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Summary

Background Combining antipsychotics is common in schizophrenia treatment, despite evidence-based guidelines generally not recommending such practice. Otherwise, evidence remains inconclusive, especially regarding specific combinations. The trial aimed to test whether a combination of amisulpride plus olanzapine is more effective than either intervention as a monotherapy.

Methods A multicentre, 16-week, randomised, double-blind, controlled trial was done at 16 psychiatric in-patient centres throughout Germany. Inclusion criteria were adults aged 18–65 years with non-first episode schizophrenia or schizoaffective disorder and with a Positive and Negative Syndrome Scale (PANSS) total score of at least 70 and at least two items of the positive symptoms subscale rated at least 4. Patients were randomly assigned to receive 16 weeks of treatment with either amisulpride plus olanzapine, amisulpride plus placebo, or olanzapine plus placebo (1:1:1), and block randomisation was stratified by study site. To keep patients and investigators masked throughout the duration of the trial, amisulpride, olanzapine, and placebo were administered as identical capsules. Flexibly dosed monotherapy of oral amisulpride (amisulpride plus placebo, 200–800 mg per day) or olanzapine (olanzapine plus placebo, 5–20 mg per day) was compared with a combination of amisulpride plus olanzapine. The primary outcome was symptom reduction measured by the PANSS total score after 8 weeks, in the modified intention-to-treat population (all patients randomly assigned to an intervention and receiving at least one study drug dose). As determined a priori, group differences were examined by t tests (Bonferroni-Holm-adjustment) followed by pre-planned Bayesian analyses as well as imputation methods based on mixed models to account for missing values and post-hoc ANCOVA adjusting for PANSS baseline scores. The study was registered on ClinicalTrials.gov, NCT01609153; the German Clinical Trials Register, DRKS00003603; and the European Union Drug Regulating Authorities Clinical Trials Database, EudraCT-No. 2011-002463-20.

Findings Between June 15, 2012, and Dec 15, 2018, 13 692 patients were assessed for eligibility. 13 364 patients were excluded (including for not meeting inclusion criteria, declining to participate, or inappropriate reasons for changing pharmacological treatment), and 328 were then randomly assigned to an intervention group. 112 patients were randomly assigned to receive amisulpride plus olanzapine, 109 were randomly assigned to receive amisulpride plus placebo, and 107 were randomly assigned to receive olanzapine plus placebo. 321 patients were analysed for the primary outcome in the modified intention-to-treat population after exclusion of screening failures and patients who did not receive the intervention (110 for amisulpride plus olanzapine, 109 for amisulpride plus placebo, and 102 for olanzapine plus placebo). Among the 321 patients who were randomly assigned to intervention groups and analysed for the primary outcome, 229 (71%) were male, 92 (29%) were female; the mean age was 40·2 years (SD 11·7); and 296 (92%) were White and 25 (8%) were classified as other ethnicity. PANSS total score improved significantly more at 8 weeks in the amisulpride plus olanzapine group (–29·6 [SD 14·5]) than in the olanzapine plus placebo group (–24·1 [13·4], p=0·049, Cohen's d=0·396). A significant difference was not observed in reduction of PANSS total score between the amisulpride and olanzapine group compared with the amisulpride and placebo group (–25·2 [SD 15·9], p=0·095, Cohen's d=0·29). After 8 weeks and 16 weeks, sexual dysfunction, weight, and waist circumference increase were significantly higher for patients receiving amisulpride plus olanzapine than for those receiving amisulpride plus placebo, with no differences in serious adverse events. Two patients died during study participation; one randomly assigned to the amisulpride plus olanzapine group, and one assigned to the olanzapine plus placebo group (both assessed with no relation to treatment).

Interpretation The advantages of amisulpride plus olanzapine have to be weighed against a higher propensity for side-effects. The use of this specific combination therapy could be an alternative to monotherapy in certain clinical situations, but side-effects should be considered.

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Introduction

Combining antipsychotics to treat schizophrenia is a frequently utilised therapeutic strategy[1] to improve efficacy in the acute illness phase, in which up to half of patients[2] do not have adequate symptom response to antipsychotic monotherapy. Furthermore, a subgroup of patients on antipsychotic combination treatment had poorer results when switched to monotherapy owing to drug discontinuation.[3] However, combinations of antipsychotic drug treatment were not superior compared with monotherapy in high-quality, blinded randomised controlled trials, and the potential for increased adverse effects demands careful use of this type of therapy.[4]

Results of most former randomised controlled trials were limited to the combination of clozapine with other antipsychotics, which is usually restricted to treatment-resistant schizophrenia. Additionally, real-world effectiveness studies using extensive registry-based data show considerable advantages of antipsychotic combination treatment.[5] However, some authors recommend earlier use of clozapine as a monotherapy instead of combining antipsychotics, particularly for treatment-resistant schizophrenia.[6]

Because there is a lack of guidance for clinicians on how to improve efficacy in patients not responding to antipsychotic monotherapy when clozapine might not be an option, we aimed to study the combination of two potentially mechanistically synergistic or complementary second-generation antipsychotics. In a previous systematic review and meta-analysis, amisulpride and olanzapine both showed the highest efficacy when compared with other antipsychotic drugs.[7] Amisulpride is associated with selective blockade of dopamine 2 and dopamine 3 receptors, while olanzapine has broader receptor interactions. Olanzapine can lead to sedation, weight gain, metabolic abnormalities, and transient increase of liver enzymes, while amisulpride has a greater propensity for prolactin elevation, sexual dysfunction, extrapyramidal side effects, and QTc prolongation. Pharmacokinetic interactions between amisulpride and olanzapine are unlikely, as amisulpride

Research in context

Evidence before this study

A Cochrane systematic review on antipsychotic combinations for schizophrenia from 2017 found low-quality evidence that antipsychotic combination therapy might be superior to monotherapy in reducing the risk of non-response. Positive results were driven by studies with clozapine or first-generation antipsychotics in both groups: the monotherapy and combination groups. There was no evidence for a difference in effects of combination treatment compared with monotherapy with non-clozapine combinations. Similarly, another meta-analysis, also published in 2017, only found superiority of antipsychotic combination treatments regarding total psychopathology in individuals with schizophrenia in low-quality studies (defined as open-label studies or those not using an intent-to-treat analysis) but not in high-quality studies. Amisulpride plus olanzapine was not compared with either monotherapy in either of these two meta-analyses. We further searched the PubMed database for publications dating from Jan 01,, 2016, to Feb 28, 2021, with the following search terms: "antipsychotic" OR "neuroleptic" OR "drug" AND "combined" OR "add-on" OR "addition" OR "supplementation" OR "supplement" OR "cotreatment" OR "co-treatment" OR "adjunctive" OR "concurrent" OR "concomitant" OR "simultaneous" OR "parallel" OR "polypharmacy" OR "polytherapy" OR "augmentation" OR "parallel" OR "combined" AND "antipsychotic". Moreover, we searched the clinical trial registry "clinicaltrials.gov" for the terms "amisulpride" and "olanzapine". The search was restricted to English terms but through PubMed might include citations from up to 40 languages. Within this search strategy there were no studies that assessed the combination treatment of amisulpride plus olanzapine in a high-quality prospective randomised controlled trial.

Added value of this study

The present study is one of the largest publicly funded trials to assess antipsychotic combination treatment in a prospective, high-quality design. It is one of very few studies that found a higher symptomatic response in combination treatment of non-clozapine second-generation antipsychotics compared to monotherapy. Because of the fact that to date, there are no guideline recommendations on which combination to choose based on high-quality evidence, the results of this study might help guide clinical decision making regarding antipsychotic combination treatment choice.

Implications of all the available evidence

There is some evidence, that antipsychotic combination treatment might be efficient in certain clinical situations. However, the benefits must be weighed against a potentially higher rate of adverse effects, which should be monitored. Combined amisulpride with olanzapine treatment might be useful for the management of acute clinical situations and might speed up the response in patients compared with antipsychotic monotherapy.

is mainly cleared renally, whereas olanzapine is metabolised hepatically.

We aimed to test the efficacy and safety of the combination of amisulpride plus olanzapine versus amisulpride plus placebo, or olanzapine plus placebo, in an adequately powered, double-blind randomised controlled trial in in-patients with acutely exacerbated schizophrenia. We hypothesised that patients treated with amisulpride plus olanzapine would show significantly greater improvements on the Positive and Negative Syndrome Scale (PANSS)[8] total score than those treated with amisulpride plus placebo, or olanzapine plus placebo, at the end of an 8-week period.

