Amisulpride, aripiprazole, and olanzapine in patients with schizophrenia-spectrum disorders (BeSt InTro): a pragmatic, rater-blind, semi-randomised trial

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Summary

Background Amisulpride, aripiprazole, and olanzapine are first-line atypical antipsychotics that have not previously been compared head-to-head in a pragmatic trial. We aimed to compare the efficacy and safety of these agents in a controlled trial.

Methods This pragmatic, rater-blind, randomised controlled trial was done in three academic centres of psychiatry in Norway, and one in Austria. Eligible patients were aged 18 years or older, met ICD-10 criteria for schizophrenia-spectrum disorders (F20–29), and had symptoms of active psychosis. Eligible patients were randomly assigned to receive oral amisulpride, aripiprazole, or olanzapine. Treatment allocation was open to patients and staff, and starting dose, treatment changes, and adjustments were left to the discretion of the treating physician. Computer-generated randomisation lists for each study centre were prepared by independent statisticians. Patients were followed up for 52 weeks after random assignment, during which assessments were done 8 times by researchers masked to treatment. The primary outcome was reduction of the Positive And Negative Syndrome Scale (PANSS) total score at 52 weeks, and primary analyses were done in the intention-to-treat population. This trial is registered with ClinicalTrials.gov, number NCT01446328.

Findings Between Oct 20, 2011, and Dec 30, 2016, we assessed 359 patients for eligibility. 215 patients were excluded (107 did not meet inclusion criteria, 82 declined to participate, 26 other reasons). 144 patients (mean baseline PANSS total estimated score 78·4 [SD 1·4]) were randomly assigned 1:1:1 to receive amisulpride (44 patients), aripiprazole (48 patients) or olanzapine (52 patients). After 52 weeks, the patients allocated to amisulpride had a PANSS total score reduction of 32·7 points (SD 3·1) compared with 21·9 points reduction with aripiprazole (SD 3·9, p=0·027) and 23·3 points with olanzapine (2·9, p=0·025). We observed weight gain and increases of serum lipids and prolactin in all groups. 26 serious adverse events (SAEs) among 20 patients were registered (four [9%] of 44 patients allocated to amisulpride, ten [21%] of 48 patients allocated to aripiprazole, and six [12%] of 52 patients allocated to olanzapine), with no statistically significant differences between the study drugs. 17 (65%) of the 26 SAEs occurred during the use of the study drug, with readmission or protracted hospital admission accounting for 13 SAEs. One death by suicide, one unspecified death, and one life-threatening accident occurred during follow-up, after cessation of treatment.

Interpretation Amisulpride was more efficacious than aripiprazole or olanzapine for reducing the PANSS total scores in adults with schizophrenia-spectrum disorders. Side-effect differences among the groups were generally small. This study supports the notion that clinically relevant efficacy differences exist between antipsychotic drugs. Future research should aim to compare first-line antipsychotics directly in pragmatic clinical trials that reflect everyday clinical practice.

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Introduction

Antipsychotic drugs are an important constituent in the treatment of schizophrenia-spectrum disorders. The introduction of antipsychotic drugs in the early 1950s was considered a breakthrough in the treatment of psychosis,[1] but effectiveness limitations and tolerability concerns continue to challenge their clinical use. Functional antagonism of striatal dopamine D2 receptors remains the core feature of all antipsychotic drugs,[2] and the availability of partial dopaminergic agonists is the most recent development in the field. Although new drugs for extradopaminergic targets would be welcome, no such agents seem to be close to registration or clinical use, which is all the more

Research in context

Evidence before this study

Choice of antipsychotic drug in the treatment of schizophrenia-spectrum disorders remains a tradeoff between expected efficacy and tolerability. Available evidence is mostly based on short-term studies with highly selected study samples and pragmatic, long-term clinical trials are scarce. Moreover, direct comparisons exist for only a few antipsychotics. We searched PubMed without language restrictions, from the start of the database until June 1, 2020, for head-to-head, pragmatic, randomised comparisons of amisulpride, aripiprazole and olanzapine in schizophrenia-spectrum disorders, using the search terms "amisulpride" AND "olanzapine" AND "aripiprazole" AND "schizophreni*, and found no clinical trials with pragmatic designs comparing all three antipsychotics.

Added value of this study

In this pragmatic, long-term, semi-randomised trial, we compared the antipsychotic efficacy of amisulpride, aripiprazole, and olanzapine. After 52 weeks, amisulpride was significantly more efficacious than aripiprazole or olanzapine in reducing overall symptoms of schizophrenia. All three drugs were generally well tolerated, with little difference in side-effects. All study drugs were associated with weight gain and increase in serum lipids, indicating that amisulpride and aripiprazole might be less metabolically favourable than previous evidence suggests.

Implications of all the available evidence

Guidelines emphasise basing clinical decision making regarding antipsychotic drugs strongly on safety and tolerability. However, meta-analyses of direct and indirect comparisons also suggest a hierarchical structure of antipsychotic efficacy, listing clozapine, amisulpride, olanzapine, and risperidone among the most efficacious antipsychotics. This study supports the notion that clinically relevant efficacy differences exist between antipsychotic drugs, and future research should aim to compare first-line antipsychotics directly in pragmatic clinical trials that reflect everyday clinical practice.

reason to optimise the use of available antipsychotic drugs.

