Examining the reliability and validity of the Clinical Assessment Interview for Negative Symptoms within the Management of Schizophrenia in Clinical Practice (MOSAIC) multisite national study

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ABSTRACT

The current study sought to expand on prior reports of the validity and reliability of the CAINS (CAINS) by examining its performance across diverse non-academic clinical settings as employed by raters not affiliated with the scale's developers and across a longer test-retest follow-up period. The properties of the CAINS were examined within the Management of Schizophrenia in Clinical Practice (MOSAIC) schizophrenia registry. A total of 501 participants with a schizophrenia spectrum diagnosis who were receiving usual care were recruited across 15 national Patient Assessment Centers and evaluated with the CAINS, other negative symptom measures, and assessments of functioning, quality of life and cognition. Temporal stability of negative symptoms was assessed across a 3-month follow-up. Results replicated the two-factor structure of the CAINS reflecting Motivation and Pleasure and expression symptoms. The CAINS scales exhibited high internal consistency and temporal stability. Convergent validity was supported by significant correlations between the CAINS subscales with other negative symptom measures. Additionally, the CAINS was significantly correlated with functioning and quality of life. Discriminant validity was demonstrated by small to moderate associations between the CAINS and positive symptoms, depression, and cognition (and these associations were comparable to those found with other negative symptom scales). Findings suggest that the CAINS is a reliable and valid tool for measuring negative symptoms in schizophrenia across diverse clinical samples and settings.

1. Introduction

Negative symptoms in schizophrenia are chronic features of the illness (e.g., Arndt et al., 1995; Fennig et al., 1996) that are related to impaired functioning (e.g., Alvarez-Jimenez et al., 2012; Milev et al., 2005; Rocca et al., 2014) and poorer quality of life (Eack and Newhill, 2007;

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Edgar et al., 2014; Lysaker and Davis, 2004). Negative symptoms have been identified as an unmet therapeutic need (Kirkpatrick et al., 2006) based on the lack of efficacious treatments for these symptoms (e.g., Fusar-Poli et al., 2015). To develop new interventions for negative symptoms, it is critical that treatment studies utilize the most valid and reliable measures to detect clinical change. Based on concerns regarding existing negative symptom measures (Blanchard et al., 2011), researchers developed the Clinical Assessment Interview for Negative Symptoms (CAINS; Horan et al., 2011; Kring et al., 2013) to provide a reliable and valid assessment interview for use in clinical and research settings. Findings across two development studies (Horan et al., 2011; Kring et al., 2013) indicate that the CAINS yields two negative symptom subscales reflecting symptoms associated with deficits in Motivation and Pleasure and symptoms associated with deficits in expressivity. These CAINS scales show high internal consistency, good rater agreement, convergent and discriminant validity, and short-term temporal stability (Kring et al., 2013). The CAINS shows great promise for use in clinical research and has already been translated into Czech, French, Spanish, Mandarin, Cantonese, Korean, Polish, Greek, Swedish, Lithuanian and German (e.g., Chan et al., 2015; Engel et al., 2014).

Though previously investigated, the generalizability and psychometric properties of the CAINS needs to be further evaluated (Kring et al., 2013). It is important to determine whether the CAINS can be successfully administered by raters who are not affiliated with the developers of the scale – this would speak to the ability to successfully deploy this new measure by other investigators. Further, as noted by Kring et al. (2013) it will be informative to show that the characteristics of the scale (e.g., reliability and convergent validity) are replicable in diverse clinical samples and settings. Another issue is that Kring et al. (2013) demonstrated test-retest reliability of the CAINS; however, the interval between testing was modest (two weeks) and it would be useful to evaluate test-retest stability over a longer period. Finally, it would be valuable to understand the relation between the CAINS and subjective quality of life (Lehman, 1988) as this has not yet been examined and could illuminate how the CAINS is associated with patient reported outcomes (Reininghaus and Priebe, 2012).

