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Differential Effectiveness of Atypical Antipsychotics on Hallucinations

A Pragmatic Randomized Controlled Trial

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Abstract:

Background: Most studies investigating antipsychotic effectiveness report either total psychopathology or symptom cluster findings. Studies focusing on a separate symptom, such as hallucinations, a hallmark symptom in schizophrenia, are scarce.

Therefore, the current study aims to compare the antihallucinatory effectiveness of 3 pharmacologically different antipsychotics: olanzapine, amisulpride, and aripiprazole.

Methods: The present study is part of the Bergen-Stavanger-Innsbruck-Trondheim study, a 12-month prospective, randomized, pragmatic antipsychotic drug trial in active-phase schizophrenia spectrum disorders. The primary outcome of the present study was change of hallucinations as measured by item P3 (hallucinatory behavior) from the Positive and Negative Syndrome Scale in the subgroup with hallucinations at baseline. Primary analyses were intention to treat.

Results: A total of 144 participants were included in the study, where 105 (72%) had a score of 3 or more on the Positive and Negative Syndrome Scale P3 item at baseline, indicating the presence of hallucinations (HALL subgroup).

In the HALL subgroup, a significantly less reduction of hallucinations was revealed for participants using olanzapine in weeks 12, 26, 39, and 52 when compared with amisulpride and in weeks 26 and 52 when compared with aripiprazole. In subanalyses for participants never exposed to antipsychotic drugs (antipsychotic-naive) and those who had used antipsychotics before entering the study, antihallucinatory differences were revealed only in the latter group.

Conclusions: A differential antihallucinatory effect of the 3 study drugs was present. The inferior effect of olanzapine seems to be driven by the subgroup of participants exposed to antipsychotic treatment before entering the study.

Key Words: antipsychotics, hallucinations, differential effectiveness, randomized trial

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Variability in the effectiveness of antipsychotic treatment remains a major clinical challenge in the treatment of schizophrenia-spectrum disorders.[1] Whereas individually tailored drug protocols are established in other medical disciplines, antipsychotic treatment is much less targeted, with a trial-and-error approach often lasting from weeks to months and even years.[2] The consequence of this trial-and-error approach may be long-term exposure to drugs without clear benefits and with possible risk of reinforcing adverse effects, prolonged suffering, and adverse impact on long-term prognosis because of sustained illness.[2] Overall antipsychotic effectiveness is thoroughly documented.[3] However, the focus in the majority of studies has been either change of total psychopathology or clusters of symptom scores.[3,4] This might conceal effectiveness differences between separate symptoms of interest. Different symptoms might have, at least in part, separate underlying psychopathology[5] and combining them might mask underlying differences. Because psychotic disorders are symptomatically heterogeneous, revealing possible differences among antipsychotics for separate symptoms would contribute to understanding symptom-specific and personalized treatment.[6]

Hallucinations are one of the hallmark symptoms of schizophrenia and related disorders. As much as 80% of patients experience hallucinations, where auditory hallucinations are reported most frequently.[7] Hallucinations in general and auditory verbal hallucinations in particular are important treatment targets, being not only a major burden to patients but might also lead to self-harm, suicide, violence or homicide.[8,9] Hallucinations respond well to

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antipsychotics, and the response is likely to appear rapidly.[10,11] In our previous study, we demonstrated that more than three-quarters of patients with clinically significant hallucinations at baseline reported vanishing of hallucinations during the first 4 weeks of treatment.[11] In a study with 362 patients with first-episode (FEP) schizophrenia, Sommer et al[10] found that hallucinations were reduced to a level of minimal-mild already after 4 weeks of treatment. After treatment with antipsychotics for 1 year, only 8% still had mild to moderate hallucinations. The authors found that olanzapine, amisulpride, ziprasidone, and quetiapine were equally effective against hallucinations; however, haloperidol was found to be slightly less effective.[10] In our previous naturalistic randomized controlled trial comparing quetiapine, ziprasidone, risperidone, and olanzapine, differential effectiveness was found among these second-generation antipsychotics for hallucinations.[12] The quetiapine and ziprasidone groups had faster reductions of mean hallucination scores compared with the risperidone group. Symptom-specific differences among antipsychotic drugs accordingly seem to exist, but empirical evidence is sparse. Diverse pharmacological properties may underlie drug different effectiveness. The common action of all antipsychotics is functional blockade of striatal dopamine D2 receptors, but with varying potencies. Some newer antipsychotics are partial agonist at the D2 receptors.[13] Furthermore, affinity for nondopaminergic receptors vary substantially among drugs. Amisulpride has the cleanest receptor profile, targeting mainly D2/D3 receptors with little effect on other receptors. Olanzapine on the other hand binds to multiple receptors including dopaminergic, serotonergic, histaminergic, adrenergic, and muscarinergic systems. Finally, aripiprazole shares the broad receptor binding profile of most second-generation antipsychotics, but is distinguished by its partial agonistic action at the D2 receptor.

