Responses to antipsychotic therapy among patients with schizophrenia or schizoaffective disorder and either predominant or prominent negative symptoms

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A B S T R A C T

Patients with schizophrenia who have predominant negative symptoms are often considered less responsive to treatment. This analysis of patients with schizophrenia or schizoaffective disorder compares changes in symptom severity between those with predominant versus merely prominent negative symptoms. Prominent negative symptoms were defined by a baseline score of ≥4 on at least 3, or ≥5 on at least 2, of the 7 Positive and Negative Syndrome Scale (PANSS) negative subscale items. Predominant negative symptoms were defined by the foregoing plus a PANSS positive score of <19, a Barnes Akathisia score of <2, a Simpson-Angus score of <4, and a Calgary Depressive Scale score of <9. Adult patients with schizophrenia (n=227) or schizoaffective disorder (n=116) received either olanzapine (10–20 mg/day, n=169) or quetiapine (300–700 mg/day, n=174) for up to 24 weeks. Data for both medications were pooled. Of the 343 patients enrolled in the study, 34.7% met the criteria for predominant negative symptoms, the remaining 65.3% being characterized by their prominent negative symptoms. Changes in the severity of negative symptoms in both patient types were similar. Positive symptoms largely followed similar trajectories during treatment, as reflected both in Marder PANSS negative subscale scores and in the Scale for Assessment of Negative Symptoms total and domain scores. Patients with either predominant or prominent negative symptoms therefore appear to respond similarly to atypical antipsychotic treatment. This distinction, incorporating an evaluation of the presence of positive, affective, and extrapyramidal symptoms, may therefore not have prognostic implications for the responsiveness of patients’ negative symptoms to treatment.

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1. Introduction

Since the original proposal to differentiate positive from negative symptoms of schizophrenia (Wing, 1978; Crow, 1980), controversy has existed over whether these represent distinct comorbid psychopathologies or merely represent different aspects of a single disorder with differing degrees of expression among patients. Positive symptoms often respond well to antipsychotic agents, whereas negative symptoms, commonly associated with poorer functioning and lower quality of life (Gourevitch et al., 2004; Lysaker and Davis, 2004), have historically been more resistant to treatment (Angrist et al., 1980; Buchanan et al., 1998; Leucht et al., 2009). As a step toward accurately identifying subpopulations of patients with schizophrenia to provide more tailored therapies, an attempt is being made to characterize treatment-resistant patients with pronounced negative symptoms based on their symptomatic profiles. However, it is still unclear whether improvement of negative symptoms reflects a specific, primary effect of treatment on negative symptoms or is secondary to an improvement of positive symptoms, a reduction of comorbid symptoms of depression or anxiety, or an alleviation of the extrapyramidal effects of previous therapy. Care must be taken during clinical studies to avoid the potentially confounding influence of this “pseudospecificity.” Accordingly, the National Institute of Mental Health (NIMH) consensus statement on negative symptoms (Kirkpatrick et al., 2006) suggests that clinical studies of new medications to treat predominant, persistent negative symptoms include patients with primary negative symptoms, and that the effects of treatment on negative symptoms be distinguishable from changes due to secondary effects.

This post hoc analysis used data from a 24-week study of patients with schizophrenia or schizoaffective disorder and treated with olanzapine or quetiapine to determine whether patients with predominant negative symptoms differ from other patients with prominent negative symptoms.
symptoms in the magnitude of improvements in their negative symptoms. (Note: neither medication is approved for the selective treatment of negative symptoms.) Relative changes in positive symptoms and quality of life were also assessed to determine whether changes in negative symptom severity are linked to changes in quality of life. If improvement of negative symptoms is secondary to an improvement in positive symptoms, less improvement of negative symptoms should be seen among patients with predominant negative symptoms because such patients, by our definition, will have a lower baseline severity of positive symptoms than patients with prominent negative symptoms. Alternatively, if we see a similar decrease in the severity of negative symptoms in the two patient groups, this would suggest a primary effect of treatment.

2. Materials and methods

2.1. Study design

This analysis was based on data from study F1D-US-HGJB, a multicenter, randomized, double-blind, parallel study conducted at 29 sites in the United States between 08 November 2000 and 15 March 2002. The methods and main results of this study have been published (Kinon et al., 2006). Participating subjects were male or female adult (18 to 65 years of age) outpatients with a Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (American Psychiatric Association, 1994) diagnosis of either schizophrenia (n = 227) or schizoaffective disorder (n = 116). Patients were recruited from residential care facilities day-hospitals, or partial hospitalization programs, and the study was conducted primarily at outpatient sites. The study was conducted in accordance with the recommendations of the Declaration of Helsinki (World Medical Association, 2000). The study protocol was approved by the institutional review boards for each site, and patients gave written informed consent before entering the study.

