Efficacy of Aripiprazole Against Hostility in Schizophrenia and Schizoaffective Disorder: Data From 5 Double-Blind Studies

Jan Volavka, M.D.; Pal Czobor, Ph.D.; Leslie Citrome, M.D., M.P.H.; Robert D. McQuade, Ph.D.; William H. Carson, M.D.; Dusan Kostic, Ph.D.; Sterling Hardy, M.S.; and Ronald Marcus, M.D.

Objective: The objective was to determine the effects of aripiprazole on hostility.

Method: A total of 1476 patients diagnosed with DSM-IV schizophrenia or schizoaffective disorder were the subjects in 5 short-term, double-blind studies comparing aripiprazole with placebo; 3 of these studies also included a comparison with haloperidol. The studies were conducted between December 1993 and January 2001. The Positive and Negative Syndrome Scale (PANSS) was the principal outcome measure in these studies. To determine the effect of aripiprazole on hostility, post hoc analyses of the hostility item from the PANSS were conducted for the first 4 weeks of treatment.

Results: Aripiprazole was superior to placebo and not significantly different from haloperidol in reducing hostility.

Conclusion: Aripiprazole is an effective treatment for hostility in patients with schizophrenia or schizoaffective disorder.

(J Clin Psychiatry 2005;66:1362–1366)

Received March 5, 2005; accepted Aug. 2, 2005. *From the Nathan Kline Institute and New York University, Orangeburg, N.Y. (Drs. Volavka, Czobor, and Citrome); DOV Pharmaceutical, Hackensack, N.J. (Dr. Czobor); Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan (Dr. McQuade); Otsuka America Pharmaceutical, Inc., Princeton, N.J. (Dr. Carson); Bristol-Myers Squibb Company, Lawrenceville, N.J. (Dr. Kostic); and Bristol-Myers Squibb Company, Wallingford, Conn. (Mr. Hardy and Dr. Marcus).*

The studies were supported by Bristol-Myers Squibb Company.

Financial disclosure appears at the end of the article.

Corresponding author and reprints: Jan Volavka, M.D., Nathan Kline Institute, 140 Old Orangeburg Rd., Orangeburg, NY 10962 (e-mail: janvolavka@gmail.com).

Aripiprazole is a novel antipsychotic with a mechanism of action that differs from those of other antipsychotics. The mechanism apparently involves partial agonist activity at D_2 and 5-HT_{1A} receptors and antagonist activity at 5-HT_{2A} receptors. Its antipsychotic efficacy and safety have been demonstrated in a series of studies.[1–4]

Assessing the antiaggressive effects of antipsychotics is important for their clinical use. Violent or threatening behavior is a frequent reason for admission to a psychiatric inpatient facility. Moreover, if such behaviors continue after admission, they can prolong hospitalization and interfere with discharge. Violence by psychiatric patients in the hospital and the community is increasingly seen as a major burden for caregivers.[5] For these reasons, prescription patterns are to a large extent driven by psychiatrists' concern about dangerous behaviors.[6] Therefore, antiaggressive effects of antipsychotics have been extensively studied.[5,7–9] Clozapine has robust antiaggressive effects.[9,10] Risperidone was superior to haloperidol in reducing hostility,[11] but this finding was not replicated in another study using a different patient population.[9] Data on other antipsychotics are not yet adequate to permit firm conclusions regarding their antiaggressive effects.

Beneficial effects of aripiprazole on the cluster of excitement/hostility symptoms derived from the Positive and Negative Syndrome Scale (PANSS)[12] have been reported.[13,14] In this report, we focus specifically on the effects of aripiprazole on hostility.

METHOD

Study Design

This report is based on pooled data from 5 short-term, double-blind, placebo-controlled trials of aripiprazole (references 1–4 and data on file; Bristol-Myers Squibb; Lawrenceville, N.J., and Wallingford, Conn.). (An analogous strategy using pooled data from the same 5 studies to assess the safety of aripiprazole was employed by Marder et al.[15]). The studies are summarized in Table 1. These multicenter studies were conducted in North America between December 1993 and January 2001 and lasted 4 to 6 weeks. The studies were approved by the local institu-

  © Copyright 2005 Physicians Postgraduate Press, Inc.

