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Hostility in schizophrenia: An integrated analysis of the combined Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) and the European First Episode Schizophrenia Trial (EUFEST) studies

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Abstract

Phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study enrolled a sample of 1493 chronic schizophrenia patients. The European First Episode Schizophrenia Trial (EUFEST) enrolled 498 patients. We have combined these two samples to study the effects of hostility on study discontinuation as well as to examine correlates and predictors of hostility. Individual data from 1154 patients with complete data were used for analyses. Survival analysis demonstrated that higher hostility was associated with earlier all-cause treatment discontinuation. Furthermore, regression analysis indicated that increased hostility was associated with more severe positive symptoms, lower adherence to pharmacological treatment, younger age, impaired insight, and more drug or alcohol consumption. The clinical implications of the results point to the importance of establishing therapeutic alliance while managing patient's symptoms of hostility with antipsychotics such as olanzapine combined with psychosocial interventions to improve insight and reduce substance use.

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Disclosure of interest

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Keywords

Schizophrenia; Antipsychotics; Hostility

1. Introduction

Hostility, broadly defined, involves unfriendly attitudes that are manifested by overt behaviors including irritability, anger, resentment, or aggression. Its narrower operational definition is provided by clinical rating scales, including, for example, the Positive and Negative Syndrome Scale (PANSS) [20], which classifies the construct as a positive symptom. Hostility is negatively related to the quality of life in schizophrenia [12], and its clinical importance is reflected by the large number of pharmacological studies using hostility as the principal treatment target [37]. Clozapine and olanzapine are particularly effective in treating hostility and aggression in schizophrenia [5]. However, the relevance of hostility to medication adherence or treatment discontinuation has not been studied extensively.

Stopping or changing medication is a problem limiting the effectiveness of schizophrenia treatment. As defined by Lieberman et al. in the CATIE study, treatment discontinuation for any cause “integrates patients’ and clinicians’ judgments of efficacy, safety, and tolerability into a global measure of effectiveness that reflects their evaluation of therapeutic benefits in relation to undesirable effects” [24]. Currently, treatment discontinuation is used widely to assess real-world effectiveness of antipsychotic treatment [18].

On the one hand, positive therapeutic relationships between patients and professionals may improve the chances that patients will evaluate treatment as effective, thus increasing the likelihood of treatment continuity [22], including when there are concerns about the efficacy, safety, or tolerability of medication regimens. Negative therapeutic relationships, on the other hand, including patient’s hostility, would be expected to impair treatment continuity. This hypothesis was supported by findings indicating that psychological treatment for early psychosis can be beneficial or harmful, depending on therapeutic alliance [14].

A recent study explored the prevalence, incidence, and predictors of hostility in a 3-year observational study of antipsychotic treatment in 10,189 schizophrenia patients [28]. Results indicated that younger age, male sex, alcohol/substance abuse, tardive dyskinesia, extrapyramidal symptoms, cognitive impairment, and nonadherence to treatment were associated with hostility during follow-up. Results from this study indicate that hostility may be an important mechanism affecting treatment outcomes in patients with schizophrenia.

The purpose of the present study was to examine the effects of hostility on treatment discontinuation as well as to investigate relationships between clinical variables and hostility in schizophrenia patients in pooled data. The opportunity for the study was provided by the availability of data from two large controlled treatment trials: the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) [24], and the European First Episode Schizophrenia Trial (EUFEST) [17]. Our approach to the pooled data can be seen as a patient-level meta-analysis. In general, the rationale for a pooled analysis is that it includes

more patients, thus reducing the chances that it is underpowered. This yields more robust and valid findings [16]. Furthermore, pooling data increase patient heterogeneity, which makes the results more generalizable. The rationale is similar to our prior study, which analyzed the CATIE and EUFEST pooled data for predictors and correlates of adherence to treatment and the effect of adherence on treatment discontinuation [7]. We now present results of analyses focusing on hostility. Aim 1 of the study was to investigate whether discontinuation of study medication was associated with the severity of hostility. Aim 2 was to examine predictors and correlates of hostility.

