The Acute Efficacy of Aripiprazole Across the Symptom Spectrum of Schizophrenia: A Pooled Post Hoc Analysis From 5 Short-Term Studies

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Objective: To evaluate the efficacy of aripiprazole across a range of symptoms—positive, negative, disorganized thought, depression/anxiety, and hostility—in schizophrenia and schizoaffective disorder.

Method: Pooled data were analyzed from 5 short-term, double-blind, multicenter studies (published between 1997 and 2007) involving patients hospitalized with acute exacerbation of schizophrenia (5 studies) or schizoaffective disorder (2 studies) and randomly assigned to aripiprazole (N = 875), haloperidol (N = 193), risperidone (N = 95), or placebo (N = 406). Aripiprazole doses ranged from 2 to 30 mg/day. Patients receiving the ineffective 2-mg dose were excluded from the primary analyses presented here. Factor analysis of Positive and Negative Syndrome Scale (PANSS) data was used to evaluate changes from baseline with aripiprazole on 5 symptom factors—positive, negative, disorganized thought, depression/anxiety, and hostility—in 2 population subsets—schizophrenia and schizoaffective disorder. Pairwise comparisons were made as follows for schizophrenia: aripiprazole versus placebo in all 5 studies; aripiprazole, haloperidol, and placebo in 3 studies; and aripiprazole, risperidone, and placebo in 1 study. Patients with schizoaffective disorder in 2 studies were included in the comparison of aripiprazole and placebo.

Results: Aripiprazole was significantly better than placebo in improving all 5 PANSS factor scores from baseline (each $p < .001$) in the schizophrenia dataset. In schizoaffective disorder, aripiprazole was significantly better than placebo for the improvement of positive ($p \leq .05$) and hostility ($p \leq .01$) factor scores. Analysis of the 3 studies involving haloperidol showed that aripiprazole was significantly better than placebo in improving all 5 factors ($p \leq .01$), whereas haloperidol produced significantly greater improvements than placebo in 3 factors (positive, disorganized thought, and hostility) (each $p < .001$). There was no difference between aripiprazole and haloperidol on any factor. Analysis of the study involving risperidone showed that both drugs were better than placebo for all 5 factors with the exception of the depression/anxiety factor, in which only risperidone separated from placebo. There was no difference between aripiprazole and risperidone on any factor.

Conclusion: In this large dataset, aripiprazole was associated with improvements in a broad range of symptom domains in the short-term treatment of schizophrenia and schizoaffective disorder.

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Schizophrenia is a complex disorder in which virtually all psychological functions may be affected (e.g., perception, mood, thoughts, and cognition).[1] Understanding the complexity of symptoms associated with this condition and how symptom domains relate to both short-term and long-term outcomes represents a continuing challenge in the management of this disorder. Schizophrenia was first identified as a discrete mental illness by Emil Kraepelin, although he used the term *dementia praecox*.[2] Later, the Swiss psychiatrist, Eugen Bleuler, used the term *schizophrenia*.[3] Bleuler was also the first to describe the symptoms as "positive" (hallucinations, delusions, disorganized speech, suspicion/persecution, hostility, and

behavior disorders) or "negative" (poverty of thought, social withdrawal, anhedonia, and apathy). This division was highly influential in the development of reliable scales for the assessment of schizophrenia and schizoaffective disorder, such as the Positive and Negative Syndrome Scale (PANSS).[4]

Further studies, however, have suggested that the positive/negative symptom structure was insufficient to fully describe the spectrum of symptoms in patients with schizophrenia and schizoaffective disorder.[5] Initially, a 3-dimensional representation of symptoms—psychotic, disorganized, and negative dimensions—was suggested as a strongly reproducible model[6] but was limited with respect to evaluation of the full range of symptoms associated with schizophrenia. While not part of the schizophrenia/schizoaffective disorder diagnostic criteria in the DSM-IV-TR, cognitive symptoms are arguably the core characteristic of the disorder[7] as well as a major determinant of functional outcome.[8] Recently, the U.S. Food and Drug Administration (FDA) and the National Institute of Mental Health (NIMH) initiative, Measurement and Treatment Research to Improve Cognition in Schizophrenia (FDA-NIMH-MATRICS),[9] convened a consensus conference to develop guidelines on how to assess these symptoms, given their importance. Currently, models involving 5 factors are thought to be more representative of the symptom range seen in the long-term, chronic course of the disorder.[10] In the 5-factor model, derived from the PANSS scale, symptoms are divided into positive, negative, depression/anxiety, disorganized thought, and hostility.[11–13] Specific evaluation of the severity of disorganized thought, depression/anxiety, and hostility domains may be of particular value in long-term assessments—given the paramount role that these symptoms play in the readaptation of patients with schizophrenia to a healthy level of functioning.[14,15] Thus, the 5-factor model has an important role in the determination of the long-term therapeutic value of antipsychotic medications.

