Efficacy of Antipsychotic Drugs Against Hostility in the European First-Episode Schizophrenia Trial (EUFEST)

Jan Volavka, MD; Pal Czobor, PhD; Eske M. Derks, PhD; Istvan Bitter, MD; Jan Libiger, MD; René S. Kahn, MD; and W. Wolfgang Fleischhacker, MD, for the EUFEST Study Group

Objective: To compare the effects of haloperidol, amisulpride, olanzapine, quetiapine, and ziprasidone on hostility in first-episode schizophrenia, schizoaffective disorder, or schizophreniform disorder.

Method: We used the data acquired in the European First-Episode Schizophrenia Trial, an open, randomized trial (conducted in 14 countries) comparing 5 antipsychotic drugs in 498 patients aged 18–40 years with first-episode schizophrenia, schizoaffective disorder, or schizophreniform disorder. *DSM-IV* diagnostic criteria were used. Patients were assessed between December 23, 2002 and January 14, 2006. Most subjects joined the study as inpatients and then continued with follow-ups in outpatient clinic visits. The Positive and Negative Syndrome Scale (PANSS) was administered at baseline and at 1, 3, 6, 9, and 12 months after randomization. We analyzed the scores on the PANSS hostility item in a subset of 302 patients showing at least minimal hostility (a score > 1) at baseline. We hypothesized (1) that the treatments would differ in their efficacy for hostility and (2) that olanzapine would be superior to haloperidol. Our primary statistical analysis tested the null hypothesis of *no difference* among the treatment groups in change in hostility over time. Secondary analysis addressed the question of whether the effects on hostility found in the primary analysis were specific to this item. All our analyses were post hoc.

Results: The primary analysis of hostility indicated an effect of differences between treatments ($F_{4,889} = 4.02$, $P = .0031$). Post hoc treatment-group contrasts for hostility change showed that, at months 1 and 3, olanzapine was significantly superior ($P < .05$) to haloperidol, quetiapine, and amisulpride in reducing hostility. Secondary analyses demonstrated that these results were at least partly specific to hostility.

Conclusions: Both hypotheses were supported. Olanzapine appears to be a superior treatment for hostility in early phases of therapy for first-episode schizophrenia, schizoaffective disorder, and schizophreniform disorder. This efficacy advantage of olanzapine must be weighed against its adverse metabolic effects and propensity to cause weight gain.

Trial Registration: ISRCTN Register Identifier: ISRCTN68736636

J Clin Psychiatry 2011;72(7):955–961

Submitted: *August 26, 2010; accepted November 15, 2010 (doi:10.4088/JCP.10m06529).*

Corresponding author: *Jan Volavka, MD, PO Box 160663, Big Sky, MT 59716 (janvolavka@gmail.com).*

Although most schizophrenia patients are not aggressive, schizophrenia does elevate the risk for aggressive behavior.[1] Aggressive behavior in schizophrenia is a frequent reason for hospital admission. If aggression continues in the hospital, discharge is delayed. Aggression is also a major burden for caregivers and health care personnel and contributes to the stigmatization of the mentally ill. Furthermore, hostility is associated with nonadherence to medication treatment.[2] For these and other reasons, antiaggressive effects of antipsychotics have been extensively studied.

A randomized double-blind trial[3] comparing clozapine, olanzapine, and haloperidol in assaultive patients with schizophrenia or schizoaffective disorder indicated superior antiaggressive efficacy of clozapine over olanzapine, and of olanzapine over haloperidol. The superiority of clozapine was demonstrated in several previous studies.[4,5] Aggressive behavior of patients participating in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study[6] has been examined[7]; it was found that all medications used in the CATIE study (perphenazine, olanzapine, quetiapine, risperidone, ziprasidone) reduced aggressive behavior without major differences in efficacy. All these studies[3–7] were conducted mostly in long-term schizophrenia patients. We are not aware of any psychopharmacologic study of hostility specifically focused on first-episode schizophrenia.

In this article, we report analyses comparing the effects on hostility of the 5 antipsychotic drugs tested in the European First-Episode Schizophrenia Trial (EUFEST).[8,9] Empirical evidence[10] and clinical experience show that increases in hostility may precede overt physical aggression. The hostility item of the Positive and Negative Syndrome Scale (PANSS)[11] has been used extensively as a proxy measure to assess potential antiaggressive effects of antipsychotics.[4,12,13]

Specific investigation of hostility was not included in the original EUFEST study design. The decision to study hostility within the EUFEST data set was made after the principal report was published.[8] Our analyses were designed to test 2 hypotheses that were stipulated explicitly a priori in 2009: (1) the treatments will differ in their efficacy for hostility and (2) olanzapine will be superior to haloperidol.

