# **THE 4-ITEM NEGATIVE SYMPTOM ASSESSMENT (NSA-4) INSTRUMENT:** A Simple Tool for Evaluating Negative Symptoms in Schizophrenia Following Brief Training

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# ABSTRACT

**Objective.** To assess the ability of mental health professionals to use the 4-item Negative Symptom Assessment instrument, derived from the Negative Symptom Assessment-16, to rapidly determine the severity of negative symptoms of schizophrenia.

**Design.** Open participation. **Setting.** Medical education conferences.

**Participants.** Attendees at two international psychiatry conferences.

**Measurements.** Participants read a brief set of the 4-item Negative Symptom Assessment instructions and viewed a videotape of a patient with schizophrenia. Using the 1 to 6 4-item Negative Symptom Assessment severity rating scale, they rated four negative symptom items and the overall global negative symptoms. These ratings were compared with a consensus rating determination using frequency distributions and Chi-square tests for the proportion of participant ratings



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that were within one point of the expert rating.

**Results.** More than 400 medical professionals (293 physicians, 50% with a European practice, and 55%who reported past utilization of schizophrenia ratings scales) participated. Between 82.1 and 91.1 percent of the 4-items and the global rating determinations by the participants were within one rating point of the consensus expert ratings. The differences between the percentage of participant rating scores that were within one point versus the percentage that were greater than one point different from those by the consensus experts was significant (p < 0.0001). Participants rating of negative symptoms using the 4-item Negative Symptom Assessment did not generally differ among the geographic regions of practice, the professional credentialing, or their familiarity with the use of schizophrenia symptom rating instruments.

**Conclusion.** These findings suggest that clinicians from a variety of geographic practices can, after brief training, use the 4-item Negative Symptom Assessment effectively to rapidly assess negative symptoms in patients with schizophrenia.

# INTRODUCTION

Negative symptoms represent an important domain of schizophrenic symptomatology that remains inadequately assessed and treated despite our best available therapies. These symptoms have been linked to poor functional and long-term outcomes.<sup>1,2</sup> Therefore, an early diagnosis is essential.

For effective identification of negative symptoms and monitoring of treatment effects, clinicians need a reliable and easy-to-use rating instrument. The most widely used tool for this purpose is the Positive and Negative Syndrome Scale (PANSS).<sup>3</sup> In this scale, 7 of 30 items relate to negative symptoms; however, this instrument does not cover a number of symptoms commonly identified as part of the domain of negative symptoms, such as decreased motivation/interests and diminished

speech/communication.<sup>3</sup> Other tools designed to measure negative symptoms and assess change over time include the Scale for the Assessment of Negative Symptoms and the 16-item Negative Symptom Assessment (NSA-16).<sup>4,5</sup> However, use of these tools by clinicians in the course of their regular practice is limited because of the time required to complete an assessment. In addition, clinicians require a substantial amount of training to properly administer these scales.

The NSA-16 examines the presence, severity, and range of negative symptoms associated with schizophrenia. It was adapted from earlier prototype versions to be a concise and easy-to-use instrument with strong psychometric properties (e.g., validity, reliability, sensitivity to change) and good clinical utility.<sup>5,6</sup> The instrument has been shown to have a five-factor dimensional structure and it has been validated in inpatients and outpatients with schizophrenia.<sup>5</sup> The NSA-16 has demonstrated high interrater and test-retest reliability as well as high concurrent validity with similar instruments when used by Englishspeaking raters.<sup>5,7,8</sup>

To simplify the instrument as a tool for rapid clinical assessment or screening of patients for negative symptoms, four items were selected verbatim from the NSA-16 (restricted speech quantity, reduced emotion, reduced social drive, and reduced interests) and an overall global rating of negative symptoms based on the rater's overall gestalt of negative symptom severity for the NSA-4 instrument (Table 1). Each of the four items and the overall global negative symptoms are rated on a 1 to 6-point scale where '1' represents no reduction from normal behaviors associated with the item and '6' represents severe reduction in or absence of the behavior, with markedly impaired functionality. The rating scale also includes a "Not Ratable" designation (denoted as

"9"). The four items were chosen based on their validity, reliability, good item response characteristics, and the ease of training clinicians to rate these items reliably.9 With respect to overall accuracy and predictive validity, the NSA-4 is comparable to the NSA-16.6 Given the need for a practical, clinical scale that can readily assess negative symptoms and track them over time, the aim of this study was to determine whether the NSA-4 can be used effectively by a diverse group of mental health professionals after only brief training.