Although early evidence suggested that the second-generation antipsychotics (SGAs) alleviate a wider range of symptoms compared with older, first-generation antipsychotic agents (FGAs),[16] findings from large studies such as the NIMH Clinical Antipsychotic Trials in Intervention Effectiveness (CATIE) suggest that the comparative efficacy is still open to question. For example, switching to SGAs was reported to improve cognition[17,18] as well as negative, depressive, and anxiety symptoms, but the effects in this group of SGAs (excluding aripiprazole) were similar to those of perphenazine.[17] In addition, aripiprazole has also demonstrated efficacy for positive symptoms, negative symptoms, and disorganized thinking associated with schizophrenia and schizoaffective disorder.[19–24] The partial-agonist activity of aripiprazole at dopamine D_2 receptors[25,26] distinguishes it from all other currently available antipsychotics, which are D_2 receptor antagonists. D_2 receptor antagonism is directly related to an increase in side effects such as hyperprolactinemia and extrapyramidal symptoms.[27] Importantly, negative symptoms may develop or worsen secondary to extrapyramidal symptoms induced by FGAs.[28] Due to its partial-agonist activity, aripiprazole acts as a functional D_2 antagonist under hyperdopaminergic conditions and as a functional D_2 agonist under hypodopaminergic conditions.[26,29–31] Aripiprazole also has potent partial-agonist activity at serotonin 5-HT_{1A} receptors and antagonist activity at 5-HT_{2A} receptors.[32] These actions may benefit mood, anxiety, and disorganized thought. Finally, aripiprazole has moderate affinity for histamine H_1 receptors and no appreciable affinity for cholinergic muscarinic receptors,[33] providing a low liability for excessive sedation[34] and cognitive impairments.[35] This distinct pharmacologic profile may provide clinical improvements in the PANSS-derived factors of positive, negative, disorganized thought, depression/anxiety, and hostility symptoms.[30,36,37] To further explore the efficacy of aripiprazole across this range of symptoms, a factor analysis was conducted. This article reports a short-term assessment and analysis of the efficacy of aripiprazole for the treatment of the 5 factors of schizophrenia and schizoaffective disorder. Analyses such as the one presented here are of relevance since they allow evaluation of broader symptom domains that are not traditionally assessed in registration trials.

METHOD

Patient Population

Factor analysis was performed on pooled efficacy data from the 5 short-term (4- or 6-week), randomized, double-blind, placebo-controlled studies (published between 1997 and 2007) in patients hospitalized for an acute exacerbation of schizophrenia or schizoaffective disorder conducted for registrational purposes (studies 31-93-202, 31-94-202, 31-97-201, 31-97-202, and 138-001). Three studies included haloperidol (31-93-202, 31-94-202, 31-97-201) and 1 included risperidone (31-97-202) as active controls with no per-protocol intention for head-to-head comparisons. Details of these studies have been reported previously[20,23,38–41] and are summarized in Table 1.

All 5 studies involved patients aged 18 to 65 years (≥ 18 years, study 5) with an acute exacerbation of schizophrenia. Two studies also included patients with schizoaffective disorder (31-97-201 and 31-97-202), and separate analyses were conducted on this subpopulation. In all 5 studies, patients were previously responsive to antipsychotic medication (i.e., were not refractory to antipsychotics, had a history of improvement produced by an antipsychotic agent other than clozapine, and had been an outpatient for at least one 3-month period during the past year).

Table 1. Summary of the Design of 5 Short-Term, Randomized, Double-Blind, Placebo-Controlled Aripiprazole Studies Used in the Pooled Factor Analysis[a]

Study	Patient Diagnosis	Dosing	Treatment Duration, wk	Treatment Arms (randomized patients)		
				Aripiprazole, Dose (N)	Active Control, Dose (N)	Placebo, N
Petrie et al (1997)[38]	Schizophrenia	Ascending	4	5–30 mg/d (34)	Haloperidol, 5–20 mg/d (34)	35
Daniel et al (2000)[39]	Schizophrenia	Fixed[b]	4	2 mg/d (59) 10 mg/d (60) 30 mg/d (61)	Haloperidol, 10 mg/d (63)	64
Kane et al (2002)[20]	Schizophrenia or schizoaffective disorder[c]	Fixed	4	15 mg/d (102) 30 mg/d (102)	Haloperidol, 10 mg/d (104)	106
Potkin et al (2003)[23]	Schizophrenia or schizoaffective disorder[c]	Fixed	4	20 mg/d (101) 30 mg/d (101)	Risperidone, 6 mg/d (99)	103
McEvoy et al (2007)[41]	Schizophrenia	Fixed	6	10 mg/d (106) 15 mg/d (106) 20 mg/d (100)	NA	108
				Total N for Each Treatment Arm		
				932	Haloperidol, 201 Risperidone, 99	416

[a]These studies were carried out in accordance with the latest version of the Declaration of Helsinki. Each study design was reviewed by an appropriate ethical committee, and the informed consent of the participants was obtained after a full explanation of the nature of the study.
[b]Half of randomized dose on day 1.
[c]117 aripiprazole patients and 54 placebo patients had schizoaffective disorder across these 2 studies.
Symbol: NA = not applicable.

Table 2. PANSS Items Included in Each Symptom Factor[42]

Positive	Negative	Depression/Anxiety	Disorganized Thought	Hostility
P1: delusions	N1: blunted affect	G2: anxiety	N5: difficulty in abstract thinking	G8: uncooperativeness
P3: hallucinatory behavior	N2: emotional withdrawal	G3: guilt feelings	G5: mannerisms and posturing	G14: poor impulse control
P5: grandiosity	N3: poor rapport	G4: tension	G10: disorientation	P4: excitement
P6: suspiciousness	N4: passive social withdrawal	G6: depression	G11: poor attention	P7: hostility
N7: stereotyped thinking	N6: lack of spontaneity		G13: disturbance of volition	
G1: somatic concern	G7: motor retardation		G15: preoccupation	
G9: unusual thought content	G16: active social avoidance		P2: conceptual disorganization	
G12: lack of judgment and insight				

Abbreviation: PANSS = Positive and Negative Syndrome Scale.

