remains unclear.

Interestingly, even though haloperidol was given in a low dose it induced Parkinsonism more than the SGAs; also more patients were prescribed anticholinergic medication while on haloperidol than patients on olanzapine and quetiapine. Indeed, the side-effects observed in this study are generally consistent with those published in other studies and meta-analyses with weight gain most pronounced in patients on olanzapine and least in those on haloperidol and ziprasidone. Interestingly, dystonia was hardly observed, even in the haloperidol group, suggesting that the low dose used in this study is well-tolerated in this regard.

In conclusion, this study found that one year discontinuation rates in an unselected sample of first-episode schizophrenia patients varied widely (between 28 and 61%) and were significantly larger on a low dose of haloperidol than on several of the SGAs. This effect could be explained by improved efficacy and tolerability of olanzapine, increased efficacy of amisulpride and ziprasidone and better tolerability of quetiapine. If patients continued their medication they did equally well on all drugs. Encouragingly, in contrast to most earlier studies in first-episode and chronic schizophrenia, continuation rates on several of the SGAs in this pragmatic trial were high (around 70%) suggesting that effective and clinically meaningful long-term antipsychotic treatment is achievable in the first stages of schizophrenia.

TABLES AND FIGURES

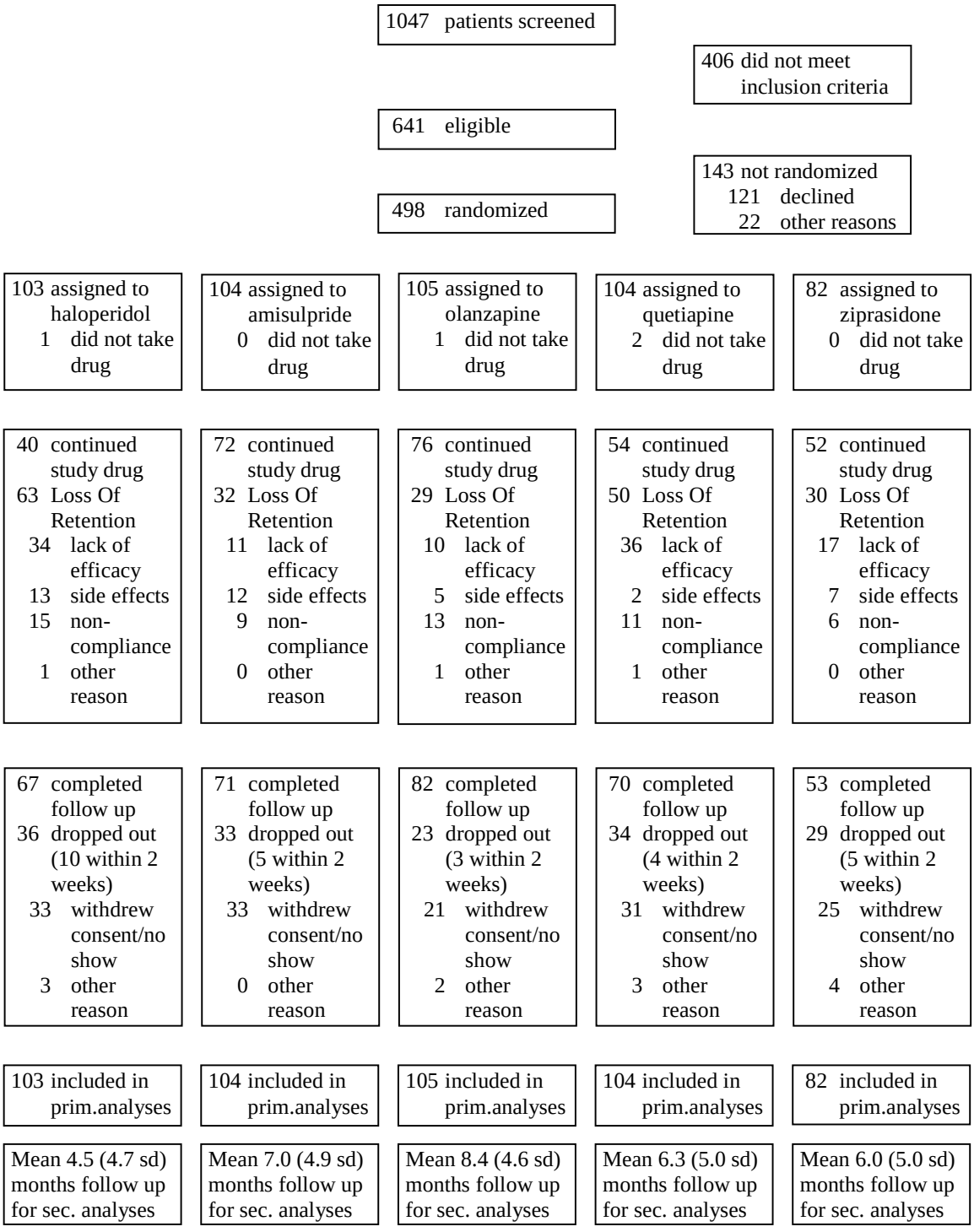

Figure 1 Trial profile
Randomisation to Ziprasidone was blocked between December 2003 and October 2004. Patients who dropped out within 14 days have not been at risk for a Loss of Retention event.

Table 1 Baseline characteristics of patients*

	Haloperidol (N=103)	Amisulpride (N=104)	Olanzapine (N=105)	Quetiapine (N=104)	Ziprasidone (N=82)	Total (N=498)
Sociodemographic characteristics						
Mean age (SD)	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%)
Caucasian	93/103 (90%)	102/104 (98%)	100/105 (95%)	97/104 (93%)	77/82 (94%)	469/498 (94%)
Mean years of education (SD)[1]	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 (includes students)	42/101 (42%)	55/104 (53%)	46/105 (44%)	46/104 (44%)	42/82 (51%)	231/496 (47%)
Diagnosis[2]						