Identifying differences between available drugs is key to evidence-based treatment. Many antipsychotic drugs have shown moderate to large group-level effect sizes for the acute treatment of schizophrenia.[3,4] Treatment guidelines emphasise tolerability and side-effect profiles as central to the choice of antipsychotic drug in the individual patient.[5,6] Agents clearly differ in propensity for causing common side-effects, such as extrapyramidal symptoms and weight gain, but meta-analyses[4] also suggest a hierarchical structure for efficacy. Based on meta-analytic findings of efficacy and tolerability, Smith and colleagues propose[7] that amisulpride, aripiprazole, and olanzapine should be among the first-choice antipsychotic drugs in schizophrenia. Amisulpride and olanzapine are among the most efficacious antipsychotic drugs in terms of antipsychotic effect sizes, whereas aripiprazole has a smaller effect size versus placebo.[7] However, aripiprazole has a more benign side-effect profile, especially for weight gain and adverse metabolic effects.[8]

Meta-analytical evidence does have important limitations. Comparisons of effect sizes across different placebo-controlled trials is complicated by steadily increasing placebo responses in trials,[9] and the effect size of newer drugs such as aripiprazole should be interpreted with this is mind. Furthermore, randomised controlled trials (RCTs) of direct head-to-head comparisons between these three antipsychotic drugs have not been done, and comparisons are based on indirect network analyses.[4] Potential pitfalls relating to the use of indirect comparisons[10] highlight the need for head-to-head comparisons of the available agents. In a meta-analysis[11] on long-term effectiveness, in which only direct comparisons between antipsychotic drugs were included, olanzapine performed similarly to amisulpride and aripiprazole for symptom reduction. Finally, meta-analyses are strongly based on industry-sponsored RCTs, prompting a need for independently funded effectiveness trials, with longer follow-up, and samples more representative of patients seen in usual clinical practice.[12,13]

To this end, we aim to compare the overall antipsychotic efficacy, tolerability, and safety of amisulpride, aripiprazole, and olanzapine in a pragmatic RCT.

Methods

Study design and participants

We did this pragmatic, rater-blind, randomised controlled trial in three academic centres of psychiatry in Norway (Bergen, Trondheim, Stavanger), and one in Austria (Innsbruck). The BeSt InTro study was approved in Norway by the Regional Committees for Medical and Health Research Ethics, and by the Norwegian Medicines Agency, and in Austria by the Etikkommission der Medizinische Universität Innsbruck, and the Austrian Federal Office for Safety in Health Care (BASG). Clinical monitoring according to ICH-GCP was done by the Department of Research and Development, Haukeland University Hospital in Norway, and by the Clinical Trial Centre at the Medical University Innsbruck in Austria.

Eligible patients for the study were aged 18 years or older, with a diagnosis within the schizophrenia-spectrum according to the ICD-10 diagnoses F20–29, and with symptoms of ongoing psychosis as defined by a score of 4 or more on at least one of the following Positive and Negative Syndrome Scale (PANSS) items: P1 (delusions), P3 (hallucinations), P5 (grandiosity), P6 (suspiciousness or persecution) or G9 (unusual thought content).[14] Diagnoses were based

on the Structured Clinical Interview for DSM-IV axis I disorders by trained physicians and psychologists. The diagnoses were converted to ICD-10 diagnoses.

Exclusion criteria were inability to understand the native language (Norwegian or German), pregnancy or breastfeeding, hypersensitivity to the active substance or to any of the excipients of the study drugs, prolactin-dependent tumours, phaeochromocytoma, concomitant use of medications which could induce torsade de pointes, use of levodopa, and known risk of narrow-angle glaucoma. Suicidal ideation or drug misuse were not exclusion criteria.

All patients were evaluated by their attending physician or psychiatrist based on their clinical condition, and eligible patients were capable of providing informed consent. All patients provided written informed consent before inclusion.

Randomisation and masking

Patients were randomly assigned (1:1:1) to receive oral amisulpride, aripiprazole, and olanzapine, at a starting dose agreed with the patient's attending physician. Computer-generated randomisation lists for each study centre were prepared by statisticians at the University of Bergen (Bergen, Norway), who were independent of the study. Randomised treatment allocation was open to the patient and the attending physician, psychiatrist, and all other staff in the clinical treatment team, but was concealed from the research team that assessed study participants. To mimic clinical decision making as closely as possible, the randomisation was to a sequence of the study drugs, where the study drugs were listed in a random sequence. Each sequence was independently put into sealed opaque envelopes that were numbered consecutively. When a new study participant was included, the attending physician or psychiatrist opened the envelope and offered the first study drug in the sequence to the participant. If the first drug could not be used because of previous inefficacy or tolerability issues, the psychiatrist offered the next drug in the sequence, and noted the reason for rejecting the first drug. Study participants and clinicians were encouraged to provide a reason for rejecting the drug in their own words rather than according to a predefined list. The same principle was followed if the second drug in the sequence could also not be used. Previous use of a study drug did not lead to rejection of the drug unless the patient had had a negative experience. Research team members involved in participant assessments did not observe drug allocation and did not access the medical records during follow-up to secure blinded assessments. Study participants were instructed not to reveal the study drug to their assessors. The first study drug in the sequence defined the randomisation group, which was the basis of the intention-to-treat (ITT) analyses (panel). The study drug ultimately chosen from the sequence was the basis of the per-protocol (PP) analyses.

Panel: **Analysis definitions**

Intention-to-treat analyses
Analyses based on the first drug in the randomisation sequence, defining the randomisation group

Per-protocol analyses
Analyses based on the study drug actually chosen by the patient and physician

Study completers
Participants completing the 52-week follow-up, any drug

Procedures

Study medications were oral tablets prescribed according to the respective summary of product characteristics. The initiation dose and any subsequent changes or termination of the study medication were left to the discretion of the attending physician or psychiatrist. Doses ranged from 50–1200 mg per day for amisulpride, 5–30 mg per day for aripiprazole, and 2·5–20 mg per day for olanzapine.

To resemble usual clinical practice as much as possible, concomitant medications were permitted, although long-term administration of additional antipsychotics was strongly discouraged, in line with treatment guidelines that advocate monotherapy.[5,6,15] Cross-titration during antipsychotic drug switches was allowed. Termination of or change from study drug did not lead to exclusion from the study.

Patients were assessed at eight points during 52 weeks of follow-up. The study visits were at baseline, 1, 3, 6, 12, 26, 39, and 52 weeks.