Methods

Study design and participants
In this multicentre, double-blind, parallel, randomised controlled trial, patients were recruited from 16 psychiatric in-patient facilities (universities and community care) throughout Germany. Adults aged 18–65 years with non-first-episode schizophrenia or schizoaffective disorder following ICD-10 diagnosis criteria[9] and with a PANSS total score of at least 70 and at least two items of the positive symptoms subscale rated at least 4, irrespective of former antipsychotic treatment (with the exception of contraindication for treatment with study drugs amisulpride or olanzapine, or non-response to clozapine) were eligible for inclusion. Patients also had to be capable and willing to follow all study procedures (eg, sufficient German language skills) and had to provide a negative pregnancy test. All patients provided written informed consent. Exclusion criteria included first-episode schizophrenia, physical diseases with potential effects on study procedures, or any patients who were not voluntarily receiving treatment. Full inclusion and exclusion criteria are presented in the appendix (p 27). The study was approved by all local ethics committees at all sites and by the German federal medications agency (BfArM).

Randomisation and masking
Patients were recruited by study physicians. After eligibility criteria were met, a fax message was sent to the externally located Coordination Center for Clinical Trials Düsseldorf, Germany, which centrally performed randomisation using the computer program „Rancode" (IDV, Gauting Germany) in collaboration with the manufacturing pharmacy, to assure concealment of assigned groups. Randomisation was stratified by centres in blocks to the three treatment groups: patients were randomly assigned to receive 16 weeks of treatment with either amisulpride plus olanzapine, amisulpride plus placebo, or olanzapine plus placebo (1:1:1). All specific drugs were provided as identical capsules (containing amisulpride, olanzapine, or placebo) resulting in identical drug administration for each study group

(amisulpride plus olanzapine; amisulpride plus placebo; olanzapine plus placebo; double-dummy design). Masking of patients and study personnel was assured by providing additional placebo for patients randomly assigned to monotherapy (amisulpride plus placebo; olanzapine plus placebo).

Procedures
After study inclusion, formerly applied antipsychotics were stepwise tapered off and the study drugs were gradually introduced via cross-titration, without a washout period.

Amisulpride (200–800 mg per day) and olanzapine (5–20 mg per day) were administered orally as identical capsules containing specific amounts of each drug according to four pre-defined dose levels by prescribers' discretion, and according to national treatment guidelines (appendix p 27).[10]

After the baseline visit, study visits were scheduled every 2 weeks for drug dispense, adjustment, and assessments, with possible intermediate visits if necessary (especially in the early study phase for drug adjustment).

To enable a comparison of the (cumulative) antipsychotic drug potency between study groups, amisulpride dosages were converted into the olanzapine equivalent dosage according to expert consensus[11] (1 mg olanzapine≈36·6 mg amisulpride). Treating physicians were asked to rate adherence to pharmaco-treatment at every visit with "Compliance to pharmaco-therapy—yes, or no". Additionally, dispensed and returned drug pills were counted and antipsychotic drug plasma concentrations were assessed after 2, 8, and 16 weeks (visit 1, 4, and 8).

Adverse events and serious adverse events were measured once every 2 weeks with spontaneous patient reporting, together with clinical measurements of blood pressure, waist circumference, body weight and body-mass index (BMI), Simpson Angus Scale (extrapyramidal side effects),[12] Dosage Record and Treatment Emergent Symptom Scale,[13] Derogatis Interview for Sexual Functioning–Self Reporting,[14] Subjective Well-being under Neuroleptics Scale–Short form (SWN-K),[15] and electrocardiography (ECG), each measured at baseline, week 8, and week 16.

Assessment of routine clinical laboratory parameters included a full blood count, and concentrations of sodium, potassium, aspartate-aminotransferase, alanine-aminotransferase (ALT), gamma-glutamyl-transferase, creatinine, creatinine kinase, haemoglobin A_{1c}, fasting glucose, triglycerides, total cholesterol, low-density cholesterol, high-density cholesterol, and C-reactive protein. Urinary measurements included beta-human chorionic gonadotropine, glucose, proteins, and drug screening (cannabinoids, amphetamines, and opiates). Antipsychotic drug blood concentrations were ascertained. Blood and urinary assessments were carried out

at baseline, week 2, week 8, and week 16. Additional inflammatory and genetic parameters were collected for an expanded scientific programme to answer further questions on predictable responsiveness (appendix p 28). A history of changes to the protocol is summarised in the appendix (pp 15–16).

Outcomes

The primary efficacy endpoint was change in PANSS total score from baseline to week 8, and was analysed in the modified intention-to-treat population, which was all participants who received therapy (at least one dose of the study drug).

Secondary endpoints were PANSS total score at week 16; PANSS subscores (Positive, Negative, General), and the Five Factors by Marder[16] and van der Gaag[17] at week 8 and week 16; Clinical Global Impression-Severity scale (CGI-S) and CGI-improvement (CGI-I) scale;[18] the time course of total and sub-score PANSS symptom change (treatment response), defined as changes of PANSS total scores compared with assessments at any visit (2 week intervals) up to week 16 defined by cut-offs (0%; >0–24%; 25–49%; 50–74%; 75–100%); and safety and tolerability (including the SWN-K side-effect measure, appendix pp 43–58). The results of the secondary outcome changes of PANSS total score compared with week 2 as a predictor for changes of PANSS scores after 8 weeks will be presented in a separate article. All secondary outcomes as well as the safety and tolerability outcomes were analysed in the modified intention-to-treat population (patients receiving at least one dose of study drugs).

Choice of primary measure

The PANSS is one of the most widely used instruments for measuring efficacy of antipsychotic treatments in clinical studies and was assessed by trained staff (psychologists or clinicians). It is especially suitable to gather a broad representation of the symptoms of patients with schizophrenia, and is made up of 30 items, which assess positive, negative, general, and affective symptoms. The interview takes about 45 minutes for a trained interviewer, and the assessment covers symptoms of the past 7 days. The total score reflects the severity of the disease. Findings that linked the PANSS with the CGI-S found that being considered mildly ill on the CGI-S corresponded to an approximate PANSS total score of 57–61, moderately ill to 73–78, markedly ill to 93–96, and severely ill to 115–118 points.[19] On the CGI-I, ratings of minimally improved corresponded to a PANSS score reduction of 19–28%, much improved to 40–53%, and very much improved to 71–81%.[20] Reliability and validity of the PANSS have been tested and confirmed multiple times. The scale has been translated into more than 40 languages and is obtainable under license fees.

Statistical analysis

We powered the study a priori on an effect size difference between the combination treatment and monotherapy of 0·50 on the basis of empirical evidence of controlled trials of antipsychotic treatment in patients with schizophrenia. On the basis of an effect size of 0·50, power of 90%, and a two-sided t test with p=0·025 (two comparisons at level 0·050), the sample size calculations resulted in 101 patients in each of the three treatment groups. Because two hypotheses were tested (amisulpride plus olanzapine vs amisulpride plus placebo; and amisulpride plus olanzapine vs olanzapine plus placebo) an overall significance level of 0·050 was kept for both hypotheses. Therefore, the sample size calculation resulted in N=3×101=303 patients to be analysed. The analyses for the primary and secondary outcomes were based on the modified intention-to-treat sample (all patients randomly assigned to an intervention who received at least one dose of study drug).

As determined a priori in the study protocol and the statistical analysis plan (available from the corresponding author), the primary hypothesis (higher reduction in PANSS total score after 8 weeks for combination treatment than amisulpride monotherapy or olanzapine monotherapy) was tested with two t tests adjusted by the Bonferroni-Holm procedure,[21] underlying the sample size calculation. Analysis dealing with missing data for the primary outcome was done by a Bayesian sensitivity analysis for the difference of means between treatments. A pattern-mixture model was used to assess the deviation of the assumptions of missing at random from the assumption of missing not at random and how this deviation might influence the trial conclusion (appendix p 13). Bayesian analyses included sensitivity analyses of the previous specification. An ANCOVA including PANSS baseline score as covariate was conducted post-hoc for the observed cases and for the imputed values under the missing at random and missing not at random assumptions. Additionally, an analysis based on a mixed effects model for repeated measures was done under the missing at random assumption (appendix 16–19).

Analyses on secondary outcomes were done by pre-specified one-way ANOVA and post-hoc comparisons for metric measures, and χ^2 tests (including exact tests in case of low cell frequencies) for frequencies or proportions.