The aim of the present study was to extend the generalizability and test-retest reliability findings of Kring et al. (2013) by assessing these variables within the Management of Schizophrenia in Clinical Practice (MOSAIC; Nasrallah et al., 2015) schizophrenia registry. MOSAIC affords a unique opportunity to examine the CAINS as MOSAIC was developed to observe patients receiving usual care in a variety of treatment settings. MOSAIC involved the use of multiple negative symptom scales in a diverse sample of over 500 participants across 15 geographically dispersed centers with 69% of sites located at community mental health centers. This study also sought to replicate the two-dimensional structure and psychometric properties of the CAINS as demonstrated by Kring et al. (2013). A more robust assessment of temporal stability of the CAINS will be conducted by examining the baseline and 3-month follow-up assessments from MOSAIC. Convergent validity was examined using other negative symptom rating scales, assessment of community functioning, and subjective quality of life ratings. Discriminant validity was explored with measures of non-negative symptoms and cognitive performance.

2. Methods

2.1. MOSAIC schizophrenia registry

Full details of the MOSAIC schizophrenia registry can be found in Nasrallah et al. (2015). Briefly, the MOSAIC registry involved 15 centralized Patient Assessment Centers each with up to 10 clinical treatment centers representing a variety of practice settings including community mental health centers (69%) and academic departments of psychiatry (38%). Independent evaluators who were not the treating clinicians conducted symptom and functional assessments. Assessors were required to have a minimum of a bachelor's degree and rating experience in psychiatry. Evaluators were trained at a single national meeting by PhD-level assessors using case vignettes. Throughout the course of the study, participants continued their usual care with their treating physician. Assessments were conducted on study entry (baseline) and at subsequent 3-month intervals for the first year. The current report focuses on ratings of symptoms, functioning, quality of life, and cognition at baseline and 3-month follow-up.

2.2. Participants

To obtain a representative sample of individuals with schizophrenia receiving treatment in the US, the MOSAIC had broad inclusion criteria and minimal exclusion criteria. Individuals with DSM-IV-TR diagnosis of schizophrenia, schizoaffective disorder, or schizophreniform disorder who were presenting for care in usual treatment settings, aged ≥ 18 years, able to read and speak English, able and willing to provide informed consent, and able to comply with the study protocol were eligible. Individuals were excluded if they were participating in a clinical treatment trial at registry enrollment (they were permitted to become involved in clinical trials after enrollment) or if they were expected to be unable to participate in study assessments.

2.3. Study assessments

The 13-item Clinical Assessment Interview for Negative Symptoms (CAINS; Kring et al., 2013) assesses the severity of five consensus-derived negative symptoms: asociality, avolition, anhedonia, affective flattening, and alogia. Each item is scored on a 5-point scale ranging from symptoms being absent (0) to severe (4). The CAINS is comprised of two scales (the nine-item Motivation and Pleasure scale and the four-item Expression scale) that are scored separately.

The 4-item Negative Symptom Assessment (NSA-4; Alphs et al., 2010) scale is derived from the NSA-16 to evaluate negative symptoms of schizophrenia (restricted speech quantity, reduced emotion, reduced social drive, and reduced interests). The NSA-4 provides a rating based on the total of the four negative symptom items.

The Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) was used to evaluate a broad range of psychopathology including negative symptoms, positive symptoms, depression, disorganization, and excitement. Subscale scores were based on the factor results of Wallwork et al. (2012) including a single subscale score reflecting negative symptom severity.

The Personal and Social Performance (PSP; Morosini et al., 2000) scale assesses patient's functioning in four areas: 1) socially useful activities; 2) personal and social relationships; 3) self-care; and 4) disturbing and aggressive behaviors. Each of these four domains is rated on a 6-point severity scale: absent, mild, manifest, marked, severe and very severe.

The Schizophrenia Quality of Life Scale (SQLS; Wilkinson et al., 2000) is a self-report questionnaire measuring quality of life specific to patients with schizophrenia. We used the Psychosocial (15 items) and Motivation and Energy (7 items) scales. Each scale is scored such that lower scores indicate better functioning.

The Brief Cognitive Assessment Tool Score (B-CATS; Mansbach et al., 2012) is a cognitive screening tool that provides a broad assessment of cognitive functioning. The B-CATS utilizes four existing cognitive tests: Trail Making Test A and B, WAIS-III Digit Symbol, and Animal Fluency.