# **METHODS**

**Participants and preparation.** At the American Psychiatric Association (APA) 159th Annual Meeting (Toronto, Canada, May 20–25, 2006) and the 19th European College of

Neuropsychopharmacology (ECNP) congress (Paris, France, September 16-20, 2006), attendees who visited an educational display on negative symptoms were invited to participate in this research. Following collection of participants' professional credentialing data, practice pattern information, and determination of whether they were familiar with the use of schizophrenia symptom rating scales, the potential participants were given the NSA-4 instrument (in English) and a brief set of instructions (also in English) on how to perform the ratings. After reading the instructions, the participants viewed a videotape of a patient with negative symptoms of schizophrenia that were previously determined by a panel of two experts to be of intermediate severity (to avoid ceiling and floor effects). Participants then rated the severity of each of the four items as well as overall global negative symptom severity. The severity ratings of each of the four items and the overall global negative symptoms rating by the participants after viewing the patient videotape were compared with a consensus rating provided by two expert raters. Participants were also queried at the conclusion of the

#### TABLE 1. Negative Symptom Assessment items and instructions for use: Listing includes 16 items on the NSA-16 with highlighted lines being the four items on the NSA-4

#### 1. Prolonged time to respond

#### 2. Restricted speech quantity

#### 1. Normal speech quantity

- 2. Minimal reduction in quantity; may be extreme side of normal
- 3. Speech quantity is reduced, but more obtained with minimal prodding
- 4. Flow of speech is maintained only by regularly prodding
- 5. Responses usually limited to a few words, and/or detail is only obtained by prodding or bribing
- 6. Responses usually nonverbal or limited to 1 or 2 words despite efforts to elicit more
- 9. Not ratable

#### 3. Impoverished speech content

#### 4. Inarticulate speech

#### 5. Emotion: Reduced range (specify time frame for this assessment)

## 1. Normal range of emotion

- 2. Minimal reduction in range; may be extreme side of normal
- 3. Range seems restricted relative to a normal person, but during the specified time period subject convincingly reports at least four emotions
- 4. Subject convincingly identifies two or three emotional experiences
- 5. Subject can convincingly identify only one emotional experience
- 6. Subject reports little or no emotional range
- 9. Not ratable

#### 6. Affect: Reduced modulation of intensity

#### 7. Affect: Reduced display on demand

## 8. Reduced social drive

- 1. Normal social drive
- 2. Minimal reduction in social drive; may be extreme side of normal
- 3. Desire for social interactions seems somewhat reduced
- 4. Obvious reduction in desire to initiate social contacts, but a number of social contacts are initiated each week
- 5. Marked reduction in desire to initiate social contacts, but a few contacts are maintained at subject's initiation (as with family)
- 6. no desire to initiate any social interactions
- 9. Not ratable

#### 9. Poor rapport with interviewer

#### 10. Sexual interest

#### 11. Poor grooming and hygiene

#### 12. Reduced sense of purpose

#### 13. Reduced interests

#### 1. Normal interests

- 2. Minimal reduction in interests; may be extreme side of normal
- 3. Range of interests and/or commitment to them seems diminished
- 4. Range of interests is clearly diminished and subject is not particularly committed to interests held
- 5. Only one or two interests reported, and these pursued superficially
- 6. Little or nothing stimulates interest

9. Not ratable

#### 14. Reduced daily activity

#### 15. Reduced expressive gestures

#### 16. Slowed movements

# GLOBAL NEGATIVE SYMPTOMS RATING

- 1. No evidence of this symptom
- 2. Minimal evidence of this symptom
- 3. Mild evidence of this symptom
- 4. Moderate evidence of this symptom; apparent to the casual observer
- 5. Marked evidence of this symptom; readily apparent to casual observer
- 6. Severe; not only obvious but has marked impact on functioning
- 7. Extremely severe symptom; it is incapacitating for subject

INSTRUCTIONS FOR NSA-4 USE: The NSA-4 rates behavior, not psychopathology. Do not alter your ratings because you consider the symptoms or behaviors observed to be caused by something other than schizophrenia (e.g., medication, institutionalization, or depression). Rate the presence or absence of each symptom compared with a normal young person in his or her 20s. Each item has its own specific set of "anchors" to help you rate the severity of that symptom/item. In general, severity of behavior is assessed using a 1 to 6-point rating; however, if despite heroic efforts, the patient cannot be rated using one of the six ratings below, designate the rating as "9"-not ratable:

- 1. Behavior is not reduced compared with a healthy young person.
- 2. Behavior is minimally reduced; significance is questionable.
- 3. Behavior is mildly reduced.
- 4. Behavior is moderately reduced.
- 5. Behavior is markedly reduced and definitely interferes with subject's functioning.
- 6. Behavior is severely reduced or entirely absent; it is glaring and markedly interferes with functioning.

symptom rating as to whether or not they regarded the NSA-4 instrument as a valuable tool for the rapid clinical assessment of negative symptoms of schizophrenia and whether or not they would use it to assess negative symptoms of schizophrenia in their own practice patients.

