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Antidepressive Effectiveness of Amisulpride, Aripiprazole, and Olanzapine in Patients With Schizophrenia Spectrum Disorders

A Secondary Outcome Analysis of a Pragmatic, Randomized Trial (BeSt InTro)

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Abstract:

Background: Depressive symptoms are frequent in schizophrenia and associated with a poorer outcome. Currently, the optimal treatment for depressive symptoms in schizophrenia remains undetermined. Amisulpride, aripiprazole, and olanzapine all have antidepressive pharmacodynamic properties, ranging from serotonergic affinities to limbic dopaminergic selectivity. Consequently, in a 12-month pragmatic, randomized clinical trial, we aimed to investigate differences in antidepressive effectiveness among amisulpride, aripiprazole, and olanzapine as a secondary outcome, measured by change in the Calgary Depression Scale for Schizophrenia sum score in patients within the schizophrenia spectrum.

Methods: Psychotic patients within the schizophrenia spectrum were included, and effectiveness was analyzed with latent growth curve modeling.

Results: Of the 144 patients, 51 (35%) were women, the mean age was 31.7 (SD 12.7), and 39% were antipsychotic naive. At inclusion, 68 (47%) participants had a Calgary Depression Scale for Schizophrenia sum score >6, indicating severe depressive symptoms. Across the 12-month follow-up, there was a depressive symptom reduction in all medication groups, but no statistically significant differences between the study drugs. Separate analyses of the subcohort with elevated depressive symptoms at inclusion also failed to find differences in depressive symptom reduction between study drugs. The reduction in depressive symptoms mainly occurred within 6 weeks after randomization.

Conclusions: There was a reduction in depressive symptoms under treatment with amisulpride, aripiprazole, and olanzapine in acutely psychotic patients with schizophrenia spectrum disorder, but no differences between the drugs.

Key Words: depression, schizophrenia, antipsychotic, randomized clinical trial, amisulpride, aripiprazole, olanzapine

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The rate of depression in schizophrenia is considerable, varying from 7% to 75%,[1] and depressive symptoms are associated with a poorer outcome.[2] Depressive symptoms reduce quality of life,[3] adherence to treatment,[4] and chance of recovery,[5] while boosting unemployment, risk of relapse,[6] frequency of self-harm,[7,8] and suicide.[9,10] Depressive symptoms are particularly prevalent in the acute and subacute phase of schizophrenia spectrum disorders, making this a highly relevant phase of illness for investigating differential antidepressive efficacy of psychotropics.[11,12]

Despite the massive impact of depression in schizophrenia, treatment guidelines are often not focused on the subject.[13] However, some guidelines and algorithms[14–16] give helpful advice, for instance to evaluate the effect of antipsychotic treatment on depressive symptoms during a psychotic episode before introducing antidepressant drugs. Although prescribing antidepressants for depression in schizophrenia is frequently recommended,[13] a recent meta-analysis concluded that treatment effects are modest.[17] Evidence for nonpharmacological interventions such as physical activity and cognitive behavioral therapy, electroconvulsive treatment, and transcranial magnetic stimulation for depression in schizophrenia is limited.[18–24] Given the modest effect size of antidepressants and attempting to limit superfluous polypharmacy with antidepressants, the antidepressive potential of atypical antipsychotics[25–27] is of clinical importance.[14,15] Knowledge gaps remain, however.

Antipsychotic drugs have documented antidepressive effects in bipolar depression,[27] in treatment-resistant depression,[28] and in schizophrenia.[26,29,30] Several pharmacological actions of atypical antipsychotics indicate an antidepressive potential, particularly for drugs with pronounced 5-HT_{2A}–antagonistic properties such as aripiprazole, olanzapine, and clozapine, or drugs with limbic selectivity, and that increase dopamine in the limbic system by blocking α_2-presynaptic receptors, for example, amisulpride.[31–33] Additional properties relevant for the antidepressant effects are,

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for amisulpride, its potent competitive antagonism on 5-HT7A receptors[34,35]; for olanzapine, activation of dopamine D1 receptors and facilitated NMDA and AMPA-induced currents in pyramidal cells in combination with fluoxetine[36] and 5-HT2C–antagonistic property, which facilitates effects on extracellular levels of DA and NA in the prefrontal cortex[37]; and for aripiprazole, a partial agonistic effect on 5-HT1A receptors; antagonistic effects on 5-HT2A receptors with a partial dopamine D2/D3 agonist effect; and affinity for dopamine D4, 5-HT2C and 5-HT7, α1-adrenergic, and histamine H1 receptors[38] may contribute. Antidepressant-like effects have been documented for some antipsychotic drugs, for example, quetiapine and ziprasidone, that is, the inhibition of transmembrane monoamine transporters, which increases levels of serotonin and/or norepinephrine.[39–41] First-generation antipsychotics (FGAs) are generally not recommended in the presence of depressive symptoms due to a greater likelihood of extrapyramidal adverse effects such as akinesia and inhibited expression.[15,42] Antipsychotics with a high degree of dopaminergic D_2-receptor blockade have been linked to dysphoria.[15,43–45] Finally, depression after a psychotic episode—postpsychotic depression—occurs in some patients.[46] We have previously shown a significant reduction of depressive symptoms in acute psychotic episodes for olanzapine, quetiapine, risperidone, and ziprasidone, albeit with no significant differences between the drugs.[47] Half of the participants with depressive symptoms at study inclusion had persistent depressive symptoms.[48]

Amisulpride,[44] aripiprazole,[49] and olanzapine[50,51] have all demonstrated superior antidepressive effectiveness in schizophrenia compared with placebo, risperidone, and haloperidol. However, only amisulpride and olanzapine have been compared directly,[52–54] with nonsignificant differences on depressive symptoms. Our limited knowledge of which treatment to choose for patients with a current psychotic episode and depressive symptoms indicates a need for more head-to-head clinical trials comparing atypical antipsychotics. Thus, we aimed to investigate antidepressive effectiveness in a randomized clinical trial of atypical antipsychotics.

The decision to investigate amisulpride, aripiprazole, and olanzapine in the BeSt InTro was primarily because of hypotheses regarding the primary outcome: antipsychotic effectiveness.[55–58] Olanzapine and amisulpride have proven to be among the most effective in meta-analyses of antipsychotic efficacy.[59,60] However, the distinct pharmacologic differences between these 3 drugs are also highly relevant with regards to the comparison of their antidepressive effectiveness.[31,32,61] Amisulpride, aripiprazole, and olanzapine were all significantly superior to FGAs for depressive symptom improvement in a review by Leucht et al.[30] However, they have not previously been investigated head-to-head in a clinical trial for antidepressive effectiveness in schizophrenia spectrum disorders.

The primary aim of this article was to investigate overall differences in antidepressive effectiveness among amisulpride, aripiprazole, and olanzapine as measured by the change of the Calgary Depression Scale for Schizophrenia (CDSS) sum score in patients with a current psychotic episode within schizophrenia spectrum disorder. The CDSS was a secondary outcome measure in the BeSt InTro trial. Further objectives were to investigate differences in antidepressive effectiveness between the study drugs in the subgroup of participants with pronounced depressive symptoms at inclusion and conducting sensitivity analyses.