For Clinical Use

- Olanzapine appears to be a superior treatment for hostility and aggression in first-episode schizophrenia spectrum disorders.
- The superiority of olanzapine is expressed mostly in the first 3 months of treatment.
- The efficacy advantage of olanzapine must be weighed against its propensity to cause adverse metabolic effects and weight gain.

The second hypothesis was based on a previous finding of superiority of olanzapine over haloperidol for aggression in a randomized, double-blind trial.[3]

METHOD

The European First-Episode Schizophrenia Trial was an open, randomized trial (ISRCTN Register Identifier: ISRCTN68736636) that tested the comparative effectiveness of haloperidol (1–4 mg/d; n = 103), amisulpride (200–800 mg/d; n = 104), olanzapine (5–20 mg/d; n = 105), quetiapine (200–750 mg/d; n = 104), and ziprasidone (40–160 mg/d; n = 82) in 498 patients from 14 countries who met *DSM-IV* diagnostic criteria for first-episode schizophrenia, schizoaffective disorder, or schizophreniform disorder.[8] Patients, aged 18–40 years, were assessed for eligibility between December 23, 2002, and January 14, 2006. Most subjects joined the study as inpatients and then continued with follow-ups in outpatient clinic visits. The primary outcome measure was loss of retention, also termed all-cause treatment discontinuation. Secondary measures of efficacy included the PANSS, the Clinical Global Impressions scale,[14] the Global Assessment of Functioning,[15] the Calgary Depression Scale for Schizophrenia,[16] and the Manchester Short Assessment of Quality of Life.[17] Efficacy data were collected at baseline and at 1, 3, 6, 9, and 12 months after randomization. All participants—or their legal representatives—provided written informed consent. The trial complied with the Declaration of Helsinki and was approved by the ethics committees of the participating centers. The Julius Centre for Health Sciences and Primary Care, Utrecht, The Netherlands, monitored the trial according to Good Clinical Practice and International Conference on Harmonisation guidelines.

Comparisons of the 4 second-generation antipsychotics with haloperidol showed lower risks for all-cause discontinuation for each of the 4 second-generation antipsychotics. However, symptom reductions (from baseline) at 12 months, assessed by the PANSS total score, were virtually the same in all the groups—around 60%. On the other hand, the Clinical Global Impressions scale and the Global Assessment of Functioning showed statistically significant differences among the 5 treatment arms at 12 months.

The current article focuses on the *hostility* item of the PANSS. This item is scored on a scale ranging from 1 (indicating no hostility) to 7 (indicating extreme hostility that includes manifest anger resulting in extreme uncooperativeness or in 1 or more episodes of physical assault against others). A score of 3 is assigned when the patient shows a guarded or openly distrustful attitude but interactions and behavior are minimally affected.

Statistical Procedures

Two basic approaches were adopted to analyze all available data from the sample: (1) random-regression hierarchical linear modeling (HLM), which allows the use of observations with incomplete data and (2) traditional analysis-of-covariance (ANCOVA) analysis of change over time (end-point or last-observation-carried-forward [LOCF] analysis for observed change at study end point for each subject). The HLM analysis was chosen as the primary statistical approach for the study. The ANCOVA analysis with the LOCF approach was applied for sensitivity analyses.

Specifically, longitudinal multilevel linear mixed-effects regression modeling, also termed *random-regression HLM*,[18–20] a longitudinal data-analytic approach that permits the use of observations with incomplete repeated-measures data (eg, patients who discontinue before completing the study), was adopted as the primary statistical model for the study. The HLM method, in contrast to the traditional ANCOVA, makes allowance for heterogeneity among treatment groups in terms of both initial (baseline) values and covariance structure (ie, the relationship between baseline severity and change). This technique was also used in the parent study for continuous efficacy outcomes.[8(p1090)] Our primary statistical analysis tested the null hypothesis of *no difference* among the treatment groups in change in hostility over time during the treatment period.

In the HLM analysis, change in hostility over time across study visits (ie, the primary-measure hostility score change based on the PANSS scale) served as the dependent variable. The independent factors included treatment group, time, and patient disposition (completed study or discontinued for lack of efficacy, adverse events, or nonadherence). This latter factor was included in the model since the heterogeneity of outcomes was expected to exhibit an association with the change in hostility in the trial.[21(p1032)] Our statistical approach adopted for this study is analogous to the pattern-mixture approach described by Hedeker and Gibbons,[22] which includes missing data patterns as a grouping (between-subject) variable in the analyses.

