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Treatment adherence in schizophrenia: A patient-level meta-analysis of combined CATIE and EUFEST studies

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Abstract

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) obtained a sample of 1493 chronic schizophrenia patients. The European First Episode Schizophrenia Trial (EUFEST) studied a sample of 498 patients. We have combined these two samples to study the predictors and correlates of adherence to treatment. Here we report on adherence to pharmacological treatment at the six and twelve month assessments of these trials with a combined subsample of 1154 schizophrenia patients. Individual patients' data were used for analyses. We used logistic regression to examine the effects of substance use, akathisia, parkinsonism, dyskinesia, hostility,

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Contributors

RSK and WWF had a leading role in the design of the EUFEST study; RAVD had a key contribution to prior analyses of the CATIE study. JV, PC, RAVD, and LC developed the study concept, and designed the analyses. PC and JV analyzed the data. All authors contributed to the interpretation of the results. JV and PC drafted the report. PC and JV prepared the tables and figures. All authors participated in the critical revision of the manuscript, and approved the final version.

Conflict of interest

PC reports no conflict of interest.

RAVD reports no conflict of interest.

LC has engaged in collaborative research with, or received consulting or speaking fees, from: Actavis (Forest), Alexza, Alkermes, AstraZeneca, Avanir, Bristol-Myers Squibb, Eli Lilly, Forum, Genentech, Janssen, Jazz, Lundbeck, Merck, Medivation, Mylan, Novartis, Noven, Otsuka, Pfizer, Reckitt Benckiser, Reviva, Shire, Sunovion, Takeda, Teva, and Valeant.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.euroneuro.2015.04.003>.

and insight on pharmacological adherence. The results showed that reduced adherence to pharmacological treatment was associated with substance use ($p=0.0003$), higher levels of hostility ($p=0.0002$), and impaired insight ($p<0.0001$). Furthermore, poor adherence to study medication was associated with earlier discontinuation in the combined data. The clinical implications of the results point to the importance of routine assessments and interventions to address patients' insight and comorbid substance use and the establishment of therapeutic alliance.

Keywords

Schizophrenia; Antipsychotic; Adherence; Compliance; Insight; Hostility

1. Introduction

Adherence to medication treatment is critically important for its effectiveness. Non-adherence to antipsychotic treatment increases the risk of hospitalization (Weiden et al., 2004), substance use, violent behavior, arrests, victimization, and other adverse outcomes in patients with schizophrenia (Ascher-Svanum et al., 2006a). Partial non-adherence to medication treatment also increases the likelihood of complete treatment discontinuation (Lindenmayer et al., 2009). Estimates of frequency and extent of non-adherence vary with the assessment methods (Velligan et al., 2003, 2009a). In general, approximately 50% of schizophrenia patients do not fully adhere to treatment (Perkins, 2002).

The association between *insight* and medication adherence was examined in the CATIE data (Mohamed et al., 2009). Insight was assessed using the Insight and Treatment Attitudes Questionnaire (ITAQ) (McEvoy et al., 1989). Improved insight was associated with improved adherence (Mohamed et al., 2009, Table 4, p. 343). Poor insight (assessed as a PANSS item) was associated with non-adherence to treatment in the EUFEST study (Czobor et al., 2013). Both insight into mental illness and positive attitudes towards treatment were associated with satisfactory adherence (Hofer et al., 2006).

Related to insight, negative attitudes toward medication are associated with non-adherence (Lacro et al., 2002; Rettenbacher et al., 2004; Perkins et al., 2006; Velligan et al., 2009a). Furthermore, negative attitudes towards medication were shown to predict discontinuation of initiated treatment in a subsample of 228 patients participating in the EUFEST trial (Gaebel et al., 2010).

Younger age, male gender, lower socioeconomic status, minority status, poorer social functioning, and difficulties in building a therapeutic alliance are associated with adherence problems (Velligan et al., 2009b).

Combination of *substance use problems* and non-adherence to medication treatment in severe mental illness is frequent, and it increases the risk of adverse outcomes including violent behavior (Swartz et al., 1998a, 1998b). Relationships between substance use and treatment non-adherence have been documented in first episode of psychosis (Coldham et al., 2002) as well as in patients with established schizophrenia (Ascher-Svanum et al., 2006b; Cooper et al., 2007). In a study of patients with first episode of schizophrenia or

schizoaffective disorder, individuals with substance abuse stopped medications more than those without substance use, but the difference was not statistically significant (Robinson et al., 2002). Although the association between substance use and treatment non-adherence in severe mental illness has been established, causation remains unclear. It is possible that substance use causes non-adherence, or that non-adherence causes substance use, or that the relation is not causative and the association is due to other factors, perhaps some personality characteristics.