MATERIALS AND METHODS

Study Design

BeSt InTro is a multicenter, randomized, rater-blind head-to-head comparison of amisulpride, aripiprazole, and olanzapine with a 1-year follow-up.[55] The aim was to include patients with ongoing psychosis who were eligible for oral antipsychotic drug treatment. Depressive symptom change was a secondary outcome measure. Participants were consecutively recruited from 4 participating centers (Bergen, Trondheim, and Stavanger in Norway and Innsbruck in Austria). Inclusion took place between October 20, 2011, and December 21, 2017.

Sample

Eligible patients were ≥18 years fulfilling diagnostic criteria within the schizophrenia spectrum F20–29 according to the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* (*ICD-10*), with symptoms of ongoing psychosis defined by a score of 4 or more on at least one of the following Positive and Negative Syndrome Scale (PANSS)[62] items: P1 (delusions), P3 (hallucinations), P5 (grandiosity), P6 (suspiciousness/persecution), or G9 (unusual thought content), as scored on the basis of a conducted Structured Clinical Interview for the PANSS (SCI-PANSS) interview.[63] This and very similar definitions of ongoing psychosis have been applied in former trials.[64,65] All candidates were deemed eligible for oral antipsychotic drug treatment by their attending psychiatrist. Trial participants had to be capable of providing written informed consent before inclusion. Exclusion criteria were inability to understand spoken site language, organic psychosis, hypersensitivity to the active substances, pregnancy, or breastfeeding. Additional drug-specific exclusion criteria for amisulpride were as follows: concomitant prolactin-dependent tumors, for example, pituitary gland prolactinomas and breast cancer; pheochromocytoma; and lactation and combination with medications, which could induce torsade de pointes. Exclusion criteria for olanzapine were a known risk of narrow-angle glaucoma.

Study Medication and Randomization

Study medications were administered as oral tablets and according to the respective summary of product characteristics. Dosing intervals were for amisulpride 50–1200 mg/d, aripiprazole 5–30 mg/d, and olanzapine 2.5–20 mg/d. Serum levels were measured at study visits to determine if effective concentrations were achieved and as a measure of medication adherence.

The randomization was open to the patients and their attending psychiatrist and wider clinical treatment team, whereas the assessment research team remained blinded. Participants were randomized to a sequence, listing the study drugs in a random sequence. These sequences were sealed in separate envelopes, numbered consecutively, and opened by the attending psychiatrist when a new participant was included. If the first study drug in the sequence was inapplicable due to previous negative experience, the next study drug in the sequence was offered and the reason for not selecting the first drug was noted. The same principle applied if the next listed study drug was also deemed inappropriate. The first study drug in the sequence defined the randomization group, which served as the basis for the intention-to-treat (ITT) analyses. The attending physician or psychiatrist made the decisions concerning initiation, dosing, and changes or termination of the study medication.

In line with usual clinical practice, concomitant medications were permitted with the exception of additional antipsychotic drugs. This is in line with leading treatment guidelines, which advocate antipsychotic monotherapy.[14,66,67] However, cross-titration during antipsychotic drug switches was permitted.

Measures

We assessed patients at inclusion; 1, 3, and 6 weeks; and 3, 6, 9, and 12 months. Diagnoses were based on a conducted Structured Clinical Interview (SCID) for the *DSM-IV* (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; American Psychiatric Association). *ICD-10* diagnoses were extracted by trained, experienced psychiatrists and psychologists from the SCID interview and information from hospital records based on the *ICD-10* research criteria.

The BeSt InTro trial was designed with the reduction of psychotic symptoms (PANSS) as the primary outcome, with results previously published.[55] The outcome measure in this article is the sum score of the CDSS.[68] The CDSS was conducted at all study visits as a separate semistructured interview and consists of 9 items scored on a 0 to 3 range. The CDSS is specifically developed to assess the level of depressive symptoms in schizophrenia as depression rating scales used in mood disorders may not sufficiently distinguish depressive symptoms from positive and negative symptoms and extrapyramidal adverse effects of medications in psychosis.[69,70] Addington and Addington[71] have previously shown that a CDSS sum score cutoff >6 has a specificity of 82% and a sensitivity of 85% for detecting a major depressive episode. Consequently, we applied this cutoff in subanalyses to investigate the subcohort with more pronounced depressive symptoms. There is no consensus concerning which magnitude of depressive reduction that may be considered clinically significant. Moreover, there are no established thresholds for response or remission of depression for the CDSS, which are more clearly defined in major depressive disorder, such as a score below a defined threshold on various psychometric scales for depression.[72–76]

Furthermore, the patients completed a PANSS interview[62,77] and the Clinical Drug Use Scale (CDUS) and Clinical Alcohol Use Scale (CAUS).[78] The Clinical Global Impression–Severity of Illness Scale (CGI-S)[79] was applied to assess illness severity. Global functioning was measured by the Global Assessment of Functioning Scale (GAF) (*DSM-IV*), and the scores were split into symptom and function scores.[80,81] Use of concomitant psychotropic medication was registered. Participants not previously treated with antipsychotic medication were considered medication naive. The CDSS, PANSS, CGI, and GAF were administered at all study visits. The SCI-PANSS was used, and all investigators conducting assessments were trained and calibrated by the PANSS Institute (panss.org) until satisfactory interrater reliability was achieved. Tolerability outcomes were measured by the UKU–Side Effect Rating Scale,[82] as well as clinical and biochemical assessments. These have been reported in a previous publication.[55] Scales and psychometric interviews were applied in valid, approved translations in Norwegian in the Norwegian sites (English in the few English-fluent participants) and German in Austria.

Statistical Procedures

Analysis Strategy

Baseline data were analyzed using SPSS version 24[83] by means of exact χ^2 tests for categorical data and one-way analyses of variance (ANOVAs) for continuous data. The latent growth curve modeling (LGCM)[84,85] was used to analyze the level and change in CDSS with Mplus 8.3.[86] First, a linear change model was fitted and evaluated based on fit indices, residual variances, and visual inspection of individual data. Model fit was evaluated based on the threshold values: comparative fit index (CFI) and Tucker-Lewis index (TLI) beyond 0.95; root mean error of approximation (RMSEA) < 0.05 as close fit, RMSEA < 0.08 as fair fit, and RMSEA < 0.10 as mediocre fit.[87] The standard LGCM incorporates both mean level and change, as well as the level and change at individual level, represented as intercept and slope variance. As the power analysis below was based on a linear model, these results will be reported independent of the model fit results. In addition to fitting a linear change, latent contrast score models were tested, analyzing change in each study visit interval and thus allowing the data to govern the form of change. First, this model was estimated as a random intercept and fixed slope model (no slope variance). Then, based on modification indices, individual variation (random slopes) was freed up in some intervals to improve model fit. Residual variance was set equal over time.

The 3 study drugs were analyzed with amisulpride as the reference category and aripiprazole and olanzapine tested against this reference medication. In addition, model constraints in Mplus were used to test for differences in changes between aripiprazole and olanzapine.

The primary analyses were ITT analyses[88] based on the randomization groups. In ITT analyses, trial participants are analyzed in the trial drug group they were randomized to regardless of which treatment they actually received. Next, per protocol (PP) analyses were based on the antipsychotic drug that ultimately was chosen. The estimator was maximum likelihood with robust standard errors, which handles nonnormality.[87] The full information maximization likelihood method uses all available data under the missing at random assumption.[89] However, the missing data (MD) could be related to the unobserved values and thus missing not at random (MNAR). Missing not at random models (Diggle-Kenward[90] and pattern mixture[89]) were tested as sensitivity models to investigate potential biases in the estimated parameters. The Diggle-Kenward model tests both whether MD is missing completely at random or missing at random and if MD is MNAR or not. Standard procedure was used, with constrained parameters over time.