In case of relevant pre-treatment or baseline group differences, additional analyses were done (as planned a priori) controlling for respective parameters (including them as co-variates based on ANCOVA or logistic regression). Additionally, a post-hoc exploratory logistic regression analysis was done to identify predictors (out of a broad set of baseline characteristics) for responders to amisulpride plus olanzapine (≥50% reduction in PANSS total score after 8 weeks) compared with

13 692 patients were assessed for eligibility

13 364 excluded
  6482 did not meet inclusion criteria
  1278 declined to participate
  3285 change of pharmacological treatment was not reasonable
  2319 for other reasons

328 were randomised

112 were randomly assigned to receive amisulpride plus olanzapine

2 excluded
  1 did not receive the intervention
  1 screening failure

110 included in analysis of the primary outcome

41 dropped out before visit 4 (8 week primary endpoint)
  11 retracted informed consent
  6 side effects
  12 non-compliance
  4 lack of efficacy
  6 lost to follow-up
  1 not specified
  1 other reasons

69 completed visit 4

23 dropped out before visit 8 (secondary endpoint)
  2 retracted informed consent
  2 side effects
  5 non-compliance
  5 lack of efficacy
  4 lost to follow-up
  2 not specified
  3 other reasons

46 completed visit 8

109 were randomly assigned to receive amisulpride plus placebo

109 included in analysis of the primary outcome

41 dropped out before visit 4 (8 week primary endpoint)
  7 retracted informed consent
  7 side effects
  9 non-compliance
  8 lack of efficacy
  6 lost to follow-up
  1 not specified
  3 other reasons

68 completed visit 4

25 dropped out before visit 8 (secondary endpoint)
  3 retracted informed consent
  6 side effects
  3 non-compliance
  7 lack of efficacy
  4 lost to follow-up
  1 not specified
  1 other reasons

43 completed visit 8

107 were randomly assigned to receive olanzapine plus placebo

5 excluded
  4 did not receive the intervention
  1 screening failure

102 included in analysis of the primary outcome

37 dropped out before visit 4 (8 week primary endpoint)
  9 retracted informed consent
  7 side effects
  7 non-compliance
  4 lack of efficacy
  7 lost to follow-up
  2 not specified
  1 other reasons

65 completed visit 4

22 dropped out before visit 8 (secondary endpoint)
  5 retracted informed consent
  4 side effects
  4 non-compliance
  3 lack of efficacy
  2 lost to follow-up
  2 not specified
  2 other reasons
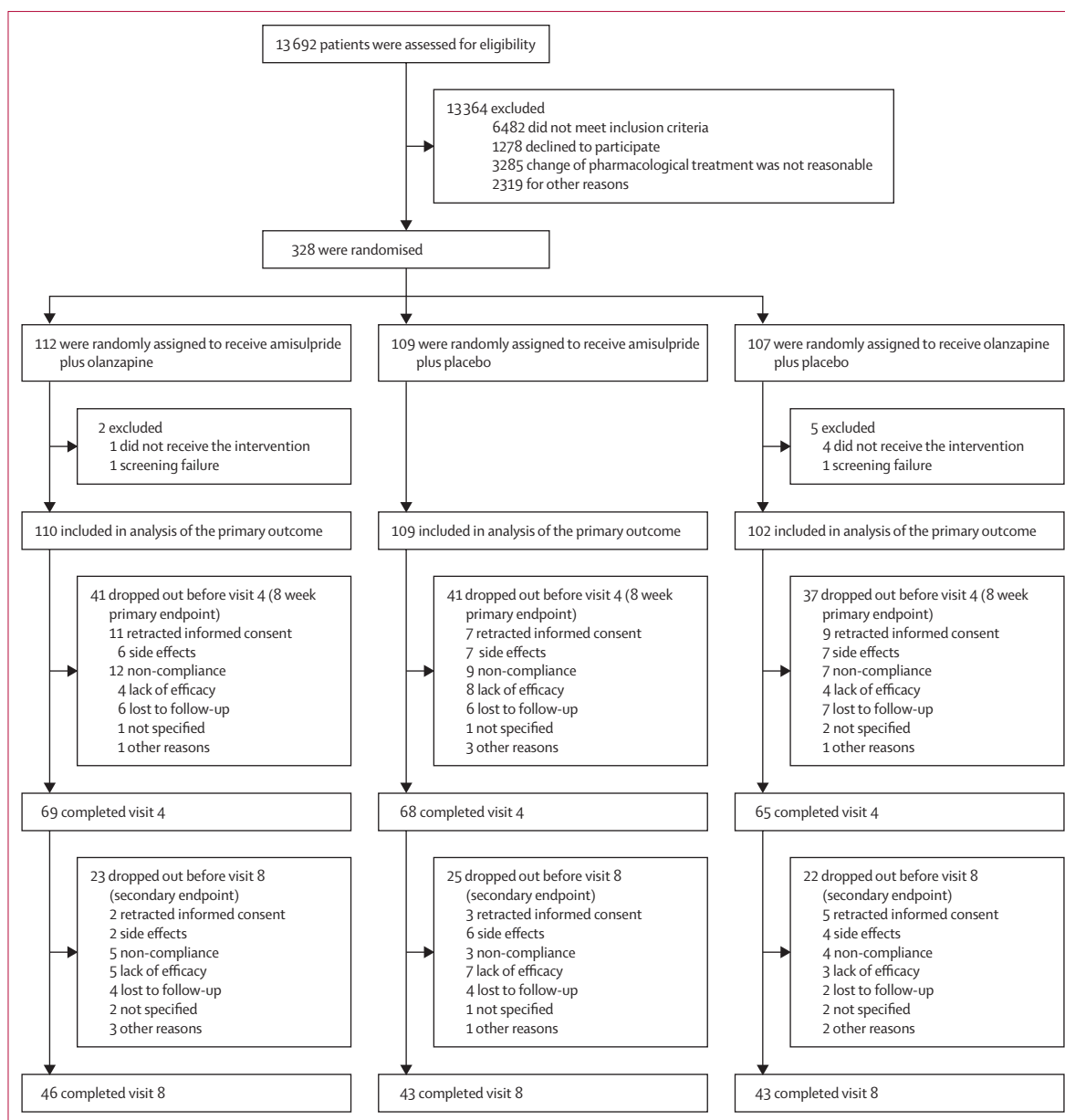
43 completed visit 8

Figure 1: Trial profile

responders to monotherapy (amisulpride plus placebo or olanzapine plus placebo).

R software (version 3.4.0), JAGS (version 4.3.0), and IBM-SPSS (version 25) were used for all statistical computations.

A data monitoring committee consisting of two external clinical experts and one statistician from Germany supervised proceedings throughout the study. The study was registered on ClinicalTrials.gov, NCT01609153, on May 31, 2012; the German Clinical Trials Register, DRKS00003603, on May 18, 2012; and the European Union Drug Regulating Authorities Clinical Trials Database, EudraCT-No. 2011-002463-20.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between June 15, 2012 and Dec 15, 2018, 13 692 patients were assessed for eligibility at 16 psychiatric facilities in Germany. After exclusion of 13 364 patients (including for not meeting inclusion criteria, declining to participate, or inappropriate reasons for changing pharmacological treatment), 328 were randomly assigned to receive double-blind treatment. 112 patients were randomly

	Amisulpride plus olanzapine group (n=110)	Amisulpride plus placebo group (n=109)	Olanzapine plus placebo group (n=102)	Total (n=321)
Age, years*	39·8 (12·1)	39·2 (10·8)	41·8 (12·3)	40·2 (11·7)
Sex†				
Male	77 (70%)	79 (72%)	73 (72%)	229 (71%)
Female	33 (30%)	30 (28%)	29 (28%)	92 (29%)
Ethnicity†				
White	100 (91%)	102 (94%)	94 (92%)	296 (92%)
Other	10 (9%)	7 (6%)	8 (8%)	25 (8%)
Weight, kg	85·2 (19·1)	79·1 (15·7)	80·9 (16·9)	81·7 (17·4)
Height, cm	175·1 (7·9)	175·4 (9·4)	175·4 (8·6)	175·3 (8·6)
Body-mass index, kg/m²	27·5 ± 6·1	25·7 ± 4·6	26·3 ± 5·2	26·5 ± 5·4
Partnered†	24 (22%)	18 (17%)	23 (23%)	65 (20%)
Employed†	27 (25%)	32 (29%)	25 (25%)	84 (26%)
Smoking				
Smokers†	91 (83%)	92 (84%)	68 (67%)	251 (78%)
Number of cigarettes per day‡	18·9 (11·8)	19·9 (10·1)	18·3 (8·8)	19·1 (10·4)
Diagnosis§				
Schizophrenia	95 (86)	94 (86%)	82 (80%)	271 (84%)
Schizoaffective disorder	14 (13%)	14 (13%)	19 (19%)	47 (15%)
Missing	1 (1%)	1 (1%)	1 (1%)	3 (1%)
Age at first psychiatric treatment, years*	26·3 (10·3)	25·2 (10·4)	27·9 (10·6)	28·2 (10·5)
Age at first in-patient psychiatric treatment, years*	28·0 (10·4)	28·3 (10·1)	29·8 (10·4)	28·7 (10·3)
Number of in-patient treatments¶	4·7 (5·3)	5·8 (6·4)	4·7 (5·2)	5·1 (5·7)
Treatment status at randomisation				
In-patient	110 (100%)	106 (97%)	98 (91%)	314 (98%)
Out-patient	0	3 (3%)	4 (4%)	7 (2%)
Substance misuse or dependency				
Previous substance misuse	54 (49%)	64 (59%)	47 (46%)	165 (51%)
Previous substance dependency	28 (25%)	29 (27%)	23 (23%)	80 (25%)
Substance misuse at study inclusion	21 (19%)	21 (19%)	18 (18%)	60 (19%)
Reason for admission to hospital†				
Impending deterioration	80 (73%)	83 (76%)	78 (76%)	241 (75%)
Suicidality	7 (6%)	6 (6%)	7 (7%)	20 (6%)
Hostility	1 (1%)	2 (2%)	4 (4%)	7 (2%)
Psychosocial distress	18 (16%)	15 (14%)	11 (11%)	44 (14%)
Insufficient treatment response	1 (1%)	1 (1%)	0	2 (1%)
Unwanted side-effects	1 (1%)	0	0	1 (<1%)
Other reason	2 (2%)	0	1 (1%)	3 (1%)
Missing	0	2 (2%)	1 (1%)	3 (1%)

(Table 1 continues on next page)

assigned to receive amisulpride plus olanzapine, 109 were randomly assigned to receive amisulpride plus placebo, and 107 were randomly assigned to receive olanzapine plus placebo. 321 patients were analysed for the primary outcome in the modified intention-to-treat population after exclusion of screening failures and patients never receiving the intervention (110 for amisulpride plus olanzapine, 109 for amisulpride plus placebo, and 102 for olanzapine plus placebo; figure 1).

