

## An Industry Perspective on the NIMH Consensus Statement on Negative Symptoms

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**Negative symptoms of schizophrenia remain an area of substantial unmet clinical need. By convening a consensus conference in January 2005, the NIMH has taken a leading role in stimulating a resurgence of interest in methodological considerations related to development of new medications for treating negative symptoms. One audience for this work is clinical researchers in industry. They must take ideas, like those emerging from this consensus meeting, and determine whether they can be applied to their global trials in order to meet the needs of a broad group of customers, which include patients, clinicians, regulators, and payers. This article takes the ideas that surfaced from the NIMH consensus work and interprets them in terms of issues that industry faces for its clinical trials. Particular emphasis is given to addressing hurdles to study design and analysis that come when developing broad-spectrum or adjunctive agents that may be effective for negative symptoms.**

*Key words:* negative symptoms/schizophrenic/  
trial design

### Basis and Goals for Study of Negative Symptoms

#### *NIMH Consensus Points*

- Negative symptoms constitute a distinct therapeutic indication.
- Persistent and clinically significant negative symptoms are an unmet therapeutic need in a large proportion of cases.

In the current environment for developing medications that treat negative symptoms, there are at least three prerequisites for regulatory and commercial success: 1) evidence that negative symptoms are readily identifiable by

clinicians across diverse cultures and are readily measurable so that clinical response can be monitored; 2) evidence of unmet need for treating these symptoms; and 3) sound scientific evidence that negative-symptom efficacy for the investigational treatment is differentiable from a justifiable alternative.

The DSM-IV codifies negative symptoms as one of the key symptoms for diagnosing schizophrenia,<sup>1</sup> and a number of specific scales have been developed to assess these symptoms and measure change in their severity.<sup>2–7</sup> Consequently, negative symptoms are broadly identifiable, and clinical response to their treatment can be tracked by treating clinicians. Thus, a key condition for drug development is met.

Although there is limited evidence that currently available drugs may provide some degree of relief from negative symptoms,<sup>8–11</sup> this evidence is incomplete, and many are not persuaded. In any case, there is broad consensus that there is much unmet need. For any proposed treatment, clinicians, regulators, and payers must be convinced that relief seen from newly developed medications is specific for negative symptoms and distinct from a reduction in confounding symptoms like EPS, sedation, and depression.<sup>12</sup>

The development of convincing evidence for efficacy of new products for treating negative symptoms is constrained by our incomplete understanding of clinical aspects of negative symptoms. This lack of knowledge limits clinical trial designs and impedes broad regulatory acceptance of trial results. Examples of such unanswered questions include the following: “Are the symptom profiles for specific negative symptoms (e.g., blunted affect, social withdrawal, and amotivation) similar across all patients who are diagnosed with this condition?” “How do these symptoms relate to other symptom domains of schizophrenia (e.g., positive symptoms, cognitive symptoms, and mood symptoms)?” “Does the course of negative symptoms vary, peaking at some times and diminishing at others?” “Is the underlying pathophysiology of negative symptoms of schizophrenia similar to conditions seen in non-schizophrenic disorders; for instance, the amotivation of depression?” “How does the presence of negative symptoms predict long-term outcome?”

Prospective, well-conducted epidemiological and longitudinal trials that address these questions are needed

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to assist with the design and interpretation of efficacy trials for treatment of negative symptoms. Such studies would be valuable in 1) formulating our best questions about efficacy; 2) identifying appropriate selection criteria and endpoints for treatment trials; 3) identifying the patients most in need of treatment and where to find them; 4) selecting appropriate endpoint analyses; and 5) optimally interpreting the results obtained from treatment trials.

#### *NIMH Consensus Point*

- Negative symptoms have face validity as disease manifestations and represent loss or diminution of normal functions.