Per protocol analyses of CDSS single-item change and analyses restricted to data of the de facto periods of administration of the trial antipsychotics were also conducted. A multisample analysis (PP) was conducted, separating participants into a less depressed and a more depressed group, with a cutoff CDSS sum score of >6 for the latter group, then analyzing antipsychotic antidepressant differences between the study drugs. Finally, a model including level and change in PANSS positive as predictors was conducted. To reduce the model complexity, these models were analyzed as linear, however with estimated time factors.[85] A nonlinear model may be indicated if time factors are found to deviate from values of the actual time points. The CDSS sum score and PANSS-positive subscale models were first analyzed separately, then combined in a multivariate model that regressed the level and change in CDSS on level and change in PANSS positive in addition to the PP medications. Effect sizes (Cohen *d*) were calculated for the ITT data by estimating the difference in CDSS reduction for the drugs and dividing the difference by the pooled standard deviation (SD).[91] For the reference drug, the model estimated baseline level was subtracted from the 52-week mean level (intercept values). Then, regression values were added on the intercept values to compute the estimates for the other 2 medications. The pooled SD was based on baseline SD and 52-week SD. The 52-week SD was extracted from a time reversed model to place the intercept factor to the last point of time.

Power Analysis

Power estimations for the linear change model were conducted in R[92] by means of linear mixed effects models[93]: a statistical power of 90% and an overall *P* value at the 5% level were entered into the model. The initial CDSS total score, slopes, and within-person variation were based on the results of a previous

model where the overall reduction of the CDSS sum score was 58%.[47] In the BeSt InTro power analysis, we defined assumed clinically relevant differences between the study drugs as CDSS sum score reductions of 10%, 35%, and 70% during the 52 weeks in the respective drug groups. The corresponding slopes were entered into the model. The initial CDSS sum score was set at 5.67 points, and an estimated dropout rate of 5% per month was used. For each level of power, 10,000 simulations were run. Based on these premises for the power calculations, the trial should have 92% power to detect statistically significant differences among the drugs with 48 subjects in each of the 3 treatment groups.

Ethical Considerations, Monitoring, and Funding

The study was carried out in accordance with ethical principles for medical research involving humans (Declaration of Helsinki)[94] and approved in Norway by the Regional Committees for Medical and Health Research Ethics and the Norwegian Medicines Agency. In Austria, the trial was approved by the Etikkommission der Medizinische Universität Innsbruck and the Austrian Federal Office for Safety in Health Care. Clinical monitoring according to the Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use–Good Clinical Practice Guideline[95] was in Norway conducted by the Department of Research and Development, Haukeland University Hospital. In Austria, clinical monitoring was conducted by the Clinical Trial Centre at the Medical University of Innsbruck. The project was publicly funded by the Research Council of Norway, the Western Norway Regional Health Trust, as well as by the participating hospitals and universities. No pharmaceutical company imbursed the trial.

RESULTS

The patient flowchart is displayed in Figure 1. A total of 144 patients were enrolled and randomized to one of the study drugs. Demographic and clinical characteristics at inclusion are presented in Table 1. Fifty-one of the 144 patients were women (35%), the mean age was 31.7 (SD 12.7) years, and 39% were antipsychotic-naive. Sixty-eight participants (47%) had a Calgary depression sum score >6 at inclusion, and the mean total PANSS score was 81.0, both reflecting a pronounced symptom level. The descriptive statistics for the CDSS is presented in Supplementary Table S1, http://links.lww.com/JCP/A848.

A total of 24 patients (16.7%) chose another study drug than the first one in the sequence, with no statistically significant difference among the randomization groups (Fisher exact test: $P = 0.143$). The mean study drug doses used with SDs were for amisulpride 396.9 (206.9) mg, aripiprazole 14.6 (7.0) mg, and olanzapine 12.3 (3.8) mg. The corresponding defined daily doses (DDDs) with SDs were 1.0 (0.5), 1.0 (0.5), and 1.3 (0.4) for amisulpride, aripiprazole, and olanzapine, respectively. The overall DDD in the olanzapine group was statistically significantly higher than in the amisulpride group (1-way ANOVA: $P = 0.018$; mean difference, 0.28; 95% confidence interval [CI], 0.04–0.53) and the aripiprazole group (1-way ANOVA: $P = 0.008$; mean difference, 0.32; 95% CI, 0.07–0.57). Study drug serum levels were mostly within the reference concentration range for the drugs; however, with lower levels in the start of and the end of the study year and a tendency toward lower concentrations in Austria than in the Norwegian study sites.[55] Serum levels were measured in one half to two thirds of participants attending study visits and showed for the majority of patients that the serum levels were within accepted reference range for the drugs. Among amisulpride-treated participants, around one fourth did not reach the lower reference level for the study drug until 12 weeks into the participation, and among aripiprazole-treated patients, one fifth did not reach this level before 6 weeks. Olanzapine-treated patients reached this level faster (>90% within 1 week).

Coprescriptions of psychotropic drugs including antidepressants, mood stabilizers, benzodiazepines/anxiolytics/hypnotics, and anticholinergics, with results published previously,[55] were generally equal among the study drug groups except more patients received mood stabilizers at inclusion in the aripiprazole group (n = 5) compared with both the amisulpride (n = 1) and olanzapine groups (n = 0) (Fisher exact test: $P = 0.020$ for the ITT groups), and 3 participants received anticholinergic drugs in the ITT amisulpride group at 3 months compared with none in the other groups (Fisher exact test: $P = 0.026$).

Depressive Symptom Change—ITT Analyses

The linear model of the level and change in CDSS over 52 weeks fitted data poorly ($\chi^2 = 94.23$, $df = 31$, $P < 0.001$, CFI = 0.77, TLI = 0.79, RMSEA = 0.119, $RMSEA_{CI} = 0.092–0.147$, $RMSEA_{close\ fit} = 0.00$). The latent contrast score model improved model fit to a satisfactory level ($\chi^2 = 33.17$, $df = 23$, $P = 0.078$, CFI = 0.96, TLI = 0.96, RMSEA = 0.056, $RMSEA_{CI} = 0.000–0.095$, $RMSEA_{close\ fit} = 0.38$). The baseline overall CDSS level in the linear model was estimated to be 5.36, and the change was −0.05 per week ($P < 0.001$). Although the amisulpride group had the greatest depressive symptom reduction and the olanzapine group the smallest reduction per week, there were no statistically significant differences between the study drugs in this linear model: amisulpride (intercept): $\alpha = -0.07$, $P < 0.001$ (significance test vs time); aripiprazole: b = 0.02, $P = 0.399$ (vs amisulpride); olanzapine: b = 0.04, $P = 0.142$ (vs amisulpride); and b-weights difference = −0.02, $P = 0.525$ (aripiprazole vs olanzapine) (Supplementary Fig. S1, http://links.lww.com/JCP/A848).

The latent contrast score model is presented in Supplementary Table S2, http://links.lww.com/JCP/A848 (model fit presented in above paragraph) and showed that reduction of depressive symptoms was greatest in the first 6 weeks and flattened in the 6- to 52-week period. The results from comparing the randomized antipsychotic drugs for change in CDSS are presented in Table 2 and Figure 2. No statistically significant differences in reduction of CDSS were found among the 3 medications. Effect size differences between the study drugs were 0.353 between amisulpride and aripiprazole and 0.354 between amisulpride and olanzapine.