The fact that *extrapyramidal side effects* may reduce patients' willingness to take antipsychotics has been known for a long time (Van Putten, 1974).

Parkinsonism (but not akathisia) predicted discontinuation of antipsychotic treatment after the first relapse of schizophrenia or schizoaffective disorder (Robinson et al., 2002). Medication adverse effects independently predicted non-adherence to antipsychotic medication in 81 patients with schizophrenia (McCann et al., 2008). In a consensus survey, experts agreed that distress associated with persistent side effects (or fear of potential side effects) was often a very important contributor to medication adherence problem in schizophrenia (Velligan et al., 2009a, p. 19). On the other hand, only one out of nine older studies looking for an association between severity of side effects and non-adherence to medication in patients with schizophrenia could confirm it. The other eight studies demonstrated little or no association (Lacro et al., 2002).

A short-term randomized clinical trial has shown that higher *hostility levels* may be a predictor of non-adherence to medication in schizophrenia patients (Lindenmayer et al., 2009). Specifically, greater hostility was associated with a greater likelihood of non-adherence at the following visit. However, hostility change from baseline did not predict non-adherence at the following visit. An association between hostility and non-adherence was also reported in the EUFEST study (Czobor et al., 2013). Other risk factors for non-adherence include poor pre-morbid and current cognitive functioning, and less improvement of psychopathology (Ascher-Svanum et al., 2006b; Hofer et al., 2007; Perkins et al., 2006), as well as weight gain (Velligan et al., 2009a).

Thus, the existing literature provides strong support for impaired insight (or negative attitudes towards medication) and substance abuse as predictors of treatment non-adherence in schizophrenia. There is limited evidence for an association between non-adherence and the combined effects of increased hostility, substance abuse, and extra-pyramidal adverse effects. These latter correlates of non-adherence have not traditionally been examined in multivariable models in large and generalizable samples. The principal purpose of this study is to investigate insight, substance use, extrapyramidal effects, and hostility in a multivariate analysis using a large sample of schizophrenia patients. We also aimed to explore the relation between non-adherence and discontinuation of study medication to which the patients had been originally randomized.

2. Experimental procedures

2.1. Study settings, patients, and designs

The analyzed data were derived from two studies: CATIE and EUFEST.

2.1.1. CATIE—Phase 1 of the CATIE recruited 1493 patients with schizophrenia at 57 clinical sites in the United States. Broad inclusion and minimal exclusion criteria were used, allowing the enrollment of patients with coexisting conditions. The participants were randomly assigned to treatment with olanzapine, perphenazine, quetiapine, risperidone, or ziprasidone for up to 18 months. Patients exhibiting tardive dyskinesia were not assigned to perphenazine. Phase 1 was a double-blind trial (Lieberman et al., 2005). The participants were followed for up to 18 months as outpatients.

Information on *adherence* to study medication was obtained using the pill count and inputs from other sources. The validity of pill count is superior to subjective measures of adherence such as self-report and physicians' rating of adherence, and is comparable to the electronic pill bottle caps that record time and date of opening (Velligan et al., 2007, 2009b). We used the monthly pill count as the measure of adherence in our analyses. We quantified adherence as the proportion of the assigned amount of medication (number of tablets) that was actually used. We used this measure to characterize mean % adherence for each trial period analyzed (i.e., 6 and 12 month assessments). In order to match the CATIE and EUFEST data, where 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 (where complete refusal of treatment is scored as 1, and ready acceptance of treatment is scored as 7).

Psychopathology, including *hostility* and *insight*, was assessed with the PANSS (Kay et al., 1987) 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 *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).

Extrapyramidal side effects were assessed using the Simpson–Angus scale (Simpson and Angus, 1970), Barnes akathisia scale (Barnes, 1989), and the Abnormal Involuntary Movement Scale (Department of Health, 1974). For analytic purposes, a dichotomous variable (side effect present or absent) was created for each of the extrapyramidal side effects.