# ANALYSES

The mean and standard deviation and modal value ratings for each of the four items and the overall global negative symptoms by the participants were determined and compared with the mean ratings as determined by the two expert raters using frequency distributions and chi-square tests for the proportion of participant ratings within one point of the expert rating. In addition, participants' ratings were assessed by subgroups based on such variables as geographic location of practice, professional credentials, and prior experience with schizophrenia assessment tools.

# RESULTS

Over 400 medical professionals, the majority of whom were psychiatrists (73.5%) or listed as professions other than psychologist, primary care, other physician, nurse, or medical student (18.4%), participated in this assessment of the NSA-4. Approximately 50 percent of the participants (n=189, 49.5%)listed a European region of practice, with 21.7 percent reporting the United States as their region of practice. Other areas of practice were as follows: Other 10.0 percent, Canada 8.4 percent, South America 3.9 percent, Indian subcontinent 3.1 percent, Far East Asia 1.8 percent, and Australia or Mexico (0.8% each). Over one-half (55%) reported that they had experience with using a clinical rating scale for schizophrenia.

The consensus expert ratings of each of the four items and the overall global negative symptoms, the numbers of participants who completed each of the ratings, the mean and standard deviations for 
 TABLE 2. Negative symptom rating scores by participants and by consensus experts

	CONSENSUS	PARTIC	CIPANT RA	WITHIN 1 POINT OF		
NSA-4 ITEM	EXPERT RATING	n	Mean ± SD	Modal Value	EXPERT RATING, %*	
Reduced speech quantity	4	359	4.0±1.1	4	86.9	
Reduced emotion	4	312	4.3±1.0	4	83.7	
Reduced social drive	5	258	4.8±0.9	5	91.1	
Reduced interests	4	234	4.4±1.0	5	87.2	
Global negative symptoms	5	396	4.7±1.3	5	82.1	

n=number of scores recorded for each item on the NSA-4; some participants did not provide scores for all items.

\*For all items, percentage shown is p<0.0001 vs. percentage of participants whose ratings were more than one point away from the consensus expert rating.

each of the ratings, and the modal values for each item are summarized in Table 2. With the exception of the item "reduced interests," the modal values for each item score were identical to those of the consensus expert rating. Mean values by the participants were within 0.4 points of the consensus expert ratings (largest difference between "reduced interests" 4.4 vs. 4) on the 1 to 6point scale. For each of the items on the NSA-4, between 82.1 and 91.1 percent were rated by the participants within one point of the consensus expert rating. The percentage of participant ratings that were within one point of the consensus expert rating was significantly greater ( $p < 0.0001, \chi^2$ test) as compared to the percentage of participant ratings that were greater than one point different than the consensus expert rating.

The ratings by the participants were analyzed by variables of geographic region, professional credentials (psychiatrists vs. nonpsychiatrists), and familiarity with the use of schizophrenia symptom rating instruments. As summarized in Table 3, with the exception of the rating for "reduced emotion," which was rated as more

severe by United States raters versus European/non-United States raters  $(4.5\pm0.8 \text{ vs. } 4.2\pm1.0, p<0.05)$ , all other negative symptoms were rated similarly between the geographic regions. There were no significant differences in the mean ratings of the five negative symptom items between those who were classified as psychiatrists or non-psychiatrists (Table 4). Between the participants with and without prior experience with schizophrenia symptom rating scales, those without prior experience tended to rate the symptoms of "reduced speech quality" and "reduced social drive" as being more severe than participants with prior experience  $(4.1 \pm 1.0 \text{ vs.})$  $3.9 \pm 1.2$ , p < 0.05 and  $5.0 \pm 0.8$  vs.  $4.7\pm1.0$ , p<0.01, respectively) (Table 5). There were no notable differences in ratings by participants from the APA and ECNP meetings (data not shown). As in the overall analysis, these subanalyses showed that the frequency of scores within one point of the consensus expert rating was significantly greater than the frequency of scores more than one point away from the consensus expert rating on each NSA-4 item.