314 (98%) of the 321 patients were receiving in-patient treatment, admitted mostly (about 97%) due to symptom re-exacerbation and only few (<5%) due to other reasons (eg, insufficient treatment response, side-effects; table 1). Demographic and illness-related variables are displayed in tables 1 and 2, and the appendix (pp 28–34).

Altogether, 202 (63%) of 321 patients completed the assessment of the primary efficacy endpoint at 8 weeks (69 for amisulpride plus olanzapine, 68 for amisulpride plus placebo, and 65 for olanzapine plus placebo). Completion rates between the three groups up to week 8 were similar (p=0·94), as were reasons for drop-out (p=0·92; appendix p 35). There were no group differences regarding the time to drug discontinuation or study discontinuation (appendix p 35). No significant group differences occurred regarding antipsychotic adherence based on physician's compliance assessment up to week 8 (except for one significant advantage of combination treatment compared with amisulpride monotherapy at Visit 6), drug accountability, the proportion of detectable plasma levels of administered study antipsychotics during Visits 1, 4, and 8, or for concomitant medications (appendix pp 36–41).

Regarding the primary efficacy endpoint of difference in PANSS total score between baseline and week 8, patients receiving amisulpride plus olanzapine showed a significantly greater reduction in PANSS total score from baseline (–29·6 [SD 14·5]) than did patients receiving olanzapine plus placebo (–24·1 [13·4], p=0·025 adjusted to p=0·049 according to Bonferroni-Holm, Cohen's d=0·396; figure 2; appendix p 42). No significant difference was observed in the reduction of PANSS total scores of patients receiving amisulpride plus olanzapine compared with those receiving amisulpride plus placebo (–25·2 [SD 15·9], p=0·095, Cohen's d=0·29; figure 2; appendix p 42). Applying Bayesian methods to account for missing data, group differences between amisulpride plus olanzapine versus olanzapine plus placebo remained significant (appendix pp 23–24). Imputation of missing values applying mixed model repeated measure analyses showed a significantly greater reduction of symptoms with amisulpride plus olanzapine than with olanzapine plus placebo (p=0·026; Cohen's d=0·35) and with amisulpride plus placebo (p=0·037; Cohen's d=0·35; appendix pp 25, 42). The post-hoc ANCOVA with PANSS baseline scores as covariate resulted in no significant differences (amisulpride plus olanzapine vs amisulpride plus placebo: p=0·08; amisulpride plus olanzapine vs olanzapine plus placebo: p=0·09) in observed cases. On the basis of post-hoc ANCOVA including imputed values (for drop-outs), amisulpride plus olanzapine showed significant differences compared with both mono-therapies (p=0·018 for amisulpride monotherapy and p=0·046 for olanzapine monotherapy).

Regarding secondary efficacy endpoints at week 8, global disease severity measured with the CGI-S decreased significantly more with amisulpride plus

olanzapine than with amisulpride plus placebo (–1·4 [SD 1·0] *vs* –1·0 [1·1]; Tukey post hoc test, p=0·046 [95% CI for group difference –0·78 to –0·07]; table 3), and PANSS negative symptoms reduced significantly more with amisulpride plus olanzapine than olanzapine plus placebo (–6·4 [5·6] *vs* –4·2 [4·0]; Tukey post-hoc test, p=0·043; [95% CI for group difference –3·81 to –0·49]; table 3; appendix p 22). However negative symptoms according to Marder[16] and van der Gaag[17] did not show differences between the groups. There were no further significant group differences in symptom changes between the three groups from baseline to week 8. Furthermore, there were no differences in PANSS total scores or other secondary outcomes between baseline and week 16 (table 3; appendix pp 22, 43–45).

Regarding side-effects, amisulpride plus olanzapine and olanzapine plus placebo were both associated with greater increases in waist circumference (4·4 cm [SD 6·1] cm for amisulpride plus olanzapine; 4·0 cm [6·1] for olanzapine plus placebo) than was amisulpride plus placebo (–0·5 cm [5·8]; both p=0·001) at week 8 (appendix p 46). At week 16, waist circumference differences were significantly lower with amisulpride plus placebo compared with olanzapine plus placebo (2·6 cm [SD 5·5] *vs* 6·9 [7·4], p=0·028). At week 8, there was significantly greater weight gain with amisulpride plus olanzapine than with amisulpride plus placebo (4·4 kg [SD 6·3] vs 1·4 kg [4·2], p=0·008). At week 16, weight gain was significantly greater with amisulpride plus olanzapine (6·6 kg [SD 6·5]; p=0·004) and olanzapine plus placebo (6·5 kg [5·5]; p=0·005) than with amisulpride plus placebo (1·3±7·4 kg). At week 8, BMI scores were significantly lower for amisulpride plus placebo (25·5 kg/m² [SD 4·0]) than for amisulpride plus olanzapine (28·3 kg/m² [5·5]; p=0·01) and for olanzapine plus placebo (28·2 kg/m² [5·6]; p=0·014). At week 16, BMI was only significantly lower for amisulpride plus placebo (25·2 kg/m² [SD 4·4]) versus olanzapine plus placebo (30·1 kg/m² [5·8]; p<0·001; appendix p 46). No significant differences occurred in the prevalence and incidence of diabetes mellitus or metabolic syndrome according to IDF-criteria.[22] At week 8, patients receiving amisulpride plus placebo showed a greater reduction of the heart rate compared with baseline during ECG recordings and resting pulse than did olanzapine plus placebo (–13·4 beats per min [SD 14·8] *vs* –3·9 beats per min [15·7]; p=0·009). No significant group differences occurred in QTc-time at week 8 (amisulpride plus olanzapine, 394·4 [90·0]; amisulpride plus placebo, 407·5 [28·1]; olanzapine plus placebo, 404·4 [29·8]; p=0·48) and week 16 (amisulpride plus olanzapine, 401·9 [87·2]; amisulpride plus placebo, 416·1 [26·2]; olanzapine plus placebo, 407·9 [29·6]; p=0·56; appendix pp 47–48), and no clinically significant QTc prolongation occurred in any group at week 8 or week 16.

	Amisulpride plus olanzapine group (n=110)	Amisulpride plus placebo group (n=109)	Olanzapine plus placebo group (n=102)	Total (n=321)
(Continued from previous page)				
Pre-randomisation antipsychotics‖				
Not specified	22 (20%)	25 (23%)	22 (22%)	69 (21%)
Amisulpride	20 (18%)	11 (10%)	9 (9%)	40 (12%)
Aripiprazole	6 (5%)	11 (10%)	9 (9%)	26 (8%)
Flupentixol	3 (3%)	3 (3%)	3 (3%)	9 (3%)
Haloperidol	5 (5%)	5 (5%)	8 (8%)	18 (6%)
Olanzapine	47 (43%)	39 (36%)	42 (41%)	128 (40%)
Quetiapine	15 (14%)	13 (12%)	11 (11%)	39 (12%)
Risperidone	26 (24%)	17 (16%)	16 (16%)	59 (18%)
Other	2 (2%)	13 (12%)	7 (7%)	22 (7%)
Number of compounds**				
Not specified	22 (20%)	25 (23%)	22 (22%)	69 (21%)
One	57 (52%)	58 (53%)	59 (58%)	174 (54%)
Two	26 (24%)	24 (22%)	17 (17%)	67 (21%)
Three	5 (5%)	2 (2%)	4 (4%)	11 (3%)

Data are mean (SD) or N (%). *Reported by patients at screening interview. †Reported by patients at screening interview; other genders categorised as non-binary were not recorded. ‡Reported by patients at screening interview; data referring to smokers. §Schizophrenia (F20) and Schizoaffective disorder (F25) according to ICD-10 diagnosis criteria.[2] ¶Previous stay in psychiatric facilities for a minimum of one night; reported by patients at screening interview. ‖Multiple answers possible; reported by patients at screening interview. **Number of patients receiving one or more pharmaceutical compounds as preceding antipsychotic treatment.