Substance use and substance abuse and/or dependence were investigated via “multiple sources of information and coded hierarchically into three categories: (1) current substance use disorders (alcohol or illicit drug abuse or dependence) (2) current alcohol or illicit drug use without serious impairment, and (3) no use. For analytic purposes, a composite variable combining any substance use (categories 1 and 2) was created” (Swartz et al., 2006). The resulting dichotomous variable (no use v. any use) was assessed at baseline and then

quarterly (Van Dorn et al., 2013). All-cause treatment discontinuation was the primary outcome variable to assess effectiveness (Lieberman et al., 2005).

2.1.2. EUFEST—EUFEST was a randomized, open trial comparing the effectiveness of haloperidol, amisulpride, olanzapine, quetiapine, and ziprasidone in patients with a first episode of DSM IV schizophrenia, schizoaffective disorder, or schizophreniform disorder (Kahn et al., 2008). Patients ($N=498$) were recruited at 50 centers in 13 European countries and in Israel. The primary outcome measure was all-cause treatment discontinuation. Secondary measures included the PANSS, CGI, and a measure of adherence.

Adherence was assessed using a one-item, 7-point rating scale (sometimes referred to as Hayward scale) where complete refusal of treatment is scored as 1, and ready acceptance of treatment is scored as 7 (Kemp et al., 1996).

Hostility and insight scoring used the PANSS items as described above in the CATIE section. Extrapyramidal syndromes (parkinsonism, akathisia and dyskinesia) were assessed using the St. Hans Rating Scale (Gerlach et al., 1993). Analogous to the CATIE, a dichotomous variable (absent v. present) was created for each extrapyramidal side effect. The same procedure was employed by other researchers studying extrapyramidal side effects in the EUFEST (Rybakowski et al., 2014). Alcohol and substance abuse/dependence were examined using the Mini-International Neuropsychiatric Interview (MINI); the MINI-Plus version was used (Sheehan et al., 1998). 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). CATIE and EUFEST were approved by the Institutional Review Boards of participating institutions, following the local laws/regulations of the participating centers.

2.2. Statistical procedures

We applied multivariate logistic regression analyses in the combined sample of CATIE and EUFEST patients to investigate concurrent and predictive associations between medication non-adherence on one hand and a set of potentially important variables pinpointed by prior studies on the other hand. For concurrent associations, the dependent and independent variables were assessed at the same period in the study (first 6 or 12 months) whereas in the predictive analyses of treatment non-adherence during the study, the assessment of predictors occurred at baseline. Adherence was used as the dependent variable. Since adherence was measured as a polychotomous variable (7-point scale), with higher scores indicating better adherence, the multinomial distribution with the log-link function was specified for the logistic model.

The set of principal independent variables of interest included hostility; lack of judgment and insight; substance abuse; extrapyramidal adverse effects; and basic demographic measures such as age and sex. Side effects were rated by different scales in the two studies; to increase comparability of the side effect measures from the two studies, we applied them as dichotomous variables in the analyses. A score of 1 was assigned to a variable if a

constituting item had a non-zero entry; otherwise, the value of the variable was set to 0. In order to investigate whether the association was specific with regard to the above predictors, symptom severity on the PANSS Positive Subscale (excluding the hostility item) was used in the analysis as a covariate. Furthermore, Study (i.e., CATIE or EUFEST) was applied as an additional fixed-effect covariate in the analyses.

The odds ratio statistic was adopted to characterize the strength of the association between the dependent and each of the independent variables. Odds ratios with a value of >1 indicate that the independent variable is associated with an increased likelihood of non-adherence. A separate analysis was performed for each of the concurrent (6 and 12 month) and predictive associations of interest (baseline vs. 6 and 12 months). Analogous to the logistic regressions described above, we conducted separate analyses for the CATIE and EUFEST subsets. The investigation of concurrent association at 6 months in the pooled sample of patients from both studies was considered as the primary analysis in order to increase 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 ($N=804$). In addition, we conducted sensitivity analyses using the multiple imputation approach for missing data. We adopted the fully conditional specification (FCS) approach that allows for data sets with an arbitrary pattern of missing data. We used the logistic regression method to impute missing values since it makes allowance for classification variables which have a binary or ordinal response (van Buuren, 2007, 2012).