Schizophreniform	36/103 (35%)	42/104 (40%)	35/105 (33%)	38/104 (37%)	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 (current)[2]	9/97 (9%)	5/103 (5%)	9/103 (9%)	17/103 (17%)	6/81 (7%)	46/487 (9%)
Suicidality (current)[2]	20/98 (20%)	23/104 (22%)	29/103 (28%)	29/103 (28%)	17/81 (21%)	118/489 (24%)
Alcohol dependence/abuse (current)[2]	10/98 (10%)	3/104 (3%)	15/103 (15%)	12/103 (12%)	8/81 (10%)	48/489 (10%)
Substance dependence/abuse (current)[2]	18/98 (18%)	14/104 (13%)	18/103 (17%)	23/103 (22%)	15/81 (19%)	88/489 (18%)
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%)
Mean psychopathology - PANSS (SD)[3]						
Total	88.9 (19.8)	86.4 (19.2)	87.6 (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 (6.1)
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)
Mean severity of illness - CGI (SD)[4]	4.9 (0.7)	4.8 (0.8)	4.8 (0.8)	4.9 (0.8)	4.8 (0.8)	4.8 (0.8)
Mean overall functioning - GAF (SD)[5]	38.6 (12.2)	40.3 (12.5)	43.0 (15.1)	38.8 (14.2)	39.3 (12.9)	40.0 (13.5)
Extrapyramidal symptoms – SHRS[6]						
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%)	-	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%)	-	-	1/81 (1%)	3/490 (1%)
Sexual dysfunction – UKU[7]						
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%)	7/39 (18%)	48/192 (25%)
Weight[8]						
Overweight (BMI ≥25)	20/96 (21%)	11/101 (11%)	17/104 (16%)	20/102 (20%)	16/81 (20%)	84/484 (17%)
Mean BMI (SD)	22.3 (3.5)	21.7 (3.6)	22.0 (3.0)	22.7 (3.3)	22.5 (3.8)	22.2 (3.4)
Prolonged QTc interval[9]	2/97 (2%)	5/98 (5%)	4/99 (4%)	2/96 (2%)	1/74 (1%)	14/464 (3%)

* Denominators fluctuate due to differences in response. Because of rounding, proportions may not sum up to 100.

[1] Years in school from 6 years of age onwards.

[2] According to the Mini International Neuropsychiatric Interview Plus (MINI+); 'Depression' includes 'major depressive episode (with or without melancholic features)' and 'dysthemia'.

[3] Positive and Negative Syndrome Scale (PANSS); 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.

[4] Clinical Global Impression (CGI); theoretical scores range from 1-7; higher scores indicate greater severity of illness.

[5] Global Assessment of Functioning (GAF); theoretical scores range from 1-100; higher scores indicate better functioning.

[6] St Hans Rating Scale (SHRS).

