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Prediction of acute clinical response following a first episode of non affective psychosis: Results of a cohort of 375 patients from the Spanish PAFIP study

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ABSTRACT

Objective: Predicting response to antipsychotic treatment might optimize treatment strategies in early phases of schizophrenia. We aimed to investigate sociodemographic, premorbid and clinical predictors of response to antipsychotic treatment after a first episode of non-affective psychosis.
Method: 375 (216 males) patients with a diagnosis of non affective psychosis entered the study. The main outcome measure was clinical response at 6 weeks and variables at baseline were evaluated as predictors of response. ANOVA for continuous and chi-square for categorical data were used to compare responders and non-responders. Multivariate logistic regression was used to establish a prediction model.
Results: 53.3% of study subjects responded to antipsychotic treatment. The following variables were associated with an unfavorable response:1. — lower severity of symptoms at baseline;2. — diagnosis of schizophrenia;3. — longer DUI and DUP;4. — poorer premorbid adjustment during adolescence and adulthood;5. — family history of psychosis, and 6. — hospitalization. Patients with a family history of psychosis, longer DUP, poor premorbid functioning and lower severity of psychotic symptoms at intake have a reduced likelihood of responding to antipsychotic treatment.
Conclusion: Helping clinicians to identify those first episode patients with a lower probability of having a favorable clinical response is meant as a first step to achieve a successful initial treatment.

1. Introduction

Successful initial treatment has been found to be associated with better therapeutic alliance and clinical outcome in schizophrenia (Wyatt, 1991). Predicting the response to treatment and understanding the factors that might contribute to the variability in response may show the way to optimize treatment strategies in early phases of the illness (Gaebel, 1996). Despite good treatment compliance, approximately 40% of first episode patients will not show a significant decrease in the severity of their initial symptoms at short term (Crespo-Facorro et al., 2006). A few factors have been also associated with a favorable or unfavorable response to pharmacological treatment in first episode individuals. Lengthy duration of untreated psychosis (DUP) (Ucok et al., 2004), poor premorbid functioning in childhood and in early adolescence (Amminger et al., 1997), and the severity of psychopathology at baseline (Robinson et al., 1999) may indicate a poor early response. In a previous study, comprising 172 non-affective psychosis patients who are also included in the present research, we found that early age of onset, poor premorbid adolescent functioning and low severity of psychopathology at intake were factors associated with a poor acute clinical response to antipsychotic drugs (Crespo-Facorro et al., 2007). Premorbid, psychopathological, and psychosocial factors influencing the short-term treatment response have been widely described in relapsed schizophrenic patients (Bartko et al., 1990; Cuesta et al., 1994; Kinon et al., 1993; McEvoy et al., 1991). However, factors influencing clinical response could vary in the course of the illness.

We aimed to extend our previous research by investigating sociodemographic, premorbid and baseline clinical predictors of acute response to antipsychotic treatment in a large sample (N = 375) of first episode of non-affective psychosis who are representative of clinical practice in an epidemiological catchment area.

Abbreviations: CGI, Clinical Global Impression; DSM, Diagnostic and Statistical Manual of Mental Disorders; DUI, Duration of untreated illness; DUP, Duration of untreated psychosis; OR, Odds Ratio; PAS, Premorbid Adjustment Scale; PAFID, Epidemiological and three-year longitudinal intervention program of first-episode psychosis; SAPS, Scale for the Assessment of Positive symptoms; SANS, Scale for the Assessment of Negative symptoms; SCID, Structured Clinical Interview for DSM; SPSS, Statistical Package for Social Science.

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2. Materials and methods

2.1. Study setting and financial support

Data for the present investigation were obtained from an ongoing epidemiological and three-year longitudinal intervention program of first-episode psychosis (PAFIP) conducted at the outpatient clinic and the inpatient unit at the University Hospital Marques de Valdecilla, Spain (Pelayo-Teran et al., 2008). Conforming to international standards for research ethics, this program was approved by the local institutional review board. Patients meeting inclusion criteria and their families provided written informed consent to be included in the PAFIP. The Mental Health Services of Cantabria provided funding for implementing the program.

2.2. Subjects

From February 2001 to January 2011 all referrals to PAFIP were screened for patients who met the following criteria: 1) 15–60 years; 2) living in the catchment area; 3) experiencing their first episode of psychosis; 4) no prior treatment with antipsychotic medication or, if previously treated, a total life time of adequate antipsychotic treatment of less than six weeks; 5) DSM-IV criteria for brief psychotic disorder, schizophreniform disorder, schizophrenia, or schizoaffective disorder. The diagnoses were confirmed using the Structured Clinical Interview for DSM-IV (SCID-I) (First et al., 2001) carried out by an experienced psychiatrist 6 months on from the baseline visit. Our operational definition for a "first episode of psychosis" included individuals with a non-affective psychosis (meeting the inclusion criteria defined above) who have not received previously antipsychotic treatment regardless the duration of psychosis.