The MNAR sensitivity analyses (Supplementary Fig. S6, http://links.lww.com/JCP/A848), based on the Diggle-Kenward model,[90] showed aripiprazole with higher odds for dropout than amisulpride (b = 0.58, $P = 0.049$, OR = 1.79). Dropout at a study visit was not found to be related to y-residual level within that point of time (b = 0.09, $P = 0.734$) or with the preceding study visit: $t - 1$ (b = −0.14, $P = 0.445$), indicating no empirical support for missing completely at random and MNAR. Missing at random is supported. This model did not change the outcome at statistical level, and the magnitude of the estimates was substantially unaltered. The pattern mixture model resulted in estimation problems, but the medication differences did not reach statistical significance.

Depressive Symptom Change—Per Protocol Analyses

The results from estimating the differences in the reduction of CDSS between the 3 study drugs showed no differences in the linear model despite greatest reduction for amisulpride and smallest reduction for aripiprazole: intercept (amisulpride) = −0.05, $P = 0.008$ (significance test vs time); aripiprazole: b = 0.02, $P = 0.435$ (vs amisulpride); olanzapine: b = 0.00, $P = 0.976$ (vs amisulpride); and b-weights difference = 0.02, $P = 0.393$

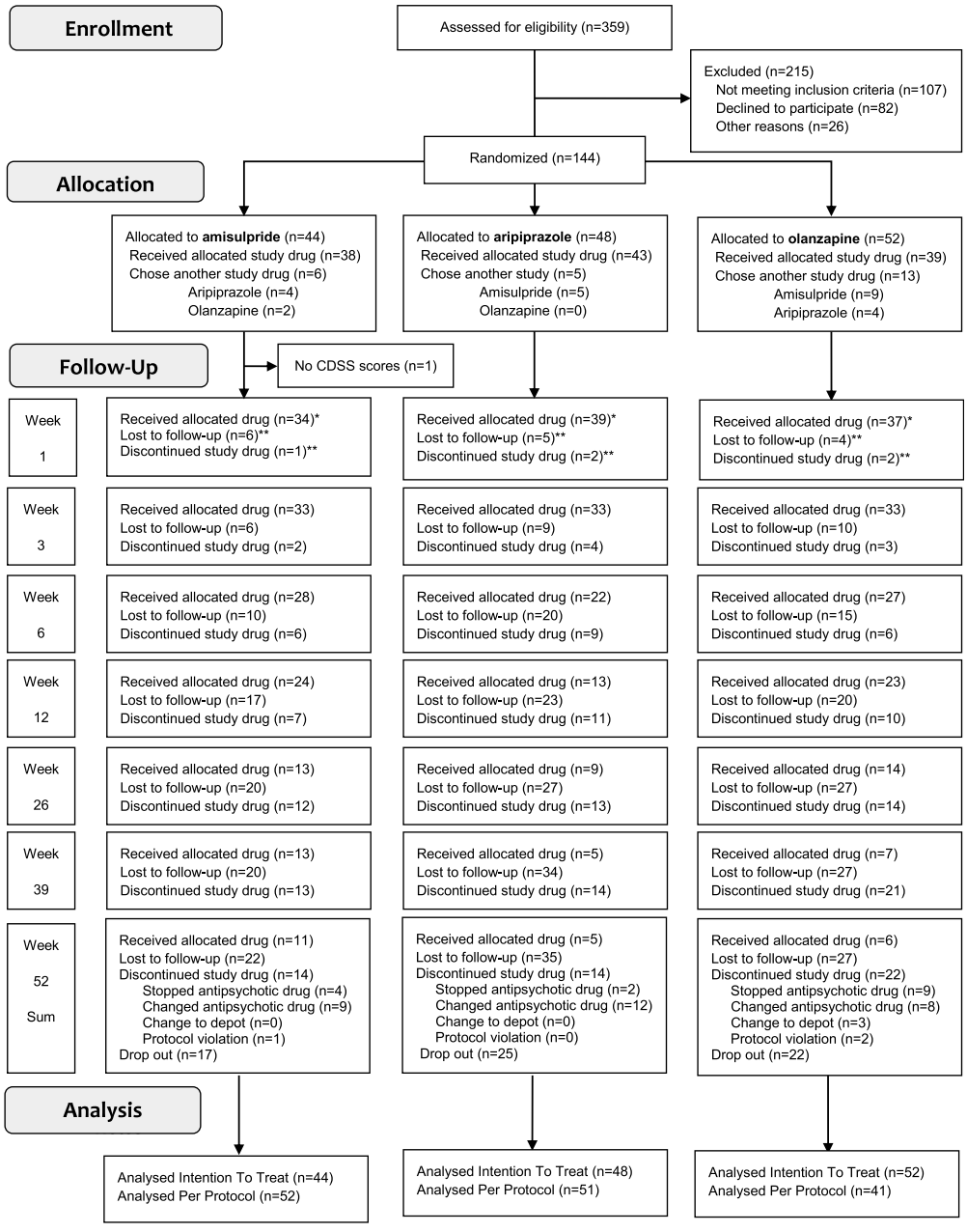

FIGURE 1. Patient flowchart. Lost to follow-up = explicit withdrawal from further participation in the study or not showing up at subsequent study visits; Depot = long-acting formulation of study drug; Protocol violation = use of dosage above upper limit according to the study protocol; Drop out = unknown study drug use status because participant is lost to follow-up. *Based on actual use of randomized drugs at each visit. **Based on originally randomized patients (ITT population).

(aripiprazole vs olanzapine) (Supplementary Fig. S2, http://links.lww.com/JCP/A848). Results from the latent difference score model are presented in Table 3 and Supplementary Figure S3, http://links.lww.com/JCP/A848. No significant differences between the study drugs were found. The Diggle-Kenward and pattern mixture analyses replicated the findings from the sensitivity MNAR ITT analyses.

In the analyses including the level and change in positive psychotic symptoms, the reduction in CDSS was found to be associated with estimated reduction in PANSS-positive subscore (b = 0.50, $P < 0.007$), but not with estimated baseline level in PANSS-positive (b = −2.80, $P < 0.38$). Reduction in CDSS was still not statistically significantly related to the PP drugs after controlling for differences in PANSS-positive reduction: amisulpride versus aripiprazole (b = −0.52, $P < 0.55$), amisulpride versus olanzapine (b = 0.16, $P < 0.84$), and aripiprazole versus olanzapine (Δb = −0.69, $P < 0.34$).