Table 1. Summary of Short-Term (4- or 6-week) Aripiprazole Trials[a]

Study Characteristic	Study 1[b]	Study 2[c]	Study 3[d]	Study 4[e]	Study 5[f]
Diagnoses	Schizophrenia	Schizophrenia	Schizophrenia or schizoaffective disorder	Schizophrenia or schizoaffective disorder	Schizophrenia
Total randomized patients included in analysis, N	101	267	401	297[g]	410
Treatment arms	Aripiprazole 5–30 mg, ascending doses (N = 33)	Aripiprazole 2 mg (N = 51) 10 mg (N = 51) 30 mg (N = 54)	Aripiprazole 15 mg (N = 99) 30 mg (N = 100)	Aripiprazole 20 mg (N = 98) 30 mg (N = 96)	Aripiprazole 10 mg (N = 103) 15 mg (N = 103) 20 mg (N = 97)
	Placebo (N = 35)	Placebo (N = 57)	Placebo (N = 103)	Placebo (N = 103)	Placebo (N = 107)
	Haloperidol 5–20 mg (N = 33)	Haloperidol 10 mg (N = 54)	Haloperidol 10 mg (N = 99)	Risperidone 6 mg (N = 95)	

[a]All studies were randomized and double-blind. Pooled studies 1 through 5 were used for the comparison of aripiprazole and placebo. Pooled studies 1, 2, and 3 were used for the comparison with haloperidol.
[b]Data from Petrie et al.[1]
[c]Data from Daniel et al.[2]
[d]Data from Kane et al.[3]
[e]Data from Potkin et al.[4]
[f]Data on file; Bristol-Myers Squibb; Lawrenceville, N.J., and Wallingford, Conn.
[g]Data from risperidone arm were not used.

tional review boards, and the subjects provided informed written consent to participate.

Study Population

The patients, aged 18 to 65 years, were diagnosed with acute relapse of schizophrenia or schizoaffective disorder as defined by DSM-IV criteria (DSM-III-R in the case of the earliest study[1]). Patients had to have a minimum total score of 60 on the PANSS (studies 3–5), 30 on the Brief Psychiatric Rating Scale (BPRS)[16] (study 1), or 36 on the BPRS (study 2) and ratings of at least "moderate" on at least 2 of the items that assess positive symptoms. They had to show prior responsiveness to antipsychotic medication other than clozapine and had to have been outpatients for at least 1 three-month period during the past year. The patients were hospitalized for the duration of their study.

Efficacy and Safety Assessments

In all 5 studies, the PANSS was administered at baseline and then weekly. The PANSS hostility item was adopted as the outcome measure. Similar to other PANSS items, hostility is scored on a scale ranging from 1 (indicating no hostility) to 7 (extreme hostility including marked anger, extreme uncooperativeness that precludes other interactions, or a physical assault). A score of 3 indicates a guarded or distrustful attitude that has no (or minimal) effect on behavior.

Spontaneously reported adverse events were recorded in all 5 studies. Daytime somnolence (sedation) was one of the events. This variable was used to assess the extent to which the aripiprazole effects on hostility were mediated by sedation.

Analysis of Pooled Data

Primary and secondary analyses. We analyzed the data collected at baseline and during the first 4 weeks of treatment. Two sets of analyses were implemented. The primary analysis compared the effects of aripiprazole and placebo. The secondary analysis compared the effects of aripiprazole, haloperidol, and placebo. The primary analysis used pooled data on aripiprazole and placebo from all 5 studies. The secondary analysis used pooled data from the 3 studies that included aripiprazole, placebo, and haloperidol treatment arms.[1–3] Demographic and clinical characteristics of patients used for primary and secondary analyses are summarized in Tables 2 and 3, respectively.