Also, antipsychotic treatment response in general might be affected by several factors, where antipsychotic naivety and illness duration are known modifiers of effect.[14] Treatment response seems to become less favorable for patients previously exposed to antipsychotics and with increasing illness duration.[14,15] The current study therefore aimed at comparing the antipsychotic effectiveness for hallucinations of 3 pharmacologically diverse antipsychotics: olanzapine, amisulpride, and aripiprazole. A secondary aim was to investigate any impact of previous antipsychotic exposure on differential effectiveness among the study drugs.

METHODS

Study Design

The present study is part of the Bergen-Stavanger-Innsbruck-Trondheim study (BeSt InTro; ClinicalTrials.org, number NCT01446328).

The BeSt InTro study aimed to compare 3 pharmacologically different antipsychotics—amisulpride, aripiprazole, and olanzapine—in a prospective, randomized, pragmatic design. The study was conducted between 2011 and 2017 at the Division of Psychiatry, at Haukeland University Hospital in Bergen, Stavanger University Hospital in Stavanger, St Olavs Hospital, Trondheim, and at the Medisinische Universität Innsbruck, Austria. The BeSt InTro study was funded by The Research Council of Norway, the Western Norway Regional Health Trust, and participating hospitals and universities and did not receive any financial or other support from the pharmaceutical industry. The study was approved in Norway by the Regional Committees for Medical and Health Research Ethics, and the Norwegian Medicines Agency, and in Austria by the Etikkommission der Medizinische Universität Innsbruck, and the Austrian Federal Office for Safety in Health Care (BASG). Further details can be found in the previous publication of the primary outcome.[16] The data presented here represent secondary outcomes in the BeSt InTro trial.

Participants

A total of 144 participants aged ≥18 years with active psychosis symptoms as determined by a score of ≥4 on one or more of the following Positive and Negative Syndrome Scale (PANSS) items: P1 (delusions), P3 (hallucinatory behavior), P5 (grandiosity), P6 (suspiciousness/persecution) or G9 (unusual thought content)[17] were included in the present study.

Participants were excluded if they were not able to use oral drugs, did not understand the native language, were hypersensitive to the active substances or to any of the excipients of the study drugs, and had prolactin-dependent tumors (eg, pituitary gland prolactinomas and breast cancer), pheochromocytoma in combination with medications that could induce torsade de pointes, and a known risk of narrow-angle glaucoma. All included participants had a diagnosis within the schizophrenia spectrum (F20–29) as defined in the *International Classification of Disease, Tenth Revision*.[18] After participants signed an informed consent form, they were randomized to 1 of 3 study drugs. The descriptive statistics for the included participants at baseline are presented in Table 1.

Study Medications and Assessments

Each participant was offered a study drug based on a sealed, opaque envelope containing a list of the study drugs organized in a random sequence. The random sequences were prepared in advance by statisticians independent of the study. The first drug in the sequence was to be offered by the attending psychiatrist and defined the randomization drug. In the case of inability to use the first offered drug based on previous negative experience, the patient was offered the second one in the sequence, with the option to choose the third drug, if the second drug could not be used either. The distribution based on the first drug in the sequence (randomization drug) was amisulpride (n = 44), aripiprazole (n = 48), and olanzapine (n = 52).

The treating psychiatrist was free to determine dosing within the following ranges as defined by the following: amisulpride 50–1200 mg/d, aripiprazole 5–30 mg/d, and olanzapine 2.5–20 mg/d. The rationale was to allow the whole dose range for all study drugs to mimic everyday clinical circumstances and allow for up-titration and down-titration of doses based on the clinical presentation. The mean 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 combination with other psychotropics, discontinuation, and any cross-titration between antipsychotics was left to the discretion of the treating psychiatrist. The use of additional psychotropic drugs was generally not different between the study drug groups. In case a participant already used an antipsychotic agent in therapeutic dosage (>0.5 defined daily dosages) at admission, no wash-out was carried out before starting on the study drug. This was the case in 28 patients at baseline, with the following distribution among the randomization groups: aripiprazole (n = 1), asenapine (n = 1), olanzapine (n = 5), and quetiapine (n = 2) for the amisulpride randomization group; aripiprazole (n = 2), olanzapine (n = 4), quetiapine (n = 4), and risperidone (n = 2) for the aripiprazole randomization group; and aripiprazole (n = 3), olanzapine (n = 1), and quetiapine for the olanzapine randomization group (n = 3). In the 3 cases where the first drug in the randomization sequence was the same as the one the patient who was already using, the next study drug in the sequence was chosen. The randomization was open to both the