The study drugs were compared in analyses for separate items of CDSS. Item score reduction at visual inspection followed the same pattern for all items, and no substantial differences were found (results not shown). Sensitivity analyses restricted to the time of de facto administration of the study drugs (Supplementary Fig. S4, http://links.lww.com/JCP/A848) showed similar results as the primary analyses, although there in the PP sensitivity analysis

TABLE 1. Descriptive Statistics for the Randomization Groups at Baseline

	Amisulpride (N = 44) n/N (%, CI)	Aripiprazole (N = 48) n/N (%, CI)	Olanzapine (N = 52) n/N (%, CI)	All (N = 144) n/N (%, CI)
Men	28/44 (64, 49–78)	32/48 (67, 54–80)	33/52 (63, 50–76)	93/144 (65, 57–73)
White	39/44 (89, 80–98)	35/48 (73, 60–86)	44/52 (85, 75–95)	118/144 (82, 76–88)
Living alone	21/44 (48, 33–63)	17/48 (35, 22–48)	23/52 (44, 31–57)	61/144 (42, 34–50)
Employed	14/44 (32, 18–46)	12/48 (25, 13–37)	10/52 (19, 8–30)	36/144 (25, 18–32)
Diagnosis: schizophrenia*	28/44 (64, 50–78)	27/48 (56, 42–70)	29/52 (56, 43–69)	84/144 (58, 50–66)
Diagnosis: schizotypal*	1/44 (2, 0–6)	0/48 (0)	1/52 (2, 0–6)	2/144 (1, 0–3)
Diagnosis: delusional disorder*	4/44 (9, 1–17)	8/48 (17, 6–28)	9/52 (17, 7–27)	21/144 (15, 9–21)
Diagnosis: brief psychotic disorder*	8/44 (18, 7–29)	3/48 (6, 0–13)	7/52 (13, 4–22)	18/144 (12, 7–17)
Diagnosis: schizoaffective*	3/44 (7, 0–15)	5/48 (10, 2–18)	2/52 (4, 0–9)	10/144 (7, 3–11)
Diagnosis: other*	0/44 (0)	1/48 (2, 0–6)	0/52 (0)	1/144 (1, 0–3)
Diagnosis: unspecified*	0/44 (0)	4/48 (8, 0–16)	4/52 (8, 1–15)	8/144 (6, 3–10)
Smoking	30/44 (68, 54–82)	29/48 (60, 46–74)	26/52 (50, 36–64)	85/144 (59, 51–67)
Abuse/dependence—alcohol†	4/44 (9, 1–17)	7/48 (15, 5–25)	2/52 (4, 0–9)	13/144 (9, 4–14)
Abuse/dependence—drugs†	10/44 (23, 11–35)	8/48 (17, 6–28)	9/52 (17, 7–27)	27/144 (19, 13–25)
APnaiv	16/44 (36, 22–50)	23/48 (48, 34–62)	17/52 (33, 20–46)	56/144 (39, 31–47)
	Amisulpride (N = 44) Mean (SD, CI)	**Aripiprazole (N = 48) Mean (SD, CI)**	**Olanzapine (N = 52) Mean (SD, CI)**	**All (N = 144) Mean (SD, CI)**
CDSS	7.5 (5.6, 5.8–9.3)	5.6 (4.8, 4.2–7.0)	7.1 (5.1, 5.6–8.5)	6.7 (5.2, 5.8–7.6)
Age	30.6 (11.7, 27.0–34.2)	32.1 (13.1, 28.3–35.9)	32.2 (13.3, 28.5–35.9)	31.7 (12.7, 29.6–33.8)
Years of education	12.7 (3, 11.8–13.7)	11.9 (2.8, 11.1–12.8)	12.2 (2.7, 11.5–13.0)	12.3 (2.8, 11.8–12.8)
PANSS total	80.0 (18.6, 74.4–85.7)	76.6 (13.4, 72.7–80.5)	78.7 (15.5, 74.4–83.0)	78.4 (15.8, 75.8–81.0)
PANSS positive	21.4 (4.8, 20.0–22.9)	21.3 (4.9, 19.9–22.7)	21.0 (4.7, 19.7–22.3)	21.2 (4.8, 20.4–22.0)
PANSS negative	18.2 (7.0, 16.1–20.3)	17.2 (5.6, 15.5–18.8)	18.1 (5.8, 16.5–19.7)	17.8 (6.1, 16.8–18.8)
PANSS general	40.4 (10.2, 37.3–43.5)	38.1 (7.2, 36.0–40.2)	39.7 (8.1, 37.4–41.9)	39.4 (8.5, 38.0–40.8)
CGI-S	5.1 (0.9, 4.8–5.4)	4.9 (0.7, 4.7–5.1)	5 (0.8, 4.8–5.2)	5 (0.8, 4.9–5.1)
GAF‡	36 (9.6, 33.1–38.9)	36 (9.6, 33.1–38.9)	35.5 (8.8, 33.1–38.0)	35.8 (9.3, 34.3–37.4)

Medication is registered as being used or not at each visit, thus the precise time of medication change or stop was not registered.

*All diagnoses are *ICD-10*.

†Abuse/dependence defined by a score ≥3 on the CDUS and CAUS.

‡GAF is reported as the mean value of GAF-S and GAF-F of the split GAF version.

was one significant difference in the 9–12 months interval where olanzapine had a greater depressive symptom reduction than aripiprazole due to a symptom increase in the aripiprazole group. Only 6 participants medicated with aripiprazole attended the 12-month visit versus 8 months with olanzapine and 16 months with amisulpride.

TABLE 2. ITT Analyses (LGCM) of Medication Differences on Level and Changes in CDSS

		Amisulpride*			Aripiprazole†			Olanzapine†			Aripiprazole vs Olanzapine	
Weeks		***I***	***P***	**CDSS´**	**b_1**	***P***	**CDSS´**	**b_2**	***P***	**CDSS´**	**$\Delta b_1 b_2$**	***P***
Baseline	I	6.65	<0.001	6.65	0		6.65	0		6.65	0	
0–1	S1	−1.43	0.046	5.23	0.75	0.379	5.97	0.31	0.705	5.53	0.44	0.479
1–3	S2	−0.25	0.441	4.73	−0.41	0.317	4.66	−0.02	0.972	5.01	−0.40	0.277
3–6	S3	−0.24	0.253	4.01	0.25	0.449	4.68	−0.09	0.735	4.02	0.34	0.241
6–12	S4	0.06	0.617	4.37	−0.20	0.319	3.87	0.14	0.474	5.20	−0.33	0.115
12–26	S5	−0.09	0.075	3.11	0.04	0.611	3.16	0.06	0.498	4.75	−0.02	0.837
26–39	S6	−0.07	0.077	2.21	0.06	0.474	3.05	−0.02	0.836	3.60	0.08	0.471
39–52	S7	0.06	0.264	3.02	0.03	0.767	4.19	−0.02	0.844	4.19	0.04	0.641

*Amisulpride = reference medication, intercept values.

†Medication tested against reference medication, presented as regression estimates.

$\Delta b_1 b_2$: model constraints used for testing differences between aripiprazole and olanzapine.

I, intercept values = level and change for amisulpride; CDSS´, predicted scores at baseline and at end of each interval.

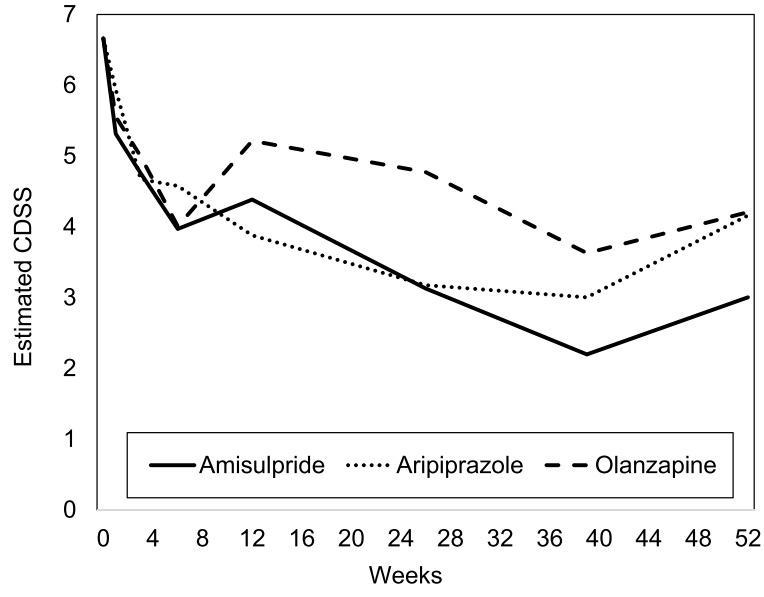

FIGURE 2. Latent contrast score model with medication differences—ITT analyses.