3. Results

3.1. Patients

Of the five hundred and fifty participants from the MOSAIC registry (Nasrallah et al., 2015) 501 completed the CAINS at baseline. Demographic characteristics are presented in Table 1. Demographic data

Table 1
Participant demographic and baseline characteristics.

Characteristic	Total sample ($N = 501$)
Diagnoses, n (%)	
Schizophrenia	250 (60%)
Schizoaffective	160 (38.6%)
Schizophreniform	4 (1%)
Gender, n (%)	
Male	351 (70%)
Female	150 (30%)
Age at entry	
Mean (SD)	42.97 (12.89)
Range	18–80
Race, n (%)	
White	315 (63%)
African-American/Black	149 (30%)
Asian	8 (2%)
American Indian or Alaska native	4 (1%)
Unknown	12 (2%)
Other	13 (3%)
Ethnicity, n (%)	
Hispanic or Latino	57 (11%)
Not Hispanic or Latino	406 (81%)
Unknown	38 (8%)
Marital status, n (%)	
Single	348 (70%)
Married/partner	66 (13%)
Divorced	73 (15%)
Separated	9 (2%)
Widowed	5 (1%)
Education, n (%)	
Less than a high school education	77 (15%)
High school graduate or equivalent (GED)	134 (27%)
Some college or vocational school	183 (37%)
College degree	80 (16%)
Graduate or professional degree	27 (5%)
Current employment, n (%)	
No	357 (71%)
Yes	143 (29%)

suggest a diverse sample as indicated by a broad age range (18–80), racial make-up (37% non-white) and range of educational achievement (42% with high school education or less, 37% with some college or vocational school, and 21% with college or graduate degree). Clinical characteristics including symptom, functioning, quality of life, and cognitive performance are presented in Table 2. At 3-month follow-up 447 participants had negative symptom ratings completed (see Table 2).

Demographic differences in baseline negative symptoms were explored focusing on sex and racial differences. At baseline, there were no sex differences in any negative symptom rating: CAINS MAP ($t = 0.255$, $p = 0.408$), CAINS EXP ($t = -0.096$, $p = 0.468$), NSA-4 ($t = 1.019$, $p = 0.309$), or PANSS ($t = 1.255$, $p = 0.210$). Racial differences were examined for the two largest racial groups in the sample (African American and White). At baseline African-American participants had higher CAINS MAP scores than did white participants ($t = -2.210$, $p = 0.028$) but there were no racial differences in the CAINS EXP ($t = 1.059$, $p = 0.290$), NSA-4 ($t = -0.645$, $p = 0.519$) or PANSS ($t = 1.095$, $p = 0.274$).

3.2. CAINS structure

Exploratory factor analysis using principle axis extraction with promax rotation was conducted on the baseline CAINS items. The scree plot for the factor analysis was most suggestive of a two-factor solution. Factor loadings are presented in Table 3. Results replicated the scale structure and item content reported by Kring et al. (2013) with one factor comprised of Motivation and Pleasure items and the second factor reflecting expression items. CAINS scale scores were moderately correlated ($r = 0.34$, $p < 0.001$).

Reliability analyses indicated high internal consistency (coefficient alpha) for the Motivation and Pleasure scale (alpha = 0.87) and the Expression scale (alpha = 0.92). These values exceeded that obtained for the NSA-4 (alpha = 0.76) and the PANSS Negative symptom scale (alpha = 0.57). Item heterogeneity (mingling motivation and expression items) and fewer items may have resulted in the lower internal consistency for the PANSS and NSA-4.

Table 2
Descriptive statistics of baseline and 3-month follow-up assessments.