2.2. Patient sample

For inclusion in the study, patients were required to have prominent negative symptoms, as defined by a baseline score ≥4 (moderate) on at least 3, or ≥5 (moderately severe) on at least 2, of the 7 negative subscale items of the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987, 2000), as proposed by Marder et al. (1997). In addition, patients were required to have a baseline score of ≤60 (moderate or worse) on the Global Assessment of Functioning Scale (GAF) (American Psychiatric Association, 2000). Patients in this analysis were characterized by the presence or absence of predominant negative symptoms, defined by the foregoing baseline entry criteria plus a PANSS positive subscale score <19, a Barnes Akathisia Scale (Barnes, 1989) global assessment score <2, a Simpson–Angus Scale (Simpson and Angus, 1970) total score for parkinsonian symptoms <4, and a Calgary Depressive Scale (Addington et al., 1992) total score <9. Patients characterized with predominant negative symptoms (“Predominant-group patients”) can therefore be considered as a subset of the overall group of patients with prominent negative symptoms but with a lesser contribution of positive symptoms to overall illness severity; the remainder are referred to as “Prominent-group patients.” The PANSS positive score of 19 was chosen as it was the median baseline value for the overall patient sample and less than the baseline mean PANSS positive subscale score, as proposed by Alphs et al., 2007. The criteria for extrapyramidal and depressive symptoms (Alphs et al., 2007) have been included to eliminate their potential confounding influences on negative symptom assessment, thereby allowing a selective assessment of changes in negative symptoms as distinct from these other symptoms of psychopathology and motor behavior (Laughren and Levin, 2006).

2.3. Treatment and assessment

Patients visited the clinic weekly for the first 4 weeks of treatment, every 2 weeks for the next 4 weeks, then monthly thereafter, for a total of 24 weeks of randomized treatment. Patients were assigned to treatment with either olanzapine (10 to 20 mg/day, n = 169) or quetiapine (300 to 700 mg/day, n = 174) in a 1:1 ratio, based on an Interactive Voice Response System computer-generated randomization code. Randomization was balanced by using permuted blocks and stratified by site. Treatment efficacy was assessed using the PANSS total score and the positive and general psychopathology subscale scores as defined by Kay et al. (1987) and the negative subscale as defined by Marder et al. (1997). PANSS measurements were obtained at each study visit. Negative symptom severity was also measured with the 1989 version of the Scale for Assessment of Negative Symptoms (SANS) (Andreasen, 1989), the predefined primary measure of efficacy in the original study on which this analysis is based. SANS scores were assessed at every visit. To assess levels of functioning, Heinrichs–Carpenter Quality of Life Scale (QLS) (Heinrichs et al., 1984) scores were measured at baseline, weeks 8 and 16, and endpoint (week 24 or discontinuation). GAF scores were measured at baseline and endpoint.

2.4. Statistical analyses

Data from both medications were pooled, and differences were examined between patients characterized by either predominant or prominent negative symptoms. Changes from baseline in symptom severity and quality of life were analyzed and compared between patient subgroups (Predominant versus Prominent) using a restricted maximum likelihood-based mixed–model repeated measures analysis with terms for visit, patient subgroup, and subgroup-by-visit interaction, adjusting for treatment, investigative site, and baseline value of the analyzed measure. To approximate inference for fixed effects, Kenward–Roger approximation (Kenward and Roger, 1997) was used for estimation of denominator degrees of freedom. Within-patient errors were modeled using an unstructured covariance matrix. Changes in quality of life measured by GAF scores were analyzed and compared between the Predominant and Prominent subgroups using analysis of covariance, adjusting for baseline score and treatment. Correlations between changes in SANS composite and QLS total scores at weeks 8, 16, and 24 were assessed using Pearson partial correlation (Pearson, 1966), adjusting for treatment, patient subgroup, and investigative site. All tests were based on a 2-tailed α significance of 0.05. Analyses were performed using SAS software (SAS Institute Inc, Cary, NC). No adjustments were made for multiple testing.

3. Results

3.1. Demographics

In total, 343 patients were enrolled in this study, 119 (34.7%) of whom met the criteria of predominant negative symptoms and the remainder (n = 224, 65.3%) characterized only by their prominent negative symptoms. Predominant-group patients did not differ significantly from Prominent-group patients in their female:male ratios, mean ages at study entry, racial or ethnic origins, or diagnoses of schizophrenia versus schizoaffective disorder (Table 1). The proportions of patients receiving olanzapine or quetiapine were also comparable in both groups.

3.2. Baseline values

Predominant-group patients did not differ significantly from Prominent-group patients in their ages at onset of psychotic symptoms (Table 2). However, Prominent-group patients had a significantly longer mean duration of illness and greater baseline severity of symptoms, as reflected in their mean GAF and PANSS (total and all 3 subscales) scores.
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