Separate Analyses of the More Depressed Subcohort and Sensitivity Analyses

In a multisample analysis separating the participants based on the CDSS scores at inclusion in a less depressed group (CDSS ≤ 6) and a more depressed group (>6) (Fig. 3), the ITT analyses showed no medication differences within the more depressed group and a minor, probably not relevant, medication difference in the less depressed group. In interval 3 (3–6 weeks), the aripiprazole and olanzapine randomized groups differed from each other (b-weights difference = 0.619, $P = 0.04$). In the PP analyses (Supplementary Fig. S5, http://links.lww.com/JCP/A848), there were no significant differences within the more depressed group nor in the less depressed group. Demographic and clinical characteristics for the more depressed versus less depressed study subgroups are presented in Table 4. The female ratio was significantly greater in the more depressed subcohort. A greater part of the more depressed patients were employed despite their more pronounced symptom levels as measured by PANSS total score, PANSS general symptom score, and CGI. Concomitant psychotropic treatment in the more depressed versus less depressed group is presented in Supplementary Table S3, http://links.lww.com/JCP/A848. There were no statistically significant differences between the study drugs in the prescription of antidepressants within the more depressed subcohort. The mean CDSS scores in study visits where participants using concomitant psychotropics were excluded showed substantially unchanged outcomes (results not shown).

DISCUSSION

We found an overall significant reduction of depressive symptoms in persons with a current psychosis within the schizophrenia spectrum randomized to amisulpride, aripiprazole, or olanzapine, steepest in the first 6 weeks and then leveling out. Thus, a linear model was an insufficient fit for the data. There were, despite greatest reduction in the amisulpride group, no statistically significant differences between the randomized

TABLE 3. Per Protocol Analyses (LGCM) of Medication Differences on Level and Changes in CDSS

		Amisulpride*			Aripiprazole†			Olanzapine†			Ari vs Olan	
Weeks		*I*	*P*	CDSS´	b_1	*P*	CDSS´	b_2	*P*	CDSS´	$\Delta b_1 b_2$	*P*
Baseline	I	6.65	<0.001	6.65	0		6.65	0		6.65	0	
0–1	S1	−1.34	0.024	5.39	0.60	0.421	5.88	0.24	0.755	5.55	0.37	0.584
1–3	S2	−0.41	0.139	4.50	−0.21	0.571	4.66	0.37	0.373	5.43	−0.58	0.131
3–6	S3	−0.20	0.309	3.83	0.02	0.935	4.09	−0.08	0.763	4.59	0.10	0.716
6–12	S4	−0.02	0.903	3.85	0.08	0.655	4.55	0.15	0.448	5.41	−0.07	0.748
12–26	S5	−0.06	0.240	3.01	0.01	0.901	3.86	−0.00	0.977	4.57	−0.01	0.897
26–39	S6	−0.05	0.133	2.32	0.02	0.849	3.34	−0.04	0.735	3.43	0.05	0.677
39–52	S7	0.10	0.008	3.66	0.05	0.500	5.31	−0.14	0.094	2.90	0.19	0.051

*Amisulpride = reference medication, intercept values.

†Medication tested against reference medication, presented as regression estimates.

$\Delta b_1 b_2$, Model constraints used for testing differences between aripiprazole and olanzapine.

I, intercept values = level and change for amisulpride; CDSS´, predicted scores at baseline and at end of each interval.

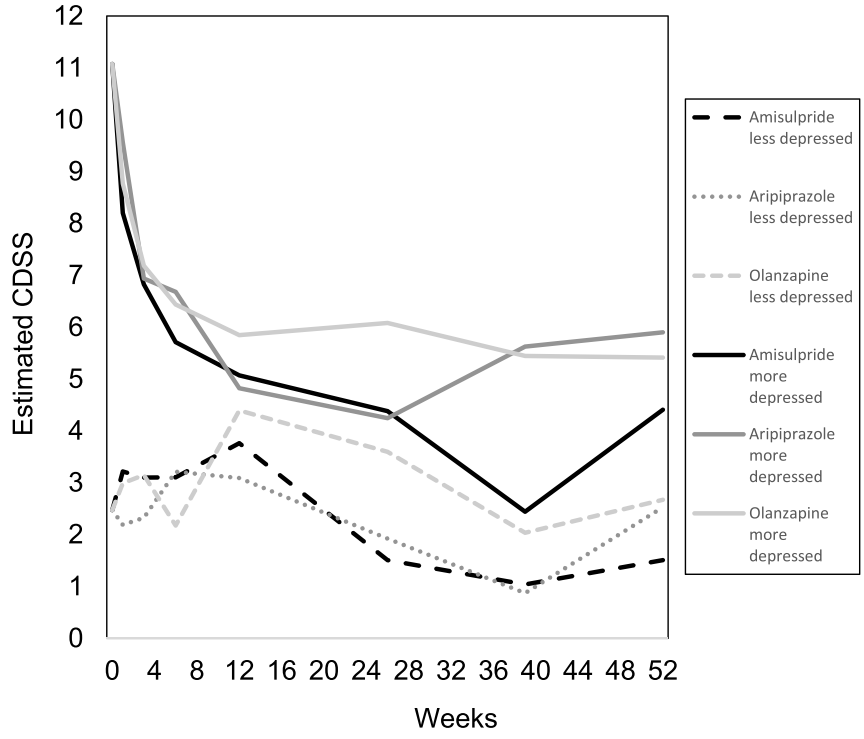

FIGURE 3. Medication differences within the more depressed versus the less depressed group—ITT. More depressed group: CDSS >6 at baseline. Less depressed group: CDSS ≤6 at baseline.

antipsychotic groups in the reduction of depressive symptoms in ITT analyses. Substantial differences were not found in PP analyses either, nor in analyses restricted to the more depressed subcohort. The BeSt InTro findings of head-to-head limited, nonsignificant antidepressive effectiveness differences in schizophrenia among amisulpride, aripiprazole, and olanzapine are novel. Our study represents the first head-to-head comparison of antidepressive effectiveness between amisulpride and aripiprazole and between aripiprazole and olanzapine.