TABLE 1. Baseline Demographic and Clinical Characteristics for the Total Sample

	Amisulpride (n = 44), Mean (SD) or n (%)	Aripiprazole (n = 48), Mean (SD) or n (%)	Olanzapine (n = 52), Mean (SD) or n (%)	All (n = 144), Mean (SD) or n (%)
Age, y	30.6 (11.7)	32.1 (13.1)	32.2 (13.3)	31.7 (12.7)
Men	28/44 (64%)	32/48 (67%)	33/52 (63%)	93/144 (65%)
White/Caucasians	39/44 (89%)	35/48 (73%)	44/52 (85%)	118/144 (82%)
Years of education	12.7 (3)	11.9 (2.8)	12.2 (2.7)	12.3 (2.8)
Living alone	21/44 (48%)	17/48 (35%)	23/52 (44%)	61/144 (42%)
Employed	14/44 (32%)	12/48 (25%)	10/52 (19%)	36/144 (25%)
Smoking	30 (68.0%)	29 (60.0%)	26 (50.0%)	85 (59.0%)
Alcohol abuse/dependence	4 (9.0%)	7 (15.0%)	2 (4.0%)	13 (9.0%)
Drug abuse/dependence	10 (23.0%)	8 (17.0%)	9 (17.0%)	27 (19.0%)
Diagnosis: schizophrenia	28/44 (64%)	27/48 (56%)	29/52 (56%)	84/144 (58%)
Diagnosis: schizotypal	1/44 (2%)	0/48 (0%)	1/52 (2%)	2/144 (1%)
Diagnosis: delusional disorder	4/44 (9%)	8/48 (17%)	9/52 (17%)	21/144 (15%)
Diagnosis: brief psychotic disorder	8/44 (18%)	3/48 (6%)	7/52 (13%)	18/144 (12%)
Diagnosis: schizoaffective	3/44 (7%)	5/48 (10%)	2/52 (4%)	10/144 (7%)
Diagnosis: other	0/44 (0%)	1/48 (2%)	0/52 (0%)	1/144 (1%)
Diagnosis: unspecified	0/44 (0%)	4/48 (8%)	4/52 (8%)	8/144 (6%)
AP−	16/44 (36%)	23/48 (48%)	17/52 (33%)	56/144 (39%)
PANSS total	80.1 (18.8)	76.6 (13.4)	78.7 (15.5)	78.4 (15.9)
PANSS positive	21.4 (4.8)	21.3 (4.9)	21 (4.7)	21.2 (4.8)
PANSS negative	18.2 (7)	17.2 (5.6)	18.1 (5.8)	17.8 (6.1)
PANSS general	40.5 (10.3)	38.1 (7.2)	39.7 (8.1)	39.4 (8.6)
CGI	5.1 (0.9)	4.9 (0.7)	5 (0.8)	5 (0.8)
GAF	36 (9.6)	36 (9.6)	35.5 (8.8)	35.8 (9.3)
CDSS	7.6 (5.7)	5.4 (4.5)	7.1 (5.1)	6.7 (5.1)

AP−, no previous exposure to antipsychotic drugs; CDSS, the Calgary Depression Scale for Schizophrenia; n, number in the total sample; n (%), number (percent) with characteristics; Smoking, daily tobacco smokers.

participant and the clinical staff, whereas the assessments were conducted by blinded research personnel.

The participants were assessed at baseline, 1 week, 3 weeks, 6 weeks, and 3 months, 6 months, 9 months, and 12 months thereafter. All PANSS raters were trained and certified by the PANSS Institute (panss.org) after satisfactory interrater and validity performance were achieved.

The primary outcome of the present study was change of hallucinations as measured by item P3 (hallucinatory behavior) in the PANSS positive subscale. A score of 3 or higher indicated the presence of hallucinations.[10] Participants with hallucinations at baseline defined the hallucination (HALL) subgroup. Whereas a threshold of 3 serves as a cutoff for presence of hallucinations per se, a score of 4 or more indicates hallucinations where thinking and behavior are affected, that is, psychosis being present. Sensitivity analyses were therefore undertaken for those with a P3 score of 4 or higher. Although the comparisons between study drugs were undertaken also in the total sample, the HALL subsample was the main group for the primary analyses in the present study.