Patients had to meet additional inclusion criteria at randomization. In studies 1 and 2, these were a PANSS-derived Brief Psychiatric Rating Scale (BPRS) total score of at least 30 (study 1) or 36 (study 2), with scores of at least 4 (moderate) on any 2 items that constitute the BPRS psychotic items subscale (hallucinations, conceptual disorganization, unusual thought content, and suspiciousness). In studies 3, 4, and 5, the criteria were a PANSS total score of at least 60 and a score of at least 4 on any 2 of the items on the PANSS psychotic items subscale (i.e., hallucinations, delusions, conceptual disorganization, and suspiciousness). In all studies, patients were hospitalized for the duration of the study. Exclusion criteria were similar across all 5 studies and included a psychiatric disorder other than schizophrenia or schizoaffective disorder requiring pharmacotherapy, a history of violence, a history of suicide attempts or serious suicidal thoughts, a clinically significant neurologic abnormality other than tardive dyskinesia or extrapyramidal symptoms, current or recent psychoactive drug or alcohol abuse or dependence, treatment with an investigational drug within 4 weeks of the washout phase, previous enrollment in an aripiprazole clinical study, or any other acute or unstable medical condition. This study was conducted in accordance with Good Clinical Practice Procedures and the Declaration of Helsinki. Approval was obtained from the institutional review board or ethics committee at each study center. All patients provided written informed consent, which was cosigned by a relative or caregiver if required by the local institutional review board.

Efficacy Assessments and Factor Analysis

In all 5 studies, PANSS assessments were performed at randomization (baseline) and weekly throughout the study period. Previous factor analytic studies have shown that the PANSS symptoms can be described according to 5 factors (dimensions): positive symptoms, negative symptoms, disorganized thought, depression/anxiety symptoms, and hostility[12,42] (Table 2). A factor analysis of the PANSS scores at each time point (up to week 4) was conducted to compare the effects of aripiprazole with placebo (5 studies), with haloperidol and placebo (3 studies), and with risperidone and placebo (1 study). Data from the last 2 weeks of study 5 were not included in this analysis.

Statistical Analyses

The PANSS data were pooled from all 5 studies and analyzed on a last-observation-carried-forward basis using the efficacy sample. Least-squares means for aripiprazole, placebo, haloperidol, and risperidone were calculated at weeks 1, 2, 3, and 4 for all 5 PANSS factors. In the pooled data from studies 1, 2, 3, 4, and 5, analyses were performed to assess differences between aripiprazole and placebo. Pooled data from studies 1, 2, and 3 were also analyzed to compare aripiprazole with haloperidol and placebo. The same approach was used in study 4 involving risperidone. Of note, the studies involving active controls (haloperidol or risperidone) were not adequately powered to show a difference between drugs as per the initial protocols. A further analysis was conducted on a subpopulation of patients with schizoaffective disorder from studies 3 and 4. The comparison of aripiprazole with risperidone in study 4 was analyzed using an analysis of covariance with treatment as main effect and baseline score as covariate. For all other subset populations, data were analyzed using an analysis of covariance with treatment and study as main effects and baseline score as covariate. In cases in which simultaneous comparisons of 3 treatment groups were performed, adjustments for multiple comparisons were made using the Tukey-Kramer method.

Aripiprazole was not efficacious at the 2-mg dose.[43] Therefore, the primary dataset excludes patients receiving the 2-mg/day dose of aripiprazole. For completeness, however, a secondary analysis was performed to investigate whether including the 2-mg/day dose would alter the results.

RESULTS

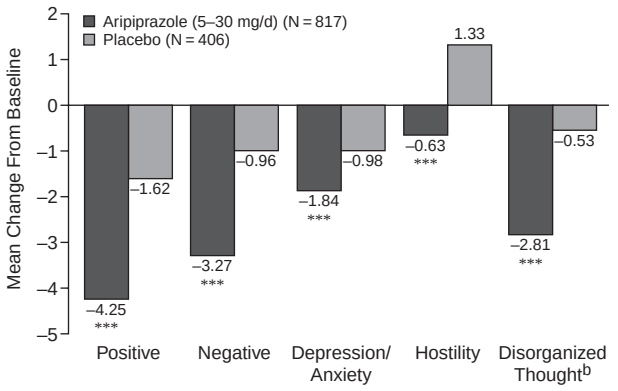
Patient Population

In the 5 studies, 932 patients were randomly assigned to aripiprazole, 201 to haloperidol, 99 to risperidone, and 416 to placebo. Sample sizes for the corresponding efficacy samples were N = 875 for aripiprazole, N = 193 for haloperidol, N = 95 for risperidone, and N = 406 for placebo. Table 1 provides an overview of the study designs and number of patients randomly assigned to each treatment arm per study. Baseline characteristics of patients were similar across the treatment groups and have been reported in a separate pooled analysis.[44] The mean age of patients in each group was approximately 39 years, and approximately 75% of patients were male. A total of 171 patients in studies 3 and 4 had a diagnosis of schizoaffective disorder (aripiprazole, N = 117; placebo, N = 54).

Factor Analysis

Aripiprazole versus placebo in schizophrenia. Aripiprazole treatment was associated with significantly greater improvements in PANSS-derived positive, negative, depression/anxiety, disorganized thought, and hostility factor scores from baseline to week 4 compared with placebo across the 5 pooled studies (Figure 1). Similar results were obtained for the analysis when the 2-mg aripiprazole dose arm was included (data not shown).

