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Drug attitude as predictor for effectiveness in first-episode schizophrenia: Results of an open randomized trial (EUFEST)

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Abstract

Effectiveness has become more and more important as a comprehensive outcome measure for (long-term) treatment in schizophrenia. Early predictors to identify patients at a high risk for not succeeding the initiated treatment would be very useful. Discontinuation of the initiated treatment was used as criterion for effectiveness and patients' drug attitude was shown to be predictive for non-adherence or discontinuation of long-term treatment in schizophrenia. Accordingly, the predictive validity of the Drug Attitude Inventory (DAI) for effectiveness should be evaluated. Based on a sub-sample of patients from the EUFEST study for whom DAI assessments were available significant predictors for effectiveness as measured by discontinuation of initiated treatment were identified based on a logistic and a Cox-regression analysis. A Receiver-Operating Characteristic- (ROC-) analysis was conducted for the DAI, prognostic / diagnostic parameters (sensitivity, specificity) were calculated and a cut-off value suggested. In a sample of 228 first-episode patients, the DAI score was the most powerful predictor for effectiveness ($p<0.001$) besides two other significant predictors (PANSS-positive score and sexual side effects). The ROC-analysis revealed an area under the curve of 0.64 ($p<0.001$). The suggested cut-off point of about 20 yielded a sensitivity of 70–75% and a specificity of 40–45%. Study results indicate that the Drug Attitude Inventory, filled in by patients early in treatment

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seems to be a valid predictor for effectiveness as measured by discontinuation of the initiated treatment. DAI scores could also serve as an (differential) indicator for the need of enhanced treatment monitoring. These findings have to be validated in other (first-episode) samples.

1. Introduction

In recent years, the concept of 'effectiveness' (e.g. Hogarty et al., 1997) has become crucial regarding the evaluation of long-term drug treatment in schizophrenia (Fleischhacker et al., 2005; Lieberman et al., 2005; Kahn et al., 2008). As a pragmatic comprehensive measure, it integrates aspects of efficacy, safety, and tolerability and considers both, the perspective of the patient and the clinician. In general, the rates of retention or (dis-) continuation serve as an appropriate indicator reflecting all of these parameters. Since non-adherence or drug discontinuation is a critical issue in the long-term treatment of schizophrenia, considerable effort has been made to identify early indicators and to provide interventions to keep patients in an (in general) effective and safe treatment. Patients' attitude towards drug treatment has emerged as one of the factors associated with drug discontinuation or non-adherence (Lacro et al., 2002), so it could be assumed, that it might be a predictor for 'effectiveness' as well. This hypothesis was tested by analyzing data from the European First-Episode Schizophrenia Trial (EUFEST; Fleischhacker et al., 2005; Kahn et al., 2008).

In recent years, several studies have identified predictors for treatment discontinuation or non-adherence in first-episode patients (Verdoux et al., 2000; Kampman et al., 2002; Robinson et al., 2002; Mutsatsa et al., 2003; Perkins et al., 2006; De Haan et al., 2007; Perkins et al., 2008; Rabinovitch et al., 2009; Miller et al., 2009). The indicators included and extracted are as manifold as in multiple episode patients: lower occupational status, substance abuse, psychopathology (more pronounced delusional symptoms and suspiciousness; Verdoux et al., 2000), negative attitudes toward drug treatment and lack of insight (Kampman et al., 2002; Mutsatsa et al., 2003), poor premorbid (cognitive) and post-acute (executive) functioning, more pronounced (extrapyramidal) side effects (Robinson et al., 2002; Perkins et al., 2008), lower expectations regarding the need for or effectiveness of general or drug-specific treatment, treatment with first (vs. second) generation antipsychotics (FGAs / SGAs; Perkins et al., 2006), hostility and uncooperativeness, involuntary admission (De Haan et al., 2007), poor treatment response, low adherence to preceding treatment, poor cognitive functioning, persisting negative or depressive symptoms, ethnicity (Perkins et al., 2008), less social support, living alone, refusing drugs at treatment initiation (Rabinovitch et al., 2009), and substance abuse (Perkins et al., 2008; Miller et al., 2009).

Based on theoretical considerations (Perkins, 2002; Weiden, 2007) and empirical findings, patients' attitude towards drug treatment was suggested to be a factor associated with treatment discontinuation both in unselected samples (mainly multiple episode patients; for a summary see Lacro et al., 2002) and in first-episode patients (Kampman et al., 2002; Mutsatsa et al., 2003; Perkins et al., 2006, 2008). Several scales have been developed for an easy and valid assessment of such attitudes (e.g. Hogan et al., 1983; McEvoy et al., 1989; Weiden et al., 1994; Kampman et al., 2000; Dolder et al., 2004). The Drug Attitude Inventory (DAI) by Hogan et al. (1983) is one of the earliest developed and most widely used scale. Patients are asked to answer 30 dichotomous items (or 10 items in the short form), reflecting various positive and negative attitudes to drug treatment. These can be summarized to an overall composite score with good psychometric properties (reliability 0.82 to 0.93, good discriminative validity; Hogan et al., 1983). Factor analyses based on different methods yielded seven dimensions: (I) subjective positive, (II) subjective negative, (III) health / illness, (IV) physician, (V) control, (VI) prevention, and (VII) harm (Hogan et al., 1983). All together, the instrument is well established, methodologically sound, and easy to use and was therefore included in EUFEST, to gather information on patients' attitude on antipsychotic drug treatment.

The main objective of this paper is to examine the predictive validity of the DAI (30 items form) regarding effectiveness in first-episode patients, as measured by discontinuation of the initiated treatment for any reason. In addition, (other) predictors for effectiveness of long-term maintenance treatment in first-episode schizophrenia aimed to be identified.

2. Experimental procedures

2.1. Study setting, patients and design

The analyzed data derived from EUFEST in which a FGA (haloperidol) was compared with four SGAs (amisulpride, olanzapine, quetiapine, and ziprasidone; open randomized design) in first-episode patients with schizophrenia spectrum disorders regarding differences in effectiveness (i.e. drug discontinuation; see below). Detailed study characteristics have been described elsewhere (Fleischhacker et al., 2005; Kahn et al., 2008). A total of 50 centers participated in 13 European countries and in Israel. Eligible patients were 18–40 years of age and met DSM-IV criteria for schizophrenia, schizophreniform, or schizoaffective disorder confirmed by the Mini International Neuropsychiatric Interview Plus (MINI+; Sheehan et al., 1998). Patients were excluded if: (1) more than two years had passed since the onset of positive symptoms; (2) any antipsychotic had been used exceeding two weeks in the previous year or six weeks lifetime; (3) patients had a known intolerance to one of the study drugs; (4) patients met any of the contraindications for any of the study drugs as mentioned in the (local) package insert texts.

Patients were included after written informed consent was obtained following a complete description of the study. The trial complied with the Declaration of Helsinki and was approved by the ethics committees of the participating centers.

Patients were randomized to: haloperidol 1–4 mg/day, amisulpride 200–800 mg/day, olanzapine 5–20 mg/day, quetiapine 200–750 mg/day, or ziprasidone 40–160 mg/day. All study medications were administered orally within the approved dose ranges at the treating physician's discretion.

Data were collected at baseline (between four weeks before and one week after randomization) and after 0.5, 1, 1.5, 2, 3, 6, 9, and 12 months. Assessments included data on demographics, diagnosis,