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Review

# Issues and perspectives in designing clinical trials for negative symptoms in schizophrenia

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ABSTRACT

A number of pharmacological agents for treating negative symptoms in schizophrenia are currently in development. Unresolved questions regarding the design of clinical trials in this area were discussed at an international meeting in Florence, Italy in April 2012. Participants included representatives from academia, the pharmaceutical industry, and the European Medicines Agency (EMA). Prior to the meeting, participants submitted key questions for debate and discussion. Responses to the questions guided the discussion during the meeting. The group reached agreement on a number of issues: (1) study subjects should be under the age of 65; (2) subjects should be excluded for symptoms of depression that do not overlap with negative symptoms; (3) functional measures should not be required as a co-primary in negative symptom trials; (4) information from informants should be included for ratings when available; (5) Phase 2 negative symptom trials should be 12 weeks and 26 weeks is preferred for Phase 3 trials; (6) prior to entry into a negative symptom study, subjects should demonstrate clinical stability for a period of 4 to 6 months by collection of retrospective information; and (7) prior to entry, the stability of negative and positive symptoms should be confirmed prospectively for four weeks or longer. The participants could not reach agreement on whether predominant or prominent negative symptoms should be required for study subjects.

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## 1. Introduction

Given their relationship to functioning and their importance for successful rehabilitation (Fenton and McGlashan, 1994; Rabinowitz et al., 2012) negative symptoms in schizophrenia are an important target for

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drug development. Negative symptoms are relatively common (Bobes et al., 2010) with one recent study finding that 57.6% of stable outpatients patients treated with second generation antipsychotics had at least one negative symptom. With the exception of amisulpride (Leucht et al., 2002) in some European countries, there are no pharmacological agents approved for the treatment of negative symptoms. As this is a relatively new therapeutic area, there are a number of unresolved questions regarding the design of clinical trials in this field. Although some of these issues have been discussed in previous publications (Kirkpatrick et al., 2006; Marder et al., 2011), a further review of methodological issues is warranted for a number of reasons: (1) considerable data have recently become available from negative symptom trials; (2) methodological issues had not been discussed in an international forum; and (3) regulatory agencies have been considering new guidelines for trials in schizophrenia.

NEWMEDS (Novel Methods leading to NeW MEdications in Depression and Schizophrenia), an academic industry collaboration funded by the Innovative Medicines Initiative Joint Undertaking (IMI JU) by the European Federation of Pharmaceutical Industries and Associations (EFPIA) and the European Union, sponsored a one day workshop on April 19, 2012 in Florence, Italy titled "Challenges, Issues, and Perspectives in Designing and Conducting Studies of Negative Symptoms in Schizophrenia". The goal of the workshop was to initiate a broad discussion of critical issues in designing clinical trials. International representatives from academia, the pharmaceutical industry, and the European Medicines Agency (EMA), a regulatory body attended. Prior to the meeting, participants submitted key questions for debate and discussion. The proposed questions focused on issues such as the selection criteria for trial participants; trial designs for medications that would be added to an antipsychotic as a co-medication and for "broad spectrum" medications that would treat both psychotic and negative symptoms; the duration of clinical trials; appropriate instruments for measuring negative symptoms and other measures that should be included in negative symptom trials. The questions were initially addressed in a survey that was administered to the meeting participants. The meeting agenda included all of the items from the survey that elicited differences of opinion. Advocates for different positions were selected from the survey and were asked to present their views at the meeting using supporting data. The survey was repeated following the meeting to determine whether the discussions had changed the opinions of participants. The goal of the meeting was not to reach a consensus on each issue that was discussed. Rather, the meeting focused on characterizing different positions that could be reconciled as new findings emerged from ongoing trials.

During the meeting, Jonathan Rabinowitz presented findings from the NEWMEDS data base of 29 placebo-controlled studies with second generation antipsychotics in schizophrenia which focused on the characteristics of individuals both at baseline and endpoint who would satisfy different inclusion and exclusion criteria for trials on negative symptoms. Stephen Marder presented an update on recent negative symptom trials that have reported results and other trials that had been registered at clinicaltrials.gov. Details from these presentations are included elsewhere in this special issue. For each issue discussed at the meeting, participants were selected to present contrasting views. This was followed by an open discussion. These discussions are summarized in this paper. Papers by David Daniel and Philip Harvey on clinical endpoints related to negative symptoms are also included in this special issue.

## 2. Issues not discussed

In addition to topics of disagreement, the pre-meeting survey identified a number of issues on which there was a consensus or a near consensus in the group. These are listed below and are not considered further.

1. Subjects entered into negative symptom trials should have no fewer than two negative symptoms and at least one should be rated as moderate or greater.
2. Subjects with notable extrapyramidal side effects from antipsychotic medications should be excluded.
3. Scales measuring the extrapyramidal syndromes should be included in negative symptom trials.
4. Subjects prescribed first and/or second-generation antipsychotics should be included in negative symptom trials of co-prescribed medication (that is, medication that is added to an antipsychotic) for negative symptoms.
5. Negative symptom trials should include an assessment battery to measure cognition.
6. Ratings for negative symptoms should include a single global score.
7. Ratings for negative symptoms should include global scores for major domains such as expressiveness and apathy/asociality.
8. Subjects currently treated with clozapine should not be excluded in negative symptom trials of co-medication.

## 3. Issues discussed

### *3.1. Issue 1. Should there be an upper age limit for subjects included in negative symptom trials?*

#### *3.1.1. Background*

Schizophrenia trials from academia and industry commonly recruit subjects with a mean age in the late 30's or 40's and with 10–15 or more years of established schizophrenia, frequently with substantial disability. For example, subjects in the NIMH (National Institute of Mental Health) CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) trial had a mean age of 40.6 years and an average of more than 14 years of illness (Lieberman et al., 2005). Such subjects are often referred to these trials because they are not satisfied with their current treatment due to side effects or inadequate efficacy. Since many of these individuals have responded poorly to multiple trials, they may be likely to show a relatively poor response to newer agents. Further, there is some evidence that, in its early stages, the schizophrenic illness is more likely to show a good response that in its later stages. For example, subjects in the EUFEST (European First Episode Schizophrenia Trial) (Kahn et al., 2008) were in a first episode and had a mean age of 26 years. These subjects had a higher response rate than the sample in the CATIE study. As suggested above, this phenomenon might be an artifact of the more heterogeneous patient samples available early in the illness. This contrasts with long-term trials where the subjects who are recruited may be more likely to be characterized by persistent, relatively resistant illness. In addition, there is the possibility that chronic treatment with pharmacologic agents (e.g. dopamine receptor antagonists) might alter the potential response to newly introduced treatments (Samaha et al., 2007).

Although well-designed epidemiologic studies are lacking, it is possible that negative symptoms increase with illness chronicity but are already present in the early phase illness, thereby making the discussion regarding stage of the disease in recruiting for studies on negative symptoms less relevant. Nevertheless a recent longitudinal study reported that although symptomatic dimensions are highly variable during the course of the illness, after the first episode the negative dimension was the most consistent and stable over time accounting for 24% of the variance at baseline and 26% at 4 weeks (Rapado-Castro et al., 2010). Perhaps it is the duration of the negative symptoms rather than the age of the patient that is the crucial issue. Whether an agent would be effective as a prophylaxis against the development of negative symptoms is another issue to be considered once effective agents are available.

#### *3.1.2. Meeting discussion*

Meeting participants agreed that it was intuitive to expect that a negative symptom compound would have a larger impact on patients who are younger and earlier in their illness. Moreover, some view schizophrenia as a progressive illness which would suggest that the