[7] Cases scored moderate/severe on selected items of the Udvalg for Kliniske Undersøgelser (UKU); for men: increased/decreased libido, orgastic dysfunction, gynaecomastia, or erectile/ejaculatory dysfunction (6 items); for women: increased/decreased libido, orgastic dysfunction, menorrhagia, amenorrhoea, galactorrhoea, or dry vagina (7 items).

[8] Body Mass Index (kg/m2); Interquartile Range.

[9] QTc prolongation: men >450 mseconds, women >470 mseconds

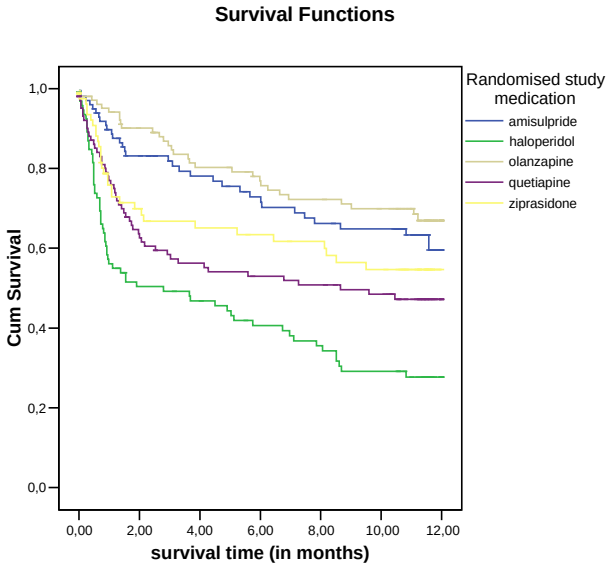

Figure 2a Time to LOR-event for any reason

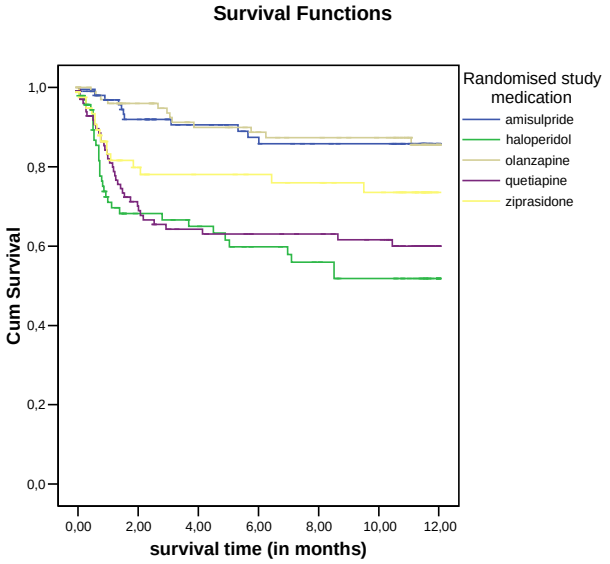

Figure 2b Time to LOR-event for lack of efficacy

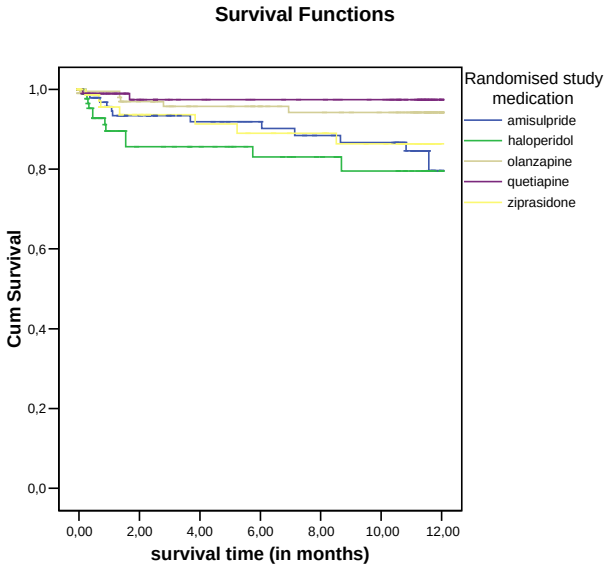

Figure 2c Time to LOR-event for side effects

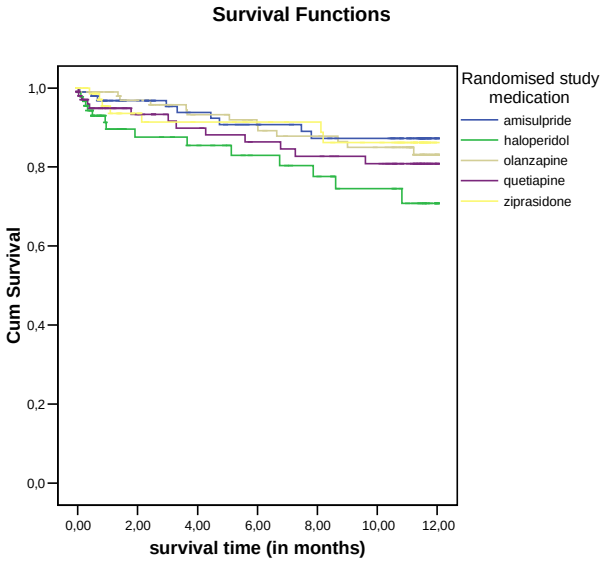

Figure 2d Time to LOR-event for non-adherence

Table 2 Loss Of Retention (LOR) according to allocated treatment[1]

	Haloperidol (N=103)	Amisulpride (N=104)	Olanzapine (N=105)	Quetiapine (N=104)	Ziprasidone (N=82)	P value[1]
Mean dose before LOR-event (mg/d, SD)	2.9 (1.2)	448.5 (175.1)	12.5 (4.9)	501.3 (201.4)	114.2 (61.8)	
≥ maximum dose before LOR-event	54/92 (59%)	25/96 (26%)	54/102 (53%)	36/99 (36%)	36/78 (46%)	<0.001
LOR for any cause	63/103 (61%)	32/104 (31%)	29/105 (28%)	50/104 (48%)	30/82 (37%)	
Months to LOR – 25th percentile (95% CI)[2]	0.5 (0.5-0.9)	5.3 (3.0-12+)	6.4 (3.8-12+)	1.2 (7.0-2.0)	1.1 (0.8-8.5)	
Cox-model treatment comparisons[3]						
Haloperidol						
Hazard Ratio (95% CI)		0.36 (.23-.55)	0.27 (.17-.42)	0.49 (.33-.73)	0.47 (.29-.76)	<0.001
P value		<0.001	<0.001	<0.001	0.002	
Quetiapine						
Hazard Ratio (95% CI)		0.74 (.45-1.19)	0.50 (.33-.87)		0.95 (.57-1.59)	
P value		0.21	0.01		0.85	
Amisulpride						
Hazard Ratio (95% CI)			0.72 (.43-1.22)		1.21 (.69-2.14)	
P value			0.23		0.51	
Ziprasidone						