The participants underwent assessments using the Structured Clinical Interview for the PANSS, the Clinical Drug and Alcohol Use Scales,[19] the "Udvalg for Kliniske Undersøgelser" Side Effects Rating Scale—Patient-Administered version,[20] the Clinical Global Impression—Severity of Illness scale (CGI-S),[21] and the Global Assessment of Functioning (GAF)—split version scores.[22] Serum levels of study drugs and the use of concomitant psychotropic medication were registered at each visit. The Calgary Depression Scale for Schizophrenia, PANSS, CGI-S, GAF, and the "Udvalg for Kliniske Undersøgelser" were administered at all visits.

Statistical Analyses

Statistical analyses were conducted according to intention-to-treat (ITT) and per-protocol (PP) groups. Intention-to-treat analysis is based on the first drug in the sequence, the randomization drug, whereas PP analysis is based on which medication participants chose. The ITT analyses were defined as the primary analyses before the start of the trial, accompanied by secondary PP analyses, as both strategies have advantages and disadvantages. Intention-to-treat analyses have the main advantage of being unbiased because they are based on randomization groups. However, patients might choose another drug than the first one in the sequence. Thus, differences between the study drugs may be leveled out. The PP analyses have the main advantage of being based on the actually study drug chosen but have the disadvantage of potential selection bias, as the randomization is no longer valid. Thus, differences found between the study drugs may be biased.

Statistical analyses for the outcome variable were conducted in statistical program software R[23] with a linear mixed-effects model (LME). The linear mixed-effects model is a preferred class of models when there are missing data because of its ability to handle both data that are missing completely at random and data that are missing at random. A random intercept was included in the model to account for intraindividual correlation, as each individual had repeated measurements for the outcome variable.[24] The model was fitted to investigate the level of the outcome variable at all visits.

The analysis strategy was as follows: first, the analyses were conducted in the HALL subgroup after an initial analysis in the

whole sample. Second, analyses for the differences among study drugs in patients who were antipsychotic-naive (AP−) and patients who were exposed to antipsychotic treatment before entering the study (AP+) were conducted in the HALL subgroup. Third, the differences for AP− and AP+ subgroups were analyzed in each study drug, in the HALL subgroup. All steps were repeated in the sensitivity analysis for patients with baseline PANSS P3 ≥4.

RESULTS

The baseline mean P3 score for the total sample was 3.64 (0.13). Discontinuation of study drug during the treatment course and lost to follow-up rates are provided in Supplementary Material S1, http://links.lww.com/JCP/A751.

A total of 105 patients (71.9%) scored 3 or more on the PANSS P3 hallucinatory behavior item at baseline (HALL subgroup). The baseline ITT distribution of study drugs at in the HALL subgroup was amisulpride (n = 33), aripiprazole (n = 33), and olanzapine (n = 39). The HALL subgroup was not substantially different from the total sample with regard to demographic or clinical descriptives, except for hallucinations. The descriptive statistics for the HALL subgroup in ITT analysis is provided in Supplementary Material 2, http://links.lww.com/JCP/A751. The baseline mean P3 score for the HALL subgroup was 4.51 (0.14; moderate/moderate severe). The decrease of hallucinations during follow-up was to 2.14 (minimal), with the reduction amounting to 61%. The mean P3 scores for each visit in the total sample and in the HALL subgroup are provided in Table 2.

Overall Analysis

Initially analyses were conducted in the whole sample to compare the study drugs on the main outcome measure P3.

No statistically significant differences among the 3 study drugs were seen for P3 score change in the ITT analysis, although a trend for statistically significant less reduction in the aripiprazole group compared with amisulpride was seen at week 3. Per-protocol analyses showed a lower baseline P3 score for the aripiprazole group and less reduction in this group compared with amisulpride at week 3 (Supplementary Material S3; Tables S3-1, S3-2, http://links.lww.com/JCP/A751).

In the HALL subgroup, the ITT analysis revealed a significantly less reduction of hallucinations for participants using olanzapine in weeks 12, 26, 39, and 52 when compared with amisulpride. A significantly less reduction of hallucinations in the olanzapine group was also seen when compared with aripiprazole in weeks 26 and 52 (Table 3). No significant differences were revealed in comparisons between amisulpride and aripiprazole. In the PP analysis, no significant differences among the 3 study drugs were seen (Supplementary Material S4, http://links.lww.com/JCP/A751).