Measure	Baseline ($N = 501$)	3-month follow-up ($N = 447$)
Negative symptom ratings, mean (SD)		
CAINS: Motivation and Pleasure	16.80 (7.29)	17.11 (7.63)
CAINS: Expression	4.68 (3.97)	4.95 (4.03)
NSA-4	12.12 (3.95)	12.35 (4.07)
PANSS: Negative	15.03 (5.58)	15.05 (5.63)
Other symptom ratings, mean (SD)		
PANSS: Positive	10.48 (4.20)	
PANSS: Depression	7.21 (3.00)	
PANSS: Disorganization	8.09 (307)	
PANSS: Excitement	6.07 (2.51)	
Personal and Social Performance, Mean (SD)		
Socially useful activities	2.46 (1.10)	
Personal and social relationships	2.11 (0.95)	
Self-care	0.92 (0.93)	
Disturbing and aggressive behaviors	0.44 (0.73)	
Schizophrenia Quality of Life Scale, Mean (SD)		
Psychosocial	32.18 (14.97)	
Motivation and Energy	21.36 (7.96)	
Brief Cognitive Assessment Tool, Mean (SD)		
Trail Making Test A	42.95 (23.25)	
Trail Making Test B	99.12 (54.19)	
WAIS III Digit Symbol	51.83 (24.51)	
Animal Fluency Score	18.20 (5.46)	

Note: CAINS = Clinical Assessment Interview for Negative Symptoms; NSA-4 = 4-item Negative Symptom Assessment; PANSS = Positive and Negative Syndrome Scale.

3.3. Convergent validity

Convergent validity was assessed by examining correlations between baseline CAINS ratings and negative symptom ratings from the NSA-4 and the PANSS (see Table 4). Both CAINS scales were significantly correlated with the NSA-4 and the PANSS Negative Symptom score. The CAINS Motivation and Pleasure scale was significantly ($z = 7.51$, $p < 0.001$) more strongly correlated with the NSA-4 ($r = 0.64$) than with the PANSS Negative symptom score ($r = 0.46$).

Table 3
Two-factor solution for the CAINS items at baseline.

CAINS item	Factor 1	Factor 2
9. MAP: Expected pleasure recreation	0.85	
8. MAP: Pleasure from past recreation	0.80	
7. MAP: Motivation for recreation	0.75	
4. MAP: Expected pleasure social	0.73	
3. MAP: Pleasure from past social	0.72	
6. MAP: Expected pleasure work/school	0.55	
2. MAP: Motivation for friendship/romantic	0.53	
5. MAP: Motivation for work/school	0.50	
1. MAP: Motivation for family/spouse/partner	0.46	
11. EXP: Vocal expression		0.93
12. EXP: Expressive gestures		0.91
10. EXP: Facial expression		0.89
13. EXP: Quantity of speech		0.71

Note: CAINS = Clinical Assessment Interview for Negative Symptoms; MAP = Motivation and Pleasure; EXP = expressivity.

Table 4
Negative symptom correlates at baseline.

	CAINS-MAP	CAINS-EXP	NSA-4	PANSS-Negative
Symptoms				
NSA-4	0.64***	0.70***	–	–
PANSS-Negative symptoms	0.46***	0.80***	–	–
PANSS-Positive symptoms	0.33**	0.06	0.23**	0.16**
PANSS-Depression	0.14**	0.07	0.07	0.12**
PANSS-Disorganization	0.30**	0.19	0.27**	0.33**
PANSS-Excitement	0.20**	-0.05	0.06	0.07
Functioning				
PSP: Socially Useful	0.60***	0.32***	0.59***	0.49**
PSP: Social Relationships	0.51***	0.30***	0.48***	0.43***
PSP: Self-Care	0.39***	0.27***	0.38***	0.38***
PSP: Disturbing Behaviors	0.22***	0.11*	0.19***	0.20***
Quality of Life				
SQLS: Psychosocial	0.35***	0.04	0.15**	0.11*
SQLS: Cognitive-Vitality	0.36***	0.05	0.16***	0.15**
Cognitive				
Trails A	0.22***	0.19***	0.18***	0.19***
Trails B	0.14**	−0.05	0.03	0.01
WAIS III Digit Symbol	−0.20***	−0.13**	−0.17***	−0.15***
Fluency	−0.23***	−0.14**	−0.22***	−0.20***

Note: CAINS-MAP = Clinical Assessment Interview for Negative Symptoms – Motivation and Pleasure; CAINS-EXP = Clinical Assessment Interview for Negative Symptoms – Expressivity; NSA-4 = 4-item Negative Symptom Assessment; PANSS = Positive and Negative Syndrome Scale; PSP = Personal and Social Performance; SQLS = Schizophrenia Quality of Life Scale.
* $p < 0.05$.
** $p < 0.005$.
*** $p < 0.001$.

