Schizophrenia Research 156 (2014) 107–114

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Treatment response heterogeneity in the predominant negative symptoms of schizophrenia: Analysis of amisulpride vs placebo in three clinical trials

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ARTICLE INFO

Article history:
Received 13 January 2014
Received in revised form 9 March 2014
Accepted 2 April 2014
Available online 29 April 2014

Keywords:
Scale for the Assessment of Negative Symptoms
Symptom response
Trajectories
Heterogeneity
Treatment
Negative symptoms

ABSTRACT

Background: The extent of heterogeneity in response to the psychopharmacological treatment of negative symptoms is unknown.
Aims: To examine the extent of heterogeneity in response to the treatment of predominantly negative symptoms of schizophrenia.
Method: Data were analyzed from three clinical trials that compared placebo or amisulpride for up to 60 days. Trial participants had predominantly negative symptoms of schizophrenia (n = 485). Heterogeneity of percentage reduction on the Scale for the Assessment of Negative Symptoms (SANS) was examined with trajectory-group based modeling followed by descriptive statistics and the prediction of trajectory group membership with logistic regression modeling. Analyses were repeated separately for the placebo and amisulpride groups.
Results: Trajectory group-based modeling identified groups of non- (n = 297, 61.2%), gradual–moderate (n = 135, 27.8%) and rapid- (n = 53, 10.9%) responders. At baseline compared to non-responders, rapid-responders had consistently significantly ($p < .05$) higher SANS total and subscale scores. Percent SANS improvement at endpoint was greatest for the rapid-responders group, a finding that replicated stratifying by placebo and amisulpride treatment groups. Similarly, in the total sample and stratifying by placebo and amisulpride groups, dropout was not significantly associated with trajectory group membership.
Conclusions: Trajectories of treatment response to the psychopharmacological medication of the negative symptoms of schizophrenia demonstrate substantial heterogeneity. Approximately half of the patients included in our analysis showed little improvement, and the most severely ill at baseline responded the most.

1. Introduction

Negative symptoms of schizophrenia (anhedonia, social withdrawal, affective flattening, and demotivation) are associated with deficits in cognitive, social and real-world functioning (Bowie et al., 2006; Harvey et al., 2006; Kirkpatrick et al., 2006). As the course of the disorder develops, negative symptoms persist in the long term to become more predominant than positive symptoms (Lieberman et al., 2001). Antipsychotics, however, are mainly effective for positive symptoms and the introduction of second-generation antipsychotics has not substantially improved this situation (Leucht et al., 2009). Therefore, there are currently intense efforts to develop psychopharmacological treatments of predominant negative symptoms. At least 15 psychopharmacological trials are currently underway to treat negative symptoms (Arango et al., 2013). A NIMH-MATRICS expert consensus group has been formed on negative symptoms with participants from academia, the Federal Drug Administration and industry (Alphs, 2006; Kirkpatrick and Fischer, 2006; Kirkpatrick et al., 2006; Marder et al., 2011), and conclusions of a recent consensus meeting reported (Marder et al., 2013). The NIMH-MATRICS consensus group has noted methodological and measurement challenges in clinical trials of negative symptoms (Kirkpatrick et al., 2006). This was elaborated on by recent directions on measurement (Daniel, 2013) backed by clinically meaningful thresholds on the SANS (Levine and Leucht, 2013). Despite these developments, little is known as to the extent of heterogeneity in negative symptoms.

Reviews and epidemiological research, however, highlight that the course of schizophrenia is heterogeneous (Tandon et al., 2008; Levine et al., 2011). Examination of heterogeneity in symptoms rather than comparing aggregated medication groups may identify (a) groups of responders, and/or non-responders, and/or placebo-responders, (b) key periods of response, (c) the extent of response is for a minority or majority of patients and/or (d) that the inferior medication showed steady but mild response for most patients. To identify the extent of

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http://dx.doi.org/10.1016/j.schres.2014.04.005
0920-9964/

heterogeneity in symptoms studies apply a statistical method known as group-based trajectory modeling (Jones and Nagin, 2007). Group-based trajectory modeling empirically identifies different groups of patients who assume similar response patterns over time, quantifies the extent of heterogeneity, and identifies key time points of change in symptom response. This method has been used to study depression (Pelayo-Terán et al., 2014) as well as schizophrenia. Re-analysis of randomized controlled trials of schizophrenia with trial participants selected on the basis of positive symptoms have shown that symptom response is heterogeneous and is typically captured by four or five symptom severity trajectory groups (Levine and Leucht, 2010; Levine and Rabinowitz, 2010; Levine et al., 2010; Case et al., 2011; Levine et al., 2011; Marques et al., 2011; Stauffer et al., 2011; Levine et al., 2012). A summary of those trajectory studies of symptom response has estimated that approximately 16% of clinical trial participants assume a trajectory course of 'dramatic response' based on approximately a 60% to 80% symptom reduction (Levine et al., 2010).

In sum, to extend the literature on heterogeneity in symptom response and on negative symptoms of schizophrenia, the current study aims to examine the extent of heterogeneity in negative symptom response in patients with predominantly negative symptoms who received amisulpride or placebo.