TABLE 2. PANSS P3 Mean Scores and SD for the Total Sample and for the HALL Subgroup

Weeks	All Participants	HALL Subgroup
Baseline	3.64 (0.13)	4.51 (0.14)
1	3.01 (0.13)	3.65 (0.14)
3	2.53 (0.14)	2.98 (0.15)
6	2.21 (0.15)	2.57 (0.15)
12	2.17 (0.15)	2.45 (0.16)
26	1.9 (0.17)	2.23 (0.18)
39	1.82 (0.17)	2.21 (0.18)
52	1.78 (0.17)	2.14 (0.19)

TABLE 3. PANSS P3 for Each Medication in the HALL Subgroup (ITT Analysis)

HALL Subgroup	Baseline	1 wk	3 wk	6 wk	12 wk	26 wk	39 wk	52 wk
Amisulpride (n = 33)	4.48 (0.244)	−0.93 (0.252)	−1.76 (0.258)	−2.22 (0.271)	−2.59 (0.289)	−2.7 (0.321)	−2.82 (0.313)	−2.74 (0.329)
Aripiprazole (n = 33)	4.55 (0.244)	−0.72 (0.253)	−1.24 (0.255)	−1.97 (0.276)	−2.07 (0.295)	−2.56 (0.307)	−2.33 (0.362)	−2.89 (0.392)
	[*P* = 0.859]	[*P* = 0.571]	[*P* = 0.156]	[*P* = 0.532]	[*P* = 0.219]	[*P* = 0.75]	[*P* = 0.309]	[*P* = 0.767]
Olanzapine (n = 39)	4.51 (0.224)	−0.94 (0.23)	−1.6 (0.237)	−1.68 (0.25)	−1.65 (0.257)	−1.71 (0.287)	−1.89 (0.272)	−1.89 (0.277)
	[*P* = 0.931]	[*P* = 0.957]	[*P* = 0.653]	[*P* = 0.148]	**[*P* = 0.017]** {0.68}	**[*P* = 0.022]** {0.70}	**[*P* = 0.026]** {0.57}	**[*P* = 0.05]** {0.62}
	[[*P* = 0.931]]	[[*P* = 0.518]]	[[*P* = 0.303]]	[[*P* = 0.432]]	[[*P* = 0.282]]	**[[*P* = 0.044]]** {0.59}	[[*P* = 0.333]]	**[[*P* = 0.037]]** {0.76}

P values in bold correspond to statistical significant findings.

Numbers in the baseline column give the estimated values, and numbers in the following columns give the estimated decrease in PANSS P3 at each visit compared with baseline. Numbers in parentheses are estimated SDs. *P* values in single brackets correspond to comparison to the reference drug amisulpride. Values in double brackets correspond to comparison to aripiprazole. Values in curly brackets are Cohen *d* for significant findings.

TABLE 4. ITT Analysis, HALL-Subgroup, AP+

	Baseline	1 wk	3 wk	6 wk	12 wk	26 wk	39 wk	52 wk
Amisulpride (n = 20)	4.45 (0.296)	−0.89 (0.309)	−2.00 (0.309)	−2.47 (0.328)	−2.98 (0.345)	−2.99 (0.395)	−3.16 (0.38)	−2.93 (0.413)
Aripiprazole (n = 16)	4.5 (0.331) [P = 0.908]	−0.64 (0.349) [P = 0.599]	−1.01 (0.358) **[P = 0.043]**	−2.05 (0.368) [P = 0.41]	−2.42 (0.408) [P = 0.308]	−2.68 (0.427) [P = 0.611]	−2.52 (0.512) [P = 0.329]	−2.56 (0.561) [P = 0.599]
Olanzapine (n = 23)	4.74 (0.276) [P = 0.476] [[P = 0.473]]	−0.6 (0.29) [P = 0.499] [[P = 0.928]]	−1.68 (0.296) [P = 0.462] [[P = 0.164]]	−1.73 (0.307) [P = 0.113] [[P = 0.52]]	−1.38 (0.314) **[P = 0.001]** **[[P = 0.049]]**	−1.2 (0.359) **[P = 0.001]** **[[P = 0.009]]**	−1.57 (0.33) **[P = 0.002]** [[P = 0.124]]	−1.69 (0.338) **[P = 0.023]** [[P = 0.189]]

P values in bold correspond to statistical significant findings.

Numbers in the baseline column give the estimated values, and numbers in the other columns give the estimated decrease in PANSS P3 compared with baseline. Numbers in parentheses are estimated SDs. *P* values in single brackets correspond to comparison to the reference drug amisulpride. *P* values in double brackets correspond to comparison to aripiprazole.

