Methodological Issues in Negative Symptom Trials

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Individuals from academia, the pharmaceutical industry, and the US Food and Drug Administration used a workshop format to discuss important methodological issues in the design of trials of pharmacological agents for improving negative symptoms in schizophrenia. The issues addressed included the need for a coprimary functional measure for registration trials; the characteristics of individuals who should enter negative symptom trials; the optimal duration for a proof-of-concept or registration trial; the optimal design of a study of a broad-spectrum agent that treats both positive and negative symptoms or a co-medication that is added to an antipsychotic; the relative strengths and weaknesses of available instruments for measuring negative symptoms; the definition of clinically meaningful improvement for these trials; and whether drugs can be approved for a subdomain of negative symptoms.

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Available antipsychotic medications are relatively ineffective for treating the negative symptoms of schizophrenia. Because these symptoms make a substantial contribution to the functional impairments that are common in schizophrenia, they represent an important target for drug development. An earlier National Institute of Mental Health (NIMH) workshop1 focused on some of the important research issues that should be addressed in designing clinical trials of pharmacological and nonpharmacological agents that may improve negative symptoms. Since that report, investigators have gained considerable experience in designing and implementing clinical trials in this area. These experiences convinced members of the International Society for CNS Clinical Trials and Methodology (ISCTM) to revisit a number of these issues with a focus on regulatory issues and instruments for measuring negative symptoms. The decision to revisit the prior consensus was based on the following concerns: (1) the prior workshop did not include representatives from industry. It was felt that industry representatives had practical experiences in designing and implementing trials as well as a different perspective on regulatory issues, rating instruments, and design issues; (2) a discussion at a prior ISCTM meeting raised concerns that the Food and Drug Administration (FDA) was reconsidering its decision to not require a functional coprimary instrument in negative symptom trials; (3) the workshop could provide greater detail about critical design issues such as a recommended sample description and trial duration; (4) there has been recent progress on new instruments for measuring negative symptoms; and (5) results and practical experiences from trials carried out since the prior workshop could be considered.

This report provides a summary of ISCTM Workshops on Methodological Issues in Negative Symptom Trials held in September, 2009, in San Diego, California, and October, 2010, in Baltimore, Maryland. Participants included individuals from academia and the pharmacological industry. Robert Levin, MD from the US FDA, participated via teleconferencing in the San Diego meeting and Karl Broich from the European Medicines Agency (EMEA) participated in the Baltimore meeting. At the Baltimore meeting, Jack Blanchard from the NIMH Collaboration to Advance Negative Symptom Assessment in Schizophrenia (CANSAS) presented an update on the development of a new instrument to measure negative symptoms2 (described in this issue). Participants were polled about the issues that they believe should be discussed in the workshops. The meeting organizers (Drs Marder, Daniel, Awad, Alphs, and Keefe) used this input to develop the meeting agendas. Each of the consensus statements is followed by background information supporting the consensus.
1. Will regulatory authorities accept evidence of improvement on a negative symptoms scale as sufficient for drug approval or will improvement on a co-primary measure associated with functioning be required as well?

Because negative symptoms can be reliably measured in clinical settings and the severity of negative symptoms reflects functional impairment, US and European Union (EU) regulators agree that appropriately designed trials using well validated assessments of negative symptoms may lead to a labeled indication of the treatment of negative symptoms without the inclusion of a coprimary measure of functional improvement.

**Background** The discussion of regulatory issues for negative symptoms has been influenced by discussions of cognitive impairment. Regulatory authorities in the United States and the EU stated that improvement on a battery of neuropsychological tests would not be sufficient to support approval of a pharmacological agent for improving cognition in schizophrenia. Instead, improvement on a coprimary measure of functioning, functional capacity, or a self-rating of cognition would also be necessary. The explanation for this additional regulatory requirement has been described by FDA representatives at public meetings: First, to the general public, neuropsychological tests may lack face validity. Although performance on these tests has been related to community functioning, it is unclear that improvement on test performance will translate to meaningful improvement in real world activities. Moreover, patients may not be aware of their cognitive impairment and clinicians without specific expertise are unable to assess it in the clinic.