Table 1: **Baseline characteristics**

Regarding sexual functioning, patients receiving amisulpride plus olanzapine had a greater reduction of the DISF-SR total score than those receiving amisulpride plus placebo (–14·5 [SD 27·6] *vs* –2·4 [23·1]; p=0·015) at week 8 (table 3). The number of adverse events and serious adverse events did not differ significantly between the groups (table 4). A graphical analysis of serious adverse events in the treatment course as well as analyses of any type of adverse event by gender are provided in the appendix (appendix p 26, 49–54).

Differences in blood laboratory parameters are presented in the appendix (pp 55–57). After 8 weeks, significant differences (all p<0·05) were observed between amisulpride plus olanzapine and olanzapine plus placebo groups regarding changes of erythrocytes (–0·03 number per pico liters [SD 0·3] *vs* 0·15 number per pico liters [0·4]), haematocrit (–0·4% [3·1] *vs* 1·0 [3·1]) and haemoglobin (–0·2 g/dL [1·0] *vs* 0·3 g/dL [1·1]), whereas the HbA_{1c} concentration was significantly different for amisulpride plus placebo versus olanzapine plus placebo (0·23%±0·7 *vs* –0·04%±0·3; p=0·037). Prolactin concentrations significantly increased with amisulpride plus olanzapine, both at week 8 (53·3 ng/ml [SD 58·2]) and week 16 (35·6 ng/ml [39·3]), and amisulpride plus placebo (week 8, 46·1±56·5 ng/ml; week 16, 38·4 ng/ml [49·3]) compared with olanzapine plus placebo (week 8, –16·8 ng/ml [39·6]; week 16, –8·4 ng/ml [33·3]; p<0·0001). At week 16, some liver parameters (ALT and gamma-GT) were significantly

	Amisulpride plus olanzapine (n=110)	Amisulpride plus placebo (n=109)	Olanzapine plus placebo (n=102)	Total (n=321)
PANSS*				
Total	90·4 (13·7)	89·2 (13·7)	87·0 (11·9)	88·9 (13·2)
Positive	22·6 (4·2)	23·4 (4·9)	22·3 (3·9)	22·8 (4·4)
Negative	23·6 (6·1)	22·3 (5·6)	22·1 (5·6)	22·7 (5·8)
General	44·1 (7·6)	43·5 (7·5)	42·6 (6·7)	43·4 (7·3)
PANSS Five-factor (Marder et al, 1997)†				
Positive symptoms	26·1 (5·4)	27·2 (6·1)	26·5 (5·1)	26·6 (5·5)
Negative symptoms	22·6 (6·8)	20·9 (6·0)	20·8 (6·7)	21·5 (6·5)
Disorganised thought	19·9 (5·2)	19·4 (4·8)	18·7 (4·7)	19·3 (4·9)
Uncontrollable hostility or excitement	9·1 (3·2)	9·2 (3·5)	8·5 (2·9)	8·9 (3·2)
Anxiety or depression	12·8 (3·8)	12·6 (3·4)	12·5 (3·0)	12·6 (3·4)
PANSS Five-factor (van der Gaag et al, 2006)‡				
Positive symptoms	22·7 (5·1)	23·7 (6·1)	23·1 (4·6)	23·2 (5·3)
Negative symptoms	23·3 (7·0)	21·7 (6·6)	21·4 (7·6)	22·2 (7·1)
Disorganised thought	29·4 (6·5)	29·3 (6·6)	28·4 (6·0)	29·0 (6·4)
Excitement	20·6 (4·8)	20·7 (4·9)	19·8 (4·4)	20·4 (4·7)
Emotional distress	25·7 (5·5)	25·2 (5·2)	24·7 (4·5)	25·2 (5·1)
CGI-severity§	5·1 (0·7)	5·0 (0·9)	4·9 (0·7)	5·0 (0·8)
SAS¶	1·3 (2·2)	1·1 (1·9)	1·3 (2·3)	1·2 (2·1)
DOTES‖	3·5 (3·9)	3·1 (3·4)	3·7 (4·4)	3·4 (3·9)
DISF-SR total**	51·3 (36·8)	50·1 (39·7)	56·3 (36·6)	52·4 (37·6)
SWN-K††				
Total	78·0 (16·3)	81·8 (17·4)	78·5 (17·3)	79·4 (17·0)
Emotional regulation	16·6 (4·6)	17·2 (4·2)	16·5 (4·8)	16·8 (4·5)
Self-control	16·4 (3·1)	17·0 (3·5)	16·2 (3·7)	16·5 (3·4)
Mental functioning	14·4 (4·3)	15·8 (4·2)	15·3 (4·9)	15·1 (4·5)
Social integration	15·1 (3·9)	15·7 (4·2)	14·8 (4·4)	15·2 (4·1)
Physical functioning	15·5 (4·6)	16·1 (5·1)	15·8 (4·3)	15·8 (4·6)

Data are mean (SD). PANSS=Positive and negative syndrome scale. CGI=Clinical Global Impression scale. SAS=Simpson Angus Scale. DOTES=Dosage Record Treatment Emergent Symptom Scale. DISF-SR=Derogatis Interview for Sexual Functioning. SWN-K=Subjective Well-Being Under Neuroleptics Scale short form. *PANSS calculated according to Kay and colleagues.[8] Total score (sum of all 30 items) ranges from 30–210; positive score (sum P1–P7) ranges from 7–49; negative score (sum N1–N7) ranges from 7–49; general score (sum G1–G16) ranges from 16–112. †Five-factor PANSS subscales calculated according to Marder and colleagues.[16] Positive score ranges from 8–56; negative score and disorganised symptoms range from 7–49; uncontrolled hostility or excitement and anxiety or depression range from 4–28. ‡Five-factor PANSS subscales calculated according to van der Gaag and colleagues.[17] Positive score and disorganised symptoms range from 10–70; negative score ranges from 9–63; excitement and emotional distress range from 8–56. §CGI scale ranging from 1–7.[18] ¶SAS of extrapyramidal symptoms ranging from 0–40.[12] ‖DOTES ranging from 0–90.[13] **DISF-SR overall score is transformed in t-standard values ranging from 20–80.[14] ††SWN-K total and sub-scores calculated according to Collegium Internationale Psychiatriae Scalarum; the SWN-K-total score ranges from 20–120.[15]

Table 2: **Baseline symptom and disease severity scales**

increased with amisulpride plus olanzapine (both 16·4 U/l [SD 48·1]), but decreased with amisulpride plus placebo (ALT, –4·3 U/l [22·6], p=0·043; gamma-GT, –2·1 U/l [18·1], p=0·08) and olanzapine plus placebo (ALT, –4·5 U/l [18·5], p=0·033; gamma-GT, –4·9 U/l [21·4], p=0·029). Conversely, C-reactive protein concentration increased with amisulpride plus placebo (2·7 U/l [SD 7·7]) and decreased with olanzapine plus placebo (–1·1 U/l [3·9]; p=0·033) at week 16.

Controlling for differences in the trial drug exposure revealed that in the initial study phase (first 2 weeks) dose levels were comparable between treatment groups (appendix p 59). After 8 weeks, the applied mean dose level was significantly lower in the amisulpride plus olanzapine group (dose level 2·9 [SD 0·9]) than in the amisulpride plus placebo group (dose level 3·3 [0·9]; p=0·04; Tukey post-hoc test) and the olanzapine plus placebo group (3·4±0·8; p=0·020; Tukey post-hoc test). After 16 weeks, dose levels were not significantly different. Regarding the overall applied antipsychotic doses (adding together the respective drug amounts in olanzapine dose equivalents), overall drug dose was significantly higher in the combination group than in the monotherapy groups at week 8 (amisulpride plus olanzapine, 28·2 mg per day [SD 8·2] vs amisulpride plus placebo, 16·5 mg per day [4·4]; p<0·001 and vs olanzapine plus placebo, 14·1 mg per day [3·8]; p<0·001) and at week 16 (amisulpride plus olanzapine, 28·4 mg per day [9·3] vs amisulpride plus placebo, 17·2 mg per day [5·0]; p<0·001 and vs olanzapine plus placebo, 14·0 mg per day [4·4];

p<0·001, appendix p 59). Exploring a potential effect of the higher drug dose equivalents in the combination group, the dose in olanzapine equivalents was not significantly associated with change in PANSS total scores (r=0·09, p=0·17 for observed scores and r=0·08, p=0·14 for imputed scores). However, additional analyses were done for PANSS total score changes adjusted for drug dose (based on analysis of co-variance). All group differences in PANSS total score changes (adjusted for drug dose) after 8 weeks according to both the observed scores (excluding missing values) and the imputed scores via mixed model repeated measures showed no significant differences between the amisulpride plus olanzapine group compared with the amisulpride and placebo group (p=0·33 and p=0·11) or the amisulpride plus olanzapine group compared with the olanzapine plus placebo group (p=0·19 and p=0·17; *t* test analyses).