Analyses for AP– and AP+ Participants

Only the HALL subgroup was chosen for further analyses. We used the same statistical analyses separately for AP− and AP+ participants. Similar results for the ITT and the PP analyses were seen in both subgroups. No differences among the 3 study drugs were found for the AP− participants (Supplementary Material S5; Tables S5–1, S5–2, http://links.lww.com/JCP/A751). In the AP+ subgroup, there were significant differences for the P3 score reduction between aripiprazole and amisulpride at week 3 for both the ITT and PP analyses (P = 0.043 and 0.012, respectively). No significant differences were seen at other time points. Olanzapine showed significantly less reduction in the P3 score when compared with amisulpride at weeks 12, 26, 39, and 52 (P = 0.001, 0.001, 0.002, and 0.023, respectively) in the ITT analysis and at weeks 3, 12, 26, and 39 (P = 0.041, 0.015, 0.004, and 0.020, respectively) in the PP analysis. Moreover, olanzapine showed less reduction in P3 score when compared with aripiprazole at weeks 12 and 26 (P = 0.040 and 0.009, respectively) in the ITT analysis and at week 12 (P = 0.007) in the PP analysis. Results for the ITT analysis are shown in Table 4 and for the PP analysis in Supplementary Material S6, http://links.lww.com/JCP/A751.

Analyses for Each Study Drug: AP+ Versus AP–

The same statistical approach was used for each study drug separately. No statistically significant differences were seen between the AP− and AP+ in participants who used amisulpride or aripiprazole, neither in the ITT nor in the PP analysis. For participants who used olanzapine, there was a significant difference in reduction of the P3 score between the AP− and AP+ subgroups at week 26 for both the ITT and the PP analyses (P = 0.034 and 0.022, respectively; Fig. 1). Furthermore, there was a significant difference at week 12 and a trend toward significance at week 39 in the PP analysis (P = 0.038 and 0.053, respectively; Supplementary Material S7; Tables S7-1, S7-2, http://links.lww.com/JCP/A751).

Sensitivity Analyses

We conducted a sensitivity analysis where patients with PANSS P3 score ≥4 were included following the same statistical approach. Similar results were found (Supplementary Material S8, http://links.lww.com/JCP/A751): in the total subgroup ITT analysis, olanzapine showed less reduction compared with amisulpride at weeks 12, 26, 39, and 52 (P = 0.004, 0.032, 0.025, and 0.02,

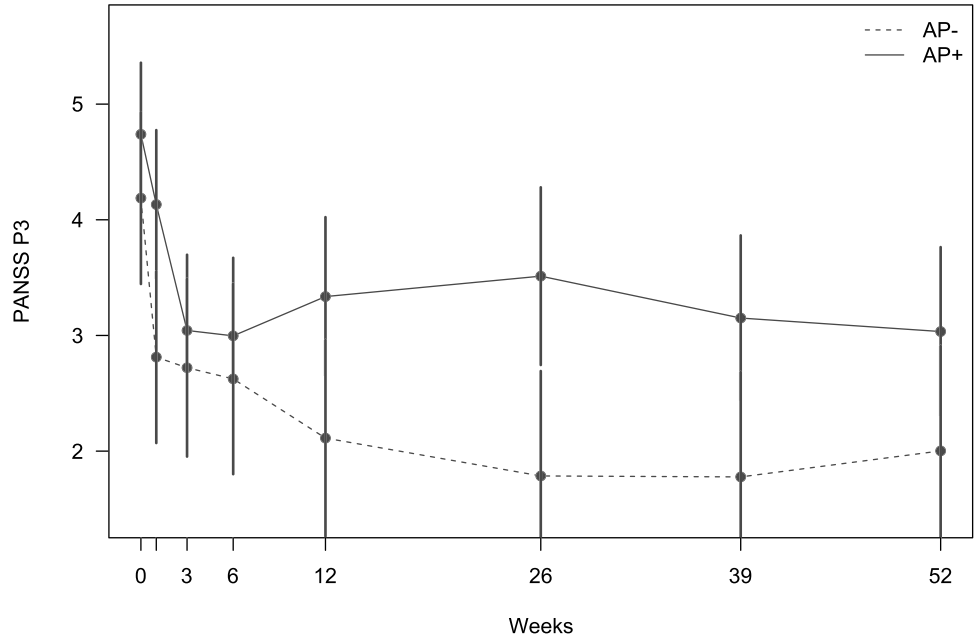

FIGURE 1. Intention-to-treat analysis. Comparing AP– and AP+ participants who were randomized to olanzapine.

