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Treatment resistant schizophrenia is associated with the worst community functioning among severely-ill highly-disabling psychiatric conditions and is the most relevant predictor of poorer achievements in functional milestones

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ABSTRACT

The aim of this work was to compare achievements in milestones of community functioning in highly disabling psychiatric conditions, including treatment resistant schizophrenia (TRS), schizophrenia (responsive to antipsychotics), bipolar disorder, and anxiety/depressive diseases. Also, we investigated the predictors of community functioning outcomes across several domains.

Among consecutive patients screened, 188 met inclusion criteria and 118 ultimately entered the study. Diagnosis of TRS was made by stringent criteria, including historic and perspective evaluations and excluding potential confounding factors. Achievements in functional milestones of everyday living were recorded. Performances in discrete cognitive tasks were assessed. The Positive and Negative Syndrome Scale, the Personal and Social Performance Scale, the Drug Attitude Inventory-10, and the Quality of Life Enjoyment and Satisfaction Questionnaire were administered.

TRS patients showed the highest impairment in community functioning among diagnostic groups. TRS was found to have more severe psychopathology, more impaired cognitive functioning, and poorer psychosocial adjustment compared to all the other groups. In the whole sample, the main predictors of community functioning were the diagnostic group (with TRS diagnosis associated with worst functioning) and achievements in the other functional milestones. In psychotic patients, however, the main predictors of community functioning were clinical and psychopathological variables.

These results may support the hypothesis that TRS represents a separate schizophrenia subtype, with its own neurobiology, psychopathology and clinical course. Our results identify a group of modifiable predictors to be addressed to prevent community disability.

1. Introduction

Treatment resistant schizophrenia (TRS) is a severe clinical condition with poor or no responsiveness to antipsychotic treatment affecting at least one third of schizophrenia patients (Lindenmayer, 2000), who do not respond or respond poorly to antipsychotic medications (Kane, 1996). The lack of response to antipsychotics is associated in these patients with persisting psychotic symptoms (both positive and negative) and cognitive dysfunctions (de Bartolomeis et al., 2013; Gilbert et al., 2014; Iasevoli et al., 2013), all of which have been regarded to predispose to social dysfunctions in schizophrenia patients (Burton et al., 2013; Galderisi et al., 2014), contributing to long-term disability and poor community functioning (Dickinson et al., 2007; Rocca et al., 2014; Rosenheck et al., 2006; Twamley et al., 2002, 2008).

Abbreviations: ADS, anxiety and depressive diseases; ANOVA, analysis of variance; BDS, bipolar disorder; BDZ, benzodiazepine; DAI-10, 10-Item Drug Attitude Inventory; DSM, Diagnostic and Statistical Manual of Mental Disorders; MCAR, Missing Completely At Random test; MLR, Multilinear Logistic Regression; PANSS, Positive and Negative Syndrome Scale; PSP, Personal and Social Performance Scale; Q-LES-Q, Quality of Life Enjoyment and Satisfaction Questionnaire; SCID-I, Structured Interview for Diagnosis Axis I; SZ-AR, schizophrenia patients antipsychotics-responsive; TRS, treatment resistant schizophrenia.

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Despite an extensive literature on inadequate social adaptations in schizophrenia patients is available (Couture et al., 2011; Harvey, 2009; Harvey et al., 2009; Strassnig et al., 2015), very few data have been to date provided on the extent of social dysfunctions and community functioning in TRS, compared to responder schizophrenia patients and to other highly disabling psychiatric conditions. High rates of unemployment in a mixed sample of TRS and schizoaffective patients were found and were related to impaired neurocognitive performances (Kaneda et al., 2010), however no comparison was given with other psychiatric conditions or with antipsychotic responder schizophrenia patients. As TRS has been regarded as a more severe subtype of schizophrenia, with putative distinct neurobiological underpinnings (Demjaha et al., 2012, 2014; Frank et al., 2015; Quarantelli et al., 2014; Szeszko et al., 2012) and poorer prognosis (Kolakowska et al., 1985; Sheitman and Lieberman, 1998), it is expected that TRS patients will suffer from more serious disability.

Quantitative evaluation of disability and social competence in schizophrenia patients has been a challenging issue. Indeed, self-reported questionnaires, such as assessment of quality of life or of skills profile, are often jeopardized by patients' lack of complete insight on their pathological conditions (Bowie et al., 2007; Sabbag et al., 2011), while increasing reliability may be granted to informants' reports, high-contact clinicians' reports, and assessments of real-word everyday functioning (Harvey and Velligan, 2011). Measurement of everyday functioning has been accomplished by two approaches: ratings of real-world functioning using structured or performance-based assessments (Harvey et al., 2007, 2011; Leifker et al., 2011), and the examination of functional achievements (e.g., marriage; independent living; competitive employment), the so-called functional milestones (Harvey et al., 2012). Therefore, milestones of real-world functioning are a reliable direct measure of everyday community functioning and may evaluate disability in multiple everyday functional domains, whose impairment is common in schizophrenia patients (Murray and Lopez, 1997), including vocational, residential, and social domains (Bowie et al., 2008; Twamley et al., 2002), and whose attainment is considered basic to social living (Wiersma et al., 2000).