Gender and age were used as covariates in the analyses. Treatment group (the 5 different treatments) and patient disposition were applied as between-subject factors. Time (in months) from baseline served as a within-subject, random-effect factor. Country was included as a between-subject random-effect factor in the HLM model. Interactions

between the 3 independent factors were also included in the model. An unstructured covariance matrix was specified in the analyses to account for the time-structured nature of the data (serial correlations across time among assessments of efficacy). The model effects were tested by the *F* statistic. If a significant main effect or interaction involving treatment group and time 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). An α level of .05 (2-sided) was adopted for all analyses of statistical significance. The Tukey-Kramer method was used for adjustment for type I error inflation due to the multiple comparisons.

In secondary analyses, we investigated whether any group differences among treatment groups identified in the study were specific with respect to hostility or could be explained by change in severity of positive symptoms over time. For the purpose of these analyses, change in positive symptoms was introduced as a time-varying covariate in the HLM model. *Change in positive symptoms* was defined as the change in the sum of the items of the PANSS positive symptoms, excluding hostility. Accordingly, the following items were included in the computation: delusions, conceptual disorganization, hallucinatory behavior, excitement, grandiosity, and suspiciousness/persecution.

Analysis of covariance using the LOCF approach was used for sensitivity analyses. Change at each time point after baseline was applied as a dependent variable, whereas treatment group served as a principal independent variable of interest in the ANCOVA model. Similar to the primary HLM analyses, gender and age were included as covariates in the ANCOVA analyses. If a significant overall effect of treatment group was detected, post hoc analyses with the Tukey-Kramer method for correction against α inflation were performed to investigate the pairwise group differences in change over time among the treatment groups.

All analyses were based on the subsample of the modified intent-to-treat population from the parent study, who displayed a baseline hostility score of at least 2 (minimal hostility). This criterion was necessary because our initial examinations showed that many patients did not have sufficient initial severity of hostility, ie, were rated as 1 (no hostility); there was no room for improvement for these patients. All our analyses were post hoc.

The Statistical Analysis System for Windows (version 9.2; SAS Institute, Cary, North Carolina) was used for the implementation of all statistical analyses, including the HLM[23] and ANCOVA analyses.[24] The computations for these data analyses were implemented at the Department of Psychiatry and Psychotherapy, Semmelweis University, Budapest, Hungary.

A complete list of EUFEST investigators has been published elsewhere.[8]

RESULTS

Sociodemographic and clinical characteristics of the patients who had a hostility score of 2 or higher at baseline and who were therefore included in the current investigation (N = 302) are displayed in Table 1. Baseline characteristics of this population were much the same between the groups and were similar to the parent population. Mean doses of trial medications were also similar to the parent population. Patient disposition is summarized in Figure 1.

The results of our *primary* analysis of hostility change from baseline indicated an effect of differences between treatments ($F_{4,889} = 4.02$, $P = .0031$), an effect of time ($F_{1,241} = 8.16$, $P = .0047$), an effect of patient disposition ($F_{3,889} = 7.43$, $P < .0001$), and an interaction between patient disposition and treatments ($F_{12,889} = 2.49$, $P = .0032$). Interactions between time and treatments, interactions between time and patient disposition, and triple interactions between time, treatments, and patient disposition were not statistically significant.

There were no statistically significant differences in hostility between treatment arms at baseline. Post hoc treatment-group contrasts for change from baseline at each subsequent time point and for overall change will now be described. At months 1 and 3, respectively, olanzapine was superior to haloperidol ($P = .0006$; $P = .0005$), quetiapine ($P = .0017$; $P = .0009$), and amisulpride ($P = .0056$; $P = .0011$) in reducing hostility. These differences at months 1 and 3 remained statistically significant ($P < .05$) after correction for multiple comparisons, and the corrected *P* values are indicated in Figure 2.

The superiority of olanzapine over haloperidol, quetiapine, and amisulpride was only nominally significant at month 6 (ie, the results were no longer significant after correction for multiple comparisons). Differences between treatments were not statistically significant at months 9 and 12. Overall change (across the entire treatment period) favored olanzapine over haloperidol and amisulpride, but the differences were not statistically significant after correction for multiple comparisons. The time course of hostility reduction for individual treatments is displayed in Figure 2, which illustrates the faster onset of action for olanzapine.

Secondary analyses investigated whether the treatment effects on hostility were specific, ie, independent of changes in other positive symptoms. The results of secondary analyses using the sum of the PANSS positive symptoms (excluding hostility) as a covariate indicated a significant effect of differences between treatments ($F_{4,888} = 2.60$, $P = .0347$) and a significant interaction between patient disposition and treatments ($F_{12,888} = 3.12$, $P = .0002$). There was a highly significant effect of positive symptoms ($F_{1,888} = 423.93$, $P < .0001$).

Post hoc treatment-group contrasts for change of hostility from baseline showed that, at months 1 ($F_{888} = 3.08$, $P = .0184$) and 3 ($F_{888} = 3.00$, $P = .0235$), olanzapine was superior to haloperidol in reducing hostility. At months 1 and 3, olanzapine was also superior to quetiapine; this superiority was only nominally significant after correction for multiple comparisons.