Significance level was set at $\alpha=0.05$ (two-tailed). 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

Sociodemographic and psychopathological characteristics at baseline are shown in Table 1 in separate columns for the CATIE and EUFEST studies.

Patient disposition and accounting of data used for the analyses from the CATIE and EUFEST studies are shown in Figure 1. The left side of the Figure provides the data separately for the two studies while the right side displays the summary data pooled across the two studies. As indicated by the pooled data depicted in the figure, 77.0% ($N=1507$) of the total of 1958 patients included in the study samples in the two studies yielded information on adherence, used as the dependent variable (DV) in the analyses. In 23.4% (353/1507) of the patients in this set, at least one of the independent variables (IVs) were unavailable for the multivariate analyses; thus, data from a total 1154 subjects were used in the statistical analyses.

In order 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 ($N=804$). The comparison is shown in Supplementary Table 1. The differences in the majority of comparisons did not reach significance after correction for multiple testing. When they did (e.g., PANSS total and positive subscale scores, and hostility), they were small; for example, the average total PANSS scores in the included and excluded subsets were, respectively, 78.0 (19.1) and 80.1(19.4) ($F=7.8$, $p=0.0052$).

3.2. Primary analysis of poor adherence to medication

The results of the primary analysis of non-adherence to medication at 6 months are shown in Table 2. This was a concurrent, cross-sectional analysis: all data were collected at 6 months in both studies. Substance use, hostility, and impaired insight were significantly related to poor adherence.

As stated in the Statistical procedures, in sensitivity analysis we investigated the robustness of our primary results with regard to potential bias due to missing data. Our results based on the multiple imputation approach revealed that the associations detected as significant in the primary analysis remained significant and in the same direction after correction for multiple testing (i.e., corrected $p<0.05$ for substance use, hostility, and impaired insight).

Logistic regression analogous to the primary analysis was performed for the 12-month data. Because of additional missing data at that time point, only 739 subjects were used for this analysis. At that time point, only impaired insight and alcohol/drug use were significantly related to non-adherence.

Data collected at baseline were used as predictors of adherence at 6 months (see Table 3). Substance use, hostility, impaired insight, and younger age at baseline predicted poor adherence at 6 months.

Analogous predictive analysis was performed using data collected at baseline as predictors of poor adherence at 12 months. Again, substance use and impaired insight at baseline predicted poor adherence at 12 months, and the association for hostility and younger age approached significance.

3.3. Effect of adherence on retention in the studies

Survival analysis using only subjects who were *not* discontinued because of non-adherence has demonstrated that poor adherence is associated with earlier discontinuation. This is shown in Figure 2, which displays the Kaplan–Meier (K–M) survival curves for the pooled analysis and separately for the CATIE and EUFEST studies. Adherence (coded as ‘yes’ below for the figure) for the purpose of the analysis was defined as score of exceeding the midpoint on the 7-point scale indexing adherence (with complete refusal of treatment coded as 1, and ready acceptance as 7). The difference in the K–M survival curves according to adherence stratum was significant in all analyses ($p<0.0001$ in the pooled, and the CATIE and EUFEST samples).

3.4. Analysis of sample heterogeneity

As shown in Table 2, the CATIE and EUFEST studies displayed significant differences in basic demographic and clinical characteristics at baseline. There were also differences in the adherence scores. At 6 months, the average scores for CATIE and EUFEST were, respectively, 6.56 (0.94), and 5.75 (1.49). Supplementary Tables 2a and b show additional descriptive data of the two study populations. The data are consistent with the differences in the respective populations (i.e., first episode vs. chronic patients with schizophrenia).

In order to investigate whether the heterogeneity of the patient samples in the two studies had an impact on our findings, the fixed-effect covariate Study (i.e., CATIE or EUFEST) was applied as an interacting covariate in the analyses. Our results indicated that while the main effect of Study reached statistical significance (as indicated by Tables 2 and 3), no interaction of Study with any of the covariates reached statistical significance ($p>0.05$ for the interaction with any of the covariates).

To further explore the heterogeneity of the two studies, we repeated the principal concurrent and predictive logistic regression analyses (displayed in Tables 2 and 3) separately for the CATIE and EUFEST studies. The results are in Supplementary Tables 3a and b (concurrent regressions) and 4a and b (predictive regressions). The results for the two studies are similar, with the ORs for alcohol/drugs, hostility, and insight going in the same direction in all four analyses.

