Examining Placebo Effects on MATRICS Battery Measures in Schizophrenia Cognition Clinical Trials

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BACKGROUND

The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Battery (MCCB) is described as the "gold standard" by members of the Psychiatry Divisions of the US FDA and the European Medicines Agency. The psychometrics of the MCCB have been increasingly well established. However, the magnitude and predictors of improvement in sequential assessments with placebo treatment is unknown.

METHODS

We combined data from 12 studies that assessed changes in MCCB performance in 753 patients with schizophrenia receiving placebo over 4 to 56 weeks. Change from baseline was investigated using a mixed-effects model of repeated measures controlling for baseline score, study, visit week nested within study, and the baseline score by study interaction. Predictors evaluated included demographics, baseline characteristics and symptoms. Practice effects were examined in a separate model using data from 7 studies (N=498) that measured cognition at screening.

RESULTS

Demographic and Baseline Characteristics of the Samples

	Mean ± SD (N)
Age	41.6 ± 11.44 (753)
Age at Onset of Illness	23.3 ± 8.34 (233)
Baseline MCCB Composite T-Score	27.4 ± 12.64 (725)
Baseline UPSA-2 Total	87.8 ± 16.10 (225)
Baseline PANSS Total	58.8 ± 14.77 (609)
Baseline NSA-16 Total	57.1 ± 11.96 (430)

	N (%)
Male	524 (70)
Race:	
White	346 (46)
Black	290 (39)
Other	117 (16)
Geographical Region:	
North America	536 (71)
Eastern Europe	58 (8)
Asia	63 (8)
Latin America	50 (7)
Western Europe	46 (6)
Post-Secondary Education	142 (28)
Current Smoker	258 (48)
Duration of Illness < 10 years	206 (36)
Baseline Antipsychotic:	
Risperidone/Paliperidone	159 (33)
Olanzapine	118 (24)
Other	89 (18)
Quetiapine	66 (14)
Aripiprazole	56 (11)

Overall Placebo Change from Baseline by Study for MCCB Composite

Study Number	1 (N=65)	2 (N=43)	3 (N=59)	4 (N=56)	5 (N=107)	6 (N=44)	7 (N=60)	8 (N=17)	9 (N=74)	10 (N=71)	11 (N=110)	12 (N=18)
Placebo Response Mean (SE)	1.8 (0.49)	0.7 (0.64)	0.8 (0.56)	2.6 (0.62)	2.9 (0.44)	1.7 (0.90)	2.1 (0.69)	2.7 (0.57)	1.4 (0.69)	1.2 (0.65)	2.7 (0.58)	1.4 (1.15)

Change from baseline was investigated with a mixed-effects model of repeated measures adjusting for baseline, study, baseline by study, and with visit nested within study.

Overall Placebo Change from Baseline for MCCB Composite and Individual Subtests

Test	Overall Composite (N=724)	Trails A (N=748)	BACS Symbol Coding (N=750)	HVLT (N=751)	Spatial Span (N=750)	Letter-number span (N=695)	NAB Mazes (N=745)	BVMT (N=751)	Fluency (N=751)	MSCEIT Managing Emotions (N=744)	CPT (N=734)
Placebo Response Mean (SE)	1.8 (0.20)	2.3 (0.35)	1.1 (0.25)	1.3 (0.28)	0.9 (0.29)	1.2 (0.26)	1.7 (0.26)	0.5 (0.32)	1.4 (0.25)	0.2 (0.33)	1.3 (0.30)

BACS, Brief Assessment of Cognition in Schizophrenia; HVLT, Hopkins Verbal Learning Test; NAB, Neuropsychological Assessment Battery; MSCEIT, Mayer-Salovey-Caruso Emotion Identification Test; CPT, Continuous Performance Test