Figure 1. Mean Change in PANSS Factor Scores From Baseline to Week 4 (LOCF analysis) in 5 Studies Comparing Aripiprazole and Placebo in Schizophrenia[a]



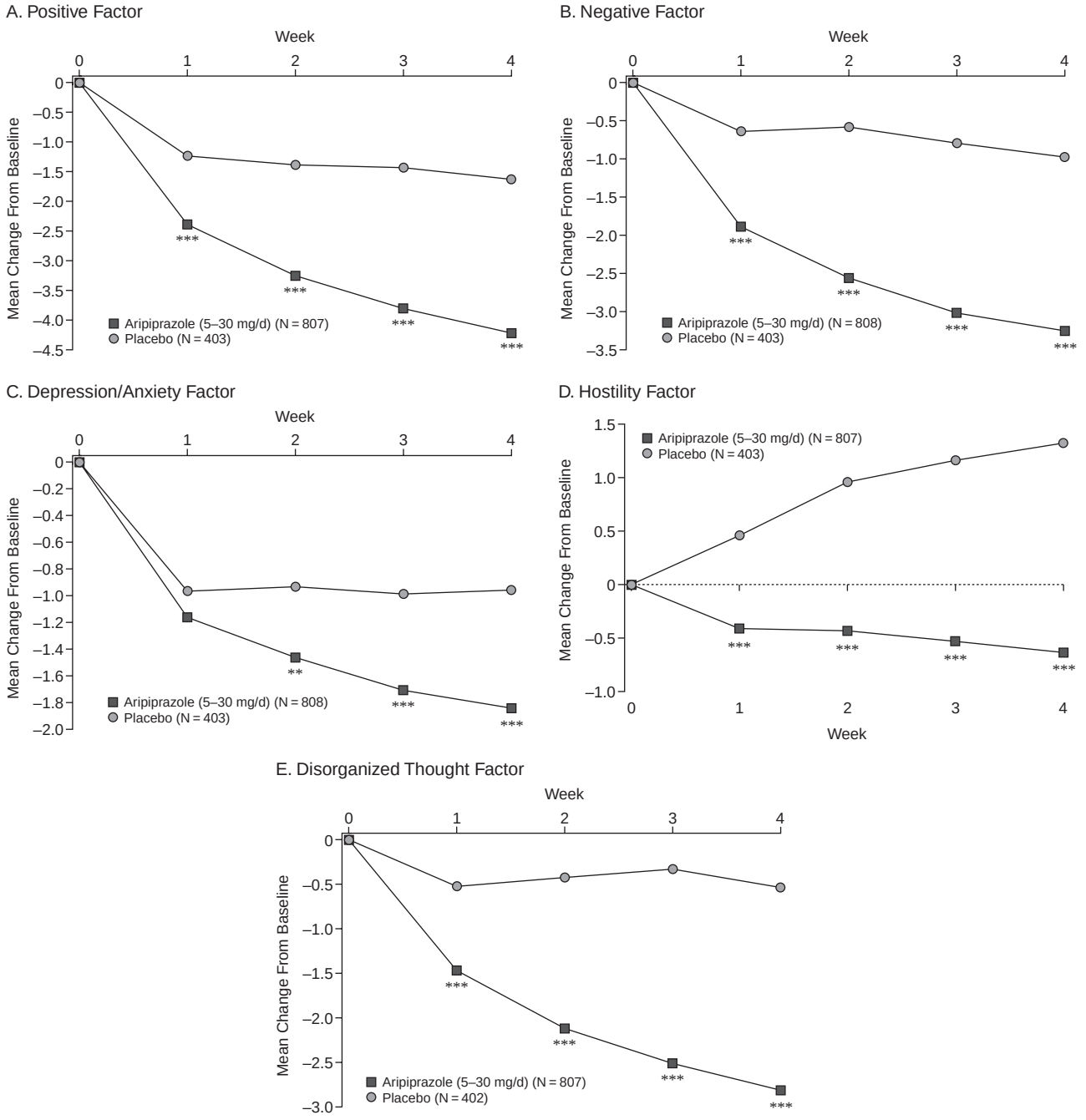
[a]Baseline PANSS subscale scores: positive factor, aripiprazole = 29.0, placebo = 28.9; negative factor, aripiprazole = 22.4, placebo = 22.2; depression factor, aripiprazole = 12.0, placebo = 12.0; hostility factor, aripiprazole = 9.4, placebo = 9.3; disorganized thought factor, aripiprazole = 21.3, placebo = 21.6.
[b]Disorganized thought factor: aripiprazole, N = 816; placebo, N = 405.
***$p \leq .001$ vs. placebo.
Abbreviations: LOCF = last observation carried forward, PANSS = Positive and Negative Syndrome Scale.

Figure 2 shows the mean change over time from baseline to week 4 for each of the 5 factors. Aripiprazole produced significantly greater improvements than placebo on the positive, negative, hostility, and disorganized thought factors as early as week 1 and significantly greater improvements on the depression/anxiety cluster from week 2 onward.

Aripiprazole versus placebo in patients with schizoaffective disorder. The mean change from baseline to week 4 for each of the 5 factors in the subset of patients with schizoaffective disorder is shown in Figure 3. Mean changes from baseline to week 4 were significantly greater for aripiprazole versus placebo in PANSS-derived positive ($p \leq .05$) and hostility ($p \leq .01$) factor scores. In this patient population, changes in positive and hostility factor scores were significantly greater with aripiprazole than with placebo from week 2 onward. Aripiprazole also produced significantly greater improvements than did placebo on the disorganized thought factor score at weeks 2 and 3 (both $p \leq .05$), although this difference was not statistically significant at endpoint. Negative and depression/anxiety factor scores for aripiprazole were not significantly different from placebo at any time point.