Depressive Symptom Change Over Time

Although all study drugs were associated with a marked improvement in depressive symptoms and even though amisulpride had the steepest reduction in both the ITT and PP analyses, the effectiveness differences between the drugs were nonsignificant. This is consistent with the recent World Federation of Biological Psychiatry guideline, which reported that all the atypical antipsychotics in our study were effective antipsychotics for depression in schizophrenia[15] and with meta-analyses determining superiority to FGAs[60] and placebo[30] for depressive symptoms. However, it may be argued that the amisulpride superior effectiveness may be clinically significant and that the trial had insufficient power to demonstrate statistical significance. The effect sizes between amisulpride and aripiprazole and between amisulpride and olanzapine were however only small to moderate (0.35) and were smaller than the effects sizes for the primary outcome.[55]

A factor potentially contributing to the shared antidepressive effectiveness and limited nonsignificant differences of the study drugs is that all 3 antipsychotics in the BeSt InTro have receptor affinities that may underlie antidepressive properties.[32] Hypothetically, the trial drugs may lead to an overall equivalent reduction of depressive symptoms, although brought about through distinctly different pharmacodynamic mechanisms: limbic selectivity for amisulpride,[31] 5-HT_{2A}–antagonistic properties for aripiprazole and olanzapine,[32,61] and for aripiprazole possibly also through its partial agonist activity at dopamine receptors.[96] Differences between the drugs in effects on, for example, 5-HT1A, 5-HT2C, and 5-HT7A receptors; D1 and D4; α1-adrenergic; and H1 receptors, may also have contributed.[34–38]

Amisulpride and olanzapine have formerly been investigated in 2 double-blind efficacy trials of 8 weeks and 6 months where both medications were found to be effective against comorbid depression in schizophrenia.[52,53] There were, however, no statistically significant differences in the antidepressive efficacy between amisulpride and olanzapine in the trials. The results of the BeSt InTro replicate the efficacy findings of this double-blind trial in a pragmatic effectiveness setting for the first time. The mean DDD of olanzapine was slightly greater (1.3) than for amisulpride and aripiprazole (1.0). This may have favored olanzapine or led to a disadvantage as excessive dopamine blockade might result in dysphoria.[15] The aripiprazole group baseline mean CDSS sum score was lower than the amisulpride and olanzapine group. Although this difference was not statistically significant, this may have contributed to less depressive symptom improvement potential in the aripiprazole group.

The reduction of positive psychotic symptoms is known to predict reduction in depressive symptoms,[15,48,97] and there were, in fact, differences in effectiveness on positive psychotic symptoms between the trial drugs, with amisulpride being more effective than aripiprazole and olanzapine.[55–57] The antipsychotic superiority of amisulpride might hypothetically underlie the nonsignificant greater depressive symptom reduction. Although the main aim of the current study was to investigate the overall antidepressive effectiveness of the BeSt InTro study drugs, we did control for effectiveness differences in positive psychotic symptoms, which did not change the overall results of nonsignificant effectiveness differences. Predictors of antidepressive effectiveness will be

TABLE 4. Descriptive Statistics at Baseline for the More Depressed Versus the Less Depressed Group

	CDSS > 6 N = 68 (%, CI)*	CDSS ≤ 6 N = 70 (%, CI)*	*P* χ^2 or Fisher (*F*)
Men	39/68 (57.4, 46–69)	52/70 (74.3, 64–85)	**0.036**
White	61/68 (89.7, 82–97)	54/70 (77.1, 67–87)	0.124 (F)
Living alone	28/68 (41.2, 30–53)	30/70 (42.9, 31–54)	0.784
Employed	21/68 (30.9, 20–42)	13/70 (18.6, 9–28)	**0.047 (F)**
Diagnosis: schizophrenia†	40/68 (58.8, 47–70)	38/70 (54.3, 43–66)	
Diagnosis: schizotypal†	0/68 (0)	2/70 (2.9, 0–7)	
Diagnosis: delusional disorder†	12/68 (17.6, 9–27)	9/70 (12.9, 5–21)	
Diagnosis: brief psychotic disorder†	5/68 (7.4, 1–14)	13/70 (18.6, 9–28)	0.155 (F)
Diagnosis: schizoaffective†	7/68 (10.3, 3–18)	3/70 (4.3, 0–9)	
Diagnosis: other†	4/68 (5.9, 0–12)	5/70 (7.1, 1–13)	
Smoking	46/68 (67.6, 56–79)	36/70 (51.4, 40–63)	0.079
Abuse/dependence—alcohol‡	9/68 (13.2, 5–21)	4/70 (5.7, 0–11)	0.129
Abuse/dependence—drugs‡	15/68 (22.1, 12–32)	12/70 (17.1, 8–26)	0.490
Antipsychotic naive	25/68 (36.8, 25–48)	30/70 (42.9, 31–54)	0.491
	CDSS > 6 Mean (SD, CI)	**CDSS ≤ 6 Mean (SD, CI)**	***t* test F (*P*)**
Age	30.8 (12, 27.8–33.7)	32.9 (14, 39.7–36.2)	0.326
Years of education	12.4 (3.1, 11.7–13.2)	12.1 (2.6, 11.5–12.7)	0.516
PANSS total	81.0 (13.2, 77.8–84.2)	74.5 (16.7, 70.6–78.5)	**0.013**
PANSS positive	21.4 (4.4, 20.3–22.5)	20.8 (5.0, 19.5–21.9)	0.430
PANSS negative	17.8 (5.6, 16.4–19.1)	17.3 (6.0, 15.9–18.8)	0.631
PANSS general	41.8 (6.9, 40.2–43.5)	36.5 (8.9, 34.4–38.6)	**<0.001**
CGI-S	5.1 (0.7, 5.0–5.3)	4.8 (0.8, 4.6–5.0)	**0.019**
GAF	36.4 (8.3, 34.4–38.4)	36.3 (9.6, 34.0–38.6)	0.950
CDSS	11.1 (3.6, 10.2–11.9)	2.5 (1.9, 2.0–2.9)	**<0.001**

CDSS > 6 applied as cutoff to define elevated depressive symptoms.

*Six participants were not classified due to missing CDSS at baseline.

†All diagnoses are *ICD-10*.

‡Abuse/dependence defined by a score ≥3 on the CDUS and CAUS.

investigated in more detail in future publications from the BeSt InTro. The phenomenon of postpsychotic depression, which may occur during remission of positive psychotic symptoms,[46] may have negatively affected depression response rates. Postpsychotic depression at the different assessments (roughly defined by a CDSS sum score ≤6 at baseline and a score >6 on at least 1 follow-up) varied from 1.6% to 10.6%, being most prevalent at 3 months. These prevalence figures did not exclude persistently psychotic participants, however. Still, this rough prevalence of postpsychotic depression did not significantly differ between the drugs at any study visit and was in the lower range compared with previous trials.[98,99] No atypical antipsychotic is known to affect the risk of postpsychotic depression more than other atypicals.[13]

The More Depressed Subcohort, Antidepressant Prescription, and Sensitivity Analyses

At time of inclusion, 49% had a CDSS sum score >6. However, no antidepressive effectiveness differences were discovered in the ITT analyses of this more depressed subgroup either. There are some possible explanations for this finding. First, there may be no differences in antidepressive effectiveness between the 3 drugs during treatment of a current psychotic episode. Second, there is a difference that is undetected due to a lack of trial power to conclude within a subcohort of the participants. Third, participants who dropped out might have a different development of symptoms, potentially giving rise to different findings if they had attended follow-up. This is further discussed under limitations. We consider the small significant antidepressive difference in the PP analyses in one interval in the less depressed subcohort to be a chance finding, not constituting a clinically meaningful difference in effectiveness, among other since such sensitivity analyses are more prone to bias due to the nonrandomized nature of the data.