Outcomes

The primary outcome was change in PANSS total score over 52 weeks, which is the minimum recommended time of antipsychotic maintenance drug therapy after an acute psychotic episode in patients with schizophrenia.[15,16]

The Structured Clinical Interview for the PANSS (SCI-PANSS) was used, and all investigators doing assessments were trained and calibrated by the PANSS Institute until inter-rater reliability was deemed satisfactory. Secondary outcomes included change in PANSS positive, negative, and general sub-scale scores; and Clinical Global Impression–Severity of Illness scale (CGI-S)[17] and Global Assessment of Functioning (GAF; split version) scores.[18] We used the split version of GAF, in which symptoms and functioning are scored in separate subscales. We analysed the mean score of the symptoms and functioning subscales. Tolerability outcomes were measured by the UKU-Side Effect Rating Scale, patient-rated version (UKU SERS-Pat; 0=no side-effects, 1=mild side-effects that do not interfere with performance, 2=side-effects that interfere moderately with performance, 3=side-effects that interfere markedly with performance).[19] Side-effects as measured by the UKU SERS-Pat were analysed

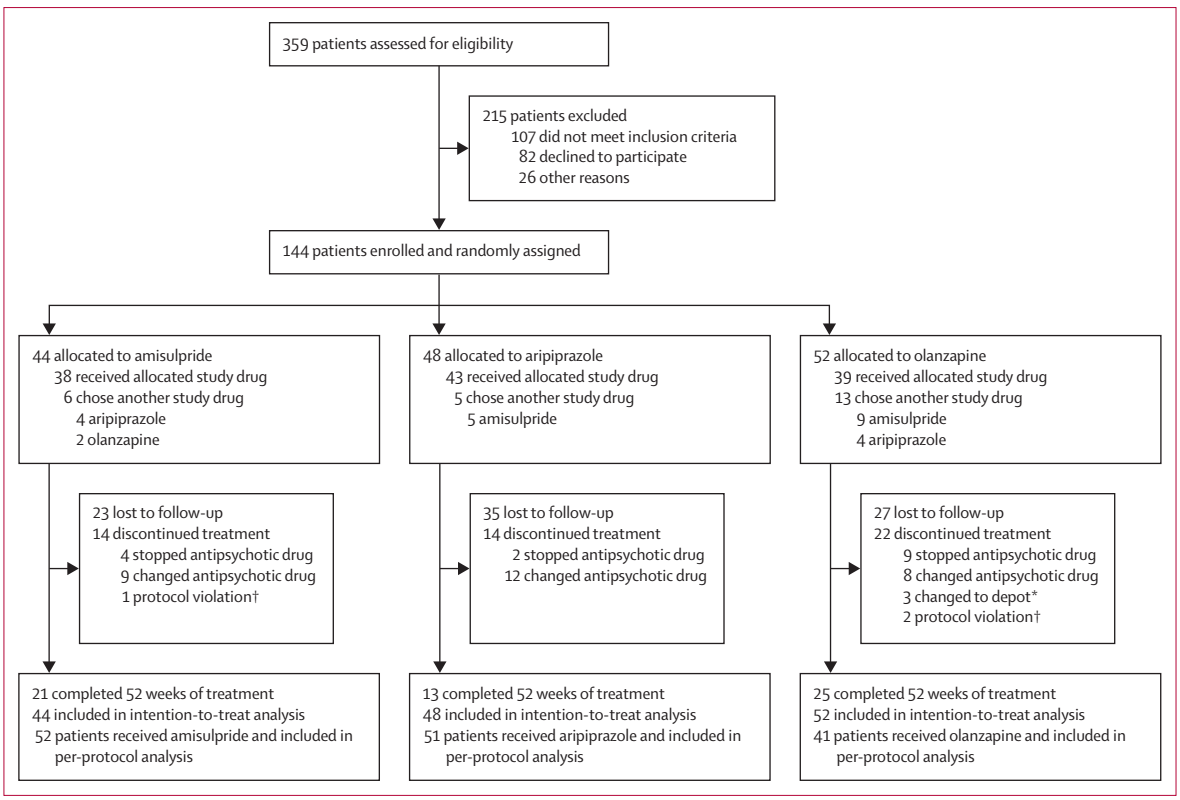

Figure: **Trial profile**
*Long-acting formulation of study drug. †Use of dose above upper limit according to the study protocol.

according to the sum scores of the modules 1 (psychic side-effects), 2 (neurological side-effects), and 3 (autonomic side-effects), as the internal consistency was sufficient (Cronbach's alpha 0·85 for module 1, 0·82 for module 2, and 0·75 for module 3). The last subdomain 4 (other side-effects) had low internal consistency, and was analysed item by item. Furthermore, metabolic analyses such as serum total cholesterol, HDL, LDL, triglycerides, glucose, bodyweight, body-mass index, blood pressure, hip and waist circumference, prolactin, the corrected QT interval on the ECG, and the occurrence of any suspected unexpected serious adverse reaction or serious adverse event (SAE) were recorded. Preplanned secondary outcomes related to mood, cognition, brain imaging, gene expression, bone turnover markers, and inflammatory markers were planned as separate subgoals in the protocol and will be reported elsewhere. There was an error in the registered trial in ClinicalTrials.gov as the secondary outcomes were not included, but they were in the pre-start planned protocol.

Statistical analysis

The power estimations and model fittings were done in R (appendix pp 21–22). With 43 patients in each treatment group, the study was calculated to have 90·1% power to detect clinically significant differences among the study drugs, the thresholds defined by the PANSS total score reductions found in an earlier study.[20] An extended power analysis description is in the appendix (p 21).

A linear mixed effects (LME) model was fitted to the PANSS total scores, and subsequently to the secondary outcomes in R. The primary analyses were accompanied by secondary PP analyses. Medication, time, and the interaction between medication and time were included as fixed effects, while a random intercept was included as a random effect to account for intra-individual dependence in the data. This model was applied in both ITT and PP analyses, and in analyses restricted to the study completers. We did an additional analysis of the PANSS total score based on ITT with baseline adjustments. To limit the number of comparisons, amisulpride was chosen as the reference drug in the drug-drug analyses. Per protocol, no adjustments were made for multiple comparisons at intermediate timepoints or secondary outcomes.

