The brief negative symptom scale (BNSS): Sensitivity to treatment effects

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A B S T R A C T

The Brief Negative Symptom Scale (BNSS) grew out of a recommendation by the NIMH-sponsored Consensus Development Conference on Negative Symptoms that a scale based on contemporary concepts be developed. We assessed sensitivity to change of the BNSS in a trial of MIN-101, which showed efficacy for negative symptoms (PANSS pentagonal model) at daily doses of 32 and 64 mg/day. Using mixed-effects model for repeated measures, we examined change in BNSS total score and in the BNSS factors of anhedonia/avolition/asociality (AAA, and expressivity (EXP). Compared to placebo, the 64 mg group (N = 83) showed a significant decrease in BNSS total score (effect size d [ES] = 0.56, p < 0.01) and both factor scores (AAA ES = 0.46, EXP ES = 0.46, p < 0.02 for both). Patients in the trial had minimal depression and positive symptom scores; covarying for disorganization, positive symptoms, or anxiety/depression did not cause a meaningful change in the significance of the BNSS total or factor scores in this group. The 32 mg group (N = 78) did not differ significantly from placebo (N = 83) on BNSS total score (ES = 0.33, p < 0.09), AAA (ES = 0.25, p < 0.20) or EXP (ES = 0.30, p < 0.12) scores. These results demonstrate the BNSS is sensitive to change.

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1. Introduction

The NIMH Consensus Development Conference on Negative Symptoms recommended that a negative symptom scale be developed that would embody recent changes in the concept of negative symptoms (Kirkpatrick et al. 2006). In response to that recommendation, the Brief Negative Symptom Scale (BNSS), which was designed for ease of use in clinical trials, was developed and tested. Psychometric studies of the BNSS have shown excellent reliability, discriminant validity, and convergent validity in English and in translation (Kirkpatrick et al. 2006). In response to that recommendation, the Brief Negative Symptom Scale (BNSS) grew out of a recommendation by the NIMH-sponsored Consensus Development Conference on Negative Symptoms that a scale based on contemporary concepts be developed. We assessed sensitivity to change of the BNSS in a trial of MIN-101, which showed efficacy for negative symptoms (PANSS pentagonal model) at daily doses of 32 and 64 mg/day. Using mixed-effects model for repeated measures, we examined change in BNSS total score and in the BNSS factors of anhedonia/avolition/asociality (AAA), and expressivity (EXP). Compared to placebo, the 64 mg group (N = 83) showed a significant decrease in BNSS total score (effect size d [ES] = 0.56, p < 0.01) and both factor scores (AAA ES = 0.46, EXP ES = 0.46, p < 0.02 for both). Patients in the trial had minimal depression and positive symptom scores; covarying for disorganization, positive symptoms, or anxiety/depression did not cause a meaningful change in the significance of the BNSS total or factor scores in this group. The 32 mg group (N = 78) did not differ significantly from placebo (N = 83) on BNSS total score (ES = 0.33, p < 0.09), AAA (ES = 0.25, p < 0.20) or EXP (ES = 0.30, p < 0.12) scores. These results demonstrate the BNSS is sensitive to change.

The BNSS consists of 13 items organized into six subscales (Table 1). Five of these subscales reflect the domains recognized as part of the construct of negative symptoms: anhedonia, avolition, asociality, blunted affect, and alogia. The Consensus Conference participants left open the possibility that other domains belong in this construct, and the BNSS contains an additional item, Lack of Normal Distress. A conceptually similar item, Diminished Emotional Range, is part of the Schedule for the Deficit Syndrome (SDS; Kirkpatrick et al. 1989). Psychometric studies of the BNSS and the SDS (Bischof et al. 2016; Kimhy et al. 2006; Kirkpatrick et al. 2011; Mané et al. 2014; Mucci et al. 2015; Nakaya and Ohmori 2008; Polat Nazli et al. 2016; Strauss and Gold 2008; Polat Nazli et al. 2016; Strauss et al. 2012b) have suggested that this item's content also belongs in the construct of negative symptoms.

The BNSS has a two-factor structure in English and in translation (Kirkpatrick et al. 2011; Strauss et al. 2012a; Mucci et al. 2015; Bischof et al. 2016) that is very similar to the factor structure of the Scale for the Assessment of Negative Symptoms (Blanchard and Cohen 2006) and the Clinical Assessment Interview for Negative Symptoms (Blanchard et al. 2017). The two BNSS factors consist of items from 1) the anhedonia, avolition, and asociality (AAA) subscales, and 2) the blunted affect and alogia subscales (expressivity; EXP). Although measures such as Cronbach’s alpha suggest the
BNSS Lack of Normal Distress item belongs in the construct of negative symptoms (Strauss et al. 2012a), it does not load as strongly on either factor as do the other BNSS items.