4. Discussion

Our analyses have confirmed the important role of insight in non-adherence to treatment in schizophrenia, and provided further support for substance use and hostility as correlates of non-adherence to pharmacological treatment in schizophrenia. The results were obtained in a combined sample whose size exceeded each of the published controlled studies addressing these issues.

Our findings relating insight to non-adherence are consistent with the extensive literature on this subject (Coldham et al., 2002; Lacro et al., 2002; Velligan et al., 2009a; Perkins et al., 2006; Chan et al., 2014). The relationship between non-adherence and substance abuse that we detected had been documented (Coldham et al., 2002; Wilk et al., 2006; Ascher-Svanum et al., 2006a). However, it is not clear whether substance use precedes non-adherence, or vice versa. Detailed prospective studies with good time resolution will be needed to answer that question. Our finding that hostility is related to non-adherence is consistent with a previous observation (Lindenmayer et al., 2009). Furthermore, we have confirmed a previous report indicating that (partial) non-adherence predicts complete treatment discontinuation (Lindenmayer et al., 2009). This is another demonstration of the importance of treatment adherence for its effectiveness in clinical practice.

The expectation that extrapyramidal symptoms would be associated with non-adherence (Robinson et al., 2002) was not supported by our analyses. However, the lack of significant correlations between extrapyramidal symptoms and adherence was consistent with the

findings of only weak (non-significant) correlations between such symptoms and attitudes towards drug treatment (Hofer et al., 2007).

The expectation of extrapyramidal symptoms relating to non-adherence makes intuitive sense: patients who suffer from adverse effects will not be enthusiastic about taking the medication causing them. However, our analyses were hampered by poor time resolution of the available assessment data. One assessment every six months cannot reliably resolve temporal relationships between non-adherence and the emergence of extrapyramidal symptoms. Thus, it is possible that while some patients indeed became non-adherent because of extrapyramidal symptoms, others first became non-adherent for other reasons; this reduced the plasma levels of medications, which *alleviated* the extra-pyramidal symptoms. This is a limitation of the study. In any event, in terms of effects on adherence, weight gain and metabolic side effects of second generation antipsychotics have, to a large extent, supplanted the concerns regarding extrapyramidal side effects associated primarily with older antipsychotics.

There are more limitations. Hostility and insight were assessed by single PANSS items. More comprehensive scales for both variables are available, but were not used. Similarly, treating continuous variables like extrapyramidal symptoms and substance abuse as dichotomous belies the complexity of their relationship with adherence.

Furthermore, neither CATIE nor EUFEST was designed to primarily study adherence and its correlates. Besides, the two studies used different instruments to assess adherence, substance use and extrapyramidal symptoms. Thus, the values of these variables are not directly comparable across the two studies. For example, the results do not inform us whether adherence was better in EUFEST or CATIE. Such comparisons were not the purpose of our study. Instead, we were interested in how variables were related to each other. In spite of the different methods used, these relationships, reflected by the results of principal analyses, are similar in the two studies.

Importantly, the subjects were clinically different: CATIE enrolled patients with chronic schizophrenia, whereas EUFEST was a first-episode study.

This would have been expected to result in substantial heterogeneity of the results. However, we observed that the ORs of independent variables yielded separately by each of the two studies were in the same direction and of very similar magnitude; the results were generally similar in both studies. Thus, the predictors and correlates of adherence to medication that we investigated showed similarities in chronic and first episode schizophrenia patients. However, we have sampled only a small portion of factors that have been linked to nonadherence.

Causal inferences cannot be made from correlations. Nevertheless, the clinical implications of the results point to the importance of routine assessment (Amador et al., 1993; McEvoy et al., 1989) and interventions (Velligan et al., 2010) to improve patients' insight, establishment of therapeutic alliance (Canas et al., 2013), as well as detection and treatment of comorbid substance use disorders (Wilk et al., 2006).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Flowchart of patient disposition.

Patient disposition and accounting of data used for the analyses from the CATIE and EUFEST studies. The left side of the Figure displays the data, respectively, for the CATIE and EUFEST studies while the right side shows the pooled summary data.

Figure 2.

Kaplan–Meier (K–M) Survival Analysis of time-to-discontinuation of study as a function medication adherence in the pooled sample and separately in the CATIE and EUFEST samples.