3.4. Discriminant validity

Discriminant validity was assessed by correlating CAINS scores with scores of non-negative symptoms (positive symptoms, depression, disorientation, excitement) and cognitive functioning (see Table 4). The CAINS Expression scale was not related to any other symptom rating. The CAINS Motivation and Pleasure scale was only modestly correlated with positive symptoms, depression, disorganization, and excitement (range of $rs = 0.14$ to 0.33, $ps < 0.005$). Similar correlations with positive symptoms and disorganization were found for the NSA-4 and the PANSS Negative symptom scale. With the exception of Trails B, all cognitive tests were correlated with negative symptom severity across rating scales (range of $rs = -0.15$ to 0.23, $ps < 0.001$), indicating that approximately 5% of the variance in negative symptom severity was shared with cognitive impairment.

3.5. Functioning and quality of life

With regard to functioning as rated with the PSP, the CAINS showed (Table 4) generally robust correlations with ratings of social relationships, useful activities, and self-care (range of $rs = 0.27$ to 0.60, $ps < 0.001$) and somewhat weaker associations with disturbing or aggressive behavior ($rs = 0.11$ and 0.22). Analyses comparing the magnitude of correlations indicated that compared to the CAINS Expression scale, the CAINS Motivation and Pleasure scale was more strongly correlated with PSP Social Relationships ($z = 6.51$, $p < 0.001$) and PSP Useful Behaviors ($z = 4.64$, $p < 0.001$). A similar pattern of correlations was obtained between PSP scales and the NSA-4 and PANSS Negative symptom scores.

Given modest correlates between CAINS scales and cognitive measures, we also examined how the CAINS was related to functioning controlling for cognitive impairment. Cognitive performance on the BCATS scales was modestly correlated with functioning measured by the PSP (range of $rs = -0.23$ to 0.22, $ps < 0.05$). After controlling for performance on all four BCATS tests, partial correlations remained significant between all PSP scores and CAINS negative symptom ratings on the MAP (Social Relationships $pr = 0.59$, Socially Useful $pr = 0.49$, Self-Care $pr = 0.36$, and Disturbing Behaviors $pr = 0.24$; all $ps < 0.001$) and EXP (Social Relationships $pr = 0.31$, Socially Useful $pr = 0.30$, Self-Care $pr = 0.26$, and Disturbing Behaviors $pr = 0.12$; all $ps < 0.05$).

Self-reported quality of life on the SQLS was significantly correlated with the CAINS Motivation and Pleasure scale but not the CAINS Expression scale (Table 4). The correlations between quality of life scores and the CAINS Motivation and Pleasure scale were significantly larger than those correlations obtained between quality of life and the NSA-4 and PANSS negative symptom score (z-scores > 5.50, $ps < 0.05$).

3.6. Test-retest reliability

Temporal stability was examined by correlating CAINS baseline scores with 3-month follow-up scores. Correlations were high for CAINS Motivation and Pleasure ($r = 0.80$, $p < 0.001$) and Expression ($r = 0.75$, $p < 0.001$) scales. Robust test-retest correlations were also obtained for the NSA-4 ($r = 0.78$, $p < 0.001$) and PANSS Negative Symptom score ($r = 0.80$, $p < 0.001$).

4. Discussion

The purpose of this study was to examine the performance of the CAINS as utilized by clinical assessors not affiliated with the scale's developers within a large and diverse sample of individuals with schizophrenia receiving usual care in a range of treatment settings. Results were promising and replicated many of the properties obtained by the CAINS' developers (Kring et al., 2013). Structural analyses indicated a two-factor solution representing Motivation and Pleasure and a factor comprised of expressive items. These structural results replicate prior findings with the CAINS (Horan et al., 2011; Kring et al., 2013) and also replicate the general bifactor solution of negative symptoms using other negative symptom scales (e.g., Liemburg et al., 2013; Messinger et al., 2011; Mueser et al., 1994; Peralta and Cuesta, 1995; Strauss et al., 2012; for a review, see Blanchard and Cohen, 2006; also see Foussias and Remington, 2010). Internal consistency analyses further indicated that that the two CAINS scales had high internal consistency.

