Schizophrenia Research 143 (2013) 60–64

Contents lists available at SciVerse ScienceDirect

Schizophrenia Research

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

Attaining and sustaining remission of predominant negative symptoms

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ARTICLE INFO

Article history:
Received 7 June 2012
Received in revised form 28 October 2012
Accepted 1 November 2012
Available online 4 December 2012

Keywords:
Schizophrenia
Remission
Antipsychotic medication
Clinical trial
Negative symptoms

ABSTRACT

Background: Evidence is lacking on remission in the presence of predominant negative symptoms.
Aims: To examine remission rates and their variation by antipsychotic medication in predominant negative symptoms.
Methods: Data were reanalyzed on patients (n = 383) who had participated in two double blind randomized placebo-controlled clinical trials of predominant negative symptoms lasting to 84 and 360 days. Symptom remission was defined with the Remission in Schizophrenia Working Group remission criteria of attaining and maintaining mild ratings on eight SANS items. Remission rates were examined to 90 days, survival analysis computed to ascertain time to attain symptom remission, binary logistic models used to predict the remission rate and 2 persistent months of symptom remission, and ANCOVA used to predict percent time in remission.
Results: Symptomatic remission rates were: 22.72% at any visit during 90 days, and 3.66% lasting 2 months. Kaplan–Meier and Cox survival models to adjust for baseline symptom severity showed that compared with the placebo group the amisulpride group attained significantly ($p<.05$) more remission sooner (HR = 2.321, 95% CI = 1.36, to 3.97, $p<.05$). ANCOVA showed that compared with placebo the amisulpride group spent significantly ($p<.05$) more percent time in remission (ES = .28). Specificity analysis showed that: across trials the negative symptom remission rate was 25.1%; and in one 360-day trial the six-month remission criteria were attained and maintained by 6.4% of participants.
Conclusions: Presented with predominant negative symptoms the Working Group Remission criteria appear not to be a pragmatic therapeutic objective. Modified remission symptom and time criteria may be an effective way to examine remission.

1. Introduction

At present, the treatment (e.g., biopertine, mGlu2/3, and SPD489) and measurement of negative symptoms are the objective of intense efforts in schizophrenia research (Bowie et al., 2006; Harvey et al., 2006; Kirkpatrick et al., 2006; Levine and Leucht, 2012). Meta-analysis reports that atypical antipsychotic medications are effective in the treatment of the positive and not negative symptoms of schizophrenia (Leucht et al., 2009a). As the course of illness develops, negative symptoms persist in the long term to become more predominant than positive symptoms (Lieberman et al., 2001). 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). The NIMH-MATRICS consensus group has noted methodological and measurement challenges in clinical trials of negative symptoms (Kirkpatrick et al., 2006), yet does not mention remission.

Remission in schizophrenia is well defined and operationalized. Remission is defined as attaining and sustaining a state free from core clinically significant symptoms (Andreasen et al., 2005; Leucht et al., 2009b). The Remission in Schizophrenia Working Group criteria (described in Table 1) aim to offer direction about the chronic course of schizophrenia, and to facilitate the comparison of the effectiveness of medications across the course of illness (Andreasen et al., 2005). Existing clinical trial remission studies are based on patients with predominantly positive symptoms. These studies report rates of attaining and sustaining six months of remission ranging from 20.3% (Beitinger et al., 2008) to 51.9% (Leucht et al., 2007). Reanalysis of CATIE (Lieberman et al., 2005) that does not have positive symptom inclusion criteria shows that at baseline 15.7% of patients were in symptomatic remission, 11.7% of patients attained and sustained six months of remission, 21% attained and sustained at least 3 months of remission, and 44.5% experienced remission for any period (Levine et al., 2011). Thus making the remission time criteria more liberal increased remission in CATIE. Also, since the length of most clinical trials is under six months, most remission studies examine symptomatic remission without the six-month time period remission criteria (Kane, 2008; Leucht et al., 2008).

In summary, negative symptoms are currently an issue, remission is well defined but at present there is no empirical evidence about remission in patients with predominant negative symptoms. Based on

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http://dx.doi.org/10.1016/j.schres.2012.11.010

Table 1
Symptomatic remission criteria of the Remission in Schizophrenia Working Group.

Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983a)	Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1983b)
Affective flattening	Delusions
Avolition-apathy	Hallucinations
Anhedonia-asociality	Positive formal thought disorder
Alogia	Bizarre behavior

Note. Operationally, remission consists of time and symptom criteria according to the Remission in Schizophrenia Working Group (Andreasen et al., 2005). The symptom criteria are to simultaneously attain eight item scores of <3 (Mild) on any of the above select items. The time criteria are to maintain the aforementioned level of symptom remission for six months, but studies often use shorter time periods (Levine et al., 2011).

the reanalysis of two double-blind randomized placebo-controlled clinical trials for the treatment of predominant negative symptoms (Loo et al., 1997; Danion et al., 1999), the current study uniquely aims to examine the course of remission in the treatment of predominant negative symptoms of schizophrenia.

2. Methods

2.1. Participants and measures

Data were reanalyzed from patients (n = 383) who participated in two double-blind randomized placebo-controlled clinical trials the primary purpose of which was to compare amisulpride with placebo for the treatment of predominant negative symptoms (Loo et al., 1997; Danion et al., 1999). The trials may be briefly summarized as follows —(i) a multicenter multinational trial, diagnoses of residual schizophrenia, exclusion of participants with substance abuse risk, 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 (ii) a multicenter trial, diagnoses of subchronic or chronic schizophrenia, exclusion of participants with risk of suicide, alcohol or drug abuse risk, and entering the trial directly for 24 weeks randomized to amisulpride (n = 69) or placebo (n = 72) (Loo et al., 1997).