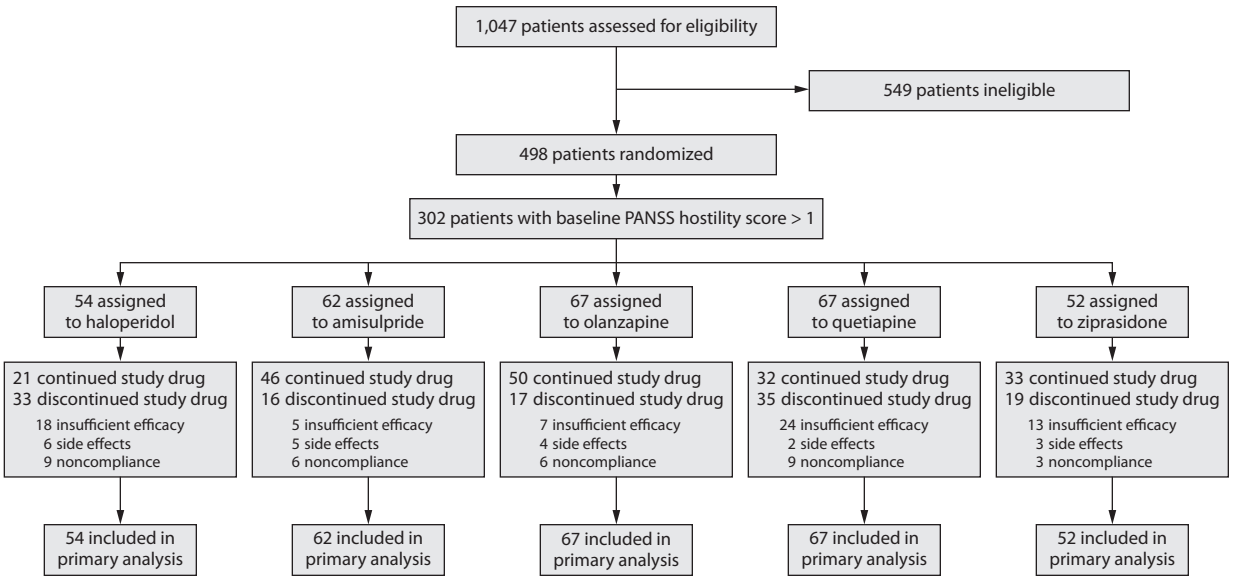
Additional post hoc analysis with correction for multiple testing indicated that the significant main effect of patient disposition was attributable to a significantly

Table 1. Sociodemographic and Clinical Characteristics of Study Participants[a,b]

Characteristic	Haloperidol (n = 54)	Amisulpride (n = 62)	Olanzapine (n = 67)	Quetiapine (n = 67)	Ziprasidone (n = 52)	Total (N = 302)
Sociodemographic characteristics						
Age, mean (SD), y	24.5 (5.4)	25.4 (5.1)	26.3 (6.1)	26.3 (5.7)	26.3 (5.5)	25.8 (5.6)
Female sex, n/N (%)	21/54 (39)	26/62 (42)	29/67 (43)	24/67 (36)	28/52 (54)	128/302 (42)
White race, n/N (%)	47/54 (87)	61/62 (98)	64/67 (96)	61/67 (91)	47/52 (90)	280/302 (93)
Years of education, mean (SD)	12.1 (2.3)	12.8 (3.1)	12.5 (3.4)	11.8 (2.8)	12.3 (2.5)	12.3 (2.9)
Diagnosis, n/N (%)						
Schizophreniform disorder	20/54 (37)	29/62 (47)	24/67 (36)	27/67 (40)	30/52 (58)	130/302 (43)
Schizoaffective disorder	0/54 (0)	3/62 (5)	5/67 (7)	6/67 (9)	4/52 (8)	18/302 (6)
Schizophrenia	34/54 (63)	30/62 (48)	38/67 (57)	34/67 (51)	18/52 (35)	154/302 (51)
Antipsychotic-naive, n/N (%)	15/54 (28)	26/62 (42)	13/67 (19)	21/67 (31)	11/52 (21)	86/302 (28)
PANSS psychopathology score, mean (SD)[c]						
Total	95.4 (20.7)	91.0 (20.3)	94.5 (17.7)	99.0 (22.0)	94.7 (18.5)	95.0 (20.0)
Positive	25.5 (5.2)	24.9 (5.9)	25.6 (5.6)	26.5 (5.9)	26.0 (4.5)	25.7 (5.5)
Negative	22.7 (8.7)	20.7 (7.1)	22.1 (6.1)	23.5 (7.2)	21.8 (9.2)	22.2 (7.6)
General	47.2 (10.1)	45.4 (11.0)	46.8 (10.0)	49.1 (12.5)	46.8 (9.3)	47.1 (10.7)
Hostility	3.1 (1.0)	3.2 (1.3)	3.3 (0.9)	3.0 (1.1)	3.2 (1.2)	3.2 (1.1)
CGI severity score, mean (SD)[d]	5.0 (0.8)	5.0 (0.8)	4.9 (0.8)	5.0 (0.9)	5.0 (0.7)	5.0 (0.8)
SHRS extrapyramidal symptom score, n/N (%)						
Akathisia	8/54 (15)	6/62 (10)	5/67 (7)	9/67 (13)	4/52 (8)	32/302 (11)
Dystonia	2/54 (4)	2/62 (3)	0/67 (0)	1/67 (1)	3/52 (6)	8/302 (3)
Parkinsonism	7/54 (13)	6/62 (10)	5/67 (7)	7/67 (10)	9/52 (17)	34/302 (11)
Dyskinesia	1/54 (2)	0/62 (0)	0/67 (0)	0/67 (0)	1/52 (2)	2/302 (1)
Dose before discontinuation of treatment, mean (SD), mg/d	3.3 (2.3)	448.4 (221.2)	11.5 (6.0)	509.7 (310.7)	96.0 (52.1)	NA