respectively; Table S8-1). Differences between olanzapine and aripiprazole were no longer significant, although a trend for less P3 score reduction for olanzapine in week 12 was observed (Table S8-1). In the PP analysis, there were no statistical significant differences (Table S8-2). As in the analyses based on a P3 score threshold ≥3, no statistically significant differences were found among antipsychotics for the AP− participants, neither in ITT nor in PP analyses (Tables S8-3, S8-4). For the AP+ participants, the ITT analysis revealed less reduction for olanzapine compared with amisulpride at weeks 12, 26, 39, and 52 (P = 0.001, 0.003, 0.025, 0.004, and 0.025, respectively) and less reduction for olanzapine compared with aripiprazole at week 26 (P = 0.021; Table S8-5). The PP analysis revealed less reduction in the olanzapine group compared with amisulpride at weeks 3, 12, and 26 (P = 0.037, 0.021, and 0.015, respectively) and less reduction in the olanzapine group compared with aripiprazole at week 12 (P = 0.01; Table S8-6). As in the separate analyses for P3 ≥ 3 of each study drug, statistically significant results were only found for olanzapine in the P3 ≥ 4 analyses. In the ITT analyses of olanzapine, the AP− participants had greater P3 score reductions than did AP+ participants in weeks 26 and 39 (P = 0.044 and 0.05). In the PP analyses, statistically significant differences were reached at weeks 12, 26, and 39 (P = 0.046, 0.031, and 0.024, respectively; Tables S8-7, S8-8).

DISCUSSION

The main objective of the study was to investigate differences in effectiveness among 3 pharmacologically different antipsychotics for reduction of hallucinations. The study showed differential effectiveness for participants who had used antipsychotics before entering the study, whereas no differences were seen in AP− participants. A faster decrease of hallucinations appeared in the amisulpride group at 3 weeks compared with aripiprazole in both the ITT and the PP analyses and to olanzapine in the PP analysis. The finding of earlier response to amisulpride might theoretically be biased by differences in the doses, as amisulpride is normally up-titrated more quickly than olanzapine. However, this was not the case in our study, where the olanzapine dose was in fact relatively higher than amisulpride and aripiprazole at 3 weeks.

The most consistent differences between the study drugs appeared later in the treatment.

The study shows that hallucinations in general respond well and rapidly to antipsychotic treatment. For participants with clinically significant hallucinations, the symptom had decreased to "mild" according to PANSS P3 after 3 weeks and continued to decrease throughout the follow-up period. This finding is consistent with our previous findings, where 80% of patients with clinically significant hallucinations at baseline were found to be "dramatic" responders, with extinction of hallucinations during the first 4 weeks of treatment.[11] The present results are also in line with findings from Sommer et al[10] where first-episode schizophrenia patients showed a mean reduction of hallucinations from 4.4 at baseline to 2.5 after 4 weeks of treatment measured by the PANSS P3 item.

Most studies investigating drug differences have used the total psychopathology score from the PANSS questionnaire or symptom clusters as outcome measures. The meta-analysis by Huhn et al[3] reveals gradual differences in effect sizes when comparing 32 antipsychotic drugs in multiepisode schizophrenia patients. The results showed that both amisulpride and olanzapine were among the most efficacious antipsychotics, whereas aripiprazole seemed to be less effective. However, a meta-analysis by Rutherford et al[25] showed that over time, there was a placebo-effect increase, together with an active medication-effect decrease. Thus, the smaller effect of aripiprazole compared with the 2 other antipsychotics in the meta-analysis may be at least in part explained by the fact that the aripiprazole studies have been conducted in more recent years.

None of the studies included in the meta-analysis by Huhn et al[3] focused on hallucinations specifically. However, Sommer et al[10] used data from the EUFEST trial where first-episode psychosis (FEP) patients were followed up for 1 year. The authors found that all the included atypical antipsychotics were equally effective against hallucinations, but haloperidol was slightly inferior. Almost half of our sample was AP− at inclusion, which may be considered a proxy for FEP. When analyzing this subgroup separately, no statistically significant differences were found among the study drugs. Thus, our study contributes to existing evidence that the antihallucinatory effectiveness among atypical antipsychotics for the subgroup of patients in an early stage of psychosis may be equal. A possible explanation may be that in this particular group, "everything works" because they are generally highly responsive to antipsychotic medication, whereas in multiepisode patients, where the drug response generally is poorer, probably also because the proportion of patients with more severe disorder is higher, the separate drugs are subject to a tougher test. Thus, differences in the effectiveness of antipsychotic drugs may appear. A previous study from our group has also shown that ziprasidone and quetiapine were superior to risperidone in reducing hallucinations, with olanzapine in an intermediate position. In this randomized controlled trial, patients were followed up for up to 2 years.[12] In the present study, olanzapine was less effective for reduction of hallucinations compared with amisulpride and, at some time points, also less effective compared with aripiprazole. This finding seems to be driven by the participants previously exposed to antipsychotics, as statistically significant differences were only seen in the AP+ subgroup.