2. Methods

Here, we present a brief review of the methods; a more detailed overview can be found elsewhere [7].

2.1. CATIE

Phase 1 of the CATIE recruited 1493 patients with schizophrenia who were randomly assigned to double-blind treatment with olanzapine, perphenazine, quetiapine, risperidone, or ziprasidone for up to 18 months. [24]. *Hostility* and *lack of judgment and insight* were assessed with the PANSS [19] at baseline and at months 1, 3, 6, 9, 12, 15, and 18. The hostility item's score range is 1–7. A Hostility item score of 1 indicates “no hostility”, whereas the highest ratings of 6 (“severe”) or 7 (“extreme”) may denote physical aggression. The *Lack of judgment and insight* item on the PANSS also is scored on a scale ranging from 1 (no impairment of insight of psychiatric illness) to 7 (emphatic denial of past and present psychiatric illness).

We used the monthly pill count as the measure of *adherence* in our analyses. In order to harmonize the CATIE and EUFEST data, where in the latter study, adherence was measured on a 7-point scale, we transformed the CATIE pill count measure by subdividing the full range (0–100%) of the continuous measure into a 7-point scale [21]. We used this measure to characterize mean % adherence for the first six months. *Extrapyramidal side effects* were assessed using the Simpson-Angus Scale [30], Barnes Akathisia Scale [4], and the Abnormal Involuntary Movement Scale [8]. For analyses, a dichotomous variable (absent vs. present) was created for each of the extrapyramidal side effects.

Substance use and abuse were investigated via multiple sources of information. For analytic purposes, a dichotomous variable (no use vs. any use) was created and assessed at baseline and then quarterly [36]. All-cause treatment discontinuation was the primary outcome variable to assess effectiveness [24]. *Discontinuation* was defined as stopping or changing medication for any cause.

2.2. EUFEST

EUFEST was a randomized, open trial comparing the effectiveness of amisulpride, haloperidol, olanzapine, quetiapine, and ziprasidone in 498 patients with a first episode of schizophrenia, schizoaffective disorder, or schizophreniform disorder [11,17]. *Hostility and insight* scoring used the PANSS items as described above. *Adherence* was assessed at the end of the first six months using a one-item, 7-Point Rating Scale where complete refusal of

treatment (equivalent to discontinuation) is scored as 1, and ready acceptance of treatment is scored as 7 [21]. *Extrapyramidal syndromes* (parkinsonism, akathisia and dyskinesia) were assessed using the St. Hans Rating Scale [13]. Analogous to the CATIE, a dichotomous variable (absent vs. present) was created for each extrapyramidal side effect.

Alcohol and substance abuse/dependence were examined using the Mini-International Neuropsychiatric Interview (MINI); the MINI-Plus version was used [29]. This resulted in a dichotomous variable (alcohol and substance abuse/dependence, yes or no). Unlike CATIE, use of alcohol or substances was not captured by this variable unless it reached the level of abuse or dependence. Data on all assessments were available at a minimum of three time points: at baseline, 6 months, and 12 months (data at 3 and 9 months were also available for some assessments). We are presenting a six-month prospective study.

The primary outcome measure was all-cause treatment discontinuation. *Discontinuation* was defined as stopping or changing medication, the use of dose outside of the predefined range, or the use of any parenteral antipsychotic drug when the drug was active for more than 14 days over 6 months.

The CATIE and EUFEST studies were approved by the Institutional Review Boards of participating institutions.

2.3. Statistical analyses

The purpose of the statistical analyses was twofold:

- to investigate whether all-cause-discontinuation of the trial was associated with the severity of hostility (aim 1);
- to examine predictors and correlates of hostility (aim 2).

For both purposes, we used concurrent and prospective statistical models in order to test the associations. For the models of concurrent associations, the dependent and independent (i.e. regressor) variables were assessed in the same time period in the study; for the prospective models, the assessment of predictors was performed at baseline. We note that that term “independent variable” in the concurrent models is used in the statistical sense, and should not be interpreted as reflecting a potentially causative factor (predictor).