Use of additional psychotropic drugs was analysed by means of chi-square tests in IBM SPSS Statistics (version 24). The effect size difference between study drugs was based on Cohen's d, ie, by estimating the difference in PANSS reduction for the drugs and dividing the difference by the pooled SD.[21] Sensitivity analyses of missing data were done in Mplus (version 8.4). An extended statistical analyses description can be found in the appendix (pp 21–22).

For the **R project** see www.R-project.org

See **Online** for appendix

	Amisulpride (N=44)	Aripiprazole (N=48)	Olanzapine (N=52)	All (N=144)
Women	16 (36%)	16 (33%)	19 (37%)	51 (35%)
Men	28 (64%)	32 (67%)	33 (63%)	93 (65%)
White ethnicity	39 (89%)	35 (73%)	44 (85%)	118 (82%)
Living alone	21 (48%)	17 (35%)	23 (44%)	61 (42%)
Employed	14 (32%)	12 (25%)	10 (19%)	36 (25%)
Daily tobacco smoker	30 (68%)	29 (60%)	26 (50%)	85 (59%)
Alcohol misuse or dependence	4 (9%)	7 (15%)	2 (4%)	13 (9%)
Drug misuse or dependence	10 (23%)	8 (17%)	9 (17%)	27 (19%)
No previous use of antipsychotics	16 (36%)	23 (48%)	17 (33%)	56 (39%)
Diagnosis				
Schizophrenia F20	28 (64%)	27 (56%)	29 (56%)	84 (58%)
Schizotypal F21	1 (2%)	0 (0%)	1 (2%)	2 (1%)
Delusional disorder F22	4 (9%)	8 (17%)	9 (17%)	21 (15%)
Acute and transient F23	8 (18%)	3 (6%)	7 (13%)	18 (12%)
Schizo-affective F25	3 (7%)	5 (10%)	2 (4%)	10 (7%)
Other nonorganic F28	0 (0%)	1 (2%)	0 (0%)	1 (1%)
Unspecified nonorganic F29	0 (0%)	4 (8%)	4 (8%)	8 (6%)
Age (n=144)	30·6 (11·7)	32·1 (13·1)	32·2 (13·3)	31·7 (12·7)
Age at psychosis onset (n=89)	23·8 (9·6)	20·7 (6·6)	24·1 (8·2)	23·1 (8·3)
Duration of illness, years (n=89)	4·9 (5·6)	6·6 (8·5)	4·4 (7·7)	5·2 (7·3)
PANSS total score (n=144)	80·1 (18·8)	76·6 (13·4)	78·7 (15·5)	78·4 (15·9)
PANSS positive score (n=144)	21·4 (4·8)	21·3 (4·9)	21·0 (4·7)	21·2 (4·8)
PANSS negative score (n=144)	18·2 (7·0)	17·2 (5·6)	18·1 (5·8)	17·8 (6·1)
PANSS general score (n=144)	40·5 (10·3)	38·1 (7·2)	39·7 (8·1)	39·4 (8·6)
CGI score (n=144)	5·1 (0·9)	4·9 (0·7)	5·0 (0·8)	5·0 (0·8)
GAF score (n=143)	36·0 (9·6)	36·0 (9·6)	35·5 (8·8)	35·8 (9·3)
CDSS score (n=135)	7·6 (5·7)	5·4 (4·5)	7·1 (5·1)	6·7 (5·1)
BMI, kg/m^2 (n=125)	25·1 (5·4)	27·0 (6·8)	24·7 (5·7)	25·6 (6·0)
Systolic blood pressure, mm/Hg (n=115)	117·8 (14·4)	121·9 (15·3)	123·8 (16·9)	121·3 (15·7)
Diastolic blood pressure, mm/Hg (n=115)	75·3 (10·3)	78·3 (8·1)	80·9 (9·8)	78·3 (9·6)
Serum tests				
Prolactin, mIU/L (n=138)	406·5 (456·8)	302·0 (219·5)	352·5 (325·9)	352·1 (343·0)
Glucose, mmol/L (n=138)	5·1 (0·6)	5·3 (1·1)	5·4 (1·7)	5·3 (1·3)
Cholesterol, mmol/L (n=138)	4·5 (1·1)	4·5 (1·0)	4·5 (1·2)	4·5 (1·1)
HDL, mmol/L (n=138)	1·3 (0·4)	1·3 (0·4)	1·4 (0·4)	1·3 (0·4)
LDL, mmol/L (n=138)	2·9 (1·0)	2·8 (0·9)	2·9 (1·0)	2·9 (1·0)
Triglycerides, mmol/L (n=138)	1·2 (0·5)	1·3 (0·7)	1·2 (0·7)	1·2 (0·6)

Data are n (%) or mean (SD). N=number in the total sample; n=number with characteristics. PANSS=Positive and Negative Syndrome Scale. CGI=Clinical Global Impression severity of illness scale. GAF=Global Assessment of Functioning scale. CDSS=Calgary Depression Scale for Schizophrenia. BMI=body-mass index.

Table 1: **Patient demographics**

Role of the funding source

The funder 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 study data and final responsibility for the decision to submit for publication.