Aripiprazole and haloperidol versus placebo. Data from the studies that included an active haloperidol comparator arm (studies 1, 2, and 3) were pooled to allow PANSS-derived factor scores to be analyzed for

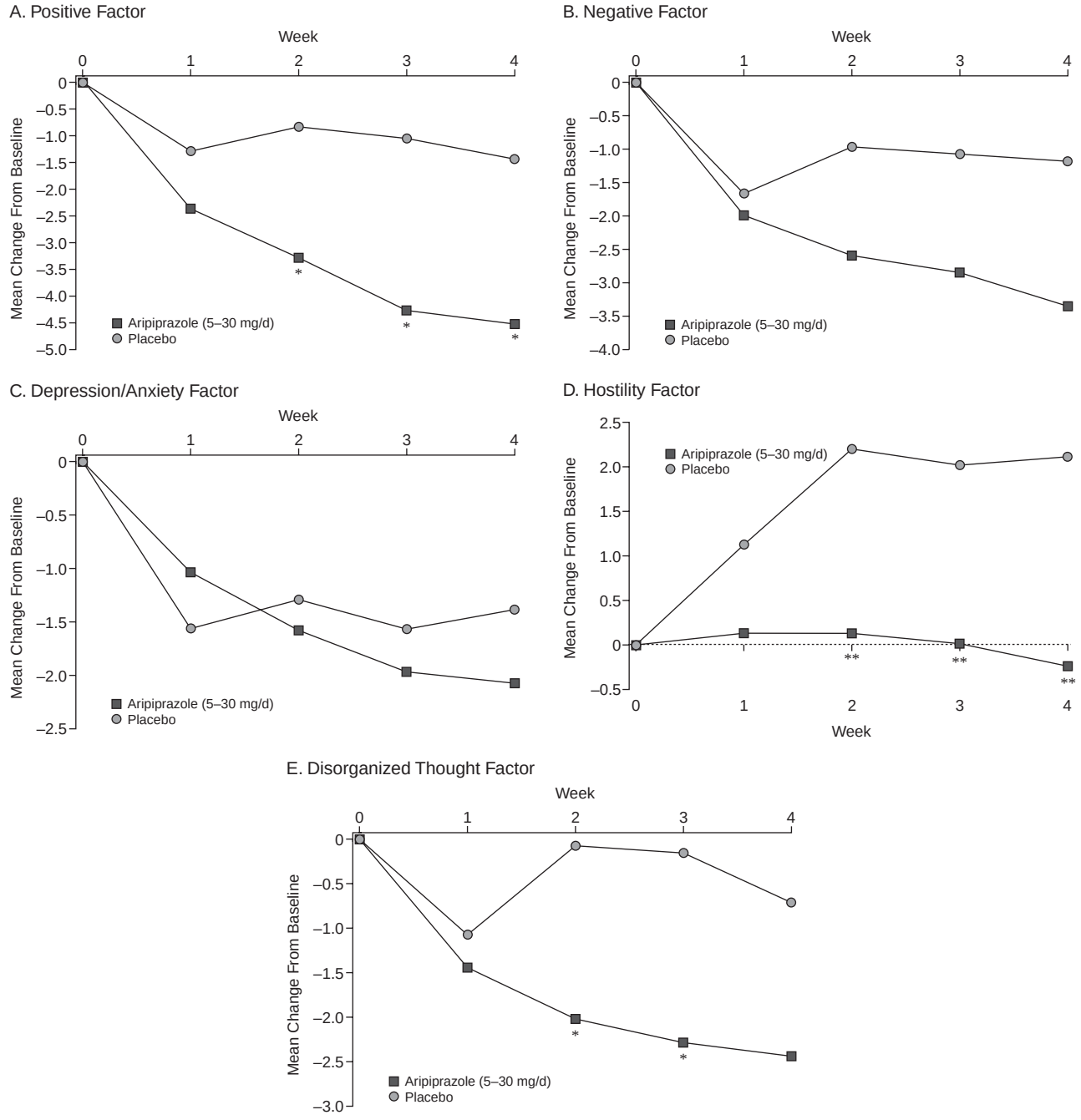
Figure 2. Mean Change in PANSS Factor Scores From Baseline to Week 4 (LOCF analysis) From 5 Pooled Studies Comparing Aripiprazole and Placebo in Schizophrenia



**p ≤ .01 vs. placebo, ***p ≤ .001 vs. placebo.
Abbreviations: LOCF = last observation carried forward, PANSS = Positive and Negative Syndrome Scale.

each antipsychotic agent compared with placebo. Mean changes from baseline to week 4 were significantly greater for aripiprazole versus placebo in all 5 factors (all p ≤ .01) (Figure 4A). Evaluation of the change over time showed that aripiprazole achieved significantly greater improvements than did placebo from week 1 for the hostility factor and from week 2 for the remaining factors (positive, negative, depression/anxiety, and disorganized thought) (Figure 5). For haloperidol, mean changes from baseline were significantly greater than for placebo from week 1 onward for the positive, hostility, and disorganized thought factors (Figure 5). Improvements in negative factor scores from baseline were significantly greater with haloperidol than with placebo at weeks 2 and 3, but not significantly

Figure 3. Mean Change in PANSS Factor Scores From Baseline to Week 4 (LOCF analysis) in 2 Studies Comparing Aripiprazole (N = 54) and Placebo (N = 117) in Schizoaffective Disorder