The BNSS has shown sensitivity to change in a psychosocial treatment trial (Choi et al. 2016), variation in multi-locus genetic profile scores reflecting elevated subcortical dopaminergic signaling capacity (Eisenstein et al. 2017), and factor-specific correlations with regional brain activation (Kirschnier et al. 2016) and real-world function (Galderisi et al. 2014). The study of real world function demonstrated the practicality of use of the BNSS in large multicenter studies. The BNSS has also shown sensitivity to groups differences in reward processing, which is currently the most influential theoretical model for negative symptoms, with the AAA factor having a specific relationship to reward (Barcl et al. 2014; Culbret al. 2016; Strauss et al. 2016b).

MIN-101 (a proprietary drug of Minerva Neurosciences, Inc.) is an antagonist of 5HT2A and sigma2 receptors (Mestre et al. 2013; Köster et al. 2013; Köster et al. 2014; Davidson et al., in press). In a 12-week, double blind phase 2b trial, two doses of MIN-101 were found to be superior to placebo as measured by the negative factor score of the pentagonal structure model (N1-N4,G5-G8 G13,14; White et al. 1997).

### 2.3. BNSS factors

As the BNSS item 4, Lack of Normal Distress, has not loaded as strongly on either the AAA or EXP factor as do other items, it was not included in either of the factor scores in the current analyses. The AAA score was therefore defined as the sum of the scores for items 1–3 and 5–8 (range: 0–42), and the EXP score was defined as the sum of the scores for items 9–13 (range 0–30).

### 2.4. Analyses

We present data related to the BNSS or its performance; details on other measures can be found in Davidson et al. (2017).

Using Mixed-Effect Model Repeated Measure (MMRM) analysis, we examined changes in BNSS total score and the AAA and EXP factors in the three treatment arms. We also examined whether the effect of MIN-101 was specific to negative symptoms or could be attributed to changes in positive symptoms and/or depression anxiety, using MMRM covarying for the positive, disorganization, and depression factors.

Using data from the endpoint ratings, confirmatory factor analysis was used to determine whether the raters separated the two factors found in previous studies. We examined the relative fits of two-factor and one-factor models of the BNSS, omitting the lack of normal distress item, using weighted least squares and maximum likelihood as methods of estimation. The comparative fit index (CFI), the Tucker Lewis Index (TLI), the root-mean-square-error-of-approximation (RMSEA), and information criteria (Akaike [AIC], Bayesian [BIC], and sample size adjusted BIC) were used to evaluate the relative fit of the two models, and of a ‘n,m,v null model, in which items are assumed to have zero covariance.

### 3. Results

Consistent with the recommendation of the Consensus Development Conference on Negative Symptoms on appropriate selection criteria for inclusion in negative symptom treatment trials (Kirkpatrick et al. 2006), patients entering the study had substantial negative symptoms but minimal positive and depressive symptoms.
The three treatment groups were also similar on demographical factors (Table 2, and see Davidson et al., in press for further details). At 12 weeks, the 64 mg treatment dose \( (N = 83) \) differed significantly from placebo on BNSS total score \( (p < 0.01) \) and on the AAA and EXP factors \( (p > 0.02 \text{ on both factors; Table 3, Figs. 1 & 2}) \). The 32 mg group \( (N = 78) \) had greater change in these three measures than did the placebo group \( (Table 2, Figs. 3 & 4) \), but these differences were not significant \( \text{total score}, p < 0.09; \text{AAA}, p < 0.20; \text{EXP}, p < 0.12; \text{Table 3, Figs. 3 & 4, Supplementary Table 1}) \).

In the 64 mg group, the BNSS had effect sizes \( \text{(Cohen’s d)} \) of 0.56, 0.48, and 0.46 for the total, AAA, and EXP scores. Among patients receiving the effective 64 mg group, the effect size for the two BNSS factors did not differ significantly, that is, the drug was not significantly more effective for one factor than for the other \( \text{(data not shown)} \). Covarying for the disorganization, anxiety/depression, and positive symptom factors from the PANSS produced no meaningful change in \( p \)-values for either the BNSS AAA or EXP factors \( (Table 4) \). In addition, removing a small number of patients with the highest scores on depression at baseline left a significant drug/placebo difference in negative symptoms, but no significant change in depression \( \text{(data not shown)} \).