Results

Between Oct 20, 2011, and Dec 30, 2016, 359 patients were assessed for eligibility. 215 patients were excluded (107 did not meet inclusion criteria, 82 declined to participate, and 26 other reasons). 144 patients were enrolled and randomly assigned to receive amisulpride (n=44), aripiprazole (n=48), or olanzapine (n=52; figure). Among those randomly assigned, a study drug other than the first one in the sequence was chosen for 24 (16·7%) of 144 patients, with no statistically significant difference among the three groups (p=0·143; figure). Reasons for rejecting the first drug in the sequence were side-effects (n=9), previous insufficient effect (n=2), and patient decision without specification of cause (n=5). For eight patients, the reason was unknown. There was no statistically significant difference among the three drugs with respect to the reasons for rejection (Fischer's exact

	Baseline	1 week	3 weeks	6 weeks	12 weeks	26 weeks	39 weeks	52 weeks
Intention-to-treat population								
Amisulpride (n=44)	80·1 (2·5)	−12·0 (2·6)	−18·6 (2·6)	−24·0 (2·7)	−24·1 (2·9)	−29·5 (3·1)	−33·5 (3·0)	−32·7 (3·1)
Aripiprazole (n=48)	76·6 (2·4); p=0·308	−8·4 (2·4); p=0·304	−11·9 (2·5); p=0·055	−12·1 (2·8); p=0·002	−17·5 (2·9); p=0·098	−21·2 (3·1); p=0·056	−19·5 (3·5); p=0·002	−21·9 (3·9); p=0·027
Olanzapine (n=52)	78·7 (2·3); p=0·686	−8·5 (2·3); p=0·298	−17·9 (2·4); p=0·839	−18·6 (2·5); p=0·135	−19·3 (2·6); p=0·206	−16·6 (3·0); p=0·002	−23·8 (3·0); p=0·020	−23·3 (2·9); p=0·025
Per-protocol analysis								
Amisulpride (n=52)	81·5 (2·3)	−11·7 (2·3)	−19·2 (2·4)	−22·1 (2·5)	−22·6 (2·6)	−26·5 (2·8)	−31·6 (2·8)	−29·1 (2·9)
Aripiprazole (n=51)	77·1 (2·3), p=0·171	−7·9 (2·4), p=0·252	−12·2 (2·5), p=0·039	−14·9 (2·7), p=0·046	−19·0 (2·9), p=0·347	−21·6 (3·2); p=0·235	−21·5 (3·6), p=0·025	−23·5 (3·9), p=0·242
Olanzapine (n=41)	76·2 (2·6), p=0·122	−8·7 (2·7), p=0·386	−17·2 (2·8), p=0·578	−17·6 (2·9), p=0·240	−18·7 (3·0), p=0·321	−17·3 (3·4), p=0·033	−22·2 (3·4), p=0·029	−24·6 (3·3), p=0·290

Data are estimate (SD). p values are comparisons to amisulpride at baseline and each assessment point.

Table 2: **Baseline PANSS scores and change in scores from baseline at eight assessment points from baseline to 52 weeks follow-up**

test: p=0·839). 85 patients were lost to follow up (23 in the amisulpride group, 35 in the aripiprazole group, 27 in the olanzapine group), and 59 patients completed the study. 144 patients were included in the ITT analysis by assigned study drug, and 144 patients were included in the PP analysis by study drug received (safety population). The mean study drug doses were 396·9 mg per day for amisulpride (SD 206·9), 14·6 mg per day for aripiprazole (7·0), and 12·3 mg per day for olanzapine (3·8). Dose details are presented in the appendix (p 2).

Mean patient age at baseline was 31·7 years (SD 12·7, range 18·0–65·6). Median age was 26·8 years (IQR 16·7). The mean age at onset of psychosis was 23·1 years (SD 8·3), and the mean interval between onset and inclusion in the study was 5·2 years (7·3). 91 (63·2%) of 144 patients were enrolled after hospital admission, and the rest were enrolled from outpatient clinics. Further demographic and clinical characteristics are presented in table 1. Additional psychotropic drugs taken, including antipsychotics, antidepressants, mood stabilisers (lithium and anticonvulsants), opioids, benzodiazepines and related anxiolytics and hypnotics, and anticholinergics, are displayed in the appendix p 3. The estimated baseline PANSS total score based on the LME model for all patients was 78·4 points (SD 1·4).

Primary and secondary outcome measures are detailed in tables 2 and 3. At 52 weeks follow-up, decrease in PANSS total score was greater in the amisulpride group than in either the aripiprazole or olanzapine groups in the ITT population (table 2 and appendix p 4). The estimates were similar when the analysis was done with adjustment for PANSS total score difference at baseline (appendix p 6).

The estimated total PANSS score in the model decreased by 32·7 points in the amisulpride group (SD 3·1), 21·9 points in the aripiprazole group (SD 3·9; p=0·027), and 23·3 points in the olanzapine group (2·9; p=0·025). The significantly larger reduction of the estimated PANSS total score for the amisulpride group compared with those on aripiprazole and olanzapine corresponded to effect sizes of 0·57 for aripiprazole and 0·54 for olanzapine (table 2). In the PP analysis, the differences in estimated PANSS score reduction between groups was not statistically significant after 52 weeks (amisulpride *vs* aripiprazole p=0·242, amisulpride *vs* olanzapine p=0·290; table 2). In the modified ITT analyses in completers only (n=59), estimated PANSS total score reduction was 33·1 points for amisulpride (SD 3·5) and 21·5 points for aripiprazole (4·6, LME p=0·04 compared to amisulpride; appendix p 7), and 24·0 points for olanzapine (3·2, LME p=0·051 compared to amisulpride; appendix p 7). Modified ITT analyses in 56 patients who had not received previous treatment showed similar results, with a significant difference after 52 weeks between amisulpride and olanzapine (LME p=0·036), but not between amisulpride and aripiprazole (LME p=0·061; appendix p 8).

Change in scores and comparisons between study drugs for the secondary outcomes of PANSS positive, negative, and general subscale scores are summarised in table 3 and appendix p 5.

In the ITT analyses, estimated PANSS positive subscale score at 52 weeks was reduced by 12·2 points for amisulpride (SD 1·0), which was statistically more efficacious than olanzapine (estimated reduction 7·7 points, SD 0·9; p=0·001) but not than aripiprazole (9·4 points, 1·2; p=0·077, table 3). The estimated PANSS negative subscale score decreased by 4·8 points for amisulpride (SD 1·1) in the ITT population, with no statistically significant differences compared with aripiprazole or olanzapine after 52 weeks (table 3). The reduction of the estimated PANSS general subscale score was 15·7 points for amisulpride (SD 1·7) in the ITT population after 52 weeks, which was significantly better than aripiprazole (estimated reduction 10·2 points, SD 2·1; p=0·042), but not olanzapine (11·6 points, 1·5; p=0·072, table 3).