2.3. Study design

This is a prospective, randomized, flexible-dose, open-label study. At study intake, all patients but 11 were antipsychotic naïve. The medication protocol was explained to the patient and family by the psychiatrist. All patients were randomly assigned to antipsychotic treatments (haloperidol, olanzapine, risperidone, aripiprazole, ziprasidone and quetiapine) (Crespo-Facorro et al., 2006, in press). Dose ranges were 5–20 mg/day for Olanzapine, 2–6 mg/day of Risperidone, 3–9 mg/day for Haloperidol, 100–600 mg/day for Quetiapine, 5–30 mg/day for Aripiprazole and 40–160 mg/day for Ziprasidone. Rapid titration schedule (5-day), until optimal dose was reached and was as a rule used unless severe side effects occurred. At the treating physician's discretion, the dose and type of antipsychotic medication could be changed based on clinical efficacy and the profile of side effects during the follow-up period. Antimuscarinic medication, lormetazepam and clonazepam were permitted for clinical reasons. No antimuscarinic agents were administered prophylactically. Antidepressants (sertraline) and mood stabilizers (lithium) were permitted if clinically needed. For the acute treatment of the illness (6 weeks) patients went through a pharmacological protocol and no particular therapeutic interventions were initiated.

2.4. Predictor measures

2.4.1. Baseline sociodemographic characteristics

The following sociodemographic information was recorded from patients and family members, and medical records: age, gender, marital status (1. — single or never married/conjugal 2. — other status); living status at psychosis onset (1. — lived with relatives; 2. — lived alone and other status); employment status during the 2 years previous initial interview (1. — employed/student and 2. — unemployed). Socioeconomic status of parents was measured by using the Hollingshead and Redlich Scale (a 5-level rating scale) and was defined as follows: 1 — high as defined by ≤3 score; and 2. — low as defined by 4–6 score. Educational level (1. — primary education as defined by up to 10 years of education; and 2. — other educational level as defined by more than 10 years of education). Urbanicity was defined as living (most of their life) in a >50,000 inhabitant city.

2.4.2. Premorbid characteristics

The following premorbid information was recorded from patients, family members, and medical records. Age of onset (the age of onset of the first continuous psychotic symptom: hallucinations, delusion and bizarre behavior). Duration of untreated illness (DUI) defined as the time from the first unspecific symptoms related to psychosis to initiation of adequate antipsychotic drug treatment. Duration of untreated psychosis (DUP) defined as the time from the first continuous psychotic symptom to initiation of adequate antipsychotic drug treatment. Cannabis use history (1. — sporadic or frequent use of cannabis, defined as one or more times a week for at least the last year; 2. — non-cannabis use). Drug use history (1. — sporadic or frequent use of cocaine or other illicit drugs, defined as one or more times a week for at least the last year; 2. — non-drug use). Alcohol use history (1. — frequent use of alcohol, defined as 1 or more times a week for at least the last year; 2. — sporadic or non-alcohol user). The first degree family history of psychosis was based on the subject and family reports.

The premorbid functioning in childhood (up to 11 years), early adolescence (12–15 years), late adolescence (16–18 years) and adulthood was measured by the Premorbid Adjustment Scale (PAS)(Cannon-Spoor et al., 1982). In each period the PAS consisted of five domains: isolation, peer relation, scholastic performance, adaptation to school, and interest. The scores on domains of each period were averaged to provide a single mean score for each age category. The last year before onset of psychosis was not taken into account in the PAS evaluation to avoid interference by functional dysfunction associated to the prodromal phase. The higher PAS scores the poorer premorbid functioning.

2.4.3. Clinical assessments

To assess the clinical response to treatment, the following scales were utilized: the Brief Psychiatric Rating Scale total (BPRS) was used to assess the severity of general psychiatric symptomatology (Overall and Gorham, 1962); the presence of psychotic, positive and negative, symptoms was evaluated by using the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983) and the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984); the Clinical Global Impression (CGI) scale was used to measure the overall severity of illness (Guy, 1976).

Assessments with the BPRS, SAPS, SANS, and CGI were completed, at least, at baseline and 6 weeks. The rate of hospitalization during the first episode was also measured. The same trained psychiatrist (BC-F) completed all clinical assessments.

2.5. Outcome measure

Responders were defined as the patients who concurrently met the following criteria in 6 weeks: 1. — 40% or greater reduction of BPRS total score from baseline; and 2. — CGI total score of ≤4 (moderately ill).

2.6. Statistical methods

Numerical data were expressed as frequency and percentage (%). Measured data were expressed as mean (SD). The association of the selected variables with treatment was assessed by comparing responders and non-responders with regard to the baseline values of the selected variables using ANOVA for continuous and chi-square for categorical data, respectively. Logistic regression was used to examine a multivariate prediction model that included all potentially useful variables for discriminating the 2 groups. An additional forward selection logistic regression was used by adding a block of relevant variables (i.e.; gender, cannabis use, parental socio-economic status and treatment at intake). All hypotheses were tested by using