Differences from placebo in the \( \text{(smaller)} \) 32 mg group were not significant, with respective effect sizes for BNSS total score, AAA, and EXP of 0.33, 0.25, and 0.30 \( \text{(Table 3)} \).

Confirmatory factor analysis showed that raters in this study separated the AAA and EXP factors. The two-factor model, which was essentially the structure found in previous studies \( \text{(Supplementary Table 2)} \), provided a fit to the data \( \chi^2 = 1199.80, p < 0.0001, \text{CFI} = 0.743, \text{TLI} = 0.854, \text{RMSEA} = 0.571 \) superior to the fit for a one-factor model \( \chi^2 = 1161.50, p < 0.0001, \text{CFI} = 0.732, \text{TLI} = 0.831, \text{RMSEA} = 0.603 \) or the null model \( \text{(Supplementary Table 3)} \).

4. Discussion

In this twelve week study of the efficacy of MIN-101 for negative symptoms in schizophrenia, the BNSS showed sensitivity to change similar in effect size to that of the negative factor score of the pentagonal structure model of the PANSS \( \text{(Davidson et al., 2017)} \). Covarying for disinhibition, positive symptom, anxiety/depression measures did not cause a meaningful change in the significance in either of the BNSS factor scores. These finding suggest that the effect of MIN-101 may not have been “pseudospecific,” that is, due to an effect on these causes of secondary negative symptoms \( \text{(Kirkpatrick et al. 2006)} \). Depression improved in the MIN-101 trial, but the drug/placebo differences remained significant after covarying for change in depression scores \( \text{(Davidson et al. 2017)} \), and removing a small number of patients with the highest scores on depression at baseline left a significant drug/placebo difference in negative symptoms, but no significant change in depression.

Both BNSS factor scores \( \text{(AAA and EXP)} \) had a significant decrease compared to placebo in the 64 mg treatment group. The confirmatory factor analysis suggests this was not due to a halo effect, that is, the raters did not tend to give high ratings on the AAA items because of high EXP ratings, or vice versa, as the raters did preserve the factor structure. This lack of a specific relationship to one of the factors contrasts with the factor-specific correlations with regional brain activation \( \text{(Kirschner et al. 2016)} \) and real-world function \( \text{(Galderisi et al. 2014)} \) in studies that used the BNSS. However, in a psychosocial treatment trial \( \text{(Choi et al. 2016)} \), both factors improved. The significance of this lack of specificity in the MIN-101 trial is not clear; future treatment studies with MIN-101 may help clarify this issue.

While results with the BNSS parallel those of the primary negative symptom measure in the MIN-101 phase 2b trial, there are limitations to this study of the BNSS. The most important limitation of this

### Table 2

Demographic and clinical characteristics of the sample.

<table>
<thead>
<tr>
<th></th>
<th>Placebo ( (N = 83) )</th>
<th>32 mg/32 mg/day ( (N = 78) )</th>
<th>64 mg/64 mg/day ( (N = 83) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ( (SD) )</td>
<td>40.0 (10.2)</td>
<td>39.8 (10.2)</td>
<td>40.6 (10.6)</td>
</tr>
<tr>
<td>% male</td>
<td>57.8</td>
<td>52.6</td>
<td>57.8</td>
</tr>
<tr>
<td>PANSS total score</td>
<td>80.2 (10.7)</td>
<td>81.2 (9.8)</td>
<td>79.7 (11.1)</td>
</tr>
<tr>
<td>PANSS pentagonal model</td>
<td>31.5 (4.7)</td>
<td>31.7 (4.2)</td>
<td>31.4 (4.3)</td>
</tr>
<tr>
<td>PANSS negative symptom score ( (SD) )</td>
<td>10.4 (2.9)</td>
<td>10.5 (3.0)</td>
<td>10.2 (2.9)</td>
</tr>
<tr>
<td>Calgary depression scale for schizophrenia ( (SD) )</td>
<td>2.2 (3.2)</td>
<td>2.2 (3.0)</td>
<td>2.0 (2.5)</td>
</tr>
</tbody>
</table>

### Table 3

Effect size and \( p \)-value of BNSS total and factor scores at 12 weeks.

