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Persistent negative symptoms in first episode patients with schizophrenia: Results from the European First Episode Schizophrenia Trial

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Abstract
Negative symptoms that do not improve following antipsychotic treatment represent a challenge for development of effective treatments. Few studies have been carried out so far, especially in first-episode schizophrenia patients, to clarify prevalence, correlates and impact of persistent negative symptoms (PNS) on short- and long-term outcome of the disease.
All patients from EUFEST study for whom both baseline and 12-month assessments were available were included (N=345). PNS were defined as the presence of at least one negative symptom of moderate or higher severity, not confounded by depression or parkinsonism, at baseline and after 1 year of treatment. Patients with PNS were compared to those with at least one negative symptom of moderate or higher severity at the baseline, not persisting after 1 year, on demographic, clinical, neurocognitive, global functioning and quality of life measures.
PNS not confounded by depression or parkinsonism were present in 6.7% of the sample. The symptom that more often persisted was blunted affect. Patients with PNS differed from those

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without PNS for a longer duration of untreated psychosis (DUP) and a more frequent discontinuation of study treatment; they also had a poorer psychopathological outcome and a worse global functioning after 1 year of treatment.
The presence of PNS was associated to poorer improvement of all psychopathological dimensions and worse global functioning after 1 year of treatment. The longer DUP in subjects with PNS suggests that programs aimed at shortening DUP might reduce the prevalence of PNS and improve prognosis of schizophrenia.

1. Introduction

Negative symptoms of schizophrenia are often associated with poor response to available treatments and functional outcome (Galderisi and Maj, 2009; Milev et al., 2005; Kirkpatrick et al., 2006). It is largely acknowledged that they represent a heterogeneous clinical construct, including primary negative symptoms, a core aspect of the illness, as well as secondary negative symptoms, due to other aspects of the disorder (e.g. positive symptoms, depression) or other factors (e.g. antipsychotic drugs, isolation). Both primary and secondary negative symptoms may be temporary or enduring. In spite of this complexity, clinical trials still tend to focus on the evaluation of the broad construct, as captured by largely used psychopathological rating scales, such as the Scale for Assessment of Negative Symptoms (SANS), the Brief Psychiatric Rating Scale (BPRS) or the Positive and Negative Syndrome Scale (PANSS). Two alternative approaches might be considered to foster research progress on pathophysiology and treatment of negative symptoms. The first approach is based on the identification of patients with primary and enduring negative symptoms, that represent the core aspect of a putative schizophrenia subtype named Deficit Schizophrenia (DS, Carpenter et al., 1988; Edwards et al., 1999; Kirkpatrick and Galderisi, 2008). Although the deficit/nondeficit categorization can be made reliably, the diagnosis of deficit schizophrenia may be difficult, especially as it applies to patients early in the course of their illness (Edwards et al., 1999; Mayerhoff et al., 1994), due to the highly fluid clinical pattern and the frequent lack of sufficient longitudinal observation allowing the distinction between primary and secondary negative symptoms. The second approach is based on the identification of persistent negative symptoms (PNS), that can be either primary to the illness, or secondary, but have not responded to the usual treatments for these symptoms, persist during periods of clinical stability and represent an unmet therapeutic need (Buchanan, 2007; Buchanan et al., 1996). This psychopathological construct is regarded as broader than the one relevant to the deficit syndrome and as having greater potential clinical utility. In fact, the classification of patients into deficit or nondeficit forms of schizophrenia requires clinicians skilled in the distinction between primary and secondary negative symptoms, trained in the use of the Schedule for the Deficit Syndrome (Kirkpatrick et al., 1989), and can be difficult when information on symptoms longitudinal course is scarce. Instead, the identification of PNS is based on rating scales largely used in clinical settings and does not require additional training than the one needed for those scales. It is recommended (Buchanan, 2007) that clinical trials on PNS should set a minimal severity level of negative symptoms and restrict severity of other symptoms that may contribute to secondary negative symptoms (positive, depressive and extrapyramidal symptoms). At odds with the criteria for the DS, the duration of negative symptoms can be less than 12 months, but preferably not less than 6 months. Criteria for the identification of subjects with PNS are actually less restrictive and easier to apply than those required for the diagnosis of deficit schizophrenia, though conceptually close to them.

The issue of PNS in patients with first episode non-affective psychoses has been addressed by previous studies using different methods. Discrepant prevalence figures were reported, ranging from 3.8% to 31.5% (Mayerhoff et al., 1994; Edwards et al., 1999; Malla et al., 2004; Chang et al. 2011), due to different definitions of PNS, but also to different clinical variables, such as the severity of positive symptoms or the duration of longitudinal assessment.

The European First Episode Schizophrenia Trial or EUFEST (Fleischhacker et al., 2005; Kahn et al., 2008), an open randomized trial, not excluding subjects with comorbidities, such as substance abuse, collected demographic, clinical, psychosocial and cognitive baseline data in a large cohort of first episode patients with schizophrenia, schizophreniform or schizoaffective disorder. Data from EUFEST may contribute to answer the following questions in a large sample of FE patients, hardly ever exposed to antipsychotics and relatively unselected: (a) How often do negative symptoms persist after one year of treatment in a large group of first episode schizophrenia patients? (b) Do first episode patients with PNS differ from those without PNS on other clinical indices, neuropsychological measures and psychosocial variables? (c) Is the frequency and severity of PNS influenced by positive symptoms remission or by the antipsychotic type? (d) Is there any indicator enabling the early identification of those who will show persistent negative symptoms in spite of treatment?

2. Experimental procedures

Data from the European First Episode Schizophrenia Trial (EUFEST, Kahn et al., 2008) were used for the present study. Details of the entry criteria have been presented elsewhere (Kahn et al., 2008). Briefly, patients included in EUFEST were 18–40 years of age, met DSM-IV criteria for schizophrenia, schizoaffective or schizophreniform disorder; recent onset of psychosis with less than two years elapsed between the onset of positive symptoms and recruitment into the trial; previous use of antipsychotic drugs less than two weeks during the preceding year and less than six weeks lifetime.