Statistical analyses. Random regression hierarchical linear modeling (HLM)[17–19] was adopted as the principal statistical approach for the study. This method permits the use of observations with incomplete data (e.g., patients who dropped out before completing the study). Furthermore, in contrast to the traditional analysis of covariance, the HLM approach makes allowance for heterogeneity among treatment groups both in terms of initial (baseline) values and in terms of covariance structure (i.e., relationship between baseline severity and change).[20] In the HLM model, repeated assessments of symptom severity over time served as the dependent variable.

The 2 independent factors of primary interest in the HLM model were treatment group and time. Treatment group (placebo and aripiprazole [and haloperidol in the secondary comparisons as described above]) served as the between-subject factor. Time (in weeks) from baseline was used as a within-subject, random-effect factor. Interaction between treatment group and time was included in the model. In addition, "protocol" (study) was applied in the model as a (categorical) covariate. The purpose of the inclusion of this covariate in the model was to assure that changes in efficacy variables over time were not confounded by variability across studies. To investigate whether the results were independent of sedation and

© Copyright 2005 Physicians Postgraduate Press, Inc.

Table 2. Demographic and Clinical Characteristics of Patients in 5 Studies Comparing Aripiprazole and Placebo

Characteristic	Placebo (N = 405)	Aripiprazole (N = 885)
Gender, N (%)		
Male	301 (74)	661 (75)
Female	104 (26)	224 (25)
Race, N (%)		
White	205 (51)	492 (56)
African American	140 (35)	260 (29)
Hispanic	29 (7)	53 (6)
Asian	23 (6)	59 (7)
Other	8 (2)	21 (2)
Diagnosis, N (%)		
Schizophrenia	351 (87)	768 (87)
Schizoaffective disorder	54 (13)	117 (13)
Age, mean (SD), y	39.09 (10.23)	39.03 (10.46)
Baseline PANSS hostility item score, mean (SD)	2.33 (1.33)	2.34 (1.37)

Abbreviation: PANSS = Positive and Negative Syndrome Scale.

Table 3. Demographic and Clinical Characteristics of Patients in 3 Studies Comparing Aripiprazole, Haloperidol, and Placebo

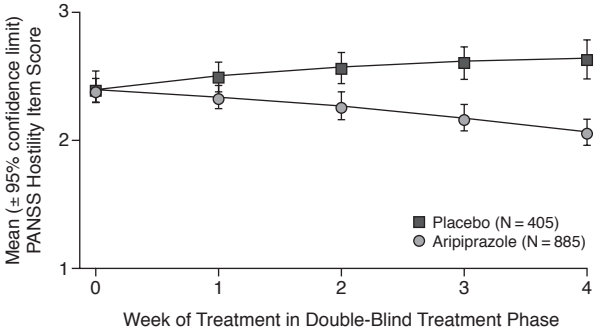
Characteristic	Placebo (N = 195)	Haloperidol (N = 186)	Aripiprazole (N = 388)
Gender, N (%)			
Male	146 (75)	137 (74)	292 (75)
Female	49 (25)	49 (26)	96 (25)
Race, N (%)			
White	99 (51)	115 (62)	216 (56)
African American	69 (35)	51 (27)	121 (31)
Hispanic	21 (11)	14 (8)	36 (9)
Asian	3 (2)	1 (1)	9 (2)
Other	3 (2)	5 (3)	6 (2)
Diagnosis, N (%)			
Schizophrenia	166 (85)	146 (78)	332 (86)
Schizoaffective disorder	29 (15)	40 (22)	56 (14)
Age, mean (SD), y	37.99 (9.24)	38.70 (9.93)	38.01 (9.90)
Baseline PANSS hostility item score, mean (SD)	2.36 (1.32)	2.34 (1.16)	2.45 (1.41)

Abbreviation: PANSS = Positive and Negative Syndrome Scale.

of an overall change in the severity of positive symptoms, sedation and improvement on the PANSS positive symptoms subscale were introduced as additional covariates in the analyses. For the purpose of this investigation, the hostility item was excluded from the subscale score of positive symptoms; this subscale score was used as an independent variable in the analysis of hostility, which was the primary measure and the dependent variable in the HLM model.