Hazard Ratio (95% CI)			0.65 (.34-1.25)			
P value			0.65			
LOR for lack of efficacy	34/103 (33%)	11/104 (11%)	10/105 (10%)	36/104 (35%)	17/82 (21%)	
Cox-model treatment comparisons[3]						
Haloperidol						
Hazard Ratio (95% CI)		0.22 (.11-.45)	0.17 (.08-.34)	0.68 (.41-1.12)	0.51 (.27-0.96)	<0.001
P value		<0.001	<0.001	0.13	0.04	
Quetiapine						
Hazard Ratio (95% CI)		0.36 (.18-.76)	0.26 (.13-.55)		0.83 (.43-1.61)	
P value		0.01	<0.001		0.58	
Ziprasidone						
Hazard Ratio (95% CI)		0.52 (.22-1.23)	0.39 (.15-.98)			
P value		0.14	0.05			
Amisulpride						
Hazard Ratio (95% CI)			0.71 (.29-1.74)			
P value			0.45			
LOR for side effects	13/103 (13%)	12/104 (12%)	5/105 (5%)	2/104 (2%)	7/82 (9%)	
Cox-model treatment comparisons[3]						
Haloperidol						
Hazard Ratio (95% CI)		0.55 (.25-1.23)	0.23 (.08-.65)	0.12 (.03-.54)	0.45 (.16-1.27)	0.02
P value		0.14	0.01	0.01	0.13	
Amisulpride						
Hazard Ratio (95% CI)			0.38 (.13-1.11)	0.21 (.05-.99)	0.90 (.30-2.66)	
P value			0.08	0.05	0.84	
Ziprasidone						
Hazard Ratio (95% CI)			0.68 (.18-2.51)	0.26 (.05-1.49)		
P value			0.56	0.13		
Olanzapine						
Hazard Ratio (95% CI)				0.35 (.06-2.00)		
P value				0.24		
LOR for non-adherence	15/103 (15%)	9/104 (9%)	13/105 (12%)	11/104 (11%)	6/82 (7%)	
Cox-model treatment comparisons[3]						
Haloperidol						
Hazard Ratio (95% CI)		0.52 (.22-1.24)	0.52 (.24-1.12)	0.40 (.17-.91)	0.46 (.16-1.31)	0.27
P value		0.14	0.10	0.03	0.14	
Amisulpride						
Hazard Ratio (95% CI)			1.01 (.41-2.45)	0.84 (.32-2.18)	0.77 (.25-2.32)	
P value			0.99	0.72	0.64	
Ziprasidone						
Hazard Ratio (95% CI)			1.32 (.45-3.91)	0.91 (.30-2.81)		
P value			0.61	0.87		
Olanzapine						
Hazard Ratio (95% CI)				0.59 (.24-1.46)		
P value				0.25		
LOR for other reason	1/103 (1%)	-	1/105 (1%)	1/104 (1%)	-	