In the logistic regression analyses regarding predictors for response to combination treatment, only pre-treatment with amisulpride remained in the model as a predictor for response to amisulpride plus olanzapine (compared with response to both monotherapies); however, this variable did not reach significance (odds ratio 2·99 [95% CI 0·87–10·27]; p=0·06).

Discussion

According to a systematic review[23] and our own literature search, no double-blind randomised controlled trials have examined the efficacy and tolerability of amisulpride plus olanzapine compared with each as a monotherapy. The present study is one of the largest publicly funded trials to assess antipsychotic combination treatment in a prospective, high-quality design. Our results in multi-episode in-patients with at least moderate, clinically relevant symptoms of schizophrenia showed that PANSS total score improved significantly more at 8 weeks in patients receiving amisulpride plus olanzapine than those receiving olanzapine plus placebo.

The effects favouring antipsychotic combination treatment in the primary outcome at week 8 are probably not due to differences in baseline characteristics. A lower proportion of smokers in the olanzapine treatment arm could have led to higher plasma concentrations of olanzapine in the monotherapy group relative to the combination group caused by slower metabolisation via the cytochrome p450 1A2 pathway. However, a higher olanzapine plasma concentration in the monotherapy group would have caused a higher risk for side-effects, but might have been an even more powerful comparator, and the analyses of olanzapine blood drug concentrations showed no significant differences of plasma concentrations between the groups. The duration of untreated psychosis was not assessed and could have affected treatment results.

Treatment groups did not differ significantly in all-cause or specific-cause discontinuation, non-compliance, drug accountability, antipsychotic blood concentrations,
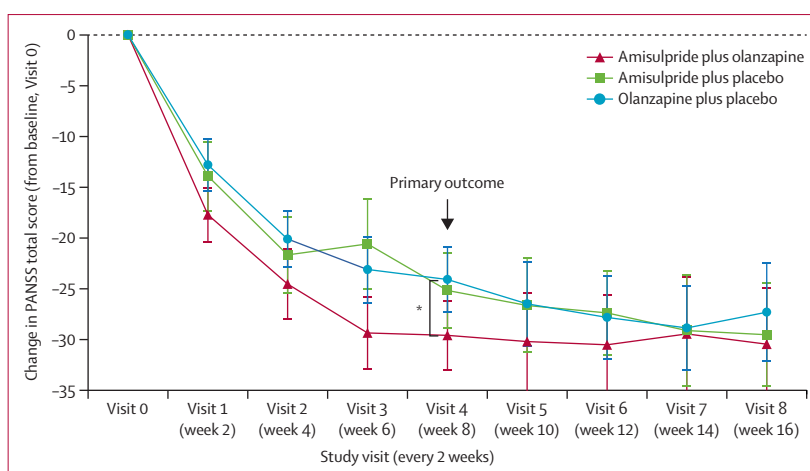

Figure 2: Changes of symptom severity per group measured by PANSS total score from baseline (Visit 0) to week 16 (Visit 8)
Points represent mean change and error bars indicate 95 CI of the mean. The primary outcome was change at Visit 4 (8 weeks). PANSS=Positive and Negative Syndrome Scale. *Amisulpride plus olanzapine versus olanzapine plus placebo: p=0·049, Cohens d=0·396 (t test with alpha error adjustment according to Bonferroni-Holm).

or serious adverse events. Even if compliance, which is a strong predictor for treatment outcome in schizophrenia especially in the longer term, was only roughly assessed, none of the indicators for treatment adherence uniformly showed any significant group differences. The main results did not differ when Bayesian methods were used to account for missing data.

Considering high prescription rates of antipsychotic combination treatment in clinical practice and various rationales[24] for this practice, the combination of olanzapine and amisulpride could offer an alternative for patients whose symptoms respond insufficiently to various antipsychotic monotherapies and who refuse or are otherwise ineligible or unsuitable for clozapine. In this population, even small differences in efficacy could be important regarding the severity of the disorder and its consequences. In case of lack of efficacy, instead of choosing antipsychotic combination treatments without evidence, our findings offer amisulpride plus olanzapine as a clinical option with some evidence to support its use in clinical situations in which combination treatment seems reasonable and is carefully justified and monitored.

The factor that would most likely predict response in combination versus monotherapy was a preceding medication with amisulpride. In the OPTiMiSE trial,[25] no significant differences occurred between open-label treatment with amisulpride followed by a change to olanzapine versus staying on amisulpride in non-remitting first-episode patients. Therefore, our results support a unique effect of combination treatment rather than a broader coverage of individuals with different responsiveness to each monotherapy.

Results of this study need to be interpreted within its limitations. The differences in the main comparisons (4·4 and 5·5 points on the PANSS total score, Cohen's *d*

	Amisulpride plus olanzapine group (n=110)	Amisulpride plus placebo (n=109)	Olanzapine plus placebo (n=102)	p value	Post-hoc comparison	
					Amisulpride plus olanzapine vs amisulpride plus placebo	Amisulpride plus olanzapine vs olanzapine plus placebo
PANSS*						
Total	–29·6 (14·5)	–25·2 (15·9)	–24·1 (13·4)	..	..	..
Positive	–9·7 (5·3)	–9·1 (5·9)	–8·0 (5·0)	0·18	..	..
Negative	–6·4 (5·6)	–4·5 (5·7)	–4·2 (4·0)	0·031	0·084	0·043
General	–13·1 (8·7)	–11·6 (8·8)	–11·9 (7·4)	0·52	..	..
PANSS Five-factor (Marder et al, 1997)†						
Positive symptoms	–10·4 (6·6)	–10·0 (6·4)	–9·3 (6·6)	0·62	..	..
Negative symptoms	–5·8 (6·6)	–4·1 (6·0)	–3·8 (4·8)	0·088	..	..
Disorganised thought	–6·0 (4·4)	–4·7 (4·8)	–4·6 (4·1)	0·13	..	..
Uncontrolled hostility or excitement	–2·8 (3·6)	–2·3 (3·7)	–2·1 (3·0)	0·52	..	..
Anxiety or depression	–4·2 (4·2)	–4·2 (3·9)	–4·3 (4·0)	0·99	..	..
PANSS Five-factor (van der Gaag et al, 2006)‡						
Positive symptoms	–9·4 (6·5)	–9·4 ± 6	–8·5 (6·3)	0·62	..	..
Negative symptoms	–5·5 (7·6)	–3·7 ± 6·7	–3·8 (5·8)	0·21	..	..
Disorganised thought	–9·1 (6·2)	–7·5 ± 6·3	–7·4 (5·6)	0·16	..	..
Excitement	–6·2 (5·4)	–5·0 ± 4·9	–4·9 (4·7)	0·29	..	..
Emotional distress	–8·9 (5·8)	–8·5 ± 6·0	–8·1 (6·0)	0·75	..	..
CGI-severity§	–1·4 (1·0)	–1·0 (1·1)	–1·1 (1·0)	0·054	0·046	..
SAS¶	–0·2 (2·6)	0·1 (2·6)	0·4 (2·6)	0·47	..	..
DOTES‖	–0·8 (4·1)	–0·3 (3·0)	–0·9 (4·7)	0·38	..	..
DISF-SR**						
Total	–14·5 (27·6)	–2·4 (23·1)	–8·0 (23·6)	0·020	0·015	..
Sexual cognition and fantasy	–5·7 (10·6)	0·2 (9·6)	–2·6 (8·9)	0·043	0·034	..
Sexual arousal	–4·1 (7·0)	0·6 (6·4)	–1·9 (7·2)	0·021	0·016	..
Sexual behaviour or experience	–2·5 (8·1)	1·5 (5·8)	1·0 (6·7)	0·030	0·045	0·081
Orgasm	–1·3 (8·6)	0·9 (6·4)	–2·8 (6·5)	0·13	..	..
Sexual drive	–3·2 (5·3)	–0·9 (5·7)	–1·8 (23·6)	0·24	..	..
SWN-K††						
Total	8·3 (13·7)	5·3 (15·9)	6·2 (15·8)	0·60	..	..
Emotional regulation	0·9 (3·2)	0·6 (4·2)	1·1 (4·3)	0·82	..	..
Self-control	1·7 (3·2)	0·9 (3·2)	1·4 (3·6)	0·48	..	..
Mental functioning	1·8 (3·5)	0·6 (4·9)	0·7 (4·6)	0·32	..	..
Social integration	2·4 (4·2)	1·3 (3·4)	1·9 (4·2)	0·36	..	..
Physical functioning	1·5 (4·9)	1·3 (4·4)	1·0 (4·7)	0·86	..	..

