Comparison of CAINS and PANSS as Assessments of Negative Symptoms in Outpatients with Schizophrenia in a Clinical Trial Setting

Longenecker, J[1]; Snipes, C[1]; Livezey, V[1]

[1]Click Therapeutics, Inc., New York, NY, USA

Methodological Issue Addressed

The Positive and Negative Syndrome Scale (PANSS) - the established outcome for clinical trials in schizophrenia - emphasizes observable behaviors, has incomplete coverage of negative symptoms, and may be less sensitive to change, particularly in populations with stable positive symptoms, compared to more contemporary assessments.

Introduction

- Negative symptoms are the primary source of functional impairment in schizophrenia, making accurate detection of therapeutic signal essential.
- While the PANSS has long served as the gold standard, its Marder Negative Factor Score (NSFS) heavily emphasizes observable behavioral deficits and the expressive domain.
- The CAINS was developed to capture contemporary models of negative symptoms with greater sensitivity and less confounding variance. It operationalizes the NIMH consensus two-factor model, differentiating the Motivation and Pleasure (MAP) and Expression (EXP) domains.
- This study provides a descriptive comparison of the convergent validity and longitudinal sensitivity of both scales.

Methods

Exploratory, post hoc analysis of the **CONVOKE RCT** evaluating CT-155 (a 16-week digital therapeutic for negative symptoms) vs. digital control in schizophrenia outpatients (n=457) and data from the **Open Label Extension** study in a subset of participants (n=73) who completed a second CT-155 course.

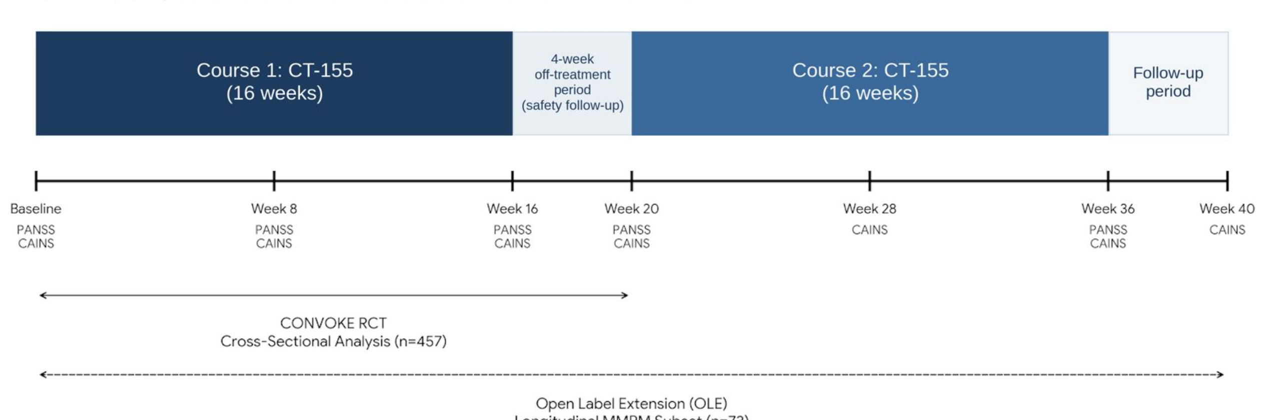
Measures

- **PANSS:** 7-item NSFS, 2-item proxy MAP, 2-item proxy EXP
- **CAINS:** MAP, EXP, total score

Statistical Analysis

- **Convergent validity** between CAINS and PANSS was compared using Spearman correlations, with 95% confidence intervals (CIs) calculated using a non-parametric bootstrap (based on the 2.5th and 97.5th percentiles of 5000 bootstrap samples).
- **Longitudinal sensitivity** of CAINS-MAP and PANSS NSFS was explored using Mixed Models for Repeated Measures (MMRM), including the fixed effects of week as a categorical variable and baseline value.