[1] Standard Deviation (SD); Confidence Interval (CI).

[2] Kaplan Meier; months at risk for the LOR event, excluding the first 14 days after randomization. For amisulpride and olanzapine no upper limit for the CI could be estimated because of low event rates.

[3] Cox proportional-hazards regression models, adjusted for gender and country.

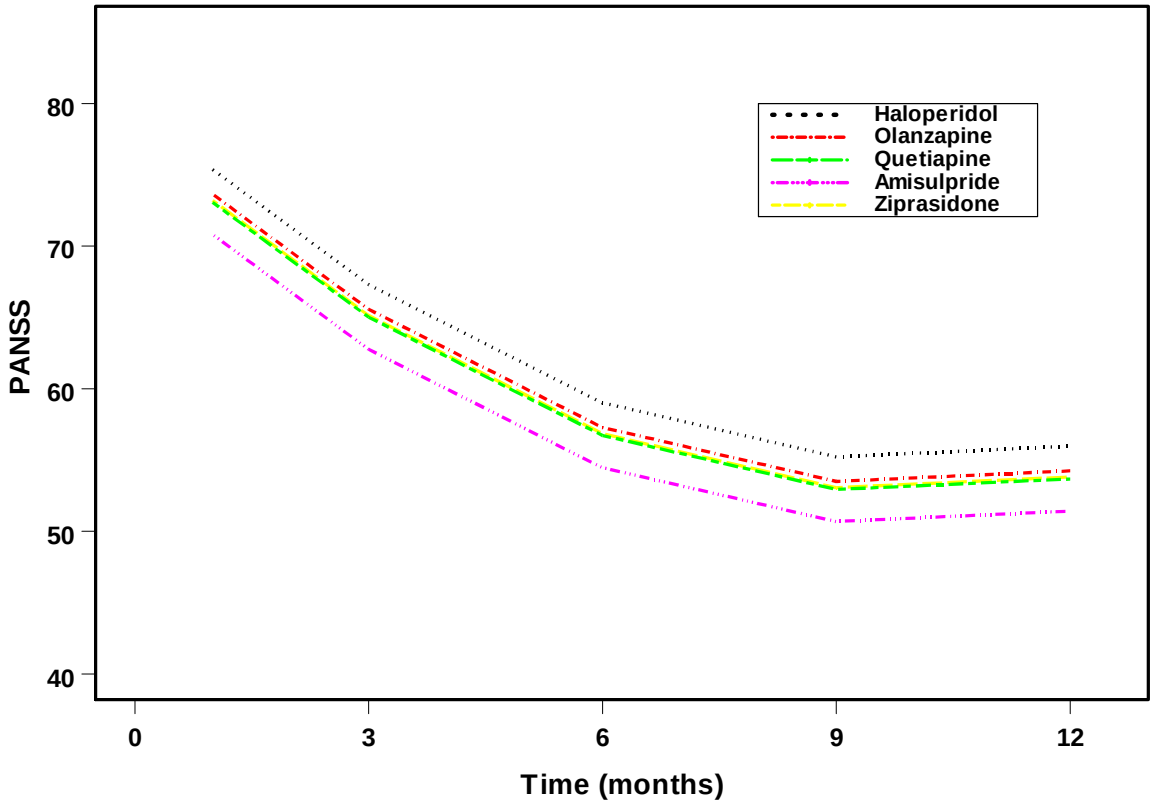

Figure 3 PANSS total score during 12 months follow up

Table 3 Outcomes of safety and tolerability*

	Haloperidol	Amisulpride	Olanzapine	Quetiapine	Ziprasidone	P-value
Psychiatric hospitalisation						
Patients admitted to hospital after randomisation / patients at risk for admission	17/66 (26%)	17/88 (19%)	19/90 (21%)	17/61 (28%)	10/60 (17%)	0.53
Number of admissions to hospital after randomisation / total patient-years at risk for admission	20/34.0	22/52.8	31/62.8	21/38.8	12/35.2	
Risk ratio	0.59	0.42	0.49	0.54	0.34	
Any serious adverse event	8/103 (8%)	3/104 (3%)	5/105 (5%)	5/104 (5%)	-	0.11
Extrapyramidal symptoms – SHRS[1]						
Akathisia	19/73 (26%)	15/94 (16%)	10/97 (10%)	11/85 (13%)	19/68 (28%)	0.01
Dystonia	1/73 (1%)	3/94 (3%)	-	1/85 (1%)	2/68 (3%)	0.44
Parkinsonism	25/73 (34%)	16/94 (17%)	6/97 (6%)	9/85 (11%)	11/68 (16%)	<0.001
Dyskinesia	2/73 (3%)	1/94 (1%)	-	-	-	0.19
Sexual dysfunction – UKU[1]						
Male	15/48 (31%)	14/48 (29%)	15/60 (25%)	16/57 (28%)	19/35 (54%)	0.04
Female	11/24 (46%)	21/45 (47%)	18/38 (47%)	10/28 (36%)	11/33 (33%)	0.65
Weight[2]						
Overweight (BMI ≥25)	17/43 (40%)	32/72 (44%)	45/83 (54%)	25/55 (45%)	15/44 (34%)	0.24
Weight gain >7% from baseline	23/43 (53%)	45/72 (63%)	71/83 (86%)	36/55 (65%)	17/44 (39%)	<0.001
Weight change (kg) from baseline						
Mean (SE)	6.4 (1.0)	8.9 (0.9)	11.6 (0.8)	8.0 (0.9)	4.0 (0.7)	<0.001