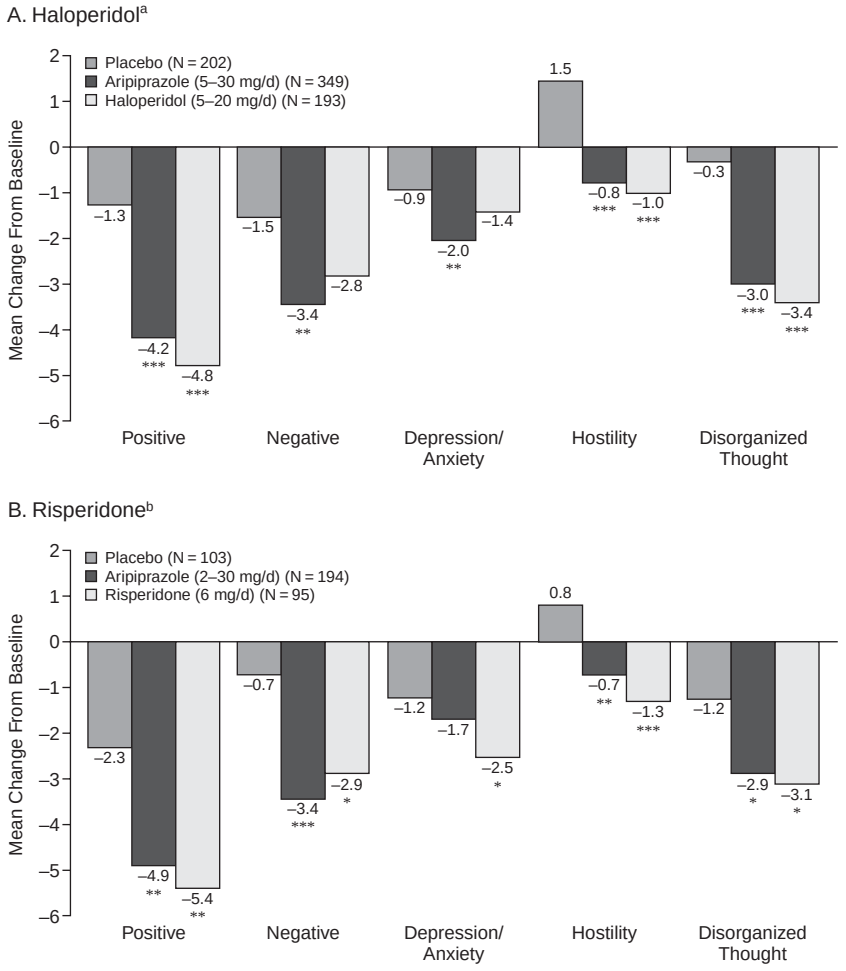
*p ≤ .05 vs. placebo, **p ≤ .01 vs. placebo.
Abbreviations: LOCF = last observation carried forward, PANSS = Positive and Negative Syndrome Scale.

different from placebo at endpoint (week 4). Improvements in the depression/anxiety factor with haloperidol did not differ significantly from placebo at any time point. Similar results were obtained for the analysis when the 2-mg aripiprazole dose arm was included (data not shown).

While a comparison of aripiprazole and haloperidol showed no significant differences between treatment arms in any factor at any time point (Figure 5), this comparison should be interpreted with caution as the original studies were not adequately powered to detect differences between aripiprazole and haloperidol.

Aripiprazole and risperidone versus placebo. Mean changes from baseline to week 4 were significantly greater for aripiprazole versus placebo on the positive,

Figure 4. Mean Change in PANSS Factor Scores From Baseline to Week 4 in 3 Studies Comparing Aripiprazole, Haloperidol, and Placebo and in 1 Study Comparing Aripiprazole, Risperidone, and Placebo (LOCF analysis)