CT-155 Studies and Assessment Timeline

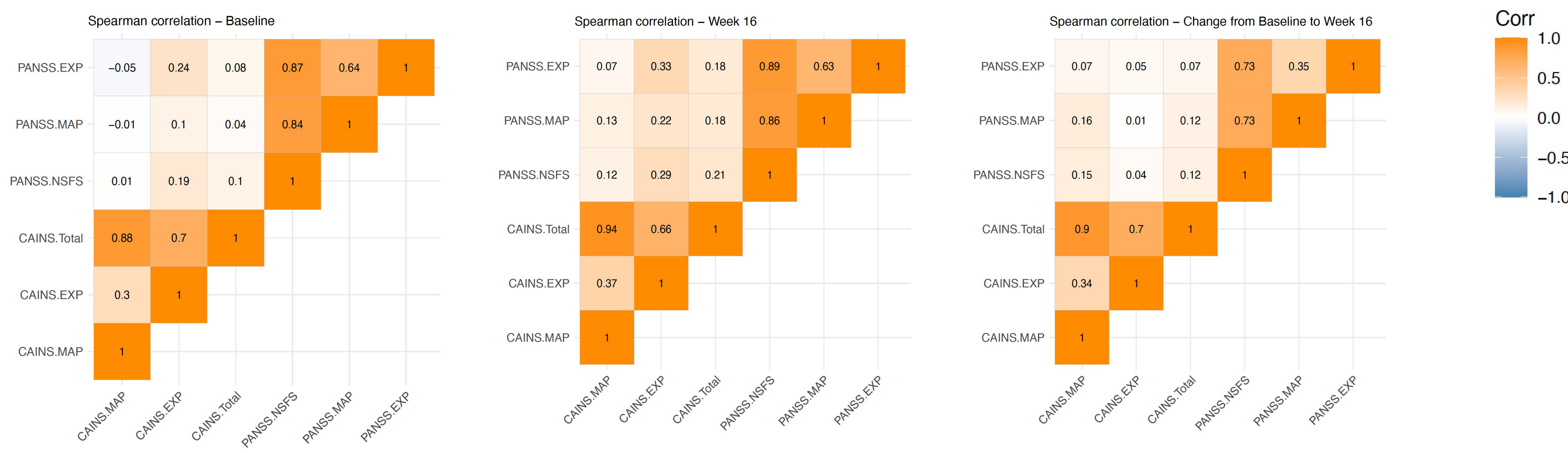

Course 1: CT-155 (16 weeks)
4-week off-treatment period (safety follow-up)
Course 2: CT-155 (16 weeks)
Follow-up period
Baseline PANSS CAINS
Week 8 PANSS CAINS
Week 16 PANSS CAINS
Week 20 PANSS CAINS
Week 28 CAINS
Week 36 PANSS CAINS
Week 40 CAINS
CONVOKE RCT Cross-Sectional Analysis (n=457)
Open Label Extension (OLE) Longitudinal MMRM Subset (n=73)

Results

Convergent validity (cross-sectional correlations)

Correlations with PANSS NSFS were stronger, and statistically significant, for CAINS-EXP (ρBL=0.19, 95% CI [0.10, 0.28]; ρw16=0.29, 95% CI [0.19, 0.38]) than CAINS-MAP (ρBL=0.01, 95% CI [-0.08, 0.11], not significant; ρw16=0.12, 95% CI [0.02, 0.22]) or Total (ρBL=0.10, 95% CI [0.01, 0.19]; ρw16=0.21, 95% CI [0.10, 0.30]) scores at Baseline and Week 16, consistent with the known overemphasis of expressive negative symptoms in PANSS.