When queried as to the value of the NSA-4 tool, 93 percent of

TABLE 3. Negative symptom rating scores by geographic subgroup participants and by consensus experts											
NSA-4 ITEM	EXPERT RATING		US RA	ATERS		EUROPEA	N AND OTH	US VS. NON-US RATERS			
		n	Mean ± SD	Modal Value	Within 1 Point of Expert Rating, %*	n	Mean ± SD	Modal Value	Within 1 Point of Expert Rating, %*	T-test	<i>p</i> -value
Reduced speech quantity	4	73	3.9±1.0	4.0	91.8	273	4.0±1.2	4.0	85.7	0.36	<i>p</i> =NS
Reduced emotion	4	74	4.5±0.8	4.0	87.8	232	4.2±1.0	4.0	82.8	2.53	<i>p</i> <0.05
Reduced social drive	5	67	4.8±0.9	5.0	91.0	187	4.8±0.9	5.0	91.4	0.05	<i>p</i> =NS
Reduced interests	4	60	4.6±0.9	5.0	85.0	169	4.4±1.0	5.0	88.2	1.75	<i>p</i> =NS
Global negative symptoms	5	83	4.7±1.1	5.0	85.5	299	4.7±1.3	5.0	82.3	0.21	<i>p</i> =NS

n=number of participants who provided scores for each item on the NSA-4; some participants did not provide scores for all items. \*For all items, percentages shown are p<0.0001 vs percentage of participants whose ratings were more than 1 point away from the consensus expert rating.

NS=not significant.

TABLE 4. Negative symptom rating scores by psychiatrist and non-psychiatrist subgroup participants and by consensus experts

NSA-4 ITEM	EVDEDT	PSYCHIATRISTS					NON-PS	PSYCHIATRISTS VS NON- PSYCHIATRISTS			
	RATING	n	Mean ± SD	Modal Value	Within 1 Point of Expert Rating, %*	n	Mean ± SD	Modal Value	Within 1 Point of Expert Rating, %*	T-test	<i>p</i> -value
Reduced speech quantity	4	265	4.0±1.1	4.0	86.4	80	3.9±1.2	5.0	87.5	0.43	<i>p</i> =NS
Reduced emotion	4	221	4.3±1.0	4.0	82.4	85	4.3±0.9	4.0	88.2	0.61	<i>p</i> =NS
Reduced social drive	5	184	4.9±0.8	5.0	92.9	71	4.8±1.0	5.0	87.3	0.71	<i>p</i> =NS
Reduced interests	4	167	4.4±1.0	5.0	88.0	62	4.4±1.1	5.0	87.1	0.25	<i>p</i> =NS
Global negative symptoms	5	280	4.8±1.1	5.0	87.1	101	4.5±1.5	5.0	70.3	1.32	<i>p</i> =NS

n=number of participants who provided scores for each item on the NSA-4; some participants did not provide scores for all items. \*For all items, percentages shown are p<0.0001 vs. percentage of participants whose ratings were more than 1 point away from the consensus expert rating.

NS=not significant.

TABLE 5. Negative symptom rating scores by participants with and without prior experience with schizophrenia rating instruments and by consensus experts

NSA-4 ITEM	EXPERT RATING	WITH PRIOR EXPERIENCE				WIT	HOUT PRIO	RATERS WITH VS. WITHOUT PRIOR EXPERIENCE			
		n	Mean ± SD	Modal Value	Within 1 Point of Expert Rating, %*	n	Mean ± SD	Modal Value	Within 1 Point of Expert Rating, %*	T-test	<i>p</i> -value
Reduced speech quantity	4	196	3.9±1.2	4.0	84.2	151	4.1±1.0	5.0	90.7	1.98	<i>p</i> <0.05
Reduced emotion	4	167	4.3±1.0	4.0	83.8	140	4.3±1.0	4.0	84.3	0.26	<i>p</i> =NS
Reduced social drive	5	143	4.7±1.0	5.0	89.5	112	5.0±0.8	5.0	93.8	3.21	<i>p</i> <0.01
Reduced interests	4	133	4.4±1.1	5.0	84.2	97	4.5±0.8	5.0	91.8	1.12	<i>p</i> =NS
Global negative symptoms	5	211	4.6±1.3	5.0	82.5	172	4.9±0.8	5.0	83.7	1.31	<i>p</i> =NS

n=number of participants who provided scores for each item on the NSA-4; some participants did not provide scores for all items. \*For all items, percentages shown are p<0.0001 vs percentage of participants whose ratings were more than 1 point away from the consensus expert rating.

NS=not significant.

participants responded that they felt that the NSA-4 was a valuable tool for the rapid clinical assessment of negative symptoms of schizophrenia. In addition, 89 percent of the participants said they would use the NSA-4 instrument to assess negative symptoms of schizophrenia in patients enrolled in their practices.