A key consideration for many of the customers for industry-initiated trials on negative symptoms is that results be translatable into clinical and/or economic values. To do this, a clear definition of the constituent domains for negative symptoms is important. Although, by definition, negative symptoms represent a loss of normal behaviors and functioning, the boundaries of the losses represented are not fully agreed upon. A general consensus within the field on these boundaries is necessary for conducting clinical trials that will lead to approval of new treatments and reimbursement for them. This common understanding of the negative syndrome is necessary so as to avoid befuddling our clinical, regulatory, and patient audiences with needless controversy about results that are based on differences in conceptualization or unclear terminology.

Initially, ideas about negative symptoms were based primarily on keen clinical observations and hypotheses that were largely untested. Over the last 25 years, however, our knowledge has increased,<sup>3-6,13</sup> and there has been growing agreement, supported by numerous factor analyses, that cognitive functioning, attention, and inappropriate affect should not be grouped under the “negative symptom” construct, even though these ideas were included in earlier definitions.<sup>2</sup> On the other hand, functional deficits in the productivity of communication, social drive, and motivation are consistently attributed to this condition.<sup>2-6</sup>

When reexamining our definition of negative symptoms, it should be recognized that this condition does not represent the simple expression of aberrant activity in a well-defined neurocircuit. Rather, these symptoms must represent the behavioral expression of interplay between neuropathology, such as aberrant neurocircuit activity, and the patient’s natural/social environment. Understanding these complex determinants is critical to designing trials, choosing scales, and interpreting clinical results. For instance, results from a scale that measures domains of negative symptoms like “asociality” are undoubtedly dependent on underlying neuropathology of the brain, social mores, and the living situation of

the subject being assessed, as well as the quality of the scale being used. Pharmacological treatments could only be expected to impact a small subset of the underlying factors responsible for the final behavioral responses being evaluated. Clinical trials must be designed to address these other factors.

#### *NIMH Consensus Points*

- As currently understood, the domains of negative symptoms include blunted affect, alogia, asociality, anhedonia, and avolition.
- Negative symptoms and cognitive impairments represent separate domains.

Because researchers in industry must convince diverse and skeptical audiences of the validity of their trials, they must be prepared to clearly present and defend the definition of negative symptoms that they employ in their studies. Careful designation of the particular domains included in and excluded from the rubric of negative symptoms is crucial to this task. This need raises interest in how consensus on negative-symptom domains was achieved by the NIMH consensus group. Although their report suggests that factor analysis was used to identify these domains, knowledge of the specific items included in these analyses, the type of analytical tools employed, and a description of the sample population from which these factors were defined are important for convincing skeptics that the most appropriate and generalizable factors have been selected.

Some factor analyses suggest that the domains proposed by the NIMH group are incomplete, and that the inclusion of other relevant domains may be beneficial when characterizing negative symptoms.<sup>3-6</sup> Emotional experience is one area that has not been completely addressed. Do persons with prominent negative symptoms experience complex emotions like pride, joy, grief, disgust, and disdain? Do they have a similar breadth of experience of the more basic emotions (sadness, happiness, fear, and anger), as do persons without this disorder? Is their ability to both express and perceive emotions disturbed? How do these symptoms relate to social cognition? Such questions should be explored before finalizing the definitional boundaries of negative symptoms. When doing so, the tools used to measure negative symptoms must accurately represent items from each putative domain so as to ensure breadth of coverage, without an over- or under-sampling of particular areas of interest.

Clinical trials that are led by industry will be cross-cultural and will not be limited to a single geographic region. Therefore, assessment tools that are developed must be applicable to these diverse venues. Results from these trials will be important for a still larger audience. Indeed, their impact will go beyond psychiatrists and psychologists working with symptomatic patients,

and will include regulatory reviewers of clinical trials, general clinicians, social workers, patient advocates, payers of medical bills, and the patient-consumers themselves. Results of investigations must be intelligible to and, hopefully, relevant to all potential consumers.

