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The NIMH-MATRICS Consensus Statement on Negative Symptoms

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The impairments now called negative symptoms have long been noted as common features of schizophrenia, and the concept of negative symptoms itself has a long history.[1,2] Patients who exhibit significant negative symptoms have particularly poor function and quality of life,[3–8] and this aspect of schizophrenia has been proposed as a separate domain with distinctive pathophysiological and therapeutic implications since at least 1974.[9] Despite the attention these problems receive, no drug has received Food and Drug Administration (FDA) approval for an indication of negative symptoms, and available data indicate that second-generation antipsychotic medications have not met early hopes for a highly effective treatment for alleviation of negative symptoms.[10]

Because of limited progress in the development of effective treatments for negative symptoms, under the auspices of the National Institute of Mental Health (NIMH), Drs. Steve Marder, Wayne Fenton, William T. Carpenter, Jr, and Brian Kirkpatrick initiated a process to examine issues that may interfere with treatment development. The NIMH had previously focused attention on impaired cognition as a therapeutic target with the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) project. The success of the MATRICS process suggested similar progress could be made in the area of negative symptoms and provided a possible model for proceeding in the area of negative symptoms.

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Marder, Fenton, Carpenter, and Kirkpatrick organized a consensus development conference, which was held at the NIMH Neuroscience Center in Rockville, Maryland, on January 26–27, 2005. Those attending are listed in the appendix. The mission statement of the meeting was:

- To review the data relating to the existence of separate domains within negative symptoms, as a prerequisite for choosing appropriate measures of these domains in clinical trials.
- To initiate a process for developing or identifying widely acceptable, evidence-based measures and methodologies needed to establish the efficacy of treatments that target negative symptoms.

Prior to the meeting, the organizers asked experts to address a series of questions:

- What are the separate components of negative symptoms?
- Are they independent, or components of the same latent construct?
- Which aspect of each domain belongs to the negative symptom construct?
- Does this area need a separate assessment?
- What is the best assessment method for clinical trials?

Since research has suggested that both negative symptoms and cognitive impairments were significant determinants of poor outcome in schizophrenia, an additional set of questions related to the relationship between these domains of psychopathology was also addressed at the conference:

- Which aspects of cognition are part of the negative symptom construct?
- Which are independent?
- Which are uncertain?

Articles that more fully address the topics of these presentations can be found in this issue of *Schizophrenia Bulletin*. Those articles address regulatory issues and negative symptoms,[11] negative symptoms as a therapeutic target,[12] the factor structure of negative symptoms,[13] restricted affect,[14] anhedonia,[15] and the relationship

between negative symptoms and cognitive impairment.[16] At the conference other presentations were also made: Wayne Fenton spoke on "Meeting Goals and Objectives: The NIMH Perspective," Robert Buchanan on "Summary of the MATRICS Process," William Carpenter, Jr, on "Study Design and the "Pseudospecificity' Problem," Michael Green on "Social Cognition," Nancy Andreasen on "Alogia," and Jeffrey Cummings on "Apathy."

Areas of Agreement

Conference participants achieved consensus on 11 points.

1. Negative symptoms constitute a distinct therapeutic indication area.

One purpose of this first statement is to encourage those involved in treatment development to target negative symptoms as a primary outcome variable in treatment trials. Historically, the main strategy for drug development has been to target "positive" psychotic symptoms (hallucinations, delusions, and disorganization) and hope that antipsychotic efficacy will extend to other aspects of schizophrenia, including negative symptoms. The underlying assumption of this approach is that positive and negative symptoms share an underlying pharmacology and hence will have a similar treatment response. The relative lack of success in developing pharmacological treatments for negative symptoms suggests this strategy is not sufficient and brings into question the assumption of a common neuropharmacology.

2. Negative symptoms and cognitive impairments represent separate domains. Aspects of interaction and overlap may be defined in the future, but documentation of substantial separation is available in current data.

There is some evidence for a relationship between cognitive impairment and negative symptoms. (For further discussion of this issue, see the accompanying article by Harvey et al.[16]) The question therefore arose whether negative symptoms and cognitive impairment constitute separate therapeutic indications.