# **DISCUSSION AND CONCLUSION**

These findings indicate that with a brief amount of training, the NSA-4 is an effective way of determining the severity of negative symptoms of schizophrenia, with no substantial differences seen in the ratings across geographic regions, professional medical credentials, or prior experience with symptom rating instruments. It is notable that the NSA-4 instrument and its instructions were provided in English to a population of attendees who were primarily European and for whom English often was not their primary language. The findings support the robustness of the items chosen for inclusion in this instrument. Furthermore, the high level of agreement between ratings by the expert consensus panel and participants of a mixed cultural/geographic background suggests that the negative symptoms construct assessed by the NSA-4 transcends cultural boundaries. A description of the interrater reliability of the NSA-16 across languages and cultures has been submitted for publication.<sup>10</sup>

Limitations to the interpretation of these findings include that participants were selected from attendees at professional medical conferences and that the same videotape interview was rated by all participants so true interrater reliability was not assessed. Future research to establish inter-rater reliability will require the use of several videotaped interviews of subjects with a range of negative symptoms that are rated by a broadly representative group of clinicians.

These findings provide preliminary evidence that clinicians from a variety of regions and professional medical backgrounds can effectively use the NSA-4 for rapid assessment of negative symptoms in patients with schizophrenia after only brief training.

In conclusion, we found a high level of consistency between ratings by experts compared to clinicians with only brief training in the use of the NSA-4. The results of the subanalyses suggest that the utility of the NSA-4 for professionally trained clinician raters is not substantially affected by geographic location of practice, professional credentials, or prior experience with ratings tools for schizophrenia. Overall, these findings indicate that the NSA-4 can be rapidly administered with minimal training. These findings support the use of the NSA-4 as a practical clinical tool for assessing the severity of negative symptoms in patients with schizophrenia and tracking their course over time.

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# **AUTHORS CONTRIBUTIONS**

Larry Alphs contributed to the development of the NSA-16 and the NSA-4, and contributed to the study design; Robert Morlock contributed to the study design and provided an initial draft of the report; Arjen van Willigenburg and John Panagides contributed to the development of the manuscript; Cheryl Hill conducted the data analyses.

# REFERENCES

1. Goeree R, Farahati F, Burke N, et al. The economic burden of schizophrenia in Canada in 2004.

Curr Med Res Opin. 2005;21:2017–2028.

- Wu EQ, Birnbaum HG, Shi L, Ball DE, et al. The economic burden of schizophrenia in the United States in 2002. J Clin Psychiatry. 2005;66:1122–1129.
- Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull. 1987;13:261–276.
- Andreasen NC. The Scale for the Assessment of Negative Symptoms (SANS): conceptual and theoretical foundations. Br J Psychiatry Suppl. 1989;49–58.
- Axelrod BN, Goldman RS, Alphs LD. Validation of the 16-item Negative Symptom Assessment. J Psychiatr Res. 1993;27:253–258.
- Alphs LD, Summerfelt A, Lann H, Muller RJ. The negative symptom assessment: a new instrument to assess negative symptoms of schizophrenia. *Psychopharmacol Bull*. 1989;25;159–163.
- Axelrod BN, Alphs LD. Training novice raters on the Negative Symptom Assessment Scale. Schizophr Res. 1993;9:25–28.
- Axelrod BN, Goldman RS, Woodard JL, Alphs LD. Factor structure of the negative symptom assessment. *Psychiatry Res* 1994;52:173–179.

- Alphs L, Hill C, Cazorla P, et al. Psychometric evaluation of the four-item Negative Symptom Assessment (NSA-4) in schizophrenic patients with predominant negative symptoms. New Clinical Drug Evaluation Unit, 47th Annual Meeting. Boca Raton, FL, 2007.
- Daniel DG, Alphs L, Cazorla P, Bartko JJ, Panagides J. Training for assessment of negative symptoms of schizophrenia across languages and cultures: comparison of the NSA-4 with the PANSS negative subscale and negative symptom factor. *Schizophren Res.* 2010 (In Development).
- Cazorla P, Panagides J, Alphs L, et al. Asenapine versus olanzapine in patients with predominant, persistent negative symptoms of schizophrenia. [Poster NR4-082] American Psychiatric Association 2008 May 3–8, Washington, DC.
- Cazorla P, Panagides J, Zhao J, et al. Long-term efficacy of asenapine in people with persistent negative symptoms of schizophrenia. [Poster NR6-29] American Psychiatric Association 2010 May 22–26, New Orleans, Louisiana.