The nomenclature identified by the NIMH consensus group raises some concerns in this regard, as it seems overly complex and is not readily understood by the novice or the non-native English speaker. This could pose problems for the larger audiences that will be exposed to and work with this terminology in the future. Although some of the terms chosen to identify negative-symptom domains have a distinguished background, their selection conveys a sense of exclusiveness, suggesting that their use can be accessed only by a privileged few. This is neither helpful nor desirable. Further, the unfamiliarity of the terminology is likely to breed idiosyncratic understandings that will actually confuse and/or inhibit communication among its users. This can be anticipated, because some of the meanings being applied to these terms are not wholly true to their Greek origins and represent the worst outcome of the negative-symptom pathology under consideration. For instance, many patients with negative symptoms are not completely alogic, asocial, amotivated/avolitional, or anhedonic. Rather, they experience diminution of capacity in these areas. Using this terminology is analogous to suggesting that a person experiencing bradycardia has an “asystolic condition.” Better terminology for these domains might include terms like “communication dysfunction,” “social dysfunction,” and “affective dysfunction.”

## Design Issues

### *NIMH Consensus Points*

- The paradigmatic design for clinical trials of persistent negative symptoms would include ... a double blind, placebo-controlled comparison of parallel groups, in which the putative negative symptom treatment is administered as a co-medication with a second generation antipsychotic.
- The paradigmatic design ... is less satisfactory when testing a broad-spectrum antipsychotic agent.... In such a study, superiority for negative symptoms would be established if the experimental treatment’s advantage were limited to negative symptoms, with psychosis and other key symptoms remaining stable and similar to the comparator drug....
- The length of a clinical trial will vary with the purpose of a trial.
- Within negative symptoms, the definition of a clinically meaningful effect size needs further review.

At this time, development programs within industry are examining both broad-spectrum and adjunctive agents as

potential solutions to the needs for treating negative symptoms. However, considering the reduced potential for drug-drug interactions, ease of use, reduced cost, and increased probability of better compliance, broad-spectrum therapy is as a rule the most desirable alternative for patient, clinician, and drug developer. This contrasts with the view of the NIMH consensus group which, based on methodological grounds, preferred trials with an adjunctive agent.<sup>14</sup> Given the clinical preference for monotherapy with a broad-spectrum agent, however, trial designs that advance their use should be exhaustively explored.

### *Design for a Broad-Spectrum Agent*

Because negative symptoms represent a chronic condition within schizophrenia, clinical trials must be long enough to demonstrate that any observed response to treatment is not transient. Further, some of the specific negative symptoms for which change is sought are dependent on interactions with the environment and may require months to see measurable, stable improvement. There is growing consensus that, to establish efficacy for treating negative symptoms, trials should be about six months long.<sup>12</sup>

If patients are randomized to monotherapeutic treatment with placebo during such a long period, patients’ positive symptoms are likely to exacerbate. This raises serious ethical and feasibility hurdles to designs that include a placebo treatment arm. Most critical are concerns about the medical and social risks that would accompany symptomatic relapse. In addition, interpretation of clinical results could be confounded. Loss of clinical stability may result in increased paranoia or other symptoms of schizophrenia that behaviorally mimic negative symptoms, e.g., social withdrawal. Conversely, emergence of psychotic agitation may be confused with a decrease in negative symptoms.

An alternative to a placebo-controlled design for monotherapy trials with broad-spectrum agents is to compare response from a novel investigational drug with that from currently used treatments that, though incompletely effective for negative symptoms, generally maintain clinical stability. Distinctive efficacy for treating negative symptoms would be demonstrated if the investigational treatment produced a superior reduction in negative symptoms compared with that for the active control.