For the secondary outcomes of changes to GAF and CGI-S scores, the GAF score increased from 36·5 points (SD 1·8) to 60·8 points (SD 3·0) for amisulpride in the ITT model after 52 weeks. The GAF score increase was not different between amisulpride and aripiprazole or

	Baseline	1 week	3 weeks	6 weeks	12 weeks	26 weeks	39 weeks	52 weeks
PANSS positive subscale								
Intention-to-treat analysis								
Amisulpride (n=44)	21·4 (0·7)	−4·5 (0·8)	−7·6 (0·8)	−8·9 (0·8)	−9·8 (0·9)	−11·4 (1·0)	−12·1 (0·9)	−12·2 (1·0)
Aripiprazole (n=48)	21·3 (0·7), p=0·915	−2·6 (0·7), p=0·078	−4·0 (0·8), p=0·002	−5·4 (0·9), p=0·004	−7·2 (0·9) [p=0·042]	−9·1 (1·0), p=0·093	−7·8 (1·1), p=0·004	−9·4 (1·2), p=0·077
Olanzapine (n=52)	21·0 (0·7), p=0·644	−2·5 (0·7), p=0·063	−5·5 (0·7), p=0·064	−6·8 (0·8), p=0·061	−7·4 (0·8) [p=0·043]	−6·9 (0·9), p=0·001	−8·3 (0·9), p=0·005	−7·7 (0·9), p=0·001
Per-protocol analysis								
Amisulpride (n=52)	21·7 (0·7)	−4·5 (0·7)	−7·3 (0·7)	−8·2 (0·8)	−9·1 (0·8)	−10·4 (0·9)	−11·0 (0·8)	−10·6 (0·9)
Aripiprazole (n=51)	21·5 (0·7), p=0·796	−2·3 (0·7), p=0·038	−4·1 (0·7), p=0·003	−6·1 (0·8), p=0·064	−7·7 (0·9), p=0·278	−9·0 (1·0), p=0·276	−8·5 (1·1), p=0·079	−10·3 (1·2), p=0·835
Olanzapine (n=41)	20·3 (0·8), p=0·179	−2·4 (0·8), p=0·049	−5·4 (0·8), p=0·102	−6·7 (0·9), p=0·211	−7·3 (0·9), p=0·169	−7·3 (1·0), p=0·027	−8·3 (1·0), p=0·053	−8·2 (1·0), p=0·076
PANSS negative subscale								
Intention-to-treat analysis								
Amisulpride (n=44)	18·2 (0·9)	−1·5 (0·9)	−2·5 (0·9)	-3·1 (1·0)	−1·4 (1·0)	−3·9 (1·1)	−4·3 (1·1)	−4·8 (1·1)
Aripiprazole (n=48)	17·2 (0·8), p=0·403	−1·7 (0·9), p=0·925	−2·3 (0·9), p=0·856	−0·6 (1·0), p=0·059	−1·2 (1·0), p=0·876	−1·0 (1·1), p=0·059	−0·8 (1·3), p=0·028	−2·3 (1·4), p=0·141
Olanzapine (n=52)	18·1 (0·8), p=0·945	−1·6 (0·8), p=0·995	−2·9 (0·9), p=0·749	−1·7 (0·9), p=0·280	−1·9 (0·9), p=0·723	−1·5 (1·1), p=0·109	−3·4 (1·1), p=0·519	−4·0 (1·0), p=0·582
Per-protocol analysis								
Amisulpride (n=52)	18·5 (0·8)	−1·6 (0·8)	−2·4 (0·8)	−2·5 (0·9)	−1·3 (0·9)	−3·1 (1·0)	−4·2 (1·0)	−4·4 (1·0)
Aripiprazole (n=51)	17·2 (0·8), p=0·230	−1·8 (0·9), p=0·905	−2·6 (0·9), p=0·907	−1·2 (0·9), p=0·328	−1·6 (1·0), p=0·818	−1·5 (1·1), p=0·270	−1·4 (1·3), p=0·070	−2·2 (1·4), p=0·178
Olanzapine (n=41)	17·8 (0·9), p=0·536	−1·4 (0·9), p=0·852	−2·7 (1·0), p=0·797	−1·8 (1·0), p=0·601	−1·6 (1·1), p=0·835	−1·4 (1·2), p=0·256	−2·6 (1·2), p=0·291	−4·3 (1·1), p=0·952
PANSS general subscale								
Intention-to-treat analysis								
Amisulpride (n=44)	40·5 (1·3)	−5·9 (1·4)	−8·6 (1·4)	−11·9 (1·4)	−12·9 (1·5)	−14·2 (1·7)	−17·1 (1·6)	−15·7 (1·7)
Aripiprazole (n=48)	38·1 (1·2), p=0·187	−4·2 (1·3), p=0·373	−5·7 (1·3), p=0·131	−6·1 (1·5), p=0·006	−9·1 (1·6), p=0·090	−11·1 (1·7), p=0·195	−10·9 (1·9), p=0·015	−10·2 (2·1), p=0·042
Olanzapine (n=52)	39·7 (1·2), p=0·643	−4·4 (1·2), p=0·422	−9·5 (1·3), p=0·643	−10·1 (1·3), p=0·355	−10·1 (1·4), p=0·189	−8·1 (1·6), p=0·010	−12·1 (1·6), p=0·030	−11·6 (1·5), p=0·072
Per-protocol analysis								
Amisulpride (n=52)	41·3 (1·2)	−5·6 (1·2)	−9·5 (1·2)	−11·4 (1·3)	−12·3 (1·4)	−13·0 (1·5)	−16·4 (1·5)	−14·1 (1·5)
Aripiprazole (n=51)	38·5 (1·2), p=0·096	−3·9 (1·3), p=0·344	−5·6 (1·3), p=0·039	−7·5 (1·4), p=0·047	−9·7 (1·5), p=0·215	−10·9 (1·7), p=0·371	−11·6 (2·0), p=0·052	−11·1 (2·1), p=0·251
Olanzapine (n=41)	38·1 (1·3), p=0·075	−5·0 (1·4), p=0·756	−9·0 (1·5), p=0·815	−9·2 (1·6), p=0·281	−9·8 (1·6), p=0·261	−8·6 (1·8), p=0·063	−11·2 (1·8), p=0·029	−12·1 (1·7), p=0·396

Data are estimate (SD). p values are comparisons to amisulpride at each assessment point.