Time to discontinuation was defined as the number of days elapsed between randomization and the time of discontinuation of the pre-assigned study medication. For the purpose of the K–M analysis adherence (coded as ‘yes’ in the Figure) was defined as a score exceeding the midpoint on the 7-point scale indexing adherence (with complete refusal of treatment coded as 1, and ready acceptance as 7). The K–M analysis included only those subjects who were *not* discontinued because of non-adherence. The difference in the K–M survival curves according to adherence stratum was significant ($p < 0.0001$) in all three study samples (pooled, CATIE, EUFEST).

Table 1Basic demographic and clinical characteristics of the study sample at baseline^a.

Characteristics	Categorical variables	N (%)	CATIE (N = 851)	EUFEST (N = 303)	Chi ²	p
Demographic male, no. (%)			629 (73.9)	174 (57.4)	28.7	<0.0001
Continuous variables: mean (SD)					<i>F</i>	<i>P</i>
Mean age, y			41.2 (11.0)	26.1 (5.5)	524.4	<0.0001
PANSS ^b						
Total score			74.5 (17.3)	87.9 (20.3)	121.9	<0.0001
Positive subscale			18.0 (5.5)	23.2 (6.0)	195.4	0.0001
Negative subscale			20.1 (6.5)	20.8 (7.4)	2.34	0.1366
General psychopathology			36.5 (9.0)	43.9 (10.7)	135.1	<0.0001
Hostility item			1.7 (1.0)	2.3 (1.3)	2.27	0.1400
Insight item			2.8 (1.3)	3.9 (1.4)	137.9	<0.0001

^aChi-square test for categorical, ANOVA for continuous variables.^bPANSS=Positive and Negative Syndrome Scale.

Table 2

Concurrent logistic regression of adherence to medication treatment at six months.

Independent variables	Odds ratio (OR) for worse non-adherence ^a	95% Confidence interval	Chi-square (<i>n</i> = 1154, <i>df</i> = 1)	<i>p</i> -Values ^b
Alcohol/drugs at 6 months ^c	2.017	1.380-2.948	13.13	0.0003
Insight at 6 months	1.420	1.264-1.596	34.69	<0.0001
Hostility at 6 months	1.372	1.160-1.623	13.64	0.0002
Akathisia at 6 months	1.332	0.885-2.004	1.89	n.s.
Parkinsonism at 6 months	0.716	0.492-1.043	3.03	n.s.
Dyskinesia at 6 months	0.737	0.471-1.152	1.79	n.s.
Positive symptoms at 6 months ^d	1.022	0.987-1.058	1.46	n.s.
Study (CATIE vs. EUFEST)	4.770	3.267-6.963	65.51	<0.0001
Age	0.992	0.978-1.006	1.33	n.s.
Male gender	1.271	0.951-1.698	2.62	n.s.

^aOR>1 and OR<1, respectively, indicate increased or decreased non-adherence.

^b*p*-Values in bold remain significant after Hochberg's correction for multiple testing.

^cAny use, combined.

^dPANSS positive symptoms excluding hostility.

Table 3

Predictive logistic regression of adherence to medication treatment at six months.

Independent variables	Odds Ratio (OR) for worse non-adherence ^a	95% Confidence interval	Chi-square (<i>n</i> = 1501, <i>df</i> = 1)	<i>p</i> -Values ^b
Alcohol/drugs at baseline ^c	1.759	1.399-2.212	23.36	<0.0001
Insight at baseline	1.122	1.035-1.217	7.80	0.0052
Hostility at baseline	1.122	1.017-1.238	5.26	0.0218
Akathisia at baseline	1.043	0.802-1.357	0.10	n.s.
Parkinsonism at baseline	0.740	0.577-0.949	5.65	0.0175
Dyskinesia at baseline	0.749	0.549-1.023	3.31	n.s.
Positive symptoms at baseline ^d	1.009	0.987-1.032	0.61	n.s.
Study (CATIE vs. EUFEST)	1.628	1.200-2.209	9.80	0.0017
Age	0.989	0.978-1.000	3.95	0.0468
Male gender	1.219	0.958-1.550	2.60	n.s.

^aOR>1 and OR<1, respectively, indicate increased or decreased non-adherence.

^b*p*-Values in bold remain significant after Hochberg's correction for multiple testing.

^cAny use, combined.

^dPANSS positive symptoms excluding hostility.