Two lines of argument suggest that negative symptoms represent a distinct therapeutic target. First, the relationship between negative symptoms and cognitive impairment is weak and varies with the domain of cognitive impairment. The second line of argument is related to the third point of consensus.

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

The cognitive impairment associated with schizophrenia has become an important focus of treatment trials in large part because of the relationship between cognitive impairment and both level of function in the community and quality of life.[17] Improvement in function and quality of life constitute the principal purpose of treatment, but cognitive impairment has an indirect relationship to impairment of significance to the patient's life. In contrast, many negative symptoms have face validity as treatment targets, as they represent a loss of normal function and/or a decrease in the quality of life that can be readily recognized by clinicians and family members.

4. Persistent and clinically significant negative symptoms are an unmet therapeutic need in a large proportion of cases. Review of the prevalence of negative symptoms sufficiently severe to merit therapeutic intervention would be useful. Longitudinal studies, which provide information on the persistence of negative symptoms, would be especially informative.

Data from treatment trials, which are usually presented as group averages, do not translate easily into estimates of the percentage of patients with a particular degree of severity. A review of existing literature, including both epidemiological and clinic-based studies, might yield a reasonable estimate of the percentage of patients meeting a criterion for significant negative symptoms, but additional studies may be needed.

5. The distinction between primary and secondary negative symptoms is not essential for the purpose of testing therapeutics for negative symptoms, if a design is used that both selects subjects with persistent negative symptoms and controls for principal sources of secondary negative symptoms.

Primary negative symptoms are those that are part of the disease process itself, that is, are not secondary to such factors as depression, drug-induced akinesia, or a suspicious withdrawal.[18] Patients with primary negative symptoms can be distinguished from other patients with negative symptoms with good reliability, and with considerable evidence for the validity of that distinction.[19] In clinical samples patients with primary negative symptoms represent about 20–25% of patients, whereas in population-based samples approximating incidence samples, they comprise 15–20% of schizophrenia patients. These figures provide a floor for estimates of the percentage of patients whose negative symptoms are sufficiently severe to merit therapeutic intervention.

The evidence showing differences in the pathophysiology of primary versus secondary negative symptoms[19] suggests that a treatment first shown to be effective for persistent negative symptoms may not prove to be effective for primary negative symptoms. However, most studies of the treatment of negative symptoms will probably focus on patients with both primary and secondary negative symptoms, in order to maximize the number of patients eligible for a treatment trial, and if an appropriate study design is used, this is a reasonable strategy.

6. The paradigmatic design for clinical trials of persistent negative symptoms would include clinically stable patients whose negative symptoms persist with adequate antipsychotic drug treatment. This would be 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.

Many antipsychotics have been shown to improve the negative symptoms of patients who enter a clinical trial during an exacerbation of their positive symptoms. In this context, an improvement in negative symptoms has an ambiguous interpretation, as dysphoria and psychotic symptoms can exacerbate negative symptoms, and if dysphoria or psychotic symptoms should improve at the same time that negative symptoms improve, it is not clear that there has been a direct effect on negative symptoms.[20] This issue is sometimes called the "pseudospecificity problem." An improvement of negative symptoms in clinically stable patients, whose psychotic symptoms have been treated to a usual clinical standard and do not change significantly, would allow an unambiguous interpretation. The rationale for parallel groups is to avoid an ambiguous interpretation due to carryover effects.

7. The paradigmatic design for a co-administered drug is less satisfactory when testing a broad spectrum antipsychotic agent, that is, one that may have superior efficacy for both positive and negative symptoms. If subjects have achieved maximum antipsychotic drug response, the patient population described above for the paradigmatic design above may be appropriate. 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. If an experimental drug is superior in multiple symptom domains, including negative symptoms, a superior efficacy claim may be appropriate, but an indication for negative symptoms may be problematic because of a lack of specificity.

The topic of an antipsychotic with superior efficacy for both positive and negative symptoms—a "broad spectrum" antipsychotic (BSA)—was the focus of considerable discussion at the conference. There was agreement that a BSA would be desirable, but the group could not envision or reach consensus on a design that, in a single study, could both establish superior efficacy for psychotic symptoms and avoid the problem of pseudospecificity discussed under point 6, above. There was consensus that, at present, the only way to establish superior efficacy for negative symptoms is with a study in which dysphoria, psychosis, sedation, and extrapyramidal symptoms, which can exacerbate negative symptoms, do not change.

