



Duration of active psychosis and functional outcomes in first-episode non-affective psychosis

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ABSTRACT

Background: The duration of untreated psychosis (DUP) has been associated with negative outcomes in psychosis; however, few studies have focused on the duration of active psychotic symptoms after commencing treatment (DAT). In this study, we aimed to evaluate the effect of DUP and DAT on functional long-term outcomes (3 years) in patients with early psychosis.

Methods: We evaluated the Scale for the Assessment of Positive Symptoms (SAPS) at frequent intervals for 3 years after presentation to determine the DAT for 307 individuals with first-episode psychosis together with DUP and clinical variables. The functional outcomes were assessed using the Disability Assessment Scale (DAS) at three years, and functional recovery was defined as minimal impairment and return to activity. Associated variables, DAT and DUP were included in logistic regression models to predict functional outcomes. Receiver operating characteristic curves and Youden's index were applied to assess the best cut-off values.

Results: DAT, (Wald: 13.974; ExpB: 1.097; $p < 0.001$), premorbid adjustment, initial BPRS score, gender, age of onset and schizophrenia diagnosis were significant predictors of social functioning, whereas only premorbid adjustment (Wald: 11.383; ExpB: 1.009), DAT (Wald: 4.850; ExpB: 1.058; $p = 0.028$) and education were significant predictors of recovery. The optimal cut-off of DAT for predicting social functioning was 3.17 months for DAT (sensitivity: 0.68; specificity: 0.64; Youden's index: 0.314).

Conclusions: DAT is strongly related to functional outcomes independent of the DUP period or other variables. As a modifiable variable, the reduction of the DAT should be considered a main focus of intervention from the onset of the illness to improve long-term outcomes.

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1. Introduction

Deterioration has historically been considered a cardinal feature of schizophrenia [1]. Nonetheless, a significant number of patients have the potential to achieve clinical remission and functional recovery after the onset of the illness [2,3]. Historical research on early detection and intervention in schizophrenia

suggested that lengthy active psychotic symptoms might prompt a worse outcome [4]. Active positive symptoms represent a dangerous mental state that might be “biologically toxic,” leading to the notion of the deleterious effect on the brain in patients with acute active psychosis [5]. Based on the weight of accumulating evidence against a uniformly deteriorating or degenerative course across time, the concept of a “critical period” proposes that most of the clinical and psychosocial deterioration occurs within the first 2 to 5 years after psychosis onset [6,7]. This period is notable for a high risk of antipsychotic treatment dropout, relapse and suicide [8,9].

A lengthy DUP may negatively influence illness prognosis with regard to symptomatic response, remission and functional outcomes [10–12]. Some cognitive [13,14] and imaging studies [15,16],

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but not all [17,18], have provided evidence to support this hypothesis, and it has been suggested that there is minimal evidence of an association between untreated psychosis and brain structure in psychosis [19,20].

Surprisingly, little attention has been paid to the likely harmful effects of the duration of active psychotic symptoms after treatment is initiated (DAT) on clinical and functional outcomes in schizophrenia. This relationship can be suspected by the association clinical and functional outcomes with time to remission or relapses in patients with a first episode of psychosis. Time to remission and non-early remission has been previously associated to both clinical and functional outcomes at long term [21–23]. Number of relapses have been previously associated to a poorer outcome in patients with schizophrenia or a first episode of psychosis [24,25]. With regard to the period of active psychosis, in a previous study, patients with first episode of psychosis and a longer DAT showed a negative intellectual course [26]. Additionally, it has been reported that the entire duration of active psychosis (DAP: DUP plus the DAT) is a better predictor of severe negative symptoms at 24 months than DUP in patients with a first episode of psychosis [27].

We aimed to investigate the effect of the DAP before or after the start of treatment (DUP or DAT, respectively) on clinical and functional outcomes in the long term (3 years) in early psychosis. We hypothesized that both variables, DUP and DAT may have an additive negative effect on the long term functional outcomes.

2. Experimental procedures

2.1. Study setting

This cohort was 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 (Cantabria, Spain) [28]. Conforming to the international standards for research ethics, this program was approved by the local Institutional Review Board and conforms to the provisions of the Declaration of Helsinki. Patients meeting the inclusion criteria provided their written informed consent to be included in the PAFIP.

