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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, 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

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interventions to address patients' insight and comorbid substance use and the establishment of therapeutic alliance.

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 e*xtrapyramidal 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 extrapyramidal 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.