Table 3: **Baseline PANSS subscale scores and change in scores from baseline at eight assessment points from start of study to 52 weeks follow-up**

amisulpride and olanzapine, except for a smaller GAF score increase for amisulpride than for aripiprazole after 52 weeks in the PP model (appendix p 9).

The estimated CGI-S score decreased from 5·1 (markedly ill; SD 0·2) to 2·9 (mildly ill; 0·3) after 52 weeks for amisulpride in the ITT population, with no statistically significant differences compared with aripiprazole and olanzapine for decrease in CGI-S score (appendix p 9).

There were no suspected unexpected serious adverse reactions. A total of 26 serious adverse events (SAEs) among 20 patients were registered during the trial (four [9%] of 44 patients receiving amisulpride, ten [21%] of 48 patients receiving aripiprazole, and six [12%] of 52 patients receiving olanzapine), with no statistically significant differences between the study drugs. 17 of the 20 patients had only one SAE (table 4). 17 (65%) of 26 SAEs occurred during use of the study drug, with readmissions or protracted hospital admissions accounting for 13 of the SAEs. Two patients died (one death by suicide, one unspecific death), and one life-threatening accident was registered, all during follow-up but after discontinuation of the study drug.

Changes in the UKU SERS-Pat are presented in the appendix (pp 10–15). The scores of modules 1, 2, and 3 all decreased over time, but with no statistically significant differences between the groups at 52 weeks (appendix p 10). Concerning the single items of module 4, olanzapine significantly reduced skin rash compared

	Amisulpride (n=44)	Aripiprazole (n=48)	Olanzapine (n=52)	Total
Intention-to-treat group				
Suicide	0	1	0	1
Death, other	0	0	1	1
Pregnancy	1	0	0	1
Exacerbation of psychosis	1	0	0	1
Re-admission	2	7	7	16
Prolonged hospital admission	0	1	1	2
Life-threatening accident	0	1	0	1
Somatic admission	0	1	2	3
Total	4	11	11	26
Per-protocol group				
Suicide	0	1	0	1
Death, other	0	0	1	1
Pregnancy	1	0	0	1
Exacerbation of psychosis	1	0	0	1
Re-admission	3	6	7	16
Prolonged hospital admission	0	1	1	2
Life-threatening accident	0	1	0	1
Somatic admission	0	1	2	3
Total	5	10	11	26

Table 4: **Serious adverse events**

with amisulpride at 52 weeks in both the ITT and PP analyses, and aripiprazole significantly reduced pruritus compared with amisulpride in the PP analysis. Patients receiving aripiprazole had statistically significantly less weight loss in the last 4 weeks, and less diminished sexual desire compared with amisulpride in the ITT analysis at 52 weeks (appendix pp 12, 14).

Weight, BMI, waist circumference, and hip circumference increased in all groups (6·8 kg overall estimated increase in weight [SD 0·7], 2·2 kg/m² overall estimated increase in BMI [SD 0·2], 6·5 cm estimated increase in waist circumference [SD 0·9], and 5·4 cm increase in estimated hip circumference [SD 1·3]), with no significant difference between the amisulpride, aripiprazole, and olanzapine groups at 52 weeks (appendix p 16).

Laboratory outcomes showed no change over time for serum glucose or the QTc interval (appendix pp 17–18). Serum total cholesterol, LDL cholesterol, and triglycerides were all increased at 52 weeks without group differences in either ITT or PP analyses, except for statistically smaller estimated total cholesterol increase for olanzapine compared with amisulpride in the PP analysis. Serum prolactin increased in all groups, but with aripiprazole and olanzapine groups showing significantly smaller increases compared with amisulpride in the PP analyses (appendix pp 18–19).

Sensitivity analyses of attrition or missingness found almost identical patterns for models assuming missing at random (full information maximum likelihood, auxilliary variables, multiple imputation), and models assuming missing not at random (Diggle-Kenward and pattern-mixture; appendix p 20), which supports the assumption that missing was at random. The model using listwise deletion seemed to exaggerate the PANSS total score reduction compared to the other models, as it followed a course with lower PANSS total scores.

Discussion

Amisulpride outperformed olanzapine and aripiprazole for reduction of PANSS total scores over 52 weeks. This is the first head-to-head comparison in a randomised, pragmatic efficacy trial for these three drugs. Only the CGI-S scale was used in the study, but the PANSS reduction found in the ITT model for amisulpride corresponds to a CGI–improvement scale score between much improved and very much improved.[22]

The reduction is larger than that reported in many double-blind, randomised antipsychotic drug trials,[23] yet is similar to more pragmatic naturalistic study findings, which might better reflect everyday clinical practice. The results of EUFEST[24] showed symptom reduction of around 60% at 1 year. Results from clinical trials without a placebo control should be interpreted with caution, and some antipsychotic drugs have even failed to separate from placebo in meta-analyses.[4] Nevertheless, it seems reasonable to surmise that in acutely psychotic patients starting treatment on a new oral antipsychotic, a substantial and clinically relevant improvement can be expected.