The CAINS scales showed good convergent validity with other negative symptom ratings obtained from the NSA-4 and the PANSS. However, comparisons of the magnitude of the correlations indicated that the CAINS Motivation and Pleasure scale was more robustly related to the NSA-4 than with the PANSS negative symptom score. These findings replicate and extend the convergent validity findings from Kring et al. (2013) obtained with the Brief Psychiatric Rating Scale (BPRS) and the Scale for the Assessment of Negative Symptoms (SANS). It should be noted that the same rater completed all symptom ratings in the current study, so the convergent correlations are likely higher than what might be expected by independent raters completing the different assessments. Consistent with this speculation, Kring et al. (2013) used independent raters and found SANS total scores to be associated with the two CAINS scales 0.48 and 0.55 (lower than the 0.46–0.80 convergent correlations in the current study).

Negative symptoms assessed with the CAINS, NSA-4, and PANSS were associated with functioning as measured by the PSP. These relations with functioning were especially robust for useful behaviors, social relationships, and self-care. This replicates the prior findings of the CAINS relationship with measures of functioning (Kring et al., 2013) and converges with a large literature indicating the association between negative symptoms and functioning (e.g., Alvarez-Jimenez et al., 2012; Kalin et al., 2015; Milev et al., 2005; Rocca et al., 2014). Within the CAINS, although both scales were correlated with functioning, the

Motivation and Pleasure scale had significantly more robust relations with functioning compared to the Expression scale. This suggests that deficits in Motivation and Pleasure may be more central to functional impairment than expressive symptoms. This finding is consistent with the results of Rocca et al. (2014) who found that avolition-related symptoms were more strongly associated with functional impairment than expressive deficits (also see Kalin et al., 2015).

With regard to self-reported quality of life, the CAINS Motivation and Pleasure scale (but not the Expression scale) was significantly correlated with SQLS ratings. Although the NSA-4 and PANSS Negative scale were also associated with subjective quality of life ratings, these correlations were significantly smaller in magnitude than those obtained with the CAINS Motivation and Pleasure scale (representing about 2% of the variance in subjective quality of life ratings versus approximately 12% of the variance in quality of life accounted for by CAINS Motivation and Pleasure scale). This result replicates prior findings indicating a contribution of negative symptoms to quality of life (Eack and Newhill, 2007; Edgar et al., 2014; Lysaker and Davis, 2004) but also demonstrates that the CAINS Motivation and Pleasure scale has a more robust relation with reports of subjective quality of life than other negative symptom scales. To the extent that treatment studies are interested in assessing patient reported outcomes (Reininghaus and Priebe, 2012) such as improvement in subjective quality of life, this result would suggest the potential advantage of utilizing the CAINS versus other negative symptom measures.

The results regarding functioning and subjective quality of life correlates of the CAINS scales also demonstrate the advantages afforded by providing separate measures of the two key facets of negative symptoms (Rocca et al., 2014). Functioning was more strongly related to Motivation and Pleasure than to Expression, and Motivation and Pleasure, but not Expression, was associated with self-reported quality of life. Negative symptom measures that were designed to only offer a single aggregate negative symptom score (like the NSA-4 and PANSS) are problematic in not being able to detect differential correlates or treatment effects across these two distinct facets of negative symptoms. Although one might try to develop subscale scores for the NSA-4 this would result in each such subscale score being based on only two items taping expression and two items tapping Motivation and Pleasure. PANSS items have been used to generate subscale scores for the two negative symptom facets (e.g., Liemburg et al., 2013; Stiekema et al., 2016) but each of these approaches includes problematic PANSS negative symptom items (e.g., active social avoidance that reflects fear, hostility or distrust) that are not conceptually related to negative symptoms (Blanchard et al., 2011) and are typically excluded in other factor work on the PANSS (Wallwork et al., 2012). When such items are excluded, like the NSA-4, the PANSS yields only two items tapping the Motivation and Pleasure domain (emotional withdrawal and passive/apathetic social withdrawal). (See supplemental material for further exploration of NSA-4 and PANSS scoring approaches.)