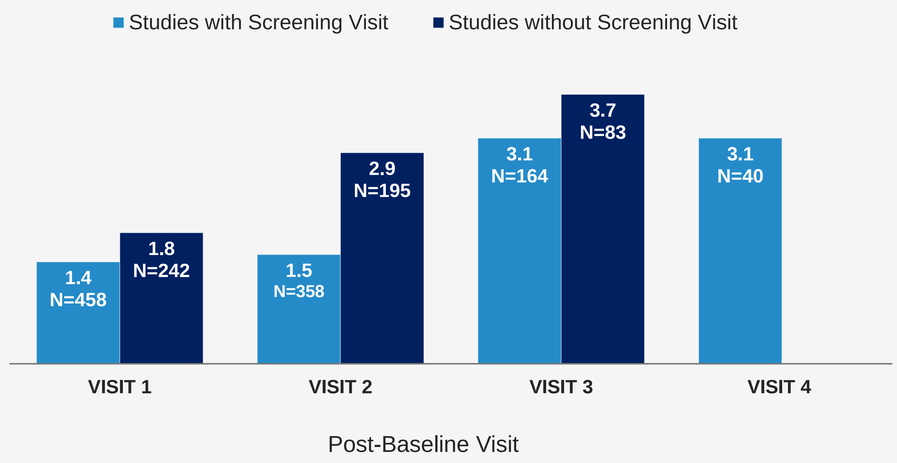
Predictors Considered for MCCB Placebo Response*

Demographics	PANSS	NSA-16	UPSA	Practice Effect
Age	PANSS Total	NSA-16 Total	UPSA-2	Change in Composite from Screening to Baseline -0.35 ± 0.040
Gender	PANSS Positive Subscale	Emotion / Affect	UPSA-2-ER	
Race	PANSS Negative Subscale	Communication		
Geographic Region	PANSS General Psychopathology	Motivation		
Education	Marder Positive Factors	Motor Retardation		
Current Smoker	Marder Negative Factors	Social Involvement		
Duration of Illness	Marder Anxiety / Depression 0.23 ± 0.081	Global Negative Symptoms		
Age at Onset of Illness	Marder Disorganized Thoughts			
Baseline Antipsychotic	Marder Hostility / Excitement			
Married				
Employed				

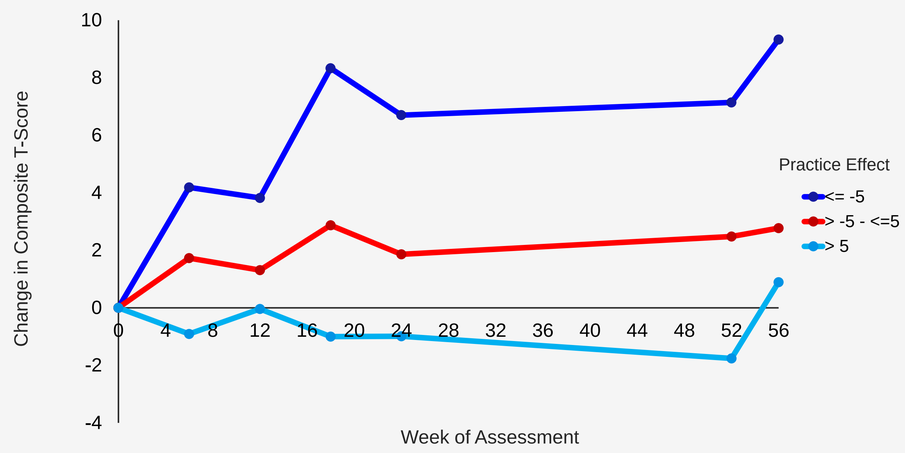
*Placebo response measured as change from baseline in the MCCB Composite T-Score using a linear mixed model repeated measures analysis with adjustment for baseline score, study, week nested within study, and the interaction between baseline and study. Regression coefficients and standard errors are given for significant effects, p-value<0.01 (highlighted).

RESULTS

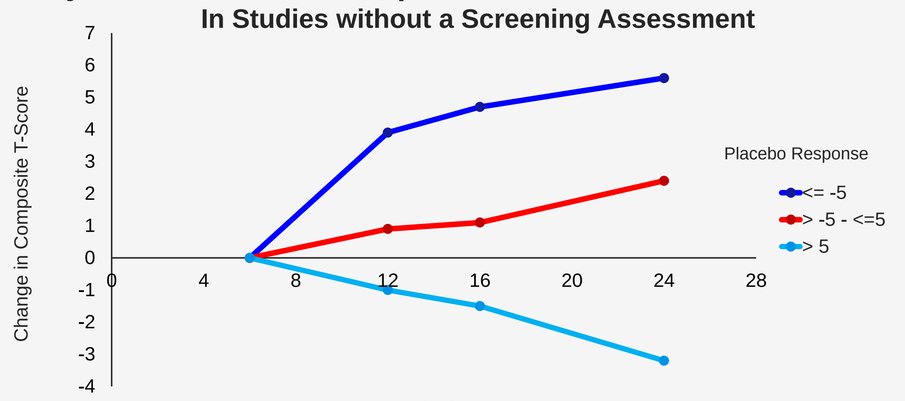
MCCB Composite T-Score Change from Baseline