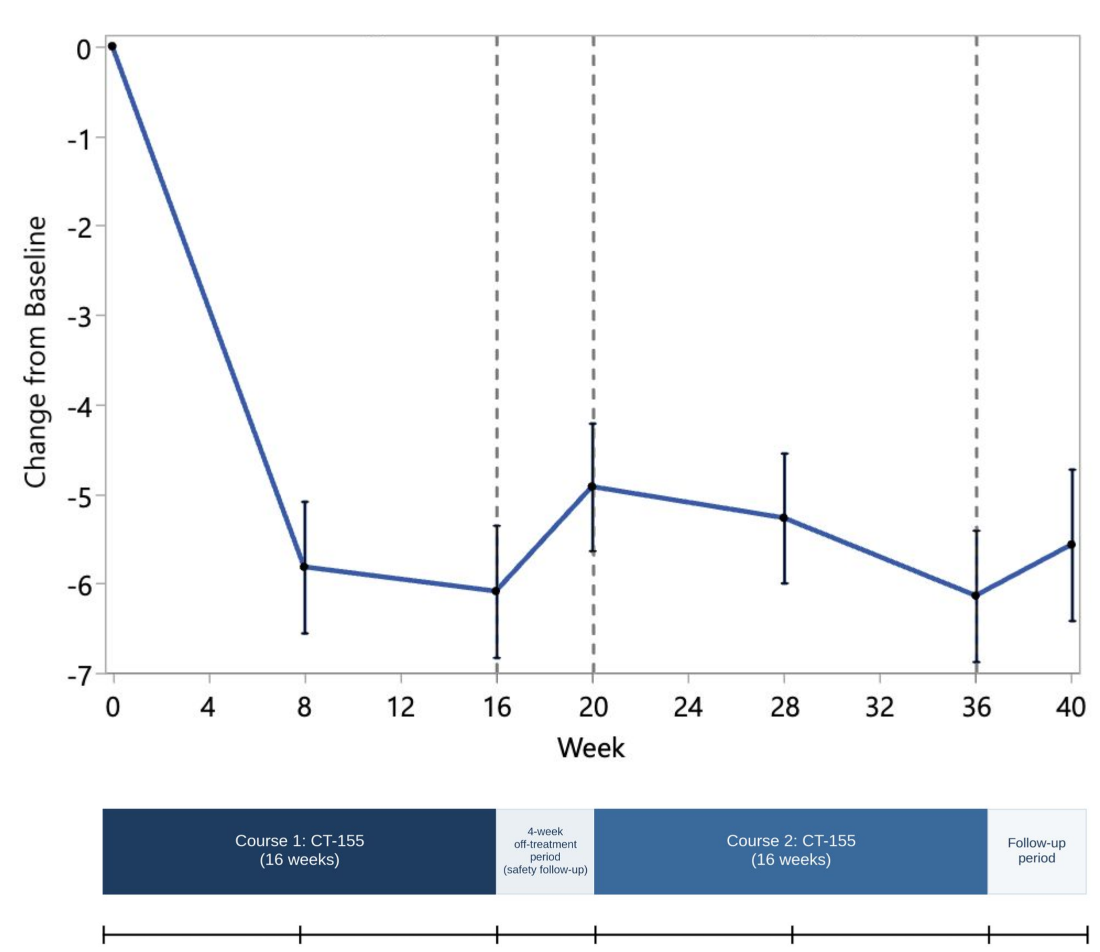
However, NSFS and CAINS-EXP change scores showed a non-significant, lower convergence (ρ=0.04, 95% CI [-0.07, 0.14]) than cross-sectional correlations at each time point.


Spearman correlation – Baseline
PANSS.EXP −0.05 0.24 0.08 0.87 0.64 1
PANSS.MAP −0.01 0.1 0.04 0.84 1
PANSS.NSFS 0.01 0.19 0.1 1
CAINS.Total 0.88 0.7 1
CAINS.EXP 0.3 1
CAINS.MAP 1
CAINS.MAP CAINS.EXP CAINS.Total PANSS.NSFS PANSS.MAP PANSS.EXP
Spearman correlation – Week 16
PANSS.EXP 0.07 0.33 0.18 0.89 0.63 1
PANSS.MAP 0.13 0.22 0.18 0.86 1
PANSS.NSFS 0.12 0.29 0.21 1
CAINS.Total 0.94 0.66 1
CAINS.EXP 0.37 1
CAINS.MAP 1
CAINS.MAP CAINS.EXP CAINS.Total PANSS.NSFS PANSS.MAP PANSS.EXP
Spearman correlation – Change from Baseline to Week 16
PANSS.EXP 0.07 0.05 0.07 0.73 0.35 1
PANSS.MAP 0.16 0.01 0.12 0.73 1
PANSS.NSFS 0.15 0.04 0.12 1
CAINS.Total 0.9 0.7 1
CAINS.EXP 0.34 1
CAINS.MAP 1
CAINS.MAP CAINS.EXP CAINS.Total PANSS.NSFS PANSS.MAP PANSS.EXP
Corr
1.0
0.5
0.0
−0.5
−1.0