[a]For data given as n/N (%), the denominators change because of incomplete data.
[b]Analysis of variance was used to compare treatment groups on continuous variables; χ^2 test was used to compare treatment groups on categorical variables. No statistically significant difference between groups was found on any of the sociodemographic characteristics.
[c]For the PANSS, theoretical scores range from 30–210 (total scale), 7–49 (positive scale), 7–49 (negative scale), 16–112 (general psychopathology scale), and 1–7 (hostility); higher scores indicate more severe psychopathology.
[d]For the CGI, theoretical scores range from 1–7; higher scores indicate greater severity of illness.
Abbreviations: CGI = Clinical Global Impressions scale, NA = not applicable, PANSS = Positive and Negative Syndrome Scale, SHRS = St Hans Rating Scale.

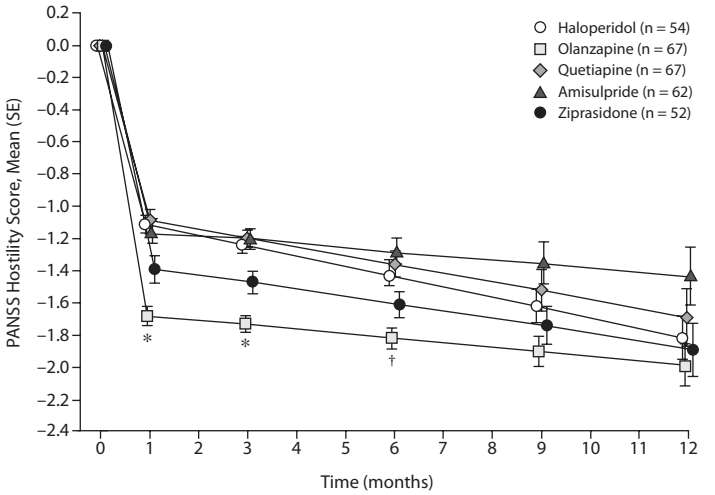
Figure 1. Flowchart of Patient Disposition in the European First-Episode Schizophrenia Trial



Abbreviation: PANSS = Positive and Negative Syndrome Scale.

greater improvement of hostility in completers as compared to patients who discontinued for lack of efficacy (Tukey-Kramer adjusted $t_{889} = 3.22$, $P = .0013$); the difference between completers and those who discontinued the study for nonadherence was marginally significant (Tukey-Kramer adjusted $t_{889} = 1.84$, $P = .067$). The estimated improvements of hostility were 1.68 (SE = 0.06) for patients who completed the study, 1.25 (SE = 0.12) for those who discontinued for lack of efficacy, 1.45 (SE = 0.18) for those who discontinued because of adverse events, and 1.59 (SE = 0.15) for those who discontinued because of nonadherence. Post hoc analysis of the interaction between patient disposition and treatment group indicated no statistically significant group difference (ie, for all Tukey-Kramer adjusted statistics $P > .05$).

Figure 2. Decrease in Hostility Over Time in the European First-Episode Schizophrenia Trial



*$P < .05$ versus haloperidol, amisulpride, and quetiapine.
†$P = .08$ versus amisulpride.
Abbreviation: PANSS = Positive and Negative Syndrome Scale.