The need for this type of coprimary measure has also been raised in studies of negative symptoms. However, there are important differences in how cognition and negative symptoms are assessed. First, negative symptoms can be evaluated by clinicians, and they can be rated reliably in clinical trials. The severity of symptoms such as restricted affect and apathy is clearly related to functional outcomes. Moreover, as noted in the 2006 consensus statement, they have face validity because they constitute a loss of normal function. Improvement in these symptoms would be apparent to clinicians and interested observers, and they would potentially result in a decrease in illness-related disability. This relationship between changes in negative symptoms and functioning has been demonstrated recently. The relationship is less clear for improvement on a cognitive test, where it remains questionable whether a small but observable improvement in a score would be clinically meaningful. Finally, the functional relevance of cognitive impairments can be determined by performance-based assessments of functioning with tasks that resemble real world tasks and are affected by cognitive deficits such as impaired memory or attention. It is less clear how apathy, asociality, or restricted affect could be translated into a performance test.

At the workshop, Dr Levin stated that FDA had reconsidered a previous position and at this time would not require a coprimary functional measure for negative symptoms. Dr Broich, representing EMEA at the Baltimore meeting, also indicated that a coprimary functional measure would not be required for EU applications.

2. What are the characteristics of subjects who should enter into trials of drugs for negative symptoms? What would be the inclusion and exclusion criteria?

The consensus opinion of the group was that a number of principles should guide the selection criteria: (1) Negative symptoms should be stable and persistent. If negative symptoms fluctuate during a trial, this may increase the proportion of subjects who improve on the control condition. It will increase the variance seen in both groups and, consequently, increase the sample size needed to detect potential differences between treatment arms; (2) Symptoms in other domains, particularly psychotic symptoms, depression, extrapyramidal symptoms, and cognitive impairment, should be stable and not predominant. This will help to assure that change during the course of the trial is not secondary to change in other domains. To help establish that this is the case and to demonstrate the specificity of any changes observed, it is valuable to have measures of psychosis, depression, extrapyramidal symptoms, and cognition in negative symptom trials; and (3) In trials addressing the use of co-medications to treat negative symptoms of schizophrenia, all antipsychotics including the simultaneous use of more than 1 antipsychotic may be allowed except when the antipsychotic has a potential pharmacokinetic or pharmacodynamic interaction with the experimental medication. In such cases, these interactions must be clarified.

3. What would be the optimal duration for a proof-of-concept or a registration trial of an agent for treating negative symptoms?

Many of the symptoms associated with negative symptoms require many months to fully stabilize. Therefore to adequately capture potential changes, the preregistrations trials should be at least 6 months in duration. A briefer duration of treatment is acceptable for proof-of-concept trials.

The time course for improvement in negative symptoms in response to pharmacological interventions continues to be unclear because there are currently no agents with demonstrated effectiveness. Among studies published over the past 10 years, the duration had varied widely from 4 weeks up to 2 years with the majority being over 8 weeks. Soliciting recent expert opinions, there seems to be an agreement that the duration of

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*Negative Symptom Trials*
pharmacological clinical trials need to be no less than 3 months but optimally 6 month or longer not including a prerandomization phase for the purpose of stabilization. The recognized challenge is how to reconcile the need for optimal duration to demonstrate meaningful clinical changes and the practical complexities of long-term trials including subject retention to endpoint and cost.

4. What is the optimal design of a trial of a broad spectrum antipsychotic or that is under evaluation for effectiveness for both psychotic and negative symptoms? What is the optimal design for a trial of a co-medication for negative symptoms that would be added to an antipsychotic?

Two types of trials that demonstrate effective drug treatments for negative symptoms can be conceptualized: (1) trials for a monotherapy indication and (2) trials for the adjunctive treatment of schizophrenia.