The HLM analysis had 2 principal objectives: (1) to assess whether a significant change in hostility severity over time occurred in any of the treatment groups and (2) to test whether there was a difference among the groups in change in hostility severity over time; this analysis is analogous to the traditional test of interaction between time and treatment effects. The time effect and the interaction effect (i.e., difference in symptom severity change in the treatment groups) were tested using the F-statistic.

Figure 1. Change in Hostility During Treatment With Aripiprazole in 5 Short-Term, Placebo-Controlled Trials[a]



[a]A significant difference in the hostility scores between aripiprazole and placebo was observed at all time points during the 4-week treatment period ($p < .05$).
Abbreviation: PANSS = Positive and Negative Syndrome Scale.

If a significant effect was detected, post hoc analyses were performed to examine the direction of changes (time effect) or the differences in change over time among the treatment groups (interaction effect).

RESULTS

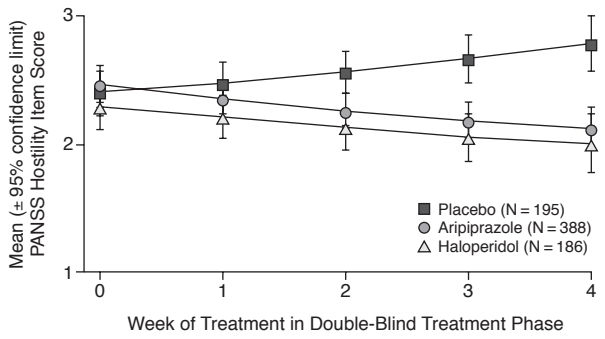
Primary Analysis

The results of the primary analysis are displayed in Figure 1. The HLM analysis indicates that the effects of aripiprazole on hostility were significantly superior to those of placebo in the overall analysis ($F = 34.25$, $df = 1,919$; $p < .0001$) and at all time points during the treatment period of 4 weeks ($p < .05$ at all time points) and that the difference between the groups tended to increase with each treatment week. These results did not change substantially when sedation and positive symptoms were used as covariates; the superiority of aripiprazole over placebo remained statistically significant during treatment weeks 2, 3, and 4.

Secondary Analysis

The results of the secondary analysis are shown in Figure 2. The analysis yielded a significant overall interaction between treatment and time ($F = 14.59$, $df = 2,568$; $p < .0001$). Post hoc analyses showed that the effects of aripiprazole and haloperidol on hostility were not significantly different from each other in the overall analysis or at any time point. The effects of aripiprazole and haloperidol were superior to those of placebo in the overall analysis. In this restricted sample, the difference between the effects of aripiprazole and placebo did not reach the level of statistical significance in the first week, but aripiprazole was significantly superior to placebo in weeks 2, 3, and 4; the difference tended to increase with each week of treatment. Haloperidol was significantly superior to placebo at all time points during the treatment period. As with the differ-

Figure 2. Change in Hostility During Treatment With Aripiprazole in 3 Short-Term, Placebo- and Active-Controlled Trials[a]



[a]The effects of aripiprazole and the active control, haloperidol, were not significantly different from each other, while both aripiprazole and haloperidol were superior to placebo. The difference between aripiprazole and placebo reached the level of statistical significance in weeks 2, 3, and 4. Haloperidol was significantly superior to placebo at all time points ($p < .05$).
Abbreviation: PANSS = Positive and Negative Syndrome Scale.

ence between aripiprazole and placebo, the difference between haloperidol and placebo tended to increase with treatment time.

When sedation and positive symptoms were used as covariates, the superiority of aripiprazole over placebo remained statistically significant during treatment weeks 3 and 4, whereas the superiority of haloperidol over placebo was statistically significant in weeks 2, 3, and 4.

DISCUSSION

We have demonstrated that the effect of aripiprazole on hostility during the first 4 weeks of treatment is superior to that of placebo and not significantly different from that of haloperidol. These short-term trial findings are important since hostile and aggressive behaviors are particularly troublesome in newly admitted patients with acute exacerbation of schizophrenia or schizoaffective disorder. Since aripiprazole clearly has a better safety profile than haloperidol,[15] it is a better choice for the treatment of hostility.