2.2. Subjects

All referrals to PAFIP between February 2001 and May 2011 were screened for eligibility with respect to the following criteria: 1) age 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 lifetime of adequate antipsychotic treatment of less than 6 weeks; and 5) DSM-IV criteria for brief psychotic disorder, schizophreniform disorder, schizophrenia, or schizoaffective disorder. Patients were excluded for any of the following reasons: 1) DSM-IV criteria for drug dependence or mental retardation and 2) a history of neurological disease or head injury. The diagnoses were confirmed using the Structured Clinical Interview for DSM-IV (SCID-I) [29] conducted by an experienced psychiatrist 6 months after the baseline visit. Our operational definition for a “first episode of psychosis” included individuals with non-affective psychosis who had not previously received antipsychotic treatment, regardless of the duration of untreated psychosis.

2.3. Study design

This prospective clinical study evaluated the effects of DUP, DAT and DAP in the clinical and functional outcomes in individuals with

first-episode non-affective psychosis (DSM-IV criteria). All patients with DUP and DAT measurements followed up in PAFIP and with clinical and functional assessments at the end point (3 years) were included in the final analysis.

2.4. Medication

This is an analysis of three different, randomized, flexible-dose and open-label clinical trials, PAFIP I, II and III [30,31]. In each trial, the patients were randomly assigned to receive olanzapine (5–20 mg/day), risperidone (2–6 mg/day), haloperidol (3–9 mg/day), aripiprazole (5–30 mg/day), ziprasidone (40–160 mg/day) or quetiapine (100–600 mg/day). A rapid titration schedule (5 days) until an optimal dose was reached was considered the rule unless severe side effects occurred. Based on the clinical efficacy and side effects during the follow-up period, the dose and type of antipsychotic medication could be changed by the treating physician. The mean equivalent chlorpromazine doses of antipsychotic medications [32] were 212.18 mg (SD: 92.22) at baseline and 294.12 mg (SD: 260.39) at the 3-year follow-up. The study protocol allowed for the use of anticholinergic agents, benzodiazepines and antidepressants for clinical reasons. Anticholinergic medication was never used prophylactically.

2.5. Assessments

2.5.1. Premorbid and sociodemographic variables

Premorbid and sociodemographic information was recorded from patients, relatives and medical records. The age at the time of onset of psychosis was defined as the age when the emergence of the first continuous (present most of the time) psychotic symptom occurred. The duration of untreated illness (DUI) was defined as the time from the first unspecific symptoms related to psychosis (for such a symptom to be considered, there should be no return to previous stable level of functioning) to initiation of adequate antipsychotic drug treatment; the duration of untreated psychosis (DUP) was defined as the time (months) from the first continuous (present most of the time) psychotic symptom to the initiation of adequate antipsychotic treatment (date when the first antipsychotic treatment in PAFIP was assigned and initiated). DUP was measured systematically to guarantee a valid and reliable measurement. Dating the onset of positive psychotic symptoms relied on information collected in a semi structured interview, based on the Symptom Onset in Schizophrenia (SOS) inventory [33] and SCID and was operationalized by estimating the date on the total SAPS score that would have met the threshold of ≥ 3 . Cross-referencing with milestones and memorable events was used to enhance the accuracy of dating. All of the interviews were conducted during the patient's first episode of psychosis. Family members and other carers also provided collateral reports for dating the onset of positive symptoms. Information gathered by a senior psychiatrist, nurses and social workers was considered to establish the DUP. After completion of all interviews, consensus-based best estimates were determined for variables in which there may have been discrepancies between clinician, patient, and family reports.

Other variables were gender; educational level (1. Primary education; 2.10 years of education or higher); living arrangements at the onset of psychosis (1. Living with relatives; 2. Living alone and other status); occupational status for 2 years prior to the initial interview (1. Employment/student; 2. Unemployed) and premorbid adjustment scale (PAS) [34].

2.5.2. Clinical variables

Clinical symptoms of psychosis were assessed using the Scale for the Assessment of Negative Symptoms (SANS) [35], the Scale for the Assessment of Positive Symptoms (SAPS) [36] and their

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