The primary analysis was based on the combined sample of CATIE and EUFEST samples. In secondary analyses, we examined the CATIE and EUFEST samples separately in order to examine the heterogeneity of the results with regard to the study.

We used Kaplan-Meier (K-M) survival analysis to investigate the association between all-cause discontinuation of the study medication to which the patient had been originally randomized (including discontinuation of the study itself) and the severity of hostility (aim 1). For the analysis of all-cause discontinuation, patients’ observation period ended when they discontinued the medication due to any reason or completed the trial. Patients who did not discontinue the study prior to the 6-month assessment (“completers” for our 6-month analytic window) were considered censored at the end of the observation period. For all non-censored observations, time to discontinuation was defined as the time elapsed from the first

dose of study medication to the premature discontinuation of the medication. For censored observations, time to discontinuation was defined as the time elapsed from the first dose of study medication to the end of our 6-month observation period. In the survival analysis, time to all-cause discontinuation was applied as the dependent variable. The set of independent variables was identical to the one used in the logistic regression analyses, including the clinical and basic demographic variables and an indicator of study, as described below.

Predictors and correlates of hostility (aim 2) were examined via multivariable logistic regression analyses with hostility as the dependent variable. Concurrent and prospective models were used. The strength of the association between the dependent and an independent variable was measured by the odds ratio (OR) statistic, which characterized the independent (partial) contribution of each of the independent variables of interest to the dependent variable hostility.

We note that since we wanted to investigate the association between nonadherence and hostility, the variable Adherence was reverse-coded for the logistic regression analyses (i.e., the values were reverse-coded, e.g., a value of 1 became 7). Accordingly, an OR with a value of > 1 shows that nonadherence is associated with an increased likelihood of hostility.

The set of principal independent variables comprised clinical and demographic variables. The clinical variables included: hostility and lack of judgment and insight (as measured by the PANSS); alcohol and substance use; extrapyramidal adverse effects including akathisia, parkinsonism and dyskinesia. Furthermore, symptom severity on the PANSS Positive Subscale (excluding the hostility item) was also included since we wanted to investigate whether an association between medication nonadherence and hostility was specific to hostility with regard to positive symptoms. Since the side effects were rated by different scales in the two studies, we used them as dichotomous variables in order to increase between-study comparability (a score of 1 was assigned to the variable with a non-zero entry; otherwise, the value of 0 was used).

The demographic variables included in the analyses were age and sex. Furthermore, Study (i.e., CATIE or EUFEST) was applied as an additional fixed-effect covariate in order to account for the between-study heterogeneity. In the prospective analyses, the assessment of predictors occurred at baseline; for the concurrent associations, both the dependent and the independent variables represented the first 6 months. In the investigation of the concurrent association, we focused on the first 6-month period since we wanted to maximize statistical power and limit the impact of missing data.

To check for bias due to missing data, we compared the subset of patients with complete data who were included in the primary analyses ($n = 1154$) with the subset excluded from the analyses because of missing data ($n = 804$). Significance level was set at $\alpha = .05$ (two-tailed). For the regression analyses, we used the Hochberg procedure for statistical adjustment to avoid inflation of Type 1 error due to multiple comparisons. All analyses were carried out using the Statistical Analysis System (SAS) version 9.4 (SAS Institute, Cary, NC).

3. Results

3.1. Sample characteristics

Baseline sociodemographic and psychopathological characteristics of the 1154 patients whose complete data were available are summarized in Table 1. Contrasting comparable items in the CATIE and EUFEST subsets at baseline, we observe that the CATIE patients were older and generally less symptomatic. These differences reflect the expected disparities between the long-term (CATIE) and first episode (EUFEST) patients.

3.2. Effect of hostility on treatment discontinuation

Although data were available for 12 months for both CATIE and EUFEST, hostility was so reduced after the first 6 months (particularly in the EUFEST study) that the joint analyses became futile. Therefore, only data and analyses up to the first 6 months are presented.