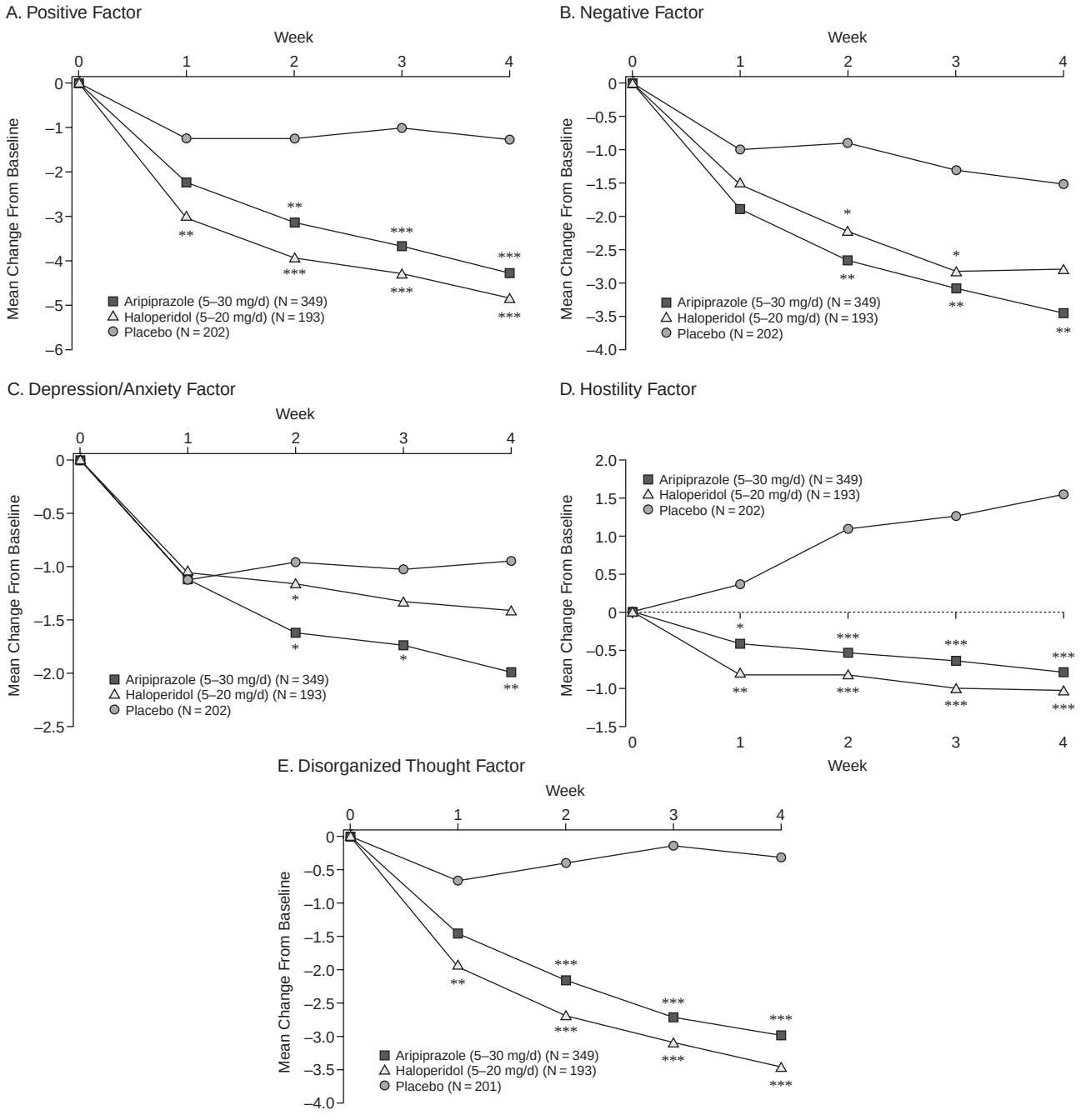


[a]Haloperidol studies' baseline PANSS subscale scores: positive factor, aripiprazole = 29.1, placebo = 28.9, haloperidol = 29.2; negative factor, aripiprazole = 22.9, placebo = 23.0, haloperidol = 22.8; depression factor, aripiprazole = 12.2, placebo = 12.0, haloperidol = 12.3; hostility factor, aripiprazole = 9.5, placebo = 9.2, haloperidol = 9.2; disorganized thought factor, aripiprazole = 21.6, placebo = 21.5, haloperidol = 21.5.
[b]Risperidone studies' baseline PANSS subscale scores: positive factor, aripiprazole = 29.0, placebo = 29.4, risperidone = 29.4; negative factor, aripiprazole = 21.8, placebo = 21.8, risperidone = 22.7; depression factor, aripiprazole = 12.1, placebo = 12.3, risperidone = 11.9; hostility factor, aripiprazole = 9.4, placebo = 9.6, risperidone = 9.6; disorganized thought factor, aripiprazole = 20.9, placebo = 21.9, risperidone = 21.1.
*p ≤ .05 vs. placebo, **p ≤ .01 vs. placebo, ***p ≤ .001 vs. placebo.
Abbreviations: LOCF = last observation carried forward, PANSS = Positive and Negative Syndrome Scale.

negative, hostility, and disorganized thought factors (all $p < .05$) (Figure 4B). For aripiprazole, mean changes from baseline were significantly greater than for placebo from week 1 onward for the positive, negative, hostility, and disorganized thought factors (all $p \leq .05$). Improvements in depression/anxiety factor scores from baseline were not significantly greater with aripiprazole than placebo at any time point. Mean changes from baseline to week 4 were significantly better for risperidone when compared with placebo in all 5 PANSS factors (all $p < .05$). For risperidone, mean changes from baseline were significantly greater than for placebo from week 1 onward for the positive and hostility factors ($p < .05$), from week 2 for the disorganized thought factor ($p < .05$), and from week 3 for the negative and depression/anxiety factors ($p < .05$).

Direct comparison of aripiprazole and risperidone showed no significant differences between treatment arms in any factor at any time point. As with the haloperidol comparisons described above, however, this finding should be interpreted with caution as the original study was not adequately powered to detect differences between aripiprazole and risperidone.

Figure 5. Mean Change in PANSS Factor Scores From Baseline to Week 4 (LOCF analysis) From 3 Pooled Studies Comparing Aripiprazole, Haloperidol, and Placebo



*p ≤ .01 vs. placebo, **p ≤ .01 vs. placebo, ***p ≤ .001 vs. placebo.
Abbreviations: LOCF = last observation carried forward, PANSS = Positive and Negative Syndrome Scale.

DISCUSSION

In this post hoc evaluation, a PANSS factor analysis of pooled data from 5 short-term aripiprazole clinical trials was used to evaluate aripiprazole's efficacy to treat positive, negative, depression/anxiety, disorganized thought, and hostility symptoms in patients with schizophrenia and schizoaffective disorder. This analysis is of clinical relevance, since it allows for evaluation of broader symptom domains not traditionally assessed in registration trials. In the pivotal clinical trials of aripiprazole, the focus was on efficacy for positive and negative symptoms of schizophrenia and schizoaffective disorder.[19–23] Treatment goals, however, should include improvement in a wider

spectrum of symptoms to maximize both short-term and long-term outcomes. In the long-term, it is particularly important to treat disorganized thought and negative and hostility symptoms, since they have important effects on functional outcome and success in rehabilitation.[14,15] Although any differences must be interpreted with caution due to imbalances between treatment groups, such comparisons provide an indication of acute treatment differences that may warrant further prospective investigation for longer-term benefits. The discussion below assesses the effects of aripiprazole on each of these factors within the context of previous factor analyses of other SGAs.

Relief of positive symptoms is often the primary short-term goal in the treatment of schizophrenia. The efficacy of aripiprazole to treat positive symptoms shown in this factor analysis is consistent with the efficacy of other antipsychotics to treat this symptom domain. Aripiprazole, haloperidol, and risperidone all provided a significantly greater change from baseline than placebo in the positive factor, and the degree of change was similar in the active treatment groups. Previously, risperidone demonstrated a significantly greater improvement over placebo and haloperidol in the positive factor.[42] Olanzapine also was superior to placebo and haloperidol for the reduction of PANSS positive factor scores.[45] Results from the subset analysis of patients with schizoaffective disorder indicate that aripiprazole also demonstrated efficacy on this factor for the treatment of patients with this specific diagnosis. These improvements over placebo on the positive factor occurred from week 2 onward. One previous factor analysis of olanzapine also included patients with schizoaffective disorder in its study population.[45] To our knowledge, however, no factor analyses of PANSS scores were conducted in schizoaffective patients specifically and thus could not be compared to our results.