<table>
<thead>
<tr>
<th></th>
<th>Placebo ( (N = 83) )</th>
<th>32 mg ( (N = 78) )</th>
<th>64 mg ( (N = 83) )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>Adjusted score change</td>
<td>Effect size</td>
<td>( p )-value</td>
</tr>
<tr>
<td>Placebo</td>
<td>−3.23</td>
<td>0.13</td>
<td>&lt;0.09</td>
</tr>
<tr>
<td>32 mg</td>
<td>−5.44</td>
<td>0.56</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>64 mg</td>
<td>−6.94</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Factor scores</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AAA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>−1.63</td>
<td>0.25</td>
<td>&lt;0.2</td>
</tr>
<tr>
<td>32 mg</td>
<td>−2.66</td>
<td>0.48</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>64 mg</td>
<td>−3.61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EXP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>−1.45</td>
<td>0.30</td>
<td>&lt;0.12</td>
</tr>
<tr>
<td>32 mg</td>
<td>−2.36</td>
<td>0.46</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>64 mg</td>
<td>−2.80</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Placebo: \( N = 83 \).
32 mg: \( N = 78 \).
64 mg: \( N = 83 \).

### Fig. 1

BNSS total score for drug \( (64 mg) \) vs. placebo: \( p < 0.01 \). W2, W4, etc. refer to weeks of the study. PLC: placebo arm.
Fig. 3. BNSS total score for drug (32 mg) vs. placebo: p < 0.09. W2, W4, etc. refer to weeks of the study. PLC: placebo arm.

Fig. 4. BNSS factor scores for drug (32 mg) vs. placebo: p < 0.20 for AAA, p < 0.12 for EXP, W2, W4, etc. refer to weeks of the study. PLC: placebo arm. AAA: anhedonia/avolition/asociality factor. EXP: expressivity factor.

Table 4  Change in p values in the BNSS AAA and EXP factors covarying for other factor scores: combined 32 mg & 64 mg groups.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Not covarying for the factor</th>
<th>Covarying for the factor</th>
<th>Not covarying for the factor</th>
<th>Covarying for the factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disorganization</td>
<td>0.0278</td>
<td>0.0240</td>
<td>0.0224</td>
<td>0.0210</td>
</tr>
<tr>
<td>Anxiety/depression</td>
<td>0.0278</td>
<td>0.0268</td>
<td>0.0224</td>
<td>0.0221</td>
</tr>
<tr>
<td>Positive symptoms</td>
<td>0.0278</td>
<td>0.0283</td>
<td>0.0224</td>
<td>0.0222</td>
</tr>
</tbody>
</table>

AAA: Anhedonia/avolition/asociality factor; EXP: Expressed emotion factor.

examination of the BNSS is that it is the first pharmacological study in which the BNSS was used that had an effect on another negative symptom measure that did not appear to be pseudospecific. The BNSS also showed sensitivity to change in one psychosocial treatment trial (Choi et al. 2016), but not in another study of a psychosocial intervention (Velligan et al. 2015), while two other scales did show a treatment effect. This discrepancy may be due to the relatively small sample (N = 51) in the study of Velligan and coworkers. Another limitation is that the MIN-101 phase 2b trial included patients with low depression and positive symptom scores, rather than a sample with more variation in symptoms.

Overall, the results of these studies suggest that the BNSS is successful in its primary intended purpose, which is to serve as a sensitive outcome measure in clinical trials. The BNSS has advantages over existing scales for use in clinical trials, including its brief interview time, a comprehensive manual, suitability for multicenter trials, crisp separation of the AAA and EXP factors, ease of training, successful translation and validation in multiple languages, standardized training materials, and implementation of recommendations of the Consensus Conference.

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Dr. Luthringer and Dr. Davidson are members of the management team of Minerva Neurosciences, Inc.

Mr. Tatsumi is an employee of ProPhase LLC, New York, NY, which provides training on the BNSS.

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Contributors

**All authors had final approval.

Brian Kirkpatrick designed the analyses and wrote the first draft.

Jay Saoud did most of the analyses and helped in interpretation of the data.

Gregory P. Strauss consulted on analyses and helped develop the concept of the paper.

Anthony O. Ahmed conducted some of the statistical analyses and helped with data interpretation.

Kaunori Tatsumi assisted in data analysis.

Mark Opler helped developed the concept of the paper.

Remy Luthringer helped design and oversee the clinical trial from which the data came.

Michael Davidson helped design and oversee the clinical trial from which the data came.

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