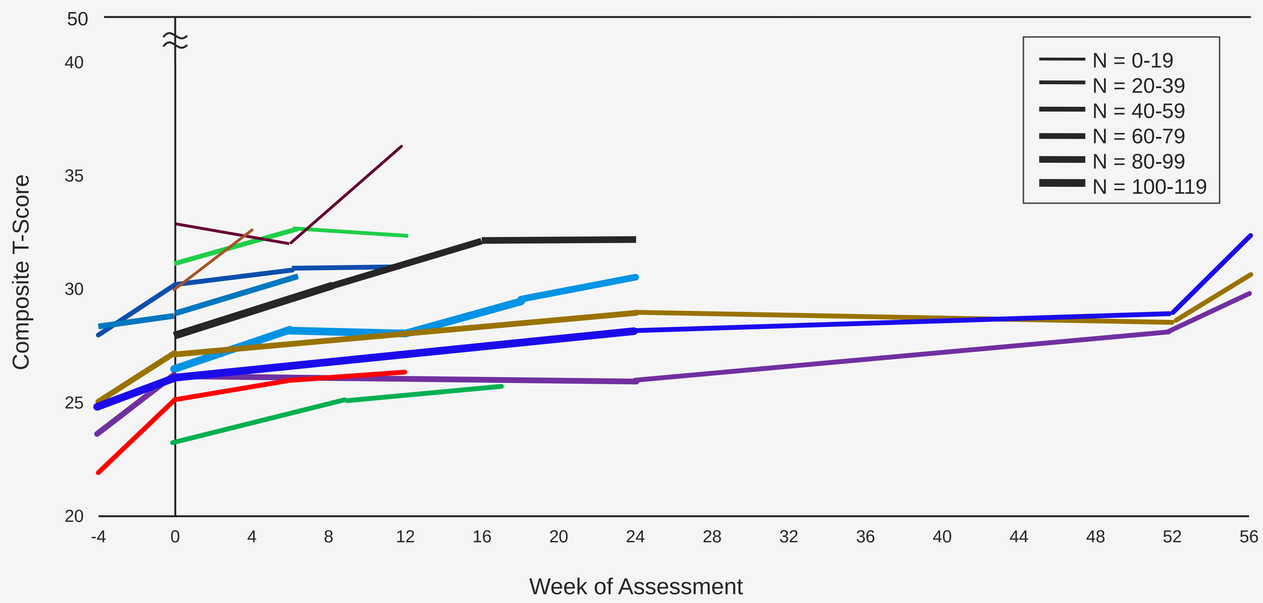
Placebo Change from Baseline in MCCB Composite T-score By Level of Practice Effect between Screening and Baseline



Placebo Change from 1st Follow-up Visit in Composite T-score By Level of Placebo Response between Baseline and Visit 1 In Studies without a Screening Assessment



Mean MCCB Composite T-Score by Study for Placebo Patients



- The overall mean change in the MCCB composite over 56 weeks, adjusting for baseline score, study and their interaction, was 1.8±0.20 T-score points, ranging from 0.7 to 2.9 points across 12 studies of schizophrenia patients treated with placebo.
- Mean change scores for the 10 subtests comprising the MCCB ranged from 0.2±0.33 (MSCEIT) to 2.3±0.35 (Trail Making) T-score points.
- Patients scoring higher on the Marder Anxiety and Depression scale at baseline were more likely to show improvement on the MCCB overall composite (p=0.004).
- Practice effect prior to randomization was negatively associated with placebo response (p<0.001).

CONCLUSIONS

- Improvement on the MCCB under placebo conditions was generally consistent with known practice effects
- The magnitude of placebo effect varied slightly across cognitive domains and individual studies
- The magnitude of placebo response was positively correlated with baseline performance on the Marder Anxiety / Depression scale and negatively correlated with improvement during a screening to baseline assessment interval
- Placebo effects beyond known practice effects are not a major barrier for designing cognitive impairment treatment trials in patients with schizophrenia
- Studies with a higher number of assessments are susceptible to greater improvement in the placebo group

DISCLOSURES

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