Monotherapy Trials

Because negative symptoms rarely, if ever, occur in isolation from positive symptoms of schizophrenia and because trials for a monotherapy indication would last 3–6 months, during which time positive symptoms would be expected to exacerbate without specific treatment, use of a placebo control in monotherapy studies is difficult in any setting and unacceptable at many research sites. Therefore, establishing a monotherapy indication for negative symptoms would likely require that both the comparator and the trial drug have previously been demonstrated to be effective for treatment of positive symptoms. Further, such trials would require additional measures of potentially confounding phenotypes (eg, depression, extrapyramidal symptoms, paranoia, cognitive dysfunction, side effects of medication) to demonstrate that the effects identified are specific to the treatment of negative symptoms. Thus, a drug that has demonstrated antipsychotic properties could theoretically also be approved for the treatment of negative symptoms if it is more effective than a comparison antipsychotic that does not impair negative symptoms. The optimal design would include patients who are stabilized on an antipsychotic who are then randomly assigned to the experimental antipsychotic or the control agent.

Background: The important challenge in a study comparing the effects of an antipsychotic with putative effects on negative symptoms (ie, a broad-spectrum antipsychotic) with a control antipsychotic would be to clearly demonstrate that the advantage of the experimental drug in negative symptoms is not a pseudospecific effect. That is, the trial should demonstrate that an advantage in negative symptoms is not related to an advantage in other domains of psychopathology that can affect ratings of negative symptoms. Separating negative symptoms that are primary and enduring from negative symptoms that are secondary to other domains of psychopathology such as psychotic symptoms or depression has been a long-standing focus of researchers. Carpenter and colleagues have used the term deficit syndrome to describe primary negative symptoms and have demonstrated that they can be reliably measured in clinical settings. Moreover, there is evidence that the deficit syndrome has a distinct psychophysiology.

There is abundant evidence from clinical trials that differences in efficacy and side effects of antipsychotic medications can appear as differences in secondary negative symptoms. When negative symptoms are measured in studies of acute schizophrenia using instruments such as the Positive and Negative Symptom Scale (PANSS), negative symptoms improve along with positive symptoms. This is likely due to decreases in symptoms such as suspiciousness that can lead to social withdrawal or a decrease in distracting hallucinations or delusional thoughts, which can lead patients to be more engaged. If, eg, a broad-spectrum antipsychotic was more effective for positive symptoms, it might appear more effective for negative symptoms. Treating acute psychosis with an antipsychotic can also decrease depressive symptoms, which can appear as an improvement in negative symptoms.

Extrapyramidal side effects (EPS) from antipsychotics can lead to akinesia, which appears as restricted emotional expression. This was an important issue when the first studies of second-generation antipsychotics (SGAs) were published (eg, Marder and Meibach). Drugs with a lower liability for EPS such as a risperidone or olanzapine were compared with high potency first-generation antipsychotics such as haloperidol. There was an apparent advantage for the SGA in negative symptoms that may have been associated with an advantage in EPS. These differences were no longer apparent when the SGA was compared with a lower dose of haloperidol. This suggests that a drug with a lower liability for causing EPS has the potential for appearing to be more effective for negative symptoms.

These considerations led to a consensus at the workshops. An agent that is being evaluated for a broad-spectrum that includes positive and negative symptoms should be compared with a comparator antipsychotic that is both effective as an antipsychotic and does not result in greater EPS liability than the experimental agent. For example, studies that used relatively high doses of high potency first-generation antipsychotics such as haloperidol tended to find that an agent with less EPS resulted in greater improvement in negative symptoms. To assure that improvement in negative symptoms is not related to improvement in positive symptoms, subjects should be stable at the time they are randomized. To provide a comparison with minimum bias, subjects could be stabilized on an antipsychotic other than the experimental drug or the comparator and then randomly assigned to a cross titration to 1 of the agents being compared.
Trials of Co-medications for Negative Symptoms

The design to establish the efficacy of a co-medication for the treatment of negative symptoms is more straightforward. Most of the conditions for an interpretable trial that are identified for monotherapy trials above would also apply to adjunctive trials. However, it would be important to establish underlying symptom stability with the concomitant antipsychotic and ensure that the antipsychotic does not produce a pharmacokinetic or pharmacodynamic interaction with the experimental medication. The dose of the antipsychotic medication should be fixed during the postrandomization phase of this trial. Because an active treatment would be used as the active comparator in such trials, a placebo control would be acceptable.