Concerning discriminant validity, the CAINS Motivation and Pleasure scale was modestly correlated with non-negative symptoms including positive symptoms. The NSA-4 and the PANSS Negative symptom score were also correlated with positive symptoms and disorganization symptoms. The relation between negative symptoms (assessed across different scales) and positive symptoms replicates the findings of Kring et al. (2013) who also found that the CAINS Motivation and Pleasure scale, the SANS, and the BPRS negative symptom score were all correlated with positive symptom severity (range of $rs = 0.25–0.35$). This suggests that positive symptoms are associated negative symptoms regardless of rating scale used, but that the contribution is typically modest with approximately 12% of the variance in negative symptoms accounted for by positive symptoms. The direction of the causal relationship between these symptom domains is complicated. Although positive symptoms may contribute error variance to the assessment of negative symptoms (i.e., positive symptoms giving rise to "secondary" negative symptoms; Carpenter et al., 1988), it is possible that negative symptoms themselves may give rise to social environments that contribute to vulnerability for the development or exacerbation of positive symptoms (e.g., Jolley et al., 2014; Saha et al., 2012). Future longitudinal research will need to further explore social and other factors that may contribute to the association between negative and positive symptoms and how these two symptom domains influence each other over time.

Cognitive impairment was modestly related to each negative symptom rating scale. Kring et al. (2013) did not find any association between the CAINS (or other negative symptom scales) and the same cognitive measures used in the current study. However, our results are consistent with prior studies that have found a weak relation between cognition and negative symptom severity (for meta-analysis, see Heinrichs and Zakzanis, 1998; for a review, see Harvey et al., 2006). Importantly, cognitive impairment accounted for no >5% of the variance in negative symptom severity as rated by the CAINS or other negative symptom scales. Further, CAINS negative symptom ratings remained robustly correlated with functioning even after controlling for cognitive impairment.

Test-retest reliability was demonstrated for each of the negative symptom scales across the 3-month follow-up. Our test-retest results for the CAINS scales ($rs = 0.75–0.80$) were somewhat higher than that (0.69) obtained by Kring et al. (2013) despite the longer follow-up period of the current study. These results are encouraging for utilizing the CAINS in treatment studies to detect improvement – that is, in the absence of intervention these negative symptom scores are rather stable over time.

The current study has several limitations. The lack of independent raters for each negative symptom measure prevents a direct evaluation of how the different scales perform when the rater only has access to the information obtained by each scale's interview. However, our results are consistent with the findings of Kring et al. (2013), who did use a more stringent independent rater design to evaluate the CAINS. Inter-rater agreement was not formally assessed in the MOSAIC protocol, so we are not able to specifically address that aspect of scale performance. Although we found only modest relations between cognition and negative symptoms, it is important to consider that the B-CATS is a brief battery of tests assessing a limited scope of cognition. Assessments of motor side effects were not included in the current study so it is not possible to directly examine the contribution of such side effects to these findings – it is notable that Kring et al. (2013) found no relation between clinician-rated motor side effects and negative symptom ratings based on the CAINS or other measures. Additionally, the MOSAIC registry did not include individuals participating in treatment trials, thus it is not possible to evaluate the sensitivity of the CAINS to treatment effects. The broad inclusion criteria utilized by MOSAIC ensures a more representative sample of individuals receiving usual care in a variety of settings and the results are encouraging for considering the CAINS in future treatment studies.

In summary, this study adds to prior reports of the CAINS as a reliable and valid clinical rating scale for negative symptoms. The present results provide an important demonstration that the CAINS can be successfully deployed across a variety of clinical settings and used with diverse patient samples. The provision of separate assessments of the two major facets of negative symptoms was shown to be an important feature of the CAINS and one that is superior to reliance on a single aggregate negative symptom score.