The main aim of this work was to evaluate whether significant differences in functional milestones' achievements can be detected among TRS, schizophrenia responders and patients with non-schizophrenic highly disabling psychiatric conditions. Additional aims were: i) to evaluate whether significant differences can be found among TRS, schizophrenia responders and the other patients of the sample in multiple demographic, clinical, therapy-related, psychopathological, cognitive and psychosocial variables; ii) to dissect, among the above-mentioned groups of variables, the predictors of outcomes in community functioning, as measured by functional milestones, in the whole sample of patients; and iii) to identify the predictors of achievement in functional milestones in the sample of psychotic patients.

2. Methods

2.1. Study design

This cross-sectional, naturalistic trial was conducted at the Outpatient Unit on Treatment Resistant Psychosis, Section of Psychiatry, Department of Neuroscience, University "Federico II" of Naples, from September 2013 to December 2014. All consecutive patients meeting criteria for eligibility were recruited. All patients signed a written informed consent form, approved by the participating institution. Patients were adequately informed of all aspects regarding the participation and the purpose of the study and had the possibility to withdraw their consent at any time of the study. All procedures carried out in the present study complied with the principles laid down by the Declaration of Helsinki, revised Hong Kong 1989.

Patients were referred to our unit since they were supposed to be non-responsive to medical treatments. All patients underwent diagnostic evaluation, made by trained psychiatrists through the Structured Interview for Diagnosis (SCID-I), and were prescribed appropriate pharmacological interventions. Prescriptions were made by FI and AdB, only. After conclusion of diagnostic evaluation and subsequent therapy prescription, patients underwent the assessments described in this study. Differential diagnosis between schizophrenia and TRS was made as described in the section below. Patients were then subdivided in four diagnostic groups that were compared for their disabilities in functional milestones of everyday living: i) TRS patients (TRS); ii) schizophrenia patients responsive to antipsychotic treatments (SZ-AR); iii) bipolar disorder (BDS); and iv) anxiety and depressive diseases (ADS). Since the primary goal of this study was to evaluate whether a diagnosis of TRS was associated with higher disability compared to other disabling psychiatric disorders, we did not include in the study a non-affected control group. All the patients included in the study suffered from serious psychopathological disturbances and had impaired social performances.

2.2. Patients

Patients eligible for enrollment were required to be 18–65 years of age, to have Personal and Social Performance Scale (PSP) score ≤ 70 (consistent with marked impairment in at least one area of psychosocial functioning), and to met DSM-5 diagnostic criteria for the following axis I diagnostic groups: i) schizophrenia (limited to the following diagnostic code: 295.9); ii) bipolar disorder (limited to the following diagnostic codes: 296.4; 296.5; 296.7; 296.89; 296.80; 310.13); and iii) anxiety and/or depressive diseases (limited to the following diagnostic codes: 296.2; 296.3; 300.4; 311; 300.02; 300.3). This latter class of heterogeneous diagnoses was included as to provide an internal control by non-psychotic non-bipolar disabling conditions.

Exclusion criteria were: i) mental retardation; ii) severe medical diseases; iii) psychiatric disorders due to another medical condition; and iv) psychiatric disorders induced by substances/medications.

2.3. Definition of TRS

Patients with a diagnosis of schizophrenia underwent an additional diagnostic process to evaluate whether they were TRS, pseudopharmacoresistant, or responsive to antipsychotic medications.

As a first step in the diagnostic procedure, all schizophrenia patients were assessed by PANSS. A score of 70 was regarded as the cut-off to consider a patient not actively symptomatic (Findling et al., 2008; Kozma et al., 2010; Leucht et al., 2006). Therefore, schizophrenia patients whose PANSS total score was inferior to 70 were considered currently responsive to antipsychotics and were diagnosed as non-TRS (thereafter we will refer to these patients as SZ-AR).

Patients whose PANSS total score was >70 were investigated for the possibility to be TRS. Diagnostic criteria for TRS were derived from previously published algorithms, such as those provided by the American Psychiatric Association (Lehman et al., 2004). These algorithms state that a schizophrenia patient should be considered resistant to treatment if he/she had failed to respond to two or three trials with antipsychotic agents (both first generation antipsychotics, such as haloperidol, and second generation antipsychotics other than clozapine, such as risperidone, olanzapine, quetiapine or aripiprazole), given at therapeutic doses (300–600 mg/day chlorpromazine equivalents) and for at least four-to-six weeks (Conley and Kelly, 2001). According to these operational criteria and to classical definitions of TRS (Meltzer, 1990), non-responsive patients in our sample were regarded as "possible TRS" if they had an history of documented non-response to at least three different antipsychotics in the past five years, given for an adequate period of time and at appropriate doses, without a period of symptomatic relief, remission, or recovery of prior levels of social functioning. Assessment of non-response to antipsychotics was made on the basis of clinical information and of previous medical records (when available). Only those cases whose medication history can be reliably reconstructed