In addition to the aforementioned analyses, we conducted a *sensitivity* analysis for our main results to examine the robustness of the findings with respect to the handling of the missing data in our primary analyses, as recommended by Schafer and Graham.[25] In particular, the primary HLM analysis was repeated with the between-subject factor "patient disposition status" omitted from the model. The result of this analysis was similar to our primary results. Specifically, the results for hostility change from baseline indicated both an effect of differences between treatments ($F_{4,904} = 3.84$, $P = .0042$) and an effect of time ($F_{1,256} = 29.93$, $P < .0001$).

The results of LOCF used for the purpose of sensitivity analysis for the first month of treatment indicated a significant effect of difference among treatments ($F = 2.46$, $P = .044$) and an effect of time ($P < .0001$). Pairwise tests showed superiority of olanzapine over haloperidol ($P = .038$) and quetiapine ($P = .004$), but the difference between olanzapine and haloperidol was not statistically significant after correction for multiple testing. There were no statistically significant effects detected by the LOCF analysis at later time points.

DISCUSSION

The results of this study indicate that, while all treatments used were successful in reducing hostility, this effect was not equal for all drugs: olanzapine was superior to haloperidol, quetiapine, and amisulpride during the first 3 months of treatment. These differences were reduced between months 3 and 6 and were no longer statistically significant in the last 6 months of the study (between months 6 and 12).

These results confirm both hypotheses that were stipulated a priori: the treatments differed in their effect on hostility, and, specifically, olanzapine was superior to haloperidol. The superiority of olanzapine over quetiapine and amisulpride had not been specifically hypothesized. Ziprasidone's efficacy against hostility, although not significantly different from any other treatment, appeared to be somewhat lower than that of olanzapine but higher than the other drugs. The effect of ziprasidone is consistent with other observations.[26]

The differences between drugs could be demonstrated for only the first 3 (or perhaps 6) months of treatment. It should be noted that, at 6 months, the average levels of hostility were already reduced to levels between 1 and 2 (minimal hostility) in all treatment arms. Further reduction would have been clinically less important and perhaps difficult to assess. In any event, faster onset of action (observed in this study for olanzapine) is an important feature for any treatment, and treatment differences in this parameter are clinically meaningful.

The results of our secondary analyses indicate a strong relationship between hostility and other positive symptoms. Nevertheless, the principal results observed in the primary analyses remained statistically significant after correction for other positive symptoms. Thus, there was still a statistically significant difference among treatments in their effect on hostility, and olanzapine was significantly superior to haloperidol in the first 3 months of treatment.

The results of primary analysis and sensitivity analyses were mutually consistent. The LOCF analysis showed a pattern of differences between medications in the early stages of treatment that was similar to that revealed by the principal analysis.

Our results are consistent with the results of one of the principal studies on which the rationale for the current analyses is based[3] but not with the results of reanalyses of the CATIE study for aggressive behavior.[7] However, the CATIE study did not investigate first-episode patients, and data on aggression specific to the 3-month time point (at which point we found the maximal differences between drugs) were not provided. A recent meta-analysis[27] did not demonstrate any difference in efficacy between first- and second-generation antipsychotics in the treatment of early psychosis. This meta-analysis apparently (1) used total scores on the PANSS or a similar scale to address symptomatic efficacy, (2) did not account for changes in time course of treatment effects, and (3) aggregated all second-generation antipsychotics into 1 group. However, in the present study, as well as in other trials,[3,4,28] effects on hostility and aggression were at least partially independent of the effects on other symptoms; significant drug differences in effects on hostility or aggression may thus occur even in the absence of effects measured by the total score on the PANSS or a similar scale. Furthermore, neither first- nor second-generation antipsychotics are a homogeneous group,[29] and aggregation of all second-generation antipsychotics into a single group for comparison with first-generation antipsychotics is not the optimal approach.[30]

This current study had some limitations. First, the EUFEST study was not originally designed for the analyses of hostility or aggression. Thus, the patients were not selected for hostile or aggressive behavior, and the baseline levels of hostility were low. Furthermore, hostility was assessed only as an item on the PANSS. No behavioral correlates, such as measures of overt aggression, were available. However, we can infer from the observed low scores on this item that overt aggression was probably infrequent. Also, there is no information about the reasons for the patients' hostility; this lack of information is a limitation since hostility and aggression in schizophrenia are etiologically heterogeneous.[31] Finally, assessments during the first month of the study were not available; these early assessments would have been helpful in terms of more exact determination of times of onset of drug action.

In summary, olanzapine appears to be a superior treatment for hostility (and, by implication, for aggression) in first-episode schizophrenia, schizoaffective disorder, and schizophreniform disorder. The superiority is mostly expressed in the first 3 months of treatment—the period when hostility and aggression are particularly difficult to control in most patients.[1] This efficacy advantage of olanzapine must be weighed against its adverse metabolic effects and propensity to cause weight gain.