Role of funding source

This study was not a Phase III registrational study with the intent to assess efficacy of an investigational agent for schizophrenia and Genentech does not currently have a medication approved for the indication of schizophrenia.

Contributors

Jack Blanchard was involved in data analyses, interpretation and writing of the manuscript. Kristen Bradshaw and Cristina P. Garcia participated in data interpretation and in

the writing of the manuscript. Henry Nasrallah participated in the writing and multiple edits of the manuscript drafts and in presenting the data at national meetings. Philip Harvey contributed to the design of the study and participated in the writing and review of the manuscript drafts. Daniel Casey and Tracey Skale reviewed the manuscript drafts. Csilla Csoboth reviewed the manuscript drafts. James Hudson was involved in the design of the study and the collection of data. Laura Julian was involved in the design of the study and the writing of protocol. Ellen Lentz participated in the design of the protocol and the Case Report Form and interpretation of the original MOSAIC results. Keith Nuechterlein contributed to the design of the study and collection of data. Diana Perkins and Sophia Vinogradov contributed to the design of the study, data interpretation, and reviewed the manuscript drafts. Lonnie Snowden and Dawn Velligan were involved in the design of the study. Rajiv Tandon and Cenk Tek participated in the conceptual development of the MOSAIC registry and study design. Cedric O'Gorman participated in the design of the original registry, the proposal of analyses, the assessment of data generated and review of the manuscript drafts.

All authors contributed to and approved the final manuscript.

Conflict of interest

Jack Blanchard has served as a paid consultant and was on a scientific advisory board for Genentech/Roche. Henry Nasrallah has received research grants from Forest, Forum, Genentech and Otsuka and has been a consultant and on the speaker's bureau for Acadia, Alkermes, Allergan, Genentech, Forum, Janssen, Lundbeck, Merck, Otsuka, Sunovion, Teva and Vanda. Philip

Harvey was an investigator on the MOSAIC Schizophrenia registry and has received consulting fees from Boehringer-Ingelheim, Forum Pharma, Genentech, Lundbeck, Otsuka-America, Roche Pharma, Sanofi, Sunovion Pharma and Takeda Pharma. Daniel Casey is a consultant to Genentech. James Hudson has received consulting fees from Genentech, Pronutria, Sunovion and Shire and has received research grant support from Genentech, Shire, and Sunovion. Keith Nuechterlein has been a paid consultant to Genentech, Janssen Scientific Affairs, Otsuka, and Takeda and has research grants from Janssen Scientific Affairs, Posit Science, and the Stanley Medical Research Institute. Diana Perkins is a consultant and research grant recipient for Genentech/Roche and a consultant for Otsuka/Lundbeck, Sunovion and Janssen Pharmaceuticals. Tracey Skale is a consultant for Sunovion and Otsuka/Lundbeck. Lonnie Snowden has no conflicts of interest related to this manuscript. Rajiv Tandon was an investigator on the MOSAIC Schizophrenia registry and has no other conflicts of interest related to this manuscript. Cenk Tek is a consultant and has received grant support from Roche. Dawn Velligan is a consultant and is on the advisory board for Genentech/Roche, a consultant, and on the advisory board and speaker's bureau for Otsuka/Lundbeck, on the advisory board for Forum Pharma and Boehringer-Ingelheim, a consultant and research grant recipient for Amgen Pharmaceuticals, a consultant and on the speaker's bureau for Janssen Pharmaceuticals, a consultant for Takeda Pharmaceuticals and a consultant for AbbVie Pharmaceuticals. Sophia Vinogradov is a site investigator on an SBIR grant to PositScience, Inc. and a consultant to Forum Pharmaceuticals. Csilla Csoboth, Laura Julian and Ellen Lentz are employees and stockholders of Genentech/Roche. At the time of the study, analyses and data generation, Cedric O'Gorman was an employee and stockholder at Roche/Genentech.

Acknowledgements

Cedric O'Gorman is currently Vice President of Medical Affairs at Intra-Cellular Therapies, Inc. 430 East 29th Street, New York City, NY 10016, USA. Dr. O'Gorman was an employee of Genentech, Inc., during the time of study conduct and data assessment.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2017.01.011.

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