The hostility items of the PANSS[9,11] and the BPRS[16,21] have been extensively used as proxy measures to estimate potential antiaggressive effects of antipsychotics. Clinical experience as well as empirical evidence[22] indicates that increased hostility may precede overt aggression.

The antihostility effects of aripiprazole were specific in the sense that they were (statistically) independent of other positive symptoms and of sedation after the first 2 weeks of treatment. This was not true for the first 2 weeks, during which the reduction of hostility was probably mediated by the general antipsychotic effects of aripiprazole and nonspecific sedation. Early reduction of symptoms in the course of antipsychotic treatment has been attributed to nonspecific sedation,[23] and it has been reported that significant specific antipsychotic effects develop only after 2 to 3 weeks of flupenthixol treatment.[24] These and similar observations led to the delayed-onset hypothesis of antipsychotic action that has been subsequently rejected on the basis of a meta-analysis[25] and empirical observations.[26] Nevertheless, our observations suggest that the relationships between various aspects of antipsychotic response appear to vary over the course of treatment.

The study has several limitations. The patients were not selected for a history of hostile and aggressive behavior, and their baseline levels of hostility were accordingly not high. Therefore, the results may not be generalizable to seriously aggressive patients. These results should encourage a study of antiaggressive effects of aripiprazole in such patients. Furthermore, the results may not generalize to treatment-resistant patients.

The patients in the 5 studies received aripiprazole daily doses of 2 to 30 mg; pooling the results has precluded examination of a dose-response relationship. Doses of 5 to 20 mg/day of haloperidol were used; the results may not generalize to other dose regimens.

Drug names: aripiprazole (Abilify), clozapine (FazaClo and others), haloperidol (Haldol and others), risperidone (Risperdal and others).

Financial disclosure: Dr. Volavka has been a consultant to and received grant/research support from Bristol-Myers Squibb, GlaxoSmithKline, and Eli Lilly; has received honoraria from Bristol-Myers Squibb, AstraZeneca, and Eli Lilly; and has served on speakers/advisory boards of Eli Lilly and Bristol-Myers Squibb. Dr. Citrome has been a consultant to Bristol-Myers Squibb, Eli Lilly, Pfizer, and GlaxoSmithKline; has received grant/research support from Bristol-Myers Squibb, Eli Lilly, Pfizer, AstraZeneca, Janssen, and Abbott; and has received honoraria from and served on speakers/advisory boards of Bristol-Myers Squibb, Eli Lilly, Pfizer, AstraZeneca, and Abbott. Dr. McQuade is an employee of Otsuka and a major stock shareholder in Bristol-Myers Squibb. Dr. Carson is an employee of Otsuka. Dr. Kostic and Mr. Hardy are employees of Bristol-Myers Squibb. Dr. Marcus is an employee of and a major stock shareholder in Bristol-Myers Squibb. Dr. Czobor reports no other financial affiliation or relationship relevant to the subject matter of this article.

REFERENCES

1. Petrie JL, Saha AR, McEvoy JP. Aripiprazole, a new typical antipsychotic: phase 2 clinical trial result [abstract]. Eur Neuropsychopharmacol 1997;7(suppl 2):S227
2. Daniel DG, Saha AR, Ingenito G, et al. Aripiprazole, a novel antipsychotic: overview of a phase II study result [abstract]. Int J Neuropsychopharmacol 2000;3(suppl 1):S157
3. Kane JM, Carson WH, Saha AR, et al. Efficacy and safety of aripiprazole and haloperidol versus placebo in patients with schizophrenia and schizoaffective disorder. J Clin Psychiatry 2002;63:763–771
4. Potkin SG, Saha AR, Kujawa MJ, et al. Aripiprazole, an antipsychotic with a novel mechanism of action, and risperidone vs placebo in patients with schizophrenia and schizoaffective disorder. Arch Gen Psychiatry 2003;60:681–690
5. Volavka J. Neurobiology of Violence. 2nd ed. Washington, DC: American Psychiatric Publishing, Inc; 2002
6. Krakowski MI, Kunz M, Czobor P, et al. Long-term high-dose neuroleptic treatment: who gets it and why? Hosp Community Psychiatry

© COPYRIGHT 2005 PHYSICIANS POSTGRADUATE PRESS, INC.