In the ITT analysis, the PANSS difference in symptom reduction between amisulpride and aripiprazole and between amisulpride and olanzapine after 52 weeks translated to a Cohen's d of approximately 0·5–0·6, which is considered moderate.[21] The efficacy found for amisulpride compared with olanzapine was more substantial than expected. This is in contrast to both meta-analyses and head-to-head comparisons published earlier. A meta-analysis of direct comparisons between antipsychotic drugs by Kishimoto and colleagues[11] found no difference between amisulpride and olanzapine. However, the study samples included in the meta-analysis differed from ours, as two studies included chronically ill patients and one study only included patients in their first episode of schizophrenia. In OPTiMiSE,[25] patients in their first episode of schizophrenia, who had not remitted following initial open treatment with amisulpride, were either continued with amisulpride or switched to olanzapine by a double-blind method. The subsequent remission rate did not differ between treatment groups.[25] Again, the sample was different from ours, and the study focused on remission rates rather than reduction in PANSS scores, although remission was defined by threshold scores on particular PANSS items:[26] see appendix (p 23) for extended discussion.

Some limitations need to be acknowledged. As the ambition of the trial was to maximise the generalisability of results, this resulted in a trade-off between scientific rigor on the one hand, and a representative sample and treatment conditions on the other. We used a pragmatic design to mimic real-life clinical practice, with broad inclusion criteria, few exclusion criteria, open-label treatment administered by the treating psychiatrist in collaboration with the patient, and long follow-up. As clinical decision making regarding choice of antipsychotic drug should consider previous experience with the drug group, random assignment was to a random sequence of the study drugs, rather than to a single drug. The first (and second) drug in the sequence might have been rejected based on a previous negative benefit:risk ratio of the drug(s) in question, with a subsequent study drug chosen instead. In favour of designing a trial reflecting everyday practice, thereby increasing clinical relevance, we sacrificed more rigorous design features, including double-blind treatment conditions. Obviously, this entailed the risk of introducing bias from both patients and raters. Although we attempted to curtail rater bias by masking raters to treatment, this masking might have been broken inadvertently in a clinical setting, in which raters and prescribing clinicians belong to the same team. Patients might have accidently discussed medication with raters, despite having been encouraged not to do so. Lastly, patients might have sought information about their medication from other sources, also a potential source of bias. However, published evidence from both RCTs and meta-analyses does not indicate efficacy advantages of amisulpride over olanzapine, and exposure to these data would have been unlikely to create bias in the direction of our findings.

The primary analysis was based on ITT. However, 16·7% chose a study drug other than the first one in the sequence, and this should also be considered when interpreting the results. Yet, there were no statistically significant differences between the ITT groups by proportion of patients choosing a study drug later in the sequence, or by the reasons for rejecting the first drug in the sequence. Furthermore, PP analyses were done for all outcomes and largely supported the findings based on ITT, although between-group differences were generally smaller. The PP analyses might better capture the effect of the actual study drug used, but have the major disadvantage of not being based on randomisation, making them susceptible to selection bias. This might explain why the improved PANSS total score reduction for amisulpride reached statistical significance at 52 weeks in the ITT analyses but not in the PP analyses. Indeed, there was a larger variance in the baseline PANSS total scores in the PP group analyses than in those based on ITT, and with lower p values for comparisons between the groups. Taken together, the similar results obtained from different analysis strategies give confidence in the robustness of the obtained results. When calculating Cohen's d, the number of patients in each group during the follow up period had to be approximated because of dropout (appendix p 22). This introduces some uncertainty, but since the SD of the decrease for each medication group was similar, these approximations should not influence the pooled SD or effect sizes substantially. Furthermore, effect sizes are typically provided for comparisons between active drug and placebo, which makes comparisons between our sample and those of placebo-controlled trials less relevant.

Co-medication is another potential source of confounding. Nevertheless, the use of additional antipsychotics, antidepressants, mood stabilisers, benzodiazepines and related drugs, and anticholinergics was similar among the three study groups. As the participants were followed up until withdrawal or study completion regardless of whether the study drug was discontinued, changes in antipsychotic treatment other than the study drug could have influenced the results. However, results of sensitivity analyses based on data restricted to the period of use of the study drug did not differ substantially from analyses of all data for any of the outcomes.

Attrition was substantial during follow-up, and larger than in some trials,[24] but not very different from what is usually found in antipsychotic drug trials.[27] The power estimates took high levels of dropout into account. Attrition has thus not caused underpowering of the trial. Another concern is that selective dropout might bias the results. However, analyses of attrition strongly indicate that missingness was at random. Accordingly, the sample after 52 weeks was representative of the sample at baseline.

We did not adjust for multiple comparisons, which is a limitation as it increases the risk of false positives. However, for the primary outcome, only two preplanned comparisons were done. Furthermore, statistically significant differences between the drugs followed an internally consistent pattern.

In conclusion, amisulpride was more efficacious than aripiprazole and olanzapine in this pragmatic trial regarding reduction of the PANSS total scores. Apart from the similar levels of significant weight gain and adverse effect on serum lipids of all study drugs, no unexpected safety concerns emerged.

Contributors

EJ designed the study, acted as principal investigator, collected data, and wrote the first draft of the manuscript with substantial input from RAK. RAK, E-ML, and SS co-designed the study and collected data. MR co-designed the study, acted as local principal investigator, and collected data. IJ collected data and acted as local study manager. TKL acted as local principal investigator. SKR collected data and acted as local principal investigator. BW, RA, LGA, FF, EK, and IS collected data. CBJ did the statistical analyses. JØB had medicinal product responsibility and acted as medical consultant in the study. JB and LS collected data and coordinated the study. KH, VMS, and WWF co-designed the study. All authors critically read the manuscript and contributed academically to the data interpretations and writing. All authors approved the final version of the manuscript before submission.

Declaration of interests

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Data sharing

According to Norwegian law, data sharing requires approvals from the Regional Committees for Medical and Health Research Ethics, and from the Data Protection Officer at Haukeland University Hospital, on the basis of specific research proposals.

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