Data are means (SD). ANOVA test was used for metric measures and followed by Tukey's post hoc test in case of significant overall group difference. p<0·05, p<0·01, p<0·001 were used to indicate significance, for the three types of analysis, respectively. The primary outcome "change in PANSS-total from Visit 0 to Visit 4" was tested by two t tests including Bonferroni-Holm adjustment. PANSS=Positive and negative syndrome scale. CGI=Clinical Global Impression scale. SAS=Simpson Angus Scale. DOTES=Dosage Record Treatment Emergent Symptom Scale. DISF-SR=Derogatis Interview for Sexual Functioning. SWN-K=Subjective Well-Being Under Neuroleptics Scale short form. *PANSS calculated according to Kay and colleagues.[8] Total score (sum of all 30 items) ranges from 30–210; positive score (sum P1–P7) ranges from 7–49; negative score (sum N1–N7) ranges from 7–49; general score (sum G1–G16) ranges from 16–112. †Five-factor PANSS subscales calculated according to Marder and colleagues.[16] Positive score ranges from 8–56; negative score and disorganised symptoms range from 7–49; uncontrolled hostility or excitement and anxiety or depression range from 4–28. ‡Five-factor PANSS subscales calculated according to van der Gaag and colleagues.[17] Positive score and disorganised symptoms range from 10–70; negative score ranges from 9–63; excitement and emotional distress range from 8–56. §CGI scale ranging from 1–7.[18] ¶SAS of extrapyramidal symptoms ranging from 0–40.[12] ‖DOTES ranging from 0–90.[13] **DISF-SR overall score is transformed in t-standard values ranging from 20–80.[14] ††SWN-K total and sub-scores calculated according to Collegium Internationale Psychiatriae Scalarum; the SWN-K-total score ranges from 20–120.[15]

Table 3: Primary and secondary outcomes—group differences in symptom reduction between baseline and Visit 4 (week 8)

between 0·3 and 0·4) are in the lower range of clinical significance and lower than the difference projected in our a priori power and sample size calculation (0·5). However, effect size differences are similar to differences between antipsychotics and placebo in general (0·38 to 0·47).[2] The difference between amisulpride plus

olanzapine versus olanzapine plus placebo was significant even if the study was not sufficiently powered, as the detected effect size was smaller than the expected effect size. The insufficient power might explain the finding that the difference between amisulpride plus

olanzapine versus amisulpride plus placebo did not reach statistical significance, especially since the sample size was further decreased by a high rate of study discontinuation. A priori planned analyses based on mixed model repeated measures imputation methods

	Amisulpride plus olanzapine (n=110)	Amisulpride plus placebo (n=109)	Olanzapine plus placebo (n=102)	p value*	Post-hoc comparison	
					Amisulpride plus olanzapine vs amisulpride plus placebo	Amisulpride plus olanzapine vs olanzapine plus placebo
Serious adverse events						
Number of patients	20 (18%)	23 (21·1)	15 (14·7)	0·48	..	..
Intensity (maximum per patient)						
Moderate	8 (7%)	9 (8%)	7 (6·9)	0·84	..	..
Serious	11 (10%)	13 (12%)	6 (5·9)	..	..	..
Life-threatening	0	1 (1%)	1 (1·0)	..	..	..
Death	1 (1%)	0	1 (1·0)	..	..	..
Assessed relation to drugs (maximum per patient)†						
Likely	0	1 (1%)	0	0·30	..	..
Possible	0	3 (3%)	2 (2%)	..	..	..
Unlikely	4 (4%)	6 (6%)	6 (6%)	..	..	..
No relation	15 (14%)	10 (9%)	7 (7%)	..	..	..
Unclear	1 (1%)	3 (%)	0	..	..	..
Frequency of serious adverse events‡	22/74 (30%)	31/74 (42%)	21/74 (28%)	0·35		
Intensity of serious adverse events						
Moderate	9/22 (40·9)	15/31 (48%)	10/21 (48%)	0·88	..	..
Serious	12/22 (55%)	15/31 (48%)	9/21 (43%)	..	..	..
Life-threatening	0	1/31 (3%)	1/21 (5%)	..	..	..
Death	1/22 (5%)	0	1/21 (5%)	..	..	..
Assessed relation to drugs†						
Likely	0	1/31 (3%)	0	0·016*	0·040*	0·024*
Possible	0	3/31 (10%)	5/21 (24%)	..	..	..
Unlikely	4/22 (18%)	9/31 (29%)	6/21 (29%)	..	..	..
No relation	17/22 (77%)	12/31 (38%)	10/21 (48%)	..	..	..
Unclear	1/22 (5%)	6/31 (19%)	0	..	..	..
Serious adverse event symptoms						
Increase of psychotic symptoms	2/22 (9%)	3/31 (10%)	2/21 (10%)	0·27	..	..
Psychotic re-exacerbation	12/22 (55%)	10/31 (32%)	6/21 (29%)	..	..	..
Suicidality	1/22 (5%)	4/31 (13%)	1/21 (5%)	..	..	..
Increase of other mental symptoms	2/22 (9%)	7/31 (23%)	4/21 (19%)	..	..	..
Extrapyramidal motor side-effects	1/22 (5%)	3/31 (10%)	0	..	..	..
Blood test or liver function test abnormalities	0	0	3/21 (14%)	..	..	..
Death	1/22 (5%)	0	1/21 (5%)	..	..	..
Other	3/22 (14%)	4/31 (13%)	4/21 (19%)	..	..	..
Adverse events						
Number of patients	101 (92%)	95 (87%)	86 (84%)	0·48	..	..
Mean frequency of adverse events per patient	8·2 (6·6)	7·4 (6·4)	8·1 (6·8)	0·90	..	..
Intensity (maximum per patient)†						
Slight	24/101 (24%)	23/95 (24%)	23/86 (27%)	0·84	..	..
Moderate	67/101 (66%)	59/95 (62%)	41/86 (48%)	..	..	..
Serious	10/101 (10%)	13/95 (14%)	22/86 (26%)	..	..	..
					(Table 4 continues on next page)	

	Amisulpride plus olanzapine (n=110)	Amisulpride plus placebo (n=109)	Olanzapine plus placebo (n=102)	p value*	Post-hoc comparison	
					Amisulpride plus olanzapine vs amisulpride plus placebo	Amisulpride plus olanzapine vs olanzapine plus placebo
(Continued from previous page)						
Assessed relation to drugs (maximum per patient)‡						
Assured	3/101 (3%)	0	3/86 (3%)	0·39	..	..
Likely	43/101 (43%)	32/95 (34%)	41/86 (48%)	..	..	..
Possible	31/101 (31%)	40/95 (42%)	27/86 (31%)	..	..	..
Unlikely	9/101 (9%)	9/95 (9%)	6/86 (7%)	..	..	..
No relation	14/101 (14%)	13/95 (14%)	9/86 (10%)	..	..	..
Unclear	1/101 (1%)	1/95 (1%)	0	..	..	..
Adverse event symptoms						
Increased psychotic symptoms	3 (3%)	6 (6%)	7 (7%)	0·37	..	..
Depressive symptoms	29 (26%)	24 (22%)	28 (27%)	0·63	..	..
Suicidality or self-violent behaviour	1 (1%)	1 (1%)	0	0·63	..	..
Sleep disturbance	29 (26%)	34 (31%)	28 (27%)	0·71	..	..
Fatigue	37 (34%)	29 (27%)	37 (36%)	0·30	..	..
Appetite increase	8 (7%)	3 (3%)	7 (7%)	0·28	..	..
Restlessness or agitation	20 (18%)	25 (23%)	20 (20%)	0·67	..	..
Drug misuse	11 (10%)	9 (8%)	3 (3%)	0·12	..	..
Other mental symptoms	2 (2%)	5 (5%)	4 (4%)	0·50	..	..
Dystonia	7 (6%)	8 (7%)	7 (7%)	0·96	..	..
Akathisia	10 (9%)	8 (7%)	11 (11%)	0·68	..	..
Rigor	27 (25%)	20 (18%)	23 (23%)	0·53	..	..
Tremor	29 (26%)	18 (17%)	23 (23%)	0·21	..	..
Hyperactivity	19 (17%)	17 (16%)	18 (18%)	0·91	..	..
Dyskinesia	8 (7%)	4 (4%)	8 (8%)	0·39	..	..
Gait	9 (8%)	3 (2%)	6 (6%)	0·22	..	..
Salivation	15 (14%)	9 (8%)	9 (9%)	0·36	..	..
Dry mouth	29 (26%)	21 (19%)	31 (30%)	0·17	..	..
Other extrapyramidal motor side-effects	15 (14%)	13 (12%)	18 (18%)	0·48	..	..
Vegetative symptoms	18 (16%)	19 (17%)	26 (25%)	0·19	..	..
Sexual dysfunction	2 (2%)	3 (3%)	4 (4%)	0·65	..	..
Weight gain	40 (36%)	21 (19%)	34 (33%)	0·01	0·005	..
Weight loss	5 (5%)	7 (6%)	7 (7%)	0·75	..	..
Obstipation	7 (6%)	6 (6%)	8 (8%)	0·79	..	..
Heart or circulatory symptoms	16 (15%)	17 (16%)	13 (13%)	0·84	..	..
Eye disorders	11 (10%)	5 (5%)	13 (13%)	0·11	..	..
Respiratory symptoms	14 (13%)	11 (10%)	12 (12%)	0·83	..	..
Gastrointestinal symptoms	13 (12%)	14 (13%)	15 (15%)	0·82	..	..
Skin symptoms	11 (10%)	19 (17%)	12 (12%)	0·24	..	..
Musculoskeletal symptoms	7 (6%)	6 (6%)	9 (9%)	0·62	..	..
Urogenital symptoms	2 (2%)	8 (7%)	2 (2%)	0·051	..	..
Neurological symptoms	4 (4%)	7 (6%)	3 (3%)	0·42	..	..
Blood test, C-reactive protein	18 (16%)	14 (13%)	11 (11%)	0·48	..	..
Blood test, creatine kinase	20 (18%)	19 (17%)	21 (21%)	0·83	..	..
Blood test, liver function	29 (26%)	20 (18%)	28 (27%)	0·23	..	..
Blood test, haematocrit	34 (31%)	29 (27%)	25 (25%)	0·57	..	..
Blood test, cells	28 (25%)	27 (25%)	26 (25%)	0·99	..	..