2. Methods

2.1. Participants and measures

Patients (n = 487) were participants in three double-blind randomized placebo-controlled clinical trials that compared amisulpride with placebo for the treatment of predominant negative symptoms as defined in each study described below (Boyer et al., 1995; Loo et al., 1997; Danion et al., 1999). The trials used similar symptom selection criteria, randomized participants to placebo or amisulpride, had similar diagnostic groups (i.e., absence of early onset), used the Scale for the Assessment of Negative Symptoms (SANS) to assess negative symptoms (Andreasen, 1983) and had overlapping visit schedules. Complete trial documentation, such as the inclusion criteria and efficacy analyses, is reported in the primary study reports (Boyer et al., 1995; Loo et al., 1997; Danion et al., 1999).

Across the three trials most participants were male (65.3% n = 318), and had a mean age of 34.04 (SD = 9.4). Each trial may be described as follows- (1) a multicenter trial, symptom inclusion thresholds of ≥75 SANS & ≤60 SAPS, diagnoses of disorganized, catatonic, undifferentiated and residual schizophrenia, and a 6-week washout phase (12-week if neuroleptics were received) followed by a six-week trial with randomization to placebo (n = 34) and or amisulpride (n = 70) conditions (Boyer et al., 1995); (2) a multicenter multinational trial, symptom inclusion thresholds of ≥60 SANS & ≤50 SAPS, diagnoses of residual schizophrenia, and a 4-week washout period followed by randomization for 12 weeks to amisulpride (n = 159) or placebo (n = 83) (Danion et al., 1999); and (3) a multicenter trial, symptom inclusion thresholds of ≥60 SANS & ≤50 SAPS, diagnoses of subchronic or chronic schizophrenia, and entering the trial directly for 24 weeks randomized to amisulpride (n = 69) or placebo (n = 72) (Loo et al., 1997).

2.2. Analytic approach

First, like prior analyses, the percentage SANS reduction (B%) at each week was calculated using the formula $B\% = (B_0 - B_i) * 100 / B_0$, where B_0 — SANS at baseline, B_i — SANS at week $_i$ (Leucht et al., 2005). This outcome was chosen since symptom response thresholds on the SANS reduction have been identified. Namely, research has shown that as 'very much improved' corresponds to a SANS percent changes of −90 to −67, 'much improved' to −50 to −42, and 'minimally improved' to −21 to −13 (Levine and Leucht, 2013).

Second, to identify subgroups of patients with similar courses of treatment response, group-based trajectory analysis was computed (Levine and Leucht, 2010; Levine and Rabinowitz, 2010; Levine et al., 2010). Using available information at each time-period, like mixed modeling (Lieberman et al., 2005), group-based trajectory analysis identifies subgroups of patients that are homogeneous on outcome criteria (i.e., SANS percent improvement) within the group, and significantly dissimilar (i.e., heterogeneous) from other subgroups in substantial ways (Haviland and Nagin, 2005). To identify the appropriate and most parsimonious number of subgroups the Bayes Information Criterion (BIC) is used. To illustrate treatment response at each week, SANS percentage improvement scores were plotted for the resultant treatment response trajectories. Analysis consisted of SANS percent improvement adjusted for baseline and treatment group as exposures, and accounted for non-random dropout (Nagin, 2005; Nagin and Odgers, 2010). Group-based trajectory analyses were computed for the aggregate (i.e., total) sample. These were implemented exactly as they had been in prior schizophrenia research (Levine and Leucht, 2010; Levine et al., 2010) except: that baseline severity and treatment group were accounted for, and the data based on this form of trajectory analysis are assumed to be not missing at random to account appropriately for systematic dropout (Haviland et al., 2011). At step three of the analysis the resultant empirically identified trajectory groups were compared at baseline with pairwise comparisons. At step four, resultant trajectory group membership was predicted using binary logistic modeling with sex, age, baseline SANS, and medication group as covariates in that order. At step five, the aforementioned steps two to five were re-computed stratifying by placebo, and amisulpride groups. At step six, the extent of trajectory group overlap was examined between the total, and stratified amisulpride and placebo samples.

3. Results

The baseline trial characteristics are presented in Table 1. Participants (n = 2) from two trials (Boyer et al., 1995; Loo et al., 1997) were removed due to missing baseline SANS scores leaving 485 participants with available scores. Next group-based trajectory modeling was computed. In the total sample, examination of the SANS total percent reduction BICs identified a three trajectory group model (Trajectories and BICs were: 1 = −6264.90, 2 = −6058.58, 3 = −6037.37 and 4 = −5886.85, respectively). Posterior probabilities of correct classification were high (.93, .83 and .92). Trajectory group 1 was labeled 'non-responders' (n = 297, 61.2%), trajectory

Table 1
Baseline characteristics across trials.

	M/n	SD/%
Male	318	(65.3)
Female	169	(34.7)
Age	34.0	(9.4)
SANS		
Affect	23.7	(5.9)
Alogia	14.2	(3.6)
Anhedonia	19.6	(3.2)
Attention	8.2	(3.0)
Apathy	13.8	(3.0)
Total	79.5	(13.4)
Randomization		
Amisulpride doses		
(100 mg)	178	(36.6)
(300 mg)	36	(7.4)
(50 mg)	84	(17.2)
Placebo	189	(38.8)

Note. Baseline characteristics of the current study pooled clinical trials.