Median (IQR)	5.0 (3.0-10.0)	8.0 (3.0-14.0)	10.0 (7.0-15.0)	6.0 (3.0-12.0)	3.0 (1.0-7.0)	
Weight change (kg) from baseline / month in the study						
Mean (SE)	1.0 (0.2)	1.3 (0.1)	1.7 (0.1)	1.5 (0.2)	0.8 (0.1)	<0.001
Median (IQR)	0.9 (0.3-1.2)	1.1 (0.5-1.9)	1.5 (1.0-2.3)	1.0 (0.5-2.5)	0.6 (0.3-1.1)	
Electrocardiographic findings						
Prolonged QTc interval[3]	1/20 (5%)	1/43 (2%)	3/46 (7%)	2/25 (8%)	-	0.61
Concomitant medication						
Lithium	-	-	3/105 (3%)	2/104 (2%)	-	0.11
Mood stabilisers / anticonvulsants	25/103 (24%)	19/104 (18%)	23/105 (22%)	27/104 (26%)	19/82 (23%)	0.74
Antidepressants	15/103 (15%)	7/104 (7%)	19/105 (18%)	6/104 (6%)	6/82 (7%)	0.01
Hypnotics, sedatives	14/103 (14%)	17/104 (16%)	20/105 (19%)	25/104 (24%)	14/82 (17%)	0.38
Anxiolytics	50/103 (50%)	54/104 (52%)	58/105 (55%)	50/104 (48%)	35/82 (43%)	0.51
Anticholinergics	37/103 (36%)	29/104 (28%)	18/105 (17%)	21/104 (20%)	17/82 (21%)	0.01

* Denominators fluctuate due to differences in response. To calculate p-values we did not yet adjust for gender and country.

[1] Percentages are based on the number of patients with at least one follow-up assessment (SHRS and UKU: 1, 3, 6, 9, 12 months) - cases scored positive at at least one evaluation; UKU: cases scored moderate/severe on severity of sexual dysfunction.

[2] Percentages and change scores are based on the data of patients with at least one post-baseline assessment (3, 6, 9, 12 months) - the maximum weight measured during follow-up was selected for the analyses. To convert weight to lb, multiply by 2.2. Body Mass Index (kg/m^2); Interquartile Range.

[3] QTc prolongation at 12 months: men >450 mseconds, women >470 mseconds.

APPENDIX

EUFEST (European First Episode Schizophrenia Trial) Study Group

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