



International Society for CNS Clinical Trials and Methodology

**Satellite Meeting on the NIMH Initiative
Regarding Treatment Development for
Negative Symptoms**

**Washington DC, USA
February 23-24, 2006**

Process of Negative Symptom Rating Scale Development

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Consensus Development Conference

**NIMH Neuroscience
Center Rockville,
Maryland
January 26 & 27,
2005**

Mission Statement

- ✓ 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.

Attending

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

Jack Blanchard, Ph.D.

William T. Carpenter, Jr., M.D.

Bruce Cuthbert, Ph.D.

Wayne Fenton, M.D.

James Gold, Ph.D.

Raquel Gur, M.D.

Robert Heinssen, Ph.D.

Daniel Javitt, M.D., Ph.D.

Brian Kirkpatrick, M.D.

Thomas Laughren, M.D.

Dolores Malaspina, M.D.

Ellen Stover, Ph.D.

Alan Bellack, Ph.D.

Robert W. Buchanan, M.D.

Jeffrey Cummings, M.D.

Steve Erhart, M.D.

Donald Goff, M.D.

Michael F. Green, Ph.D.,

Philip Harvey, Ph.D.

William Horan, Ph.D.

Shitij Kapur, M.D.

Ann Kring, Ph.D.

Robert Levin, M.D.

Steve Marder, M.D.

Outcome of the Conference

⇒ 11 points of
consensus

⇒ 3
recommendations

Consensus Point 10

- The domains of negative symptoms include:
 - blunted affect
 - alogia
 - asociality
 - anhedonia
 - avolition
- There are substantial correlations across domains, but they may to some extent have separate neurobiological substrates, and may therefore represent separate therapeutic targets.
- The structure of relationships among these domains, and their predictive validity, require further study.

Recommendation 1

- **Development of a new instrument that included the five 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.**

Recommendation 2

- ❖ **There is a need to establish a framework, leadership, and financing to accomplish the following:**
 - ❖ **form a work group for the development of a negative symptom instrument for clinical trials**
 - ❖ **test the instrument and assess its reliability and psychometric properties**
 - ❖ **test the instrument in a clinical trial to assess its sensitivity to change**

The Working Groups

- Because of evidence presented at the conference on the factor structure of negative symptoms, two groups were formed:
 - ❖ “Expressivity” group
 - ❖ Blunted affect
 - ❖ Alogia
 - ❖ “Anhedonia” group
 - ❖ Anhedonia
 - ❖ Asociality
 - ❖ Avolition
- Conference calls twice a month

Work Group Members

- **Expressivity:**
 - **Larry Alphas, M.D., Ph.D.**
 - **Raquel Gur, Ph.D.**
 - **Phil Harvey, Ph.D.**
 - **Brian Kirkpatrick, M.D.**
 - **Ann Kring, Ph.D.**
- **Anhedonia:**
 - **Jack Blanchard, Ph.D.**
 - **Georges Gharabawi, M.D.**
 - **William Horan, Ph.D.**
 - **Brian Kirkpatrick, M.D.**
 - **Ann Kring, Ph.D.**
 - **Dolores Malaspina, M.D.**
 - **Kevin Ochsner, Ph.D.**

Steering Committee

- **Will Carpenter**
- **Wayne Fenton**
- **John Kane**
- **Steve Marder**
- **Nina Schooler**

Principles for Drafting the Instrument

- ✓ **Five subscales, as in Conference Consensus Point 10:**
 - ✓ **Blunted affect**
 - ✓ **Alogia**
 - ✓ **Asociality**
 - ✓ **Anhedonia**
 - ✓ **Avolition**
- ✓ **Omit items related to disorganization**
- ✓ **Separate appetitive and consummatory aspects of anhedonia**
- ✓ **When in doubt whether to include an item, we usually included it, with the plan to examine its performance in field testing**

Recurring Issues

- **Uses of the instrument:**
 - treatment trials
 - other kinds of studies
- **Tradeoff between**
 - simplicity / ease of use
 - sophistication & completeness
- **Function vs. loss of interests, motivation, liveliness**
 - e.g., “true” asociality vs. impaired skills, suspicious withdrawal, or giving up

Summary of Progress

- **Raquel Gur: Expressivity**
 - **Blunted Affect**
 - **Alogia**
- **Ann Kring**
 - **Anhedonia**
 - **Asociality**
 - **Avolition**

Feedback from the Field

March 24, 2006

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