Survival analysis based on the non-parametric K-M approach demonstrated that higher hostility observed after baseline but before discontinuation was associated with earlier treatment discontinuation in the concurrent model during the first six-month treatment period. That is, the difference in the K-M survival curves according to hostility stratum was significant ($P < 0.0001$) in the pooled concurrent analysis. Separate analyses for the two samples showed that the direction of the difference of the survival curves was similar in both studies, with a Type I error of $P < 0.0001$ for the CATIE and $P = 0.17$ for the EUFEST study, respectively. The association is demonstrated on Fig. 1, which displays the K-M survival curves for the pooled concurrent analysis and separately for the CATIE and EUFEST studies.

When the baseline data were included in the model as predictors of discontinuation, the analysis failed to yield statistically significant results.

3.3. Analyses of hostility correlates and predictors

The results of the concurrent analysis of hostility are summarized in Table 2. This was a cross-sectional analysis: all data were collected at 6 months in both studies. Data collected at baseline were not used as predictors of hostility in these analyses. Positive symptoms (excluding hostility), lower adherence, younger age, impaired insight and substance use, were significantly related to hostility. However, lack of judgment and insight as well as substance use failed to maintain statistical significance after correction for multiple testing. The statistical significance of the study effect (CATIE vs. EUFEST) reflects the higher levels of hostility in the EUFEST study (see Table 1).

Results from the prospective analysis of hostility at 6 months are shown in Table 3. Data collected at baseline were used as predictors of hostility at 6 months. Hostility at baseline, positive symptoms, substance use, and younger age predicted hostility at 6 months. However, substance use and age failed to maintain statistical significance after correction for multiple testing. The comparisons of the missing and non-missing data are in the supplementary Table.

4. Discussion

4.1. Hostility and treatment discontinuation

The main conclusion of the study is that patient hostility predicts treatment discontinuation. As far as we know, this has not been previously reported. However, this finding is consistent with a report showing that lower persistence with antipsychotic treatment over a one-year period was associated with less positive relationships between patients and clinical staff [34]. Similarly, a topic review on medication nonadherence has concluded that a poor patient–physician relationship contributes to nonadherence [26].

Although we observed an association between hostility and treatment discontinuation, current data do not allow inferences regarding the potential for a causal mechanism. However, observations of treatment effects point to the possibility of common mechanisms shared by hostility and treatment discontinuation. We note that the patients assigned to olanzapine had the lowest all-cause rates of treatment discontinuation in both the CATIE [24] and EUFEST [17] studies. Furthermore, separate analyses indicated that olanzapine reduced hostility more than other treatments in both trials [39,40]. These effects on hostility were (statistically) independent of the effects on positive symptoms other than hostility, and in this sense were specific. Thus, it is possible that the effect of olanzapine on treatment persistence was mediated by its anti-hostility action. In other words, some patients were perhaps able to stay longer on their assigned medication because olanzapine reduced their hostility. A test of this hypothesis would require an experimental design different from both the CATIE and EUFEST studies.

The implications of our findings on treatment discontinuation and hostility point to the importance of therapeutic alliance between professionals and patients and their families, as pointed out by Goldsmith et al. [14]. Clinicians should convey a trusting, helpful, and respectful attitude in all communication with patients and families. It is important to learn about the patients' and families' attitudes to illness and to care, to respect and validate their feelings, and thus to show empathy. Respecting salient cultural issues is a necessary prerequisite to effective therapeutic alliance.

4.2. Hostility correlates and predictors

Our results showed a significant concurrent relationship between reduced medication adherence and hostility, consistent with the report by Ochoa et al. [28] that used a much larger subject sample and different assessment methods. Our findings have potential implications for better understanding, and eventually reducing community-based violence perpetrated by adults with severe mental illness, including schizophrenia. In the CATIE study, patients' medication adherence was associated with reduced violence, but this effect was limited to patients with no history of childhood antisocial conduct [32]. A prospective study of 229 individuals with schizophrenia spectrum disorders has demonstrated a reduction of violence attributable to consistent adherence to atypical antipsychotics over a 2-year period [31]. In 332 individuals with severe mental illness, the combination of medication nonadherence and alcohol or substance abuse problems was associated with serious violent acts in the community [33]. Increases in the severity of community violence