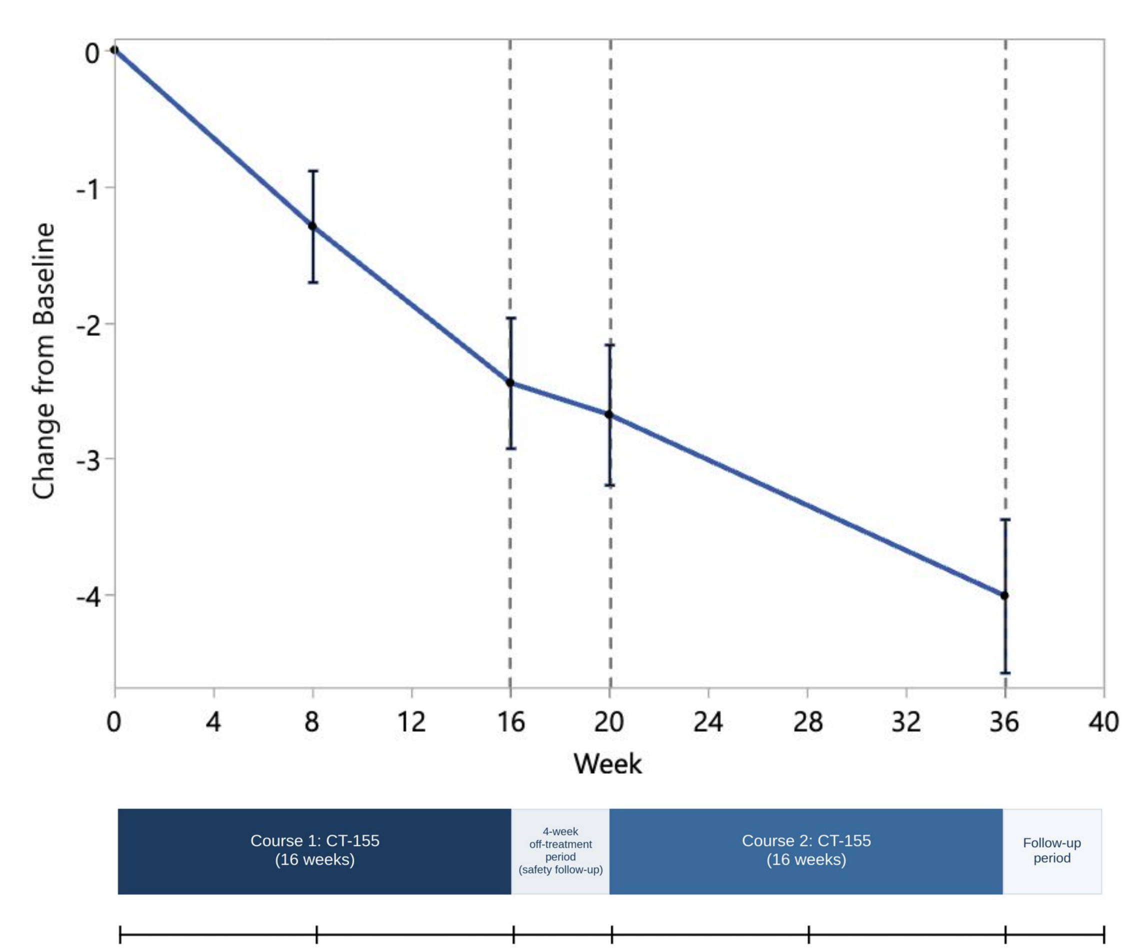
Longitudinal sensitivity (MMRM)

Within the subset of participants who completed two cycles of treatment, MMRM analysis demonstrated that CAINS-MAP captured an earlier, sustained reduction in negative symptoms, with no significant difference in scores between Week 16 and Week 36 (LS Mean diff = -0.05, 95% CI [-1.48, 1.39], p=0.95). Conversely, NSFS exhibited slower detection of symptom reduction, capturing a statistically significant continued reduction between Week 16 and Week 36 (LS Mean diff = -1.56, 95% CI [-2.56, -0.57], p=0.003).

CAINS-MAP Change from Baseline - LS Means (SE) vs Week


Change from Baseline
0
-1
-2
-3
-4
-5
-6
-7
0 4 8 12 16 20 24 28 32 36 40
Week
Course 1: CT-155 (16 weeks)
4-week off-treatment period (safety follow-up)
Course 2: CT-155 (16 weeks)
Follow-up period
Baseline
Week 8
Week 16
Week 20
Week 28
Week 36
Week 40

PANSS NSFS Change from Baseline - LS Means (SE) vs Week


Change from Baseline
0
-1
-2
-3
-4
0 4 8 12 16 20 24 28 32 36 40
Week
Course 1: CT-155 (16 weeks)
4-week off-treatment period (safety follow-up)
Course 2: CT-155 (16 weeks)
Follow-up period
Baseline
Week 8
Week 16
Week 20
Week 28
Week 36
Week 40

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Conclusions

- Newer endpoints like the CAINS may offer advantages in accurately detecting the therapeutic effects of interventions targeting negative symptoms.
- The differences in cross-sectional convergence and longitudinal sensitivity between CAINS and PANSS provide further evidence of the partial coverage of the PANSS instrument.
- Longitudinal results suggest the PANSS may show lower sensitivity to treatment-induced clinical changes, particularly in outpatients with well-controlled positive symptoms.
- These analyses provide methodological considerations for future psychosis trials, suggesting that leveraging contemporary instruments may be essential to optimizing signal detection.

References

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One or more authors report potential conflicts which are described in the program.