Drug names: clozapine (Clozaril, FazaClo, and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal and others), ziprasidone (Geodon).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents that is outside US Food and Drug Administration–approved labeling has been presented in this article.

Author affiliations: Department of Psychiatry, New York University School of Medicine, New York, New York (Dr Volavka); Department of Psychiatry and Psychotherapy, Semmelweis University, Budapest, Hungary (Drs Czobor and Bitter); Department of Psychiatry, University Medical Center Utrecht, Utrecht, The Netherlands (Drs Derks and Kahn); Psychiatric Department and Clinic, Charles University Medical Faculty and Faculty Hospital, Hradec Králové, Czech Republic (Dr Libiger); and Department of Psychiatry and Psychotherapy, Medical University Innsbruck, Innsbruck, Austria (Dr Fleischhacker).

European First-Episode Schizophrenia Trial (EUFEST) Study Group Steering Committee: R. S. Kahn, Utrecht, The Netherlands; W. W. Fleischhacker, Innsbruck, Austria; H. Boter, Utrecht, The Netherlands; I. P. M. Keet, Amsterdam, The Netherlands; C. Brugman, Utrecht, The Netherlands; M. Davidson, Tel Hashomer, Israel; S. Dollfus, Caen, France; W. Gaebel, Düsseldorf, Germany; S. Galderisi, Naples, Italy; M. Gheorghe, Bucharest, Romania; I. Gonen, Bucharest, Romania; D. E. Grobbee, Utrecht, The Netherlands; L. G. Hranov, Sofia, Bulgaria; M. Hummer, Innsbruck, Austria; J. Libiger, Hradec Králové, Czech Republic; N. Lindefors, Stockholm, Sweden; J. J. López-Ibor, Madrid, Spain; K. Nijssen, Utrecht, The Netherlands; J. Peuskens, Leuven, Belgium; D. Prelipceanu, Bucharest, Romania; A. Riecher-Rössler, Basel, Switzerland; J. K. Rybakowski, Poznan, Poland; G. Sedvall, Stockholm, Sweden; M. von Wilmsdorff, Düsseldorf, Germany.

Financial disclosure: **Dr Volavka** has received travel support and/or speaker fees and/or consultant fees from Merck and Eli Lilly. **Dr Bitter** has been an advisory board member/consultant/lecturer for AstraZeneca, Bristol-Myers Squibb, EGIS, Eli Lilly, Janssen-Cilag, Lundbeck, and Richter and has received grant/research support from Janssen-Cilag and Lundbeck. **Dr Libiger** has received speaker honoraria, travel grants, or consultant fees from Eli Lilly, Bristol-Myers Squibb, Lundbeck, and Servier; has served on the advisory boards of Eli Lilly and Bristol-Myers Squibb; and is currently a faculty member of the Lundbeck Institute (Lundbeck Neuroscience Foundation). **Dr Kahn** has served as a consultant for, has received grants from, and/or has received honoraria for education programs from Astellas, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Gedeon Richter, Janssen-Cilag, Otsuka, Pfizer, Roche, Sanofi-Aventis, and Sunovion. **Dr Fleischhacker** has received research grants from Bristol-Myers Squibb/Otsuka, Eli Lilly, and Janssen-Cilag; has received speakers fees and honoraria for educational programs from AstraZeneca, Bristol-Myers Squibb/Otsuka, Janssen-Cilag, and Pfizer; and has served on the advisory boards of and received honoraria from AstraZeneca, Bristol-Myers Squibb/Otsuka, Janssen-Cilag, Lundbeck, MedAvante, Pfizer, Gedeon Richter, NeuroSearch, and United BioSource. **Drs Czobor** and **Derks** have no personal affiliations or financial relationships with any commercial interest to disclose relative to the article.

Funding/support: The EUFEST study was funded by the European Group for Research in Schizophrenia (EGRIS), Innsbruck, Austria, which received grants from AstraZeneca, Pfizer, and Sanofi-Aventis. These companies had no role in the study design, data collection, data analysis, data interpretation, writing of the article, or the decision to submit the article for publication.

Acknowledgment: We thank all the patients who participated in the study.