were associated with medication nonadherence in forensic psychotic patients, and this relationship was independent of poor insight [1]. Greater level of hostility was found to be a significant risk factor for impaired adherence in a study of 599 patients with schizophrenia or schizoaffective disorder [25]. We reported strong relationships between nonadherence and hostility in analyses of the EUFEST and CATIE that used nonadherence as the dependent variable [7]. Thus, hostility and violence are associated with nonadherence to antipsychotic medication.

We have demonstrated that alcohol and/or drug use is concurrently associated with hostility, and also predicts its presence in the future (although this latter finding lost statistical significance after correction for test multiplicity). These findings are consistent with those reported by others [28]. Comorbid substance use disorders are frequent in schizophrenia [15]. Criminal violence by schizophrenia patients is largely (but not completely) attributable to substance abuse comorbidity [10].

We observed a significant relationship between impaired judgment and insight and hostility in the concurrent analyses, although the statistical significance was lost after correction for multiple comparisons. Similar relationships were observed by many other authors [1–3,9,23].

Our results showed that positive symptoms (with the hostility item excluded) were associated with concurrent and future hostility. The concurrent (cross-sectional) association is consistent with a similar result reported by Ochoa et al. [28]. In a study of chronic schizophrenia inpatients, positive symptom scores (on the PANSS) were significantly higher during the three days preceding an aggressive incident in comparison with inpatients without an incident [27]. Delusions are related to aggressive behavior, and this relationship is mediated by anger [6,35], which is a feature of hostility.

Finally, as expected, we found that younger age increased risk for higher hostility. This is consistent with the results of Ochoa et al. [28]. Younger age is a well-known risk factor for aggression [38]. We detected no significant relationship between patient sex and hostility. Furthermore, we were unable to replicate the reported relationship between hostility and extrapyramidal symptoms [28]. Differences in sample sizes, assessment methods, and patient selection may have been responsible for this apparent discrepancy.

4.3. Limitations and strengths of the study

Our study has certain limitations. First, neither the CATIE nor EUFEST studies were designed to examine hostility. Thus, the patients were not selected for hostility, and its levels were quite low across the pooled data. Second, although certain cross-sectional and predictive associations were observed, conclusions about causality cannot be inferred. Third, there were differences between CATIE and EUFEST in the assessment methods for alcohol and drug use, treatment adherence, and extrapyramidal symptoms. Although measures were harmonized to the extent possible, the differences in the assessment methods may have confounded the outcomes. Fourth, the definition of discontinuation in the EUFEST (but not in the CATIE) included usage of doses outside of the predefined range or usage of parenteral long-acting antipsychotics. This discrepancy of the definitions of discontinuation may have

contributed to the differences between the survival curves of the two studies apparent on Fig. 1. Furthermore, both studies used very broad definitions of discontinuation, including events like patient self-ceasing medication, adherent patients for whom switches are advised by doctors due to poor response, and other scenarios. Finally, our results may have been biased due to missing data.

Our study also has several strengths. First, the sample size was larger than in most other studies of this topic. Second, rating scales with known psychometric properties were employed for most of the assessments.

5. Conclusions

Treatment discontinuation, a major challenge in the management of schizophrenia, is linked to patient hostility. The nature of that link is not clear. However, hostility is a modifiable factor. Pharmacological and psychosocial approaches to reduce hostility are available.

Hostility in schizophrenia can arise through multiple pathways. Alcohol and drug use, impaired insight, low adherence to treatment, and positive symptoms are dynamic, modifiable variables that are associated with hostility in schizophrenia, and might have a causal role in its development and maintenance.