Olanzapine is generally found to be among the most efficacious drugs,[3] so the reduced effect compared with the other 2 study drugs in participants previously treated with antipsychotics was unexpected. However, as discussed previously, most of the antipsychotic studies have measured the effect or effectiveness of drug treatment on PANSS total psychopathology or total subscale scores. Thus, it is possible that the effect of olanzapine seen in other studies may be primarily the result of an effect on other positive symptoms than hallucinations. For example, delusions are assessed in 3 of 7 items in the PANSS positive subscale, whereas hallucinations are assessed in only 1. Accordingly, the weight of any change of hallucinations may theoretically be buried under changes of delusions.

A mechanistic explanation for the inferiority of effect for olanzapine compared with amisulpride and aripiprazole in the AP+ subgroup could be related to differences in prefrontal cortex activation. It is suggested in the neurocognitive model of hallucinations[26] that this is the result of unbalanced hyperactivation in the temporal lobe not sufficiently inhibited by frontotemporal projections because of prefrontal hypoactivation. Limited evidence also shows that both amisulpride and aripiprazole activate prefrontal cortex, whereas for olanzapine, the results are more conflicting.[27–31] Olanzapine impairs some cognitive functions; thus, possibly prefrontal also cortical activation may be low because of its sedating effects via blockade of muscarinergic, histaminergic, and adrenergic receptors. If the antihallucinatory response partly depends on activation of prefrontal cortex, then differential prefrontal cortical impairment could hypothetically contribute to the superiority of amisulpride and aripiprazole over olanzapine. Because cognitive activation is found to be reduced in more chronic patients and because the difference among antipsychotics appears only in AP+ participants, it could suggest that prefrontal activity is more sensitive to antipsychotics only in patients with reduced prefrontal cortex activity.

Limitations

Some limitations should be mentioned. The pragmatic design of the study allows for fewer exclusion criteria, thus possibly resulting in a more heterogeneous sample. However, such a study design mimics "real life," and the results can therefore be interpreted in the light of a daily clinical setting. The decision to allow for the change of antipsychotic treatment regime over the course of the study may have affected our results. However, the small number of participants who changed treatment regime makes this a less likely possibility. A high attrition rate is also a concern, which is a major problem in all antipsychotic trials.[32] A sensitivity analysis showed that using the missing-at-random assumption in the statistical analyses is plausible, both for the total sample and for the HALL subgroup. Total attrition was not associated with any of the demographic variables and did not exceed the rate found in other studies. Use of concomitant drugs might be considered as a limitation. However, there were generally no differences among the groups, and it was not considered to influence the results.

Our choice to include in the main analyses participants with P3 score ≥3 might be seen as a limitation because a score of 3 is considered below the psychosis threshold. However, a score of 3 in the PANSS scoring manual is described as "hallucinations or abnormal perceptual experiences that does not affect thinking or behavior," so even at subthreshold levels for psychosis, a score of 3 remains a symptom frequently present in psychotic populations. Considering that subpsychosis levels of symptoms have shown brain activation in functional magnetic resonance imaging studies, this threshold was chosen to better capture potential differences of antipsychotics, which theoretically would act partly via different neurotransmitter systems. However, we conducted sensitivity analyses in addition, where participants with P3 ≥ 4 were included. Interestingly, similar result were present where olanzapine showed less reduction for hallucinations in participants previously treated with antipsychotics, mainly when compared with amisulpride.

We did not correct for multiple comparisons, which might increase the chance for false-positive results. However, the statistical significant results seemed to follow an internally consistent pattern throughout the study until 52 weeks and were therefore by far more common and consistent than would have been expected to occur by chance.

Despite the relatively large number of participants and direct comparison of antipsychotics, our results should be interpreted with caution before independently replicated.

Conclusions

Hallucinations respond fairly well to antipsychotics. Differential antihallucinatory effectiveness was found for the 3 study drugs, but this was seen only in participants exposed to antipsychotic treatment before entering the study, whereas no significant differences were found for the AP− participants.

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