REFERENCES

1. Volavka J. *Neurobiology of Violence*. 2nd ed. Washington, DC: American Psychiatric Publishing; 2002.
2. Lindenmayer JP, Liu-Seifert H, Kulkarni PM, et al. Medication nonadherence and treatment outcome in patients with schizophrenia or schizoaffective disorder with suboptimal prior response. *J Clin Psychiatry*. 2009;70(7):990–996.
3. Krakowski MI, Czobor P, Citrome L, et al. Atypical antipsychotic agents in the treatment of violent patients with schizophrenia and schizoaffective disorder. *Arch Gen Psychiatry*. 2006;63(6):622–629.
4. Citrome L, Volavka J, Czobor P, et al. Effects of clozapine, olanzapine, risperidone, and haloperidol on hostility among patients with schizophrenia. *Psychiatr Serv*. 2001;52(11):1510–1514.
5. Zito JM, Volavka J, Craig TJ, et al. Pharmacoepidemiology of clozapine in 202 inpatients with schizophrenia. *Ann Pharmacother*. 1993;27(10):1262–1269.
6. Lieberman JA, Stroup TS, McEvoy JP, et al; Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005;353(12):1209–1223.
7. Swanson JW, Swartz MS, Van Dorn RA, et al; CATIE investigators. Comparison of antipsychotic medication effects on reducing violence in people with schizophrenia. *Br J Psychiatry*. 2008;193(1):37–43.
8. Kahn RS, Fleischhacker WW, Boter H, et al; EUFEST study group. Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. *Lancet*. 2008;371(9618):1085–1097.
9. Fleischhacker WW, Keet IP, Kahn RS; EUFEST Steering Committee. The European First Episode Schizophrenia Trial (EUFEST): rationale and design of the trial. *Schizophr Res*. 2005;78(2–3):147–156.
10. 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(1):109–115.
11. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13(2):261–276.
12. Volavka J, Czobor P, Citrome L, et al. Efficacy of aripiprazole against hostility in schizophrenia and schizoaffective disorder: data from 5 double-blind studies. *J Clin Psychiatry*. 2005;66(11):1362–1366.
13. Czobor P, Volavka J, Meibach RC. Effect of risperidone on hostility in schizophrenia. *J Clin Psychopharmacol*. 1995;15(4):243–249.
14. Guy W. Clinical Global Impressions (CGI) scale. In: Rush AJ Jr, Pincus HA, First MB, et al, eds. *Handbook of Psychiatric Measures*. Washington, DC: American Psychiatric Association; 2000:100-102
15. Jones SH, Thornicroft G, Coffey M, et al. A brief mental health outcome scale—reliability and validity of the Global Assessment of Functioning (GAF). *Br J Psychiatry*. 1995;166(5):654–659.
16. Addington D, Addington J, Maticka-Tyndale E, et al. Reliability and validity of a depression rating scale for schizophrenics. *Schizophr Res*. 1992;6(3):201–208.
17. Priebe S, Huxley P, Knight S, et al. Application and results of the Manchester Short Assessment of Quality of Life (MANSA). *Int J Soc Psychiatry*. 1999;45(1):7–12.
18. Bryk AS, Raudenbush SW. Application of hierarchical linear models to assessing change. *Psychol Bull*. 1987;101(1):147–158.
19. Bryk AS, Raudenbush SW. *Hierarchical Linear Models: Applications and Data Analysis Methods*. Newbury Park, CA: Sage Publications; 1992.
20. 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(3):438–443.
21. Mazumdar S, Tang G, Houck PR, et al. Statistical analysis of longitudinal psychiatric data with dropouts. *J Psychiatr Res*. 2007;41(12):1032–1041.
22. Hedeker D, Gibbons RD. Application of random-effects pattern-mixture models for missing data in longitudinal studies. *Psychol Methods*. 1997; 2(1):64–78.
23. Littel RC, Milliken GA, Stroup WW, et al. *Heterogeneous Variance Models: SAS System in Mixed Models*. 2nd ed. Cary, NC: SAS Institute; 2006:343–411.
24. Littel RC, Milliken GA, Stroup WW, et al. *Analysis of Covariance: SAS System for Mixed Models*. 2nd ed. Cary, NC: SAS Institute; 2006:243–315.
25. Schafer JL, Graham JW. Missing data: our view of the state of the art. *Psychol Methods*. 2002;7(2):147–177.
26. Citrome L, Volavka J, Czobor P, et al. Efficacy of ziprasidone against hostility in schizophrenia: post hoc analysis of randomized, open-label study data. *J Clin Psychiatry*. 2006;67(4):638–642.
27. Crossley NA, Constante M, McGuire P, et al. Efficacy of atypical v. typical antipsychotics in the treatment of early psychosis: meta-analysis. *Br J Psychiatry*. 2010;196(6):434–439.
28. Volavka J, Zito JM, Vitrai J, et al. Clozapine effects on hostility and aggression in schizophrenia. *J Clin Psychopharmacol*. 1993;13(4):287–289.
29. Leucht S, Corves C, Arbter D, et al. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *Lancet*. 2009;373(9657):31–41.
30. Volavka J. Are all antipsychotics equal? *Lancet*. 2008;372(9634):201–202, author reply 202.
31. Volavka J, Citrome L. Heterogeneity of violence in schizophrenia and implications for long-term treatment. *Int J Clin Pract*. 2008;62(8): 1237–1245.

For the CME Posttest for this article, see pages 1021–1022.