The clinical implications of the results point to the importance of detection and management of hostility, as well as to the treatment of comorbid substance use disorders. Systematic attention to the patient's adherence to treatment is particularly important in patients showing inadequate response. Insight of mental illness should be routinely assessed in schizophrenia patients, and interventions such as psycho-education should be initiated as needed. Finally, the establishment and maintenance of therapeutic alliance with the patient and their treatment-involved family members is of utmost importance. Summing up the available evidence, hostility arising from symptoms of schizophrenia or from other sources is an important impediment of treatment. Therapeutic alliance and appropriate antipsychotic medication work together to deal with the problem.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.eurpsy.2015.10.003>.

Biographies

Dr. Volavka is Professor Emeritus of Psychiatry at New York University. He was born and educated in Prague, Czechoslovakia. In 1968, he moved to the United States and was a faculty member at New York Medical College, University of Missouri, and New York University. His research has been focused on violence, schizophrenia, and psychopharmacology.

Dr. Citrome is Clinical Professor of Psychiatry & Behavioral Sciences at New York Medical College in Valhalla, NY, and has a private practice in Pomona, NY. He is a member of the Board of Directors of the American Society of Clinical Psychopharmacology. He graduated from the McGill University Faculty of Medicine and completed a Residency and Chief Residency in Psychiatry at the New York University School of Medicine, and went on to complete a Masters in Public Health at Columbia University. He is the author/co-author of over 400 published research reports, reviews, and book chapters in the scientific literature.

Prof. W. Wolfgang Fleischhacker is a certified psychiatrist and psychotherapist.

He received his medical degree and professional training at Innsbruck University and spent 18 months as a research fellow at Hillside Hospital in New York.

Dr. Fleischhacker is a co-editor/member of the editorial boards of several peer-reviewed journals. Research Interests: Dr. Fleischhacker's main research interests relate to schizophrenia and psychopharmacology. They have led to participation in WHO and WPA programs. Memberships: Chairman of the EGRIS, Fellow of the CINP; Fellow of the ACNP, Fellow of the ECNP. Member of the SIRS and the Austrian Society of Psychiatry and Psychotherapy.

Dr. Van Dorn is currently Principal Investigator of three National Institutes of Health grants (R03MH103477, R01MH093426, R34DA036791). He has been involved in clinical research at the interface of psychopharmacological medications, adherence, and relevant outcomes for adults with serious mental illnesses for the past 10 years. My core interests are at the intersection of medication effectiveness, clinical interventions, and criminal justice-related outcomes for adults with mental illness, including how to more effectively analyze data to better influence practice and policy.

Pál Czobor Ph.D. is Associate Professor and Director of Research at Semmelweis University Department of Psychiatry and Psychotherapy, Budapest. He graduated from Eötvös Lóránd University, Faculty of Natural Science in Budapest, Hungary. He spent 12 years as a full-time research scientist at the Nathan Kline Institute for Psychiatric Research, Orangeburg, New York. His principal areas of interest include biostatistics, clinical trial design, psychopharmacology and electrophysiology.

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Fig. 1.

Time to discontinuation of study as a function of hostility during the first 6 months. Kaplan-Meier (K-M) analysis of survival probabilities. For the K-M analysis, the PANSS hostility item with a score range of 1–7 was used, and the symptom ratings took place after baseline but before the time of discontinuation. The relationship between the severity of hostility and the K-M survival curves was significant ($P < 0.0001$) in the pooled concurrent analysis, and the direction of the relationship was similar in both studies ($P < 0.0001$ and $P = 0.17$ for the CATIE and the EUFEST studies, respectively). For the purpose of illustration of the direction of the relationship, the K-M curves are displayed in the Figure for two strata of hostility: “low hostility” (hostility score ≤ 2) and “high hostility” (hostility score ≥ 3).

Table 1

Basic demographic and clinical characteristics of the study sample at baseline^a.