1993;44:640–644
7. Citrome L, Nolan KA, Volavka J. Science-based treatment of aggression and agitation. In: Fishbein D, ed. The Science, Treatment, and Prevention of Antisocial Behaviors: Evidence-Based Practice. 1st ed. Kingston, NJ: Civic Research Institute, Inc; 2004:1–31
8. Volavka J, Czobor P, Nolan K, et al. Overt aggression and psychotic symptoms in patients with schizophrenia treated with clozapine, olanzapine, risperidone, or haloperidol. J Clin Psychopharmacol 2004;24:225–228
9. Citrome L, Volavka J, Czobor P, et al. Effects of clozapine, olanzapine, risperidone, and haloperidol on hostility in treatment-resistant patients with schizophrenia and schizoaffective disorder. Psychiatr Serv 2001; 52:1510–1514
10. Zito JM, Volavka J, Craig TJ, et al. Pharmacoepidemiology of clozapine in 202 inpatients with schizophrenia. Ann Pharmacother 1993;27: 1262–1269
11. Czobor P, Volavka J, Meibach RC. Effect of risperidone on hostility in schizophrenia. J Clin Psychopharmacol 1995;15:243–249
12. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull 1987;13:261–276
13. Dillenschneider A, Marcus R, Kostic D, et al. Short- and long-term effects of aripiprazole treatment on the excitement/hostility symptoms of schizophrenia [abstract]. Int J Neuropsychopharmacol 2004;7:243
14. Marcus R, Kostic D, Stringfellow J, et al. Effects of aripiprazole on excitement/hostility symptoms of schizophrenia. Presented at the 156th annual meeting of the American Psychiatric Association; May 17–22, 2003; San Francisco, Calif
15. Marder SR, McQuade RD, Stock E, et al. Aripiprazole in the treatment of schizophrenia: safety and tolerability in short-term, placebo-controlled trials. Schizophr Res 2003;61:123–136
16. Guy W. ECDEU Assessment Manual for Psychopharmacology. Rockville, Md: National Institute of Mental Health; 1976:157–169
17. Bryk AS, Raudenbush SW. Application of hierarchical linear models to assessing change. Psychol Bull 1987;101:147–158
18. Bryk AS, Raudenbush SW. Hierarchical Linear Models: Applications and Data Analysis Methods. Newbury Park, Calif: Sage Publications; 1992
19. Gibbons RD, Hedeker D, Waternaux C, et al. Random regression models: a comprehensive approach to the analysis of longitudinal psychiatric data. Psychopharmacol Bull 1988;24:438–443
20. Gueorguieva R, Krystal JH. Move over ANOVA: progress in analyzing repeated-measures data and its reflection in papers published in the Archives of General Psychiatry. Arch Gen Psychiatry 2004;61:310–317
21. Volavka J, Zito JM, Vitrai J, et al. Clozapine effects on hostility and aggression in schizophrenia [letter]. J Clin Psychopharmacol 1993;13: 287–289
22. Nolan KA, Volavka J, Czobor P, et al. Aggression and psychopathology in treatment-resistant inpatients with schizophrenia and schizoaffective disorder. J Psychiatr Res 2005;39:109–115
23. Lerner Y, Lwow E, Levitin A, et al. Acute high-dose parenteral haloperidol treatment of psychosis. Am J Psychiatry 1979;136:1061–1064
24. Johnstone EC, Crow TJ, Frith CD, et al. Mechanism of the antipsychotic effect in the treatment of acute schizophrenia. Lancet 1978;1:848–851
25. Agid O, Kapur S, Arenovich T, et al. Delayed-onset hypothesis of antipsychotic action: a hypothesis tested and rejected. Arch Gen Psychiatry 2003;60:1228–1235
26. Kapur S, Arenovich T, Agid O, et al. Evidence for onset of antipsychotic effects within the first 24 hours of treatment. Am J Psychiatry 2005;162: 939–946