

Does Placebo Response Differ Between Objective and Subjective ADHD Measures?

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Abstract

Background: Placebo response is a well-known phenomenon in CNS clinical trials^{1,2} and is becoming more recognized in ADHD research.³ To achieve registration with the US FDA,⁴ drug developers must demonstrate that their product is statistically superior to placebo. Placebo response increases the cost of clinical trials by requiring more subjects or longer observation to accomplish this crucial goal. This pilot study examined the concordance of the Quotient™ ADHD Test, a computerized assessment of hyperactivity, inattention and impulsivity,⁵ with clinical ADHD rating scales over three medication levels - placebo, low dose and medium dose.

Methods: Children aged 6 to 14 with a DSM-IV ADHD diagnosis based on clinician K-SADS-PL interview with the subject and parent were randomized to atomoxetine or extended-release methylphenidate for a 3 week double-blind trial. Subjects in each medication arm were randomized to one of two sequence groups. Sequence A: placebo, then low dose, then medium dose; Sequence B: low dose, then medium dose, then placebo.

Response to placebo was classified using three thresholds for reduction from baseline to the placebo visit on the ADHD-RS Total score or Quotient Global Score – any improvement, greater than 25% improvement, or greater than 40% improvement. The latter thresholds have been used previously in ADHD research and found to correlate with moderate and robust improvement based on CGI-S measures. Lin's concordance coefficient measured the agreement of baseline with placebo visits.

Results: Thirty subjects were included in these analyses. Placebo response rates were numerically lower when response was determined using the Quotient™ ADHD System rather than rating scales, and when the most stringent response threshold was used (i.e., >40% improvement). More subjects met any or >25% response thresholds based on the ADHD-RS at Week 3 than at Week 1. The same number of subjects met the >40% response threshold for ADHD-RS at Week 1 and Week 3. Timing of administration of placebo did not affect the number of subjects meeting response thresholds for the Quotient™ Global score.

Overall, baseline and placebo visit scores were more strongly correlated with response determined using the Quotient™ ADHD Test than ratings on the ADHD-RS. Lin's concordance correlation coefficient for the Quotient™ Global score was 0.78, compared with 0.38 for the ADHD-RS Total score. There was stronger agreement between the baseline and Week 3 placebo scores than the agreement between baseline and Week 1 placebo scores for both measures. Concordance coefficients for baseline and Week 3 placebo were 0.84 for Quotient™ Global Score and 0.45 for the ADHD-RS Total score. When comparing the baseline to week 1 placebo scores, the concordance coefficients were 0.75 for Quotient™ Global Score and 0.27 for the ADHD-RS Total score.

Conclusions: Although preliminary, the results of this study suggest that the placebo response rate is minimized by using the Quotient™ ADHD System and the >40% improvement response threshold. In addition, the timing of placebo exposure seems to affect the rate of response and the similarity of scores while on placebo to those at baseline. Of note, while it may seem intuitively obvious that objective measures would be more sensitive to treatment effects than rating scales, recent research and professional guidelines have tended to de-emphasize the need for and importance of objective measures of response. Larger parallel group design studies are needed to further elucidate the benefit of objective measures and response thresholds in differentiating placebo and drug response.

Methods

Study Design

- Children aged 6 to 14 with a DSM-IV ADHD diagnosis based on K-SADS-PL interview conducted by the clinician with the subject and parent were randomized to atomoxetine or extended-release methylphenidate for a 3-week double-blind trial.
- Subjects in each medication arm were randomized to one of two sequence groups. The timing of placebo administration was blinded.

	Medication	Week 1	Week 2	Week 3
Sequence A	Extended-Release Methylphenidate	placebo	18 mg	27 mg (subjects <50 kg) 36 mg (subjects <50 kg)
	Atomoxetine	placebo	0.5 mg/kg	0.8 mg/kg
Sequence B	Extended-Release Methylphenidate	18 mg	27 mg (subjects <50 kg) 36 mg (subjects <50 kg)	placebo
	Atomoxetine	0.5 mg/kg	0.8 mg/kg	placebo

Statistical Methods

- Comparison of the placebo effect across trials: Standardized mean difference in change from baseline on placebo was computed as mean change from baseline to endpoint on placebo divided by the standard deviation of the change.
- Comparison of the placebo effect in the primary analysis: Subjects were pooled across medication and sequence groups, ignoring the effect of time when placebo was administered.
- Response to placebo was assessed using the ADHD-RS Total Score or Quotient™ Global Score.
- Response to placebo classified using three thresholds for symptom reduction from baseline to the placebo visit:
 - Any improvement
 - Greater than 25% improvement
 - Greater than 40% improvement
 (ADHD research has demonstrated that >25% and >40% improvement thresholds correlate with moderate and robust improvement based on CGI-S measures.)
- These are nested thresholds – subjects meeting the robust improvement level are included in the other thresholds by definition.
- Lin's CCC measured the agreement of scores at the baseline and placebo visits. Secondary analyses computed response rates and concordance coefficients separately for the different treatment sequences.

Measures used to assess response:


- Quotient™ Global Score, Activity Scaled Score, and Attention Scaled Score
- ADHD-RS-investigator administered
- Conners' Parent Rating Scale-Revised Short Form
- Clinical Global Impression of Severity of ADHD (CGI-ADHD-S)
- Clinical Global Impression of Improvement in ADHD.