Across the trials most participants were male (66.3% n = 254), and had a mean age of 34.57 (SD = 9.69). Both trials had symptom inclusion criteria of >= 60 on the SANS & <= 50 on the SAPS, used the SANS as a primary efficacy measure, used the SAPS as a secondary outcome, randomized participants with predominant negative symptoms of schizophrenia to placebo or amisulpride, had similar diagnostic groups (i.e., absence of early onset), and had similar visit schedules to three months (8, 28, 60, and 90 days; Loo et al., 1997 and 14, 30, 56, 83 days; Danion et al., 1999).

In the 12 week follow up of Danion et al. (1999) 33 placebo and 29 amisulpride participants dropped out for the following reasons: loss to follow-up (placebo n = 4, amisulpride n = 4), lack of efficacy (placebo n = 10, amisulpride n = 5), adverse event (placebo n = 14, amisulpride n = 15), uncooperative patient (placebo n = 4, amisulpride n = 4), other (placebo n = 1, amisulpride n = 1). Both trials address the issue of emergence of positive symptoms during the course of the trial as a safety issue. One trial reports that if a SAPS score over 50 it was considered indicative of relapse resulting in discontinuation (Loo et al., 1997) and in the other trial safety was monitored for "reemergence of positive symptoms" (Danion et al., 1999). Collectively, 20 participants were removed for these reasons. Further trial documentation is found in the primary study reports (Loo et al., 1997; Danion et al., 1999).

Measures included in both studies were the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983a) that consists of 34 items, and the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1983b) that consists of 25 items. Scores on each SANS and SAPS item range from 0 (No abnormality) to 5 (severe). The current study used the symptom remission criteria in Table 1. Remission consists of a time criterion, thus scheduled visits from 1 to 4 were respectively merged from days 8, 28, 60, and 90 in one trial (Loo et al., 1997) and on days 14, 30, 56, 83 for the other trial (Danion et al., 1999).

A key feature of these trials was that the measures and symptom inclusion criteria in both trials ensured that negative symptoms were predominant. The symptom inclusion thresholds were SANS >= 60 and <= 50 SAPS. A paired samples t-test showed that the average SAPS scores (M = 19.94, SD = 13.1) were statistically significantly lower ($p < .05$) than the SANS scores (M = 116.0, SD = 78.38; t = 69.41, df = 379, $p < .01$; Cohen's ES d = 1.71, 95% CI = 1.5, 1.8). Accordingly it appears that the study participants had predominant negative symptoms.

2.2. Analytic plan

First, to evoke a time criterion remission scheduled visits from 1 to 4 were merged; respectively from days 8, 28, 60, and 90 in one trial (Loo et al., 1997) and on days 14, 30, 56, 84 for the other trial (Danion et al., 1999). Using all the symptomatic criteria of the Remission in Schizophrenia Working Group criteria (described in Table 1) (Andreasen et al., 2005) outcomes, based on this were (a) time to first visit with symptom remission; (b) whether or not symptom remission was attained; (c) percent time in symptomatic remission computed as the visits attended in remission divided by the number of visits attended multiplied by 100; and (d) attainment of 3 sequential visits (2 months) in symptomatic remission (i.e., partial remission). These remission outcomes resemble prior remission research (Emsley et al., 2007; Levine et al., 2011).

Placebo and amisulpride were compared on the outcomes with the following tests. Time to symptom remission was predicted with Kaplan–Meier survival modeling and with Cox regression, adjusting for baseline symptom severity (i.e., the SANS baseline total score). Whether or not remission and partial remission were attained during follow up were examined with binary logistic regression models. Percent time in remission was predicted using ANCOVA adjusting for baseline.

Specificity analyses consisted of three additional rounds of data analysis. First, to consider the effect of moderated symptom criteria the negative symptoms of the remission criteria were examined (described in Table 1). To this end only the negative symptom remission items on the SANS (i.e., Affective flattening, Avolition-apathy, Anhedonia-asociality and Alogia) were used to compute negative symptom remission. Second, the six-month remission criteria of the Remission in Schizophrenia Working Group were examined based on a 360-day follow up available in one trial (Loo et al., 1997). This trial had scheduled post-baseline visits on days 8, 30, 60, 90, 120, 150, 180, 270 and 360 (Loo et al., 1997). For this analysis the outcomes examined were: time to remission, remission rate, percent time in remission, and the six-month Remission in Schizophrenia Working Group criteria (Andreasen et al., 2005). Third, specificity analysis was conducted to account for age, a proxy for chronicity, and sex that may influence the course of illness. Analyses were conducted previously with adjustments made for sex, age and baseline SANS symptom severity.

3. Results

Trial heterogeneity was examined with a series of t-tests and a Chi-square test. Comparisons between the trials showed no significant differences on sex, age and baseline SAPS scores. SANS baseline total scores were significantly ($p < .05$) lower in the Danion et al. (1999) (M = 76.19, SE = .75) than the Loo et al. (1997) (M = 81.56, SE = 1.15) trial.

Table 2 presents the remission rates for both the trials examined. No participants were in symptom remission at baseline, 22.72% attained symptom remission at any time to 90 days, and 3.66% attained and sustained remission for 2 months. The remission rates by medication group are presented in Table 3. The remission rate