(Table 4 continues on next page)

	Amisulpride plus olanzapine (n=110)	Amisulpride plus placebo (n=109)	Olanzapine plus placebo (n=102)	p value*	Post-hoc comparison	
					Amisulpride plus olanzapine vs amisulpride plus placebo	Amisulpride plus olanzapine vs olanzapine plus placebo
(Continued from previous page)						
Blood test, lipids	43 (39%)	29 (27%)	33 (32%)	0·14	..	..
Blood test, glucose	23 (21%)	17 (16%)	14 (14%)	0·35	..	..
Blood test, other	21 (19%)	11 (10%)	11 (11%)	0·095	..	..
Inflammatory symptoms or infection	8 (7%)	10 (9%)	16 (16%)	0·12	..	..
Pain	20 (18%)	24 (22%)	21 (21%)	0·78	..	..
Other	9 (8%)	5 (5%)	5 (5%)	0·46	..	..
Frequency of adverse events§	907/2532 (35·8)	801/2532 (32%)	824/2532 (33%)	..	..	..
Intensity of adverse events‡						
Slight	669/907 (74)	605/801 (76%)	606/824 (74%)	..	..	..
Moderate	224/907 (25%)	177/801 (22%)	193/824 (23%)	..	..	..
Serious	14/907 (2%)	19/801 (2%)	25/824 (3%)	..	..	..
Assessed relation of adverse events to drugs‡						
Assured	4/907 (<1%)	0	4/824 (<1%)	..	..	..
Likely	106/907 (12%)	60/801 (7%)	90/824 (11%)	..	..	..
Possible	235/907 (26%)	217/801 (27%)	212/824 (26%)	..	..	..
Unlikely	175/907 (19%)	140/801 (17%)	168/824 (20%)	..	..	..
No relation	348/907 (38%)	364/801 (45%)	294/824 (36%)	..	..	..
Unclear	39/907 (4%)	20/801 (2%)	56/824 (7%)	..	..	..

Data are mean (SD), n (%), or n/N (%). p<0·05, p<0·01, p<0·001 were used to indicate significance. For serious adverse events, the total sample has been used as the denominator. For interpretation of adverse event severity, frequency of patients with adverse events has been used as the denominator. *p value for between group differences using χ^2 test for frequencies or proportions and one-way ANOVA for metric measures. †Categorisation according to study regularities by treating physician. ‡Assessment done by treating physician. §Expected percentages according to drug group frequencies: amilsuplride plus olanzapine, 34%; amisulpride plus placebo, 34%; olanzapine plus placebo, 32%.

Table 4: Serious treatment-emergent adverse events and adverse events by treatment groups at 16 weeks

(including the full projected sample) indicated significant differences for this comparison. Similarly, adjusting for (non-significant) differences in PANSS baseline scores did not alter the main study results.

Furthermore, differences in secondary efficacy outcome measures, especially up to 16 weeks, declined or did not reach statistical significance, partly due to a noticeably lowered sample size.

Additionally, treatment with amisulpride plus olanzapine was associated with greater weight-gain, waist circumference increase, and sexual dysfunction than was amisulpride plus placebo. Therefore, tolerability and side-effects, especially in the context of antipsychotic combination treatment—which ultimately can affect physical health, adherence, quality of life, and functioning[26]—should be considered. We emphasise that our study was not powered to primarily identify differences in adverse effects, especially those with lower frequency.

We included a mixture of partial responders and non-responders to antipsychotic monotherapy. We tested combination treatment from the start and not augmentation treatment after insufficient response to monotherapy before choosing combination treatment, which could have reduced chances to identify significant advantages of the combination treatment due to responsiveness to monotherapy. Moreover, about 35% of patients were randomly assigned to the antipsychotic they had been treated with immediately before study inclusion; however, post-hoc sensitivity analyses regarding pre-treatment (same vs other) revealed that this did not alter study results. The design of the trial did not allow for excluding the possibility that higher antipsychotic drug equivalents in the combination treatment group resulted in higher efficacy instead of the specific combination of different pharmacodynamic effects. We described this issue in a former publication on methods and design.[27] High-dose combination treatment in antipsychotic polypharmacy arms has been found to mediate superiority over antipsychotic monotherapy,[28] and, thus, one important consideration is that higher antipsychotic drug dose equivalents in the antipsychotic combination arm could be responsible for a superior outcome, rather than the combined use of two pharmacologically different antipsychotics. However, a 2018 Cochrane Review[29] argues against a major

relevance of the antipsychotic total dose. The review found that data gathered up to January, 2016, did not show a clear superiority for an increase of the antipsychotic dose versus maintaining it for people with schizophrenia whose symptoms did not respond to their initial antipsychotic treatment.[29]

Discontinuation rates in our trial were higher than in other randomised controlled trials of antipsychotics,[30] which is a major limitation of the study. We think that study dropout is a problem, especially with severely ill patients who we intended to represent in this trial. We intentionally chose broad inclusion and narrow exclusion criteria to represent patients and conditions in clinical practice as much as possible. Broad inclusion criteria might have led to a larger variance in outcome and higher discontinuation rates, which could have reduced statistical power to prove superior efficacy of the combination strategy in this trial yet enhance generalisability.

Although we chose broad inclusion criteria (eg, allowing comorbid substance dependency) and a study protocol that was designed to be easy to follow for patients and staff, of 13 692 patients initially screened, only 328 were included in the study. Two possible explanations are that many patients were excluded because their symptom severity was not high enough or that patients with higher disease severity were not able or willing to consent to the study. This fact reduces the generalisability of the results, which is a major issue in many trials on schizophrenia. Because the results mainly account for patients moderately to markedly ill, and in our view, patients with higher illness severity might benefit from combination treatment, future trials should try to integrate such patients. Besides the fact that inclusion criteria were not met, the most common reason for exclusion was that a change of pharmacotherapy was not deemed reasonable. This could be because clinicians had already started to prescribe antipsychotic medication that they found suitable in the acute phase and would not find it reasonable to change it due to participation in a clinical trial. This notion is supported by the fact that many preceding medications were either amisulpride or olanzapine.

Both amisulpride plus olanzapine and amisulpride plus placebo groups were associated with greater prolactin concentration increases than was the olanzapine plus placebo group. However, amisulpride plus olanzapine showed greater reduction in sexual function than did amisulpride plus placebo. Usually, sexual dysfunction is explained by an increase in prolactin concentrations, such as those caused by amisulpride.[7] Yet, disorders of libido, erection, and sexual experience can also be explained by direct D2-blockade (via the reward system), H1 blockade (sedation), anticholinergic, and adrenolytic effects,[31] leading to a potential summation of these unwanted side-effects in the combination therapy group. Since treatment with amisulpride plus olanzapine was associated with significant weight gain, one might suspect that treatment groups could be discerned. However, treatment with olanzapine plus placebo was also associated with weight gain in the same range; therefore, discernment of the treatment groups (especially regarding combination versus monotherapy) was unlikely.

Future research should focus on confirming the positive results of olanzapine and amisulpride combination treatment found in this study and also investigate other rational approaches to antipsychotic combination therapy. Because positive efficacy in the combination treatment arm was accomplished with lower doses of the single drugs than is usually the case with monotherapy, further reducing antipsychotic dosing equivalents in combination treatments might be promising, to maximise potential efficacy while minimising adverse effects.

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