The severity of negative and disorganized thought symptoms may have a more detrimental impact on daily functioning than positive symptoms.[46,47] Negative symptoms affect long-term functional outcomes[48,49] and unfavorably impact self-esteem.[15] In this analysis, aripiprazole demonstrated a significant improvement over placebo for negative symptoms (as did risperidone), but haloperidol did not. Aripiprazole was not associated with significant improvements in negative factor scores compared with placebo in the subset of patients with schizoaffective disorder. The ability to treat negative symptoms may be a key determinant of treatment selection (e.g., FGAs may not be as beneficial in treating negative and depression/anxiety symptoms).[28,42,45,50] Other SGAs—clozapine,[50] risperidone,[42] and olanzapine[45]—have also demonstrated significant improvements in negative symptoms compared with placebo and haloperidol in patients with schizophrenia. Long-term studies of the effects on negative symptoms are necessary, however, to draw any firm conclusions regarding this symptom domain.

Depression and anxiety symptoms are also increasingly recognized as important determinants of long-term outcome in schizophrenia. Our analyses show a differential effect of aripiprazole and haloperidol over placebo to treat depression/anxiety (i.e., aripiprazole provided a significantly greater improvement in these symptoms over placebo, but haloperidol did not). Depressive symptoms occur at a modal rate of 25% in schizophrenia[51] and are associated with a high rate of relapse, suicide, and poor quality of life.[52] Anxiety can cause social disability and is also linked to a higher suicide rate, substance/alcohol abuse, lower social adjustment, and diminished quality of life.[53] Antipsychotics with a pharmacologic profile that extends beyond simple dopamine-based mechanisms of action (e.g., 5-HT effects) may produce a greater benefit for depressive and anxiety symptoms in schizophrenia.[30] Thus, SGAs with activity other than dopamine antagonism may produce antidepressant and anxiolytic effects.[26,32] For example, previous studies showed that risperidone and olanzapine also improved this factor significantly more than placebo or haloperidol.[42,45]

Disorganized thinking is considered one of the most debilitating aspects of schizophrenia.[54] It has been suggested that enhancement of cognitive functioning may be associated with improvement in community functioning.[55] Aripiprazole, haloperidol, and risperidone all provided a significantly greater and similar change from baseline than placebo in the disorganized thought factor. The subgroup of patients with schizoaffective disorder also experienced improvements in disorganized thought factor scores, although differences reached significance only at week 2 and 3. These improvements in cognition are consistent with the significant improvements in secondary verbal memory and general cognitive ability from baseline reported with aripiprazole in an open-label comparison with olanzapine in 255 patients with chronic, stable schizophrenia.[19] Previous factor analyses also demonstrated improvements with risperidone and olanzapine compared with either placebo or haloperidol on disorganized thought.[42,45] In this analysis, aripiprazole and haloperidol provided similar improvements in the disorganized thought factor. In the CATIE study, all SGAs and perphenazine, an FGA, showed a small but significant improvement in neurocognition after 2 months; there was not, however, any differences between any pair of agents, including the FGA perphenazine.[43] One caveat is that assessment and evaluation of improvements in disorganized thought are still limited and further evolution of the tools to measure cognition are needed for patients with schizophrenia.[55,56] One limitation is that our analysis cannot rule out the possibility that these improvements in disorganized thought are secondary to improvements in positive and/or negative symptoms.

Aggression and hostility are often accompanied by violence, which can lead to social alienation, rehospitalization, and imprisonment.[57] Patients manifesting these

behaviors (e.g., threatening behaviors, escalating or urgently distressing behavior, or self-exhausting behavior) often impede proper diagnosis and care.[36] Aripiprazole showed efficacy in this domain (in both schizophrenia and schizoaffective disorder), as did risperidone and haloperidol. This result is consistent with previous analyses of the PANSS hostility factor from the studies reported here[44] and analyses of other SGAs in patients with schizophrenia. Hostility, in previous factor analyses of SGAs, was assessed by the impulsivity/hostility cluster[45] or the uncontrolled hostility/excitement cluster.[42] Both olanzapine and risperidone significantly improved this symptom domain compared with either placebo or haloperidol. In addition, quetiapine[58] and olanzapine[59] demonstrated significant improvements in BPRS-derived factors, including hostility/suspiciousness. In a factor analysis of 157 inpatients with schizophrenia or schizoaffective disorder and a history of suboptimal treatment response, clozapine also demonstrated a relative advantage over haloperidol, risperidone, and olanzapine as a specific antihostility agent.[60]

Analyses such as those presented here are always limited by their post hoc nature. Although interrater reliability between the studies was not determined and may have influenced the results to a certain degree, it should be noted that the PANSS scale has demonstrated high interrater reliability (0.83 to 0.87).[61] In addition, the data originate from short-term studies. Longer-term evaluation of factors would be of substantial value to determine the impact of this treatment on patients with schizophrenia. Such short-term analyses, however, can be clinically valuable in determining the spectrum of symptoms most improved with a particular treatment and are supportive of the primary analyses of pivotal registrational studies.

CONCLUSION

Significantly greater improvements were seen for aripiprazole compared with placebo from week 1 on the positive, negative, hostility, and disorganized thought factors and from week 2 on the depression/anxiety factor. This result is clinically relevant, as the rapid resolution of acute symptoms (especially positive and hostility symptoms) is the goal of acute treatment and important to an optimal return of functioning.[62] Deficits in daily functioning (including social disability as a result of persistent affective symptoms, disorganized thought, or hostility symptoms) are a major barrier to outcome in patients with schizophrenia and are yet to be effectively treated. When compared with placebo, both aripiprazole and risperidone improved all factors, whereas haloperidol was associated with improvements in just 3 factors. There were no significant differences between aripiprazole and risperidone or haloperidol on any factor. Although derived from short-term, post hoc analyses, our results confirm the efficacy of aripiprazole across a range of symptom domains in schizophrenia and schizoaffective disorder.

Drug names: aripiprazole (Abilify), clozapine (Fazaclo, Clozaril, and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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