In the event that one of the study drugs had inferior antidepressive effects, we would expect antidepressant prescription rates to be greater in participants treated with this antipsychotic. Coprescription of antidepressants was however not significantly different between the study drugs neither within the RCT overall nor in the more depressed subcohort, lending further support to the main finding that these drugs have similar effects. The frequency of antidepressant prescription was surprisingly low even in the subcohort more depressed at inclusion (10%–25%), and markedly lower than in an earlier trial we conducted where, at different assessments, 22%–88% of the more depressed participants were administered antidepressants.[48] Despite the partly unresolved question regarding the magnitude of antidepressant effectiveness for depressive symptoms in schizophrenia, we consider the antidepressant prescription rate as too low in the present trial, possibly indicating that insufficient attention is paid upon the depressive symptoms in the aftermath of a psychotic episode.

Some adverse effects such as weight gain and hyperprolactinemia as a result of antipsychotic treatment may affect mood and contribute to depressive symptoms. These associations

have been investigated in a few other trials[100–102] and may thus weaken the antidepressive effectiveness. We have reported adverse effects in the BeSt InTro study in a previous publication,[55] and based on these findings, a potential prodepressive psychological reaction to weight gain would be greatest for amisulpride and olanzapine at some assessments; however, overall weight gain differences were small. Hyperprolactinemia was greatest for amisulpride, as expected. Both these effects may in fact have contributed to a smaller antidepressive effectiveness of amisulpride, and greater weight gain may have contributed to smaller antidepressive effectiveness of olanzapine. Overall adverse effect differences were small, thus we consider the implications for the antidepressive effectiveness as small.

Design Aspects

The study design, which allowed the prescription of anxiolytics, mood stabilizers, antidepressants, and anticholinergic drugs, may have contributed to a greater depressive symptom reduction. Thus, only part of the depressive symptom reduction may be attributed to antipsychotic treatment, and the size of this part remains unknown. However, as the trial was randomized, allowing concomitant medication should not lead to confounding in the comparison of the antidepressive effectiveness of the antipsychotics. This assumption is strengthened by results from an earlier publication,[55] showing only minuscule differences in concomitant medication. A placebo control group would have represented an informative comparison for study drug effectiveness and for quantification of the antidepressive effectiveness attributable to the study drugs, but would not be compatible with the pragmatic design that aims to resemble usual clinical practice. Randomizing to a sequence of the study drugs was chosen to aid the pragmatic design. This decision may have introduced bias, both from the patients' and the raters' perspective. The blinding of raters may unintentionally have been broken in particular circumstances. In clinical trials, a fraction of patients always end up not taking the assigned randomized drug or a different drug. This circumstance was facilitated in the BeSt InTro with the randomization to a sequence approach, potentially resulting in more frequent rejection of the first randomized drug, leading to less transparent and interpretable results. If clinicians or patients had preferences for particular drugs, bias may have been introduced. For instance, in the BeSt InTro, among the participants randomized to aripiprazole and olanzapine who chose another study drug, the majority chose amisulpride (14/18 = 78%). Hypothetically, amisulpride may have been the preferred drug at the study sites. However, a more probable cause is that amisulpride in the years 2012–2017 among the study drugs in Norway by a large margin was the least prescribed, aripiprazole in-between, and olanzapine by far the most frequent.[103] These patients had probably tried more atypical antipsychotics than participants not changing the drugs, indicating more treatment failures, possibly contributing to a smaller probability of symptom improvement. We consider the BeSt InTro findings due to the demography and health systems, as well as BeSt InTro's wide inclusion criteria and few exclusion criteria, as most representative for North and Central European schizophrenia populations, however also for other high-income countries. Gender distribution, drug abuse, and alcohol abuse were similar to former schizophrenia trials. The mean age was in-between first-episode trials and trials with more chronically ill participants, thus representing a mixed group. Although trial participants were substantially ill, the most severely ill patients were probably not included in the study. Thus, the results may not be necessarily be extrapolated to this subgroup and not to patients eligible for antipsychotic injection treatment and clozapine treatment.

Strengths and Limitations

The main strengths of this study is that it (1) was not supported by the pharmaceutical industry, which strengthens the independence of the results, (2) included participants with pronounced symptoms, and (3) had few exclusion criteria, which all add to the clinical applicability of the results to a severely ill patient group. A further strength contributing to clinical validity was that participants were included prospectively from a clinical setting and with treatment circumstances resembling usual clinical practice. The most valid and specific depression rating instrument for schizophrenia was applied. The design with short intervals for testing after randomization allowed for a more detailed overview over the fast initial improvement. Secondary outcome research may be hampered with limitations.[104] However, few of such limitations applied to this study, thus consisting strength: the available secondary outcome measure was the desired one, the antidepressive reduction hypotheses were prespecified and inherent to the study designs, and thus guided by research hypotheses rather than availability of data.

Some limitations apply. The attrition rate was substantial with close to one third of randomized participants dropping out in the first 6 weeks and 58% at 1 year. Clinical trials investigating psychosis are well known to be hampered by high dropout rates, but the BeSt InTro dropout rate was in fact lower than in some comparable trials.[47,105,106] If resulting MD in variables of interest are related to information in other variables, this may constitute a problem concerning validity of the analyses. However, the full information maximization likelihood method uses all available data under the "missing at random" assumption.[86,87] This is preferable in contrast to methods assuming MD being completely at random. We did not have permission to recontact participants who withdrew from the trial or to request the reason for withdrawn consent or drop out. Despite its moderate size, the clinical representativeness of this trial is superior to many previous efficacy trials,[107] only 40% of those assessed for eligibility were included and randomized. Approximately 23% of all eligible participants were not included as they declined to participate. In daily clinical practice, patients are even more severely ill, and antipsychotic medication probably has a better effect than clinical trials indicate. This is a perpetual challenge in consent-based trials, where there will remain a substantial amount of severely ill patients of which knowledge based on clinical trials is scarce. This reduces the external validity of the results. The power analysis for the CDSS outcome was not conducted in the study protocol, but in the planning of this manuscript. The statistical analysis plan was not prepublished and was not described in detail for secondary outcomes. Inherent to the secondary outcome design,[104] the study was not "enriched" for depressive symptoms, possibly contributing to less power.

CONCLUSIONS

Of clinical importance, there was a reduction of depressive symptoms in the amisulpride, aripiprazole, and olanzapine groups, particularly during the acute phase of psychosis in schizophrenia spectrum disorders. Antidepressive differences between the drugs were not significant.

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The authors declare no conflicts of interest.

Data availability statement: 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.

Trial Registration: ClinicalTrials.gov NCT01446328; URL: http://www.clinicaltrials.gov/.

Authors' contributions: E.K. drafted the manuscript, participated in the data collection, and participated in the data analyses; R.G. helped draft the manuscript, provided statistical analyses, and made substantial contributions to the analysis and interpretation of the data; F.F., I.S., R.A., L.G.A., I.J., M.R., and R.A.K. participated in the data collection and helped draft the manuscript; E. M.L. participated in designing the study and helped draft the manuscript; S.K.R. and T.K.L. was a principal investigator and helped draft the manuscript; M.R. was a principal investigator; J.Ø.B. was the medical supervisor and helped draft the manuscript; O. B.F. supervised and helped draft the manuscript; R.A.K. participated in designing the study; E.J. participated in designing the study, was a principal investigator, participated in the data collection, and helped draft the manuscript; all authors read and approved the final manuscript.

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