5. Which rating instruments are preferred for trials of negative symptoms?

The Scale for the Assessment of Negative Symptoms (SANS), the Negative Symptom Assessment Scale (NSA-16),13 and subscales from the PANSS are reliable and valid measures of negative symptoms for clinical trials. The 2006 consensus did not consider the NSA-16 that had not received substantial use at the time. Recent use of this instrument indicates that it can be reliably administered in large multisite trials and scores are related to the PANSS negative symptom factor14,15 and to levels of functional outcome.3 It has the advantage of measuring reductions in social interest and sense of purpose that are not measured adequately in other instruments. It has the advantage of measuring reductions in sense of purpose and global severity of negative symptoms more adequately than the SANS or PANSS. It has also been demonstrated to be sensitive to change in long-term trials.

A recent report16 (discussed in this issue) found that a newly developed Brief Negative Symptom Scale demonstrated good psychometric characteristics. In addition, the NIMH CANSAS group is using a data-driven process to develop the Clinical Assessment Interview for Negative Symptoms.2,17 Both of these new instruments will measure all the 5 domains—blunted affect, alogia, asociality, anhedonia, and avolition—described in the report from the 2006 NIMH workshop. These instruments may represent an important advance in this therapeutic area because they eliminate items such as attention that are not a component of negative symptoms. These instruments also address an important limitation of available instruments that focus on quantifying behavior in the assessment of asociality and avolition. These new instruments focus more directly on the lack of interest in these behaviors and thereby emphasize a more fundamental aspect of negative symptoms that may have a greater capacity to improve with treatment. The advantages and limitations of each of these instruments are likely to become clear because new studies of promising medications for negative symptoms are reported. Each of these newer instruments should be evaluated in terms of its sensitivity to clinical change and its ability to cover the important domains of negative symptoms (including restricted affect, apathy, anhedonia, and asociality).

The prevailing opinion at the meeting was that the original PANSS negative symptom items do not provide adequate coverage and that the PANSS negative factors that have emerged from factor analyses are preferred. There was also a consensus that studies should report a global rating of negative symptoms in addition to the scale scores. If a scale does not include a global measure of negative symptoms, then an external global measure of negative symptoms should be added as an additional item.

6. How should a clinically meaningful improvement in negative symptoms be defined?

Cohen defined a medium effect size (Cohen’s $d = 0.5$) as one that is “visible to the naked eye.”18 This amount of change during treatment is often used to define a difference that is clinically meaningful.19 The consensus opinion was that this effect should be demonstrated in the absence of effects of (or in addition to) the experimental drug on potentially confounding phenotypically overlapping syndromes, eg, depression, extrapyramidal symptoms, paranoia, cognitive dysfunction, side effects of medication.

7. If a pharmacological agent improves a single subdomain of negative symptoms (e.g., social withdrawal), should it be approved as a treatment for negative symptoms of schizophrenia?

At this time, there is not an adequate consensus regarding the subdomains that comprise the negative symptoms syndrome and their relationship to each other. (A recent review of factor analyses suggests that there are at least 2 subdomains [diminished expressiveness and anhedonia/asociality] and up to 5 subdomains.20) Therefore, the consensus opinion was that improvement in negative symptoms should be defined by a global improvement in negative symptoms. Scales that do not have a global negative symptom score should be supplemented by a “clinical global impression” of negative symptoms.

Summary

Individuals from academia, industry, and the US FDA were able to reach consensus on a number of important issues that affect the design of negative symptoms trials. These included the importance of a coprimary functional
measure, the description of subjects who should be included in these trials, the duration of trials, and the design of trials for adjunctive and broad-spectrum agents. Other issues such as the best instrument for these trials and the meaning of improvement in a subdomain can be addressed when data from current and future trials are available.

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Dr Awad provides research consultations to Pfizer, Eli Lilly Janssen-Ortho, Astra Zeneca, and Novartis. Dr Alphs is an employee of Johnson & Johnson and has worked for Pfizer and Novartis in the past. He holds the copyright to the NSA-16 and the NSA-4, 2 instruments developed to assess negative symptoms.

Dr Daniel is an employee of United BioSource Corporation.

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References