Characteristics Categorical variables n (%)	Study		CATIE vs. EUFEST	
	Pooled n = (1154)	CATIE (n = 851)	EUFEST (n = 303)	Chi ² P
Demographic				
Male, number (%)	803 (69.6)	629 (73.9)	174 (57.4)	28.7 < .0001
Continuous variables Mean (SD)				F P
Mean age, y	37.2 (11.8)	41.2 (11.0)	26.1 (5.5)	524.4 < .0001
PANSS				
Total Score	78.0 (19.1)	74.5 (17.3)	87.9 (20.3)	121.9 < .0001
Positive subscale	19.4 (6.1)	18.0 (5.5)	23.2 (6.0)	195.4 .0001
Negative subscale	20.3 (6.8)	20.1 (6.5)	20.8 (7.4)	2.34 .1366
General psychopathology	38.4 (10.0)	36.5 (9.0)	43.9 (10.7)	135.1 < .0001
Hostility item	1.9 (1.1)	1.7 (1.0)	2.3 (1.3)	2.27 .1400
Insight item	3.1 (1.4)	2.8 (1.3)	3.9 (1.4)	137.9 < .0001

CATIE: Clinical Antipsychotic Trials of Intervention Effectiveness; EUFEST: European First Episode Schizophrenia Trial; PANSS: Positive and Negative Syndrome Scale.

^aChi² test for categorical, ANOVA for continuous variables.

Table 2

Concurrent logistic regression for hostility at six months. All data were collected at 6 months in both studies.

Independent variables (regressors)	Odds ratio (OR) for higher hostility ^c	95% confidence interval	Chi ² (<i>n</i> = 1154, <i>df</i> = 1)	<i>p</i> ^d
Alcohol/drugs at 6 months ^a	1.509	1.005–2.265	3.94	0.047
Insight at 6 months	1.132	1.019–1.259	5.30	0.021
Adherence at 6 months	0.834	0.751–0.927	11.37	0.0007
Akathisia at 6 months	1.231	0.867–1.750	1.35	n.s.
Parkinsonism at 6 months	0.757	0.551–1.041	2.94	n.s.
Dyskinesia at 6 months	1.089	0.757–1.565	0.21	n.s.
Positive symptoms at 6 months ^b	1.225	1.187–1.263	166.6	<0.0001
Study (CATIE vs. EUFEST)	0.510	0.348–0.748	11.89	0.0006
Age	0.982	0.971–0.995	8.10	0.004
Male gender	0.842	0.646–1.099	1.60	n.s.

CATIE: Clinical Antipsychotic Trials of Intervention Effectiveness; EUFEST: European First Episode Schizophrenia Trial; PANSS: Positive and Negative Syndrome Scale; n.s.: not significant.

^a Any use, combined.

^b PANSS positive symptoms excluding hostility.

^c OR > 1 and OR < 1, respectively, indicate increased or decreased hostility.

^d *P*-values in bold remain significant after Hochberg's correction for multiple testing.

Table 3

Predictive logistic regression for hostility at six months.

Independent variables	Odds ratio (OR) higher for hostility ^c	95% confidence interval	Chi ² (<i>n</i> = 1154, <i>df</i> = 1)	<i>P</i> ^d
Alcohol/drugs at a baseline ^a	1.332	1.062–1.671	6.16	0.013
Insight at baseline	0.972	0.897–1.054	0.46	n.s.
Hostility at baseline	1.946	1.760–2.152	169.31	<0.0001
Akathisia at baseline	0.870	0.679–1.115	1.21	n.s.
Parkinsonism at baseline	1.219	0.967–1.537	2.80	n.s.
Dyskinesia at baseline	1.044	1.793–1.374	0.09	n.s.
Positive symptoms at baseline ^b	1.051	1.028–1.074	19.42	<0.0001
Study (CATIE vs. EUFEST)	0.163	0.116–0.228	110.02	<0.0001
Age	0.988	0.977–0.998	5.33	0.021
Male gender	1.042	0.825–1.316	0.12	n.s.

CATIE: Clinical Antipsychotic Trials of Intervention Effectiveness; EUFEST: European First Episode Schizophrenia Trial; PANSS: Positive and Negative Syndrome Scale; n.s.: not significant.

^a Any use, combined.

^b PANSS positive symptoms excluding hostility.

^c OR > 1 and OR < 1, respectively, indicate increased or decreased hostility.

^d *P*-values in bold remain significant after Hochberg's correction for multiple testing.