Because the interpretation of studies in which a drug simultaneously exhibited superior efficacy for both positive and negative symptoms cannot escape the pseudospecificity problem, FDA approval for a separate indication for negative symptoms would be unlikely. However, a "superior efficacy" claim might be approved. Laughren and Levin of the FDA discuss this issue further in their accompanying article.[11]

These considerations are not intended to serve as a disincentive for the development of a BSA. Even without an approved indication for negative symptoms, a drug labeling of "superior efficacy" should not be a disincentive, and other solutions to the pseudospecificity problem may be found. Alternative designs deserve further consideration, such as treatment of negative symptoms in a schizoid group without psychotic symptoms, or in a validated human model of primary negative symptoms, should such a model be developed.

8. Within negative symptoms, the definition of a clinically meaningful effect size needs further review.

Given the current poor therapeutic results, which means that few patients improve with treatment in the absence of a change in psychotic and depressive symptoms, it is difficult to judge the meaning of a particular effect size. Both clinical experience and correlations with other measures of level of function and quality of life are lacking.

9. The length of a clinical trial will vary with the purpose of a trial. Proof of concept studies may be brief. Preliminary efficacy studies may be 4–12 weeks. Registration trials are likely to be substantially longer (in the range of 6 months), in order to document persistent efficacy.

Registration trials are those used to support an application for approval of a therapeutic indication in package inserts and advertising for a drug marketed in the United States.

10. As currently understood, the domains of negative symptoms include blunted affect, alogia, asociality, anhedonia, and avolition. There are substantial correlations across these domains, but they may have separate neurobiological substrates and may represent separate therapeutic targets. The structure of relationships among these domains and their predictive validity require further study.

The relationship among the domains of negative symptoms is an important issue for treatment trials. It is unusual for negative symptom domains to be analyzed separately in the context of clinical trials or other studies. If the domains of negative symptoms consistently respond to treatment in a similar manner, detailed assessment of all the domains would be unnecessary. On the other hand, if the domains respond differently to treatment, assessment of a single domain, or use of a combined negative symptom score, might conceal meaningful improvement in a single domain, leading to a false negative finding. (See the accompanying articles in this issue for further discussion of the relationships among negative symptom domains.)

This issue also has implications for the development of animal models. If the negative symptom domains have a single or very similar underlying pharmacology, a valid model of one domain may provide accurate predictions about the treatment response of all negative symptoms. However, if the domains have significant differences in their neuropharmacological substrates,

predictions based on a model for one domain may be misleading with regard to other domains.

Psychometric studies offer important but limited information on this issue. The evidence reviewed during the consensus conference suggested that although these domains are intercorrelated and/or load onto a single factor, there may also be an important degree of independence within groups of these domains. Specifically, there is evidence that blunted affect and poverty of speech comprise a separable grouping or factor, while anhedonia, asociality, and avolition may comprise another. (See the accompanying articles in this issue.)

Consideration of social cognition led to the conclusion that as usually defined, it is not part of the negative symptom construct. "Social cognition" refers to the mental operations underlying social interactions, which include the ability and capacity to perceive the intentions and dispositions of others.[21] Most of the social cognitive research in schizophrenia has focused on emotion processing, theory of mind, social perception, social knowledge, and attributional bias. Asociality, which is a domain of negative symptoms, refers to a withdrawal from social contact that derives from indifference or lack of desire to have social contact.

Other domains were considered in the discussion of negative symptoms, and this point should not be construed to represent a consensus that no other domains should in the future be included in the concept of negative symptoms.

11. The structure of the Scale for the Assessment of Negative Symptoms (SANS)[22] is preferred to that of the Positive and Negative Symptom Scale (PANSS)[23] 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.

The SANS has played an important role in the study of negative symptoms. Its inclusion of more than 1 item improves the psychometric properties of the scale. Although an instrument with multiple domains and multiple items in each domain should be considered preferable when negative symptoms are the primary focus of a clinical trial, important and valid information can result from the use of other instruments.