Objective Technology for ADHD Assessment


- FDA-cleared device that objectively measures hyperactivity, inattention and impulsivity to aid in the assessment of ADHD.
- Provides objective, direct measurement of the same functions assessed by conventional, subjective evaluation methods used currently, such as DSM-IV criteria and symptom rating checklists.
- Individualized assessment analyses are available in minutes for initial evaluation and ongoing management of ADHD.



Child Test:
1 target, 1 non-target




Press **SPACE BAR**




Don't press any key

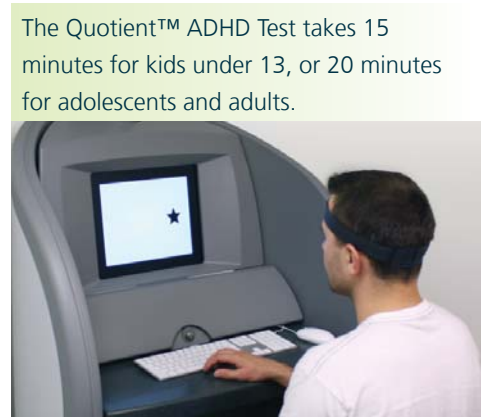
Adolescent/Adult Test:
3 targets, 1 non-target

Press **SPACE BAR**
when the star is:



Don't press any key
when the star is:

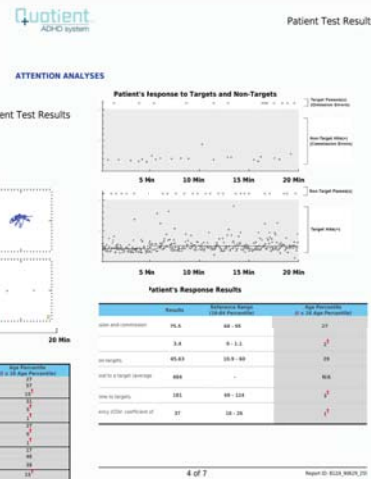




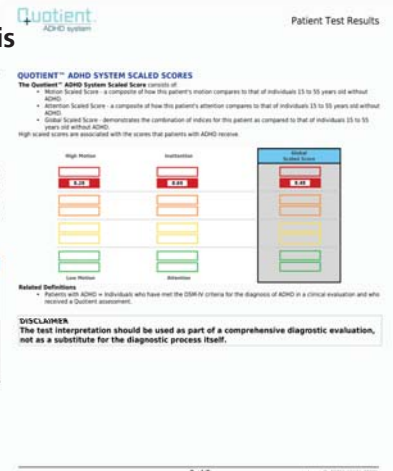
The Quotient™ Report

- The clinician uploads the data via the internet. Results are compared to a database of age- and gender-matched cohorts. Graphical and numerical results are presented in the report, including percentile scores for easy comparison to the peer group.
- The Quotient™ Motion and Attention Scaled Scores are normalized calculations on a 10-point scale. Higher Scaled Scores indicate deficit in control of motion and attention compared to age and gender matched subjects.
- The Global Scaled Score is an average of the motion and attention scores.

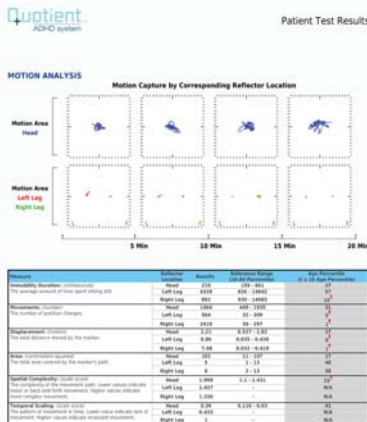
Attention Analysis



Scaled Scores & Global Score



Motion Analysis



Results

Patient Demographics (N=30)

Age Mean (SD)	9.4 (2.13)
	N (%)
Race	
Caucasian	16 (53.3%)
Black	11 (36.7%)
Asian	2 (6.7%)
Unknown	1 (3.3%)
Male	25 (83.3%)

Severity at Baseline Assessment

Assessment Tool	Scale	Mean (SD)
ADHD-RS Total	0-54	42.2 (9.66)
ADHD-RS Hyperactive/Impulsive	0-54	19.2 (6.87)
ADHD-RS Inattention	0-54	23.0 (4.14)
CGI-ADHD-S	0-10	5.3 (0.79)
Quotient Global Score	0-10	7.99 (1.71)
Quotient Activity Score	0-10	7.87 (1.74)
Quotient Inattention Score	0-10	8.10 (2.02)

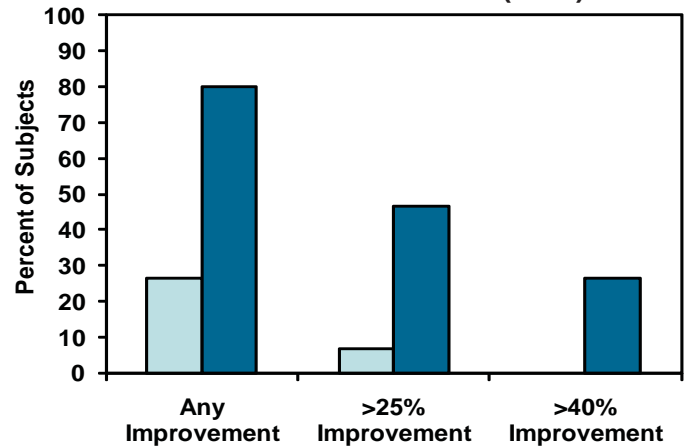
Comparison of Placebo Response Rate by Assessment Tool

- Placebo response rates were numerically lower with the Quotient™ ADHD System compared to rating scales.
- Placebo response rates were lowest