Objections have been raised to this approach based on concerns that effects seen with the novel agent may represent a “pseudospecific” response rather than a distinctive therapeutic effect on negative symptoms. It is argued that, because of the failure to include a placebo or a “no-effect” control, any apparent advantage of the novel broad-spectrum agent could be due to competing interpretations. For instance, the broad-spectrum agent may not improve negative symptoms but, instead, may

reduce side effects that mimic negative symptoms (e.g., parkinsonism, sedation/somnolence) compared with the control. Alternatively, the broad-spectrum agent may provide better treatment of paranoia or depression, but this effect may be misidentified as treatment of negative symptoms. Or, the standard therapeutic agent may worsen negative symptoms, whereas the broad-spectrum agent may have no effect or may worsen them less.

A number of counter-arguments to these objections can be raised. For instance, the distinction between primary and secondary negative symptoms is often difficult to make and, in some cases, may not be etiologically valid. It is possible that symptoms resembling negative symptoms that are seen in patients with depression (like blunted affect or anhedonia) may have an underlying pathophysiology identical to that for negative symptoms of schizophrenia. If this is the case, then treatment effects seen with the broad-spectrum agent should not be considered “pseudospecific,” as they represent the same physiological process. Furthermore, if a drug is shown to have effects on both positive and negative symptoms of schizophrenia, and the particular effect on negative symptoms can be distinguished from that of a fairly tested active comparator, this latter effect remains highly clinically relevant. Indeed, additional improvement observed in positive symptoms may have been driven by the treatment effect on negative symptoms, and not the converse. Whatever the source of the effect, the bottom line is that the patient’s negative symptoms have distinctively improved and this outcome should be recognized.

#### *Addressing Design Hurdles for Broad-Spectrum Agents*

The objections raised by pseudospecificity arguments can be addressed more directly by specific trial design considerations. To reduce confounds from differences in side-effect profiles, comparators to the investigational treatment can be selected that have minimal side effects. Also, procedures for dosing and titration should be employed that minimize expression of side effects.<sup>8–10</sup> Specifically, comparator drugs associated with minimal sedation and parkinsonian side effects should be selected.

To reduce misinterpretation from potential alternative treatment effects (e.g., that treatment response represents effects on depression or better treatment for positive symptoms), patients with significant levels of depression or positive symptoms can be excluded by specifying restrictive exclusion criteria. A problem with this approach is that it limits generalizability of trial results. Clinicians are interested in improving significant symptoms in all patients, not just those in persons who have an arbitrarily higher score on a negative-symptom scale than on a positive- or depression-symptom scale. Therefore, additional consideration must be given to designing trials that generalize to all persons who are significantly impacted by negative-symptom pathology.

Comparing results to a documented, stable baseline may allay concerns that one or both agents actually worsen negative symptoms. In truth, this particular worry seems more hypothetical than real, since evidence from clinical trials with several atypical antipsychotic agents suggests that they produce limited improvement of negative symptoms rather than worsening them.<sup>8–11</sup> Such agents could be chosen as the hurdle above which a clinically distinctive negative-symptom response must be demonstrated.

Use of special analytic approaches such as stratification techniques, covariate analysis, and partial sums of squares analysis can also be employed to help determine if the observed treatment effects are specific for negative symptoms and are not due to confounding effects of the trial medications. When applying these analyses, clinical interest focuses on determining whether a distinctive effect on negative symptoms has been identified, not their etiology. Indeed, with this design it may be impossible to fully discern whether the treatment effects have some overlap with mechanisms that are also related to treating depression or positive symptoms.

#### *Appropriate Selection of Dose*

To convincingly demonstrate superiority over a comparator agent, evaluations must fairly represent the effective dose ranges for each drug. Superior effects of the broad-spectrum agent must be demonstrated relative to doses of the comparator that optimally treat the patient’s symptoms. This may be accomplished by using multiple fixed-dose treatment cohorts or, alternatively, with a design in which clinicians are allowed to flexibly dose patients to optimal risk:benefit response within a predefined therapeutic window. The latter approach mimics clinical practice and reduces the number of treatment arms, permitting a more feasible study.

#### *Design for an Adjunctive Agent*

The NIMH consensus group has suggested that the preferred design for negative-symptom clinical trials is one using an adjunctive agent. Given the unmet need and the likelihood that pharmacological properties beyond those exhibited by standard antipsychotic agents may be necessary for alleviation of some of these symptoms, adjunctive agents represent important treatment alternatives to explore. Overall, designing these trials is less complicated and placebo use is acceptable as a treatment arm. However, many of the concerns raised about interpretation of trials with broad-spectrum agents also apply to adjunctive trials. For instance, the putative adjunctive agent could alleviate parkinsonism or depression rather than treat negative symptoms. Or, the primary therapy might worsen negative symptoms, and the adjunctive agent might mitigate that worsening without improving the underlying disease condition.

### *Studying Negative Symptoms in Alternative Populations*

It has been suggested that evidence for efficacy in treating negative symptoms might be established by evaluation of symptoms resembling negative symptoms in other psychiatric populations (e.g., persons with schizoid personality disorders). This approach is attractive, as use of placebo in such populations is less problematic. However, the underlying pathophysiology of these symptoms may be different from those for schizophrenia, raising concerns regarding false negative results, false positive results and, so, their generalizability to persons with schizophrenia.

### *Effect Size*

A clinically meaningful effect size for treating negative symptoms has not been well characterized. Currently available non-pharmacological treatments for negative symptoms have effect sizes that are often less than 0.5 standard deviations (SD).<sup>7</sup> Given the large unmet need, effect sizes as low as 0.2 SD might represent clinically relevant treatment effects in this population. Assigning clinical relevance to an observed effect requires careful review of the data regardless of the size of the effect, but it is particularly important when the effect size is small. To assess the clinical relevance of the treatment effect, changes in the endpoint measure compared with changes in clinician perception and patient perception can be measured. The effect size should be further checked for consistency across studies. Internal consistency may add credence to a small effect size (i.e., does the  $i^{\text{th}}$ -ranked item in treatment X consistently fall below the  $i^{\text{th}}$ -ranked item in treatment Y?). Finally, the distribution of responses should be examined to see if the small effect size is due to a larger response in a subpopulation of patients.

### **Assessment Tools**

#### *NIMH Consensus Point*

- The structure of the SANS is preferred to that of the PANSS in that several negative-symptom constructs are ascertained, with multiple items related to each. However, the PANSS, SANS, and perhaps other assessment approaches are appropriate for application in current clinical trials.

Because industry-based trials are multi-site, multi-language, and multicultural, the choice of tools for assessing negative symptoms in these trials is especially critical. In addition to standard requirements for validity and reliability, scales that are selected must have good psychometric properties that broadly and evenly sample the relevant domains within the negative-symptom construct. Instruments need to be developed that both sensitively identify negative symptoms and are responsive to

change following treatment interventions. These instruments should use concepts that are readily understood by the general clinician and are not limited to a small cadre of experts. If they are to be used in global trials, they must be translated into many languages with sensitivity to the nuances used to capture the negative-symptom construct. Overall, these instruments should be insensitive to cultural bias. To increase inter- and intrarater reliability, training materials should be provided that include well-defined rules for rating. Semi-structured interviews will facilitate the consistent collection of data across a heterogeneous group of raters.

### **Conclusions**

There is general agreement that negative symptoms should be the target for drug development and regulatory claims, and either broad-spectrum or adjunctive treatments would provide valuable additions to our treatment options. To get these, future research for negative-symptom treatments should employ optimal clinical trial designs. Interpretation of clinical trial results from both broad-spectrum and adjunctive treatments is complicated, but hurdles can be managed by the use of appropriate selection criteria, sensitive assessment tools, and good analytical techniques. Better understanding of these results would also be facilitated by better understanding of neuropathology of negative symptoms, more research on its epidemiology, and a better definition of the domain.

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