Unresolved Issues and Future Directions

At the Consensus Development Conference, there was also agreement on 3 recommendations that were intended to facilitate future work on the development of treatments for negative symptoms.

1. Development of a new instrument that included the 5 agreed-upon domains would advance work in this area. Such an instrument needs to be applicable in both in-patient and outpatient clinical trials and needs to be sensitive to change. The negative symptom domains need to be clearly defined for the purposes of instrument development. This task is also essential to encourage development of preclinical models and laboratory-based, human assessments of negative symptoms, and to stimulate translation from neuroscience to the clinical study of negative symptoms.

Much of the conference focused on the SANS, which was considered the most important negative symptom rating scale. The SANS was thought to have certain weaknesses, especially the inclusion of items that were not considered to belong to the negative symptom construct, specifically items related to inappropriate affect, attentional impairment, and poverty of content of speech.[24] As revision of the SANS seemed desirable, there was also general agreement that a careful reconsideration of items for the 5 domains was justified. For instance, in the area of anhedonia, the concept of appetitive and consummatory aspects of anhedonia has been extended to the study of schizophrenia[15]; in a negative symptom rating scale it may be desirable to distinguish between these 2 aspects of anhedonia. In the area of asociality, a measure of the subject's desire for relationships is currently absent from most rating scales, but this is a prominent feature in some patients with schizophrenia and appears to be strongly related to other negative symptoms.[25,26]

2. There is a need to establish a framework, leadership, and financing to accomplish the following:

a. form a work group for the development of a negative symptom instrument for clinical trials;
b. test the instrument and assess its reliability and psychometric properties; and
c. test the instrument in a clinical trial to assess its sensitivity to change.

NIMH has made a commitment to serve as a convening body in support of the process envisioned in this point. Marder and Kirkpatrick will organize a working group that would develop the instrument. Marder will also organize a second group composed of senior figures in the field who will provide oversight for the process but will not be involved in the details of instrument development. Participation of representatives from the pharmaceutical industry will be important, as it is hoped that drug companies will use the resulting instrument.

3. There is also a need to establish a framework to promote the identification and testing of drugs for a negative symptom indication. It is likely that this process would be similar to the MATRICS process for drug discovery for the treatment of cognitive impairment in schizophrenia.

Prior to the conference, the organizers judged that the conference should not attempt to review the neurobiology of negative symptoms, as this would be such a formidable undertaking that doing so would interfere with the principal goals of the conference, namely, to consider the measurement and definition of negative symptoms.

In discussions of this third recommendation, a group composed of experts in clinical treatments and basic neuroscientists was envisioned. The MATRICS process, which has a similar group, was seen as the model for this group. Again, participation by the pharmaceutical industry was envisioned because of the important role of drug companies in developing treatments for patients with schizophrenia.

Conclusion

The treatment of the negative symptoms of schizophrenia is generally disappointing, but patients with negative symptoms, whether or not these symptoms are primary, suffer a disproportionate amount of impairment. The hope of those attending the conference was that pointing out areas of consensus and recommending processes for future work would facilitate the development of treatments for negative symptoms. The NIMH decision to continue to support the instrument development and drug identification processes is very promising in this regard.

Appendix

Participants in the Consensus Development Conference

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Presentations at the Consensus Development Conference on Negative Symptoms, January 26–27, 2005

Meeting Goals and Objectives: The NIMH Perspective Wayne Fenton, M.D.

Regulatory Issues and Negative Symptoms Thomas Laughren, M.D.

Negative Symptoms as a Therapeutic Target Steve Marder, M.D.

Summary of the MATRICS Process Robert Buchanan, M.D.

Study Design and the ''Pseudospecificity'' Problem William Carpenter, M.D

Factor structure and Psychometrics Jack Blanchard, Ph.D.

Social Cognition Michael Green, Ph.D.

Alogia Nancy Andreasen, M.D., Ph.D.

Restricted Affect Brian Kirkpatrick, M.D., M.S.P.H.

Anhedonia William Horan, Ph.D.

Are Negative Symptoms and Cognitive Impairment Distinct? Philip Harvey, Ph.D.

Apathy Jeffrey Cummings, M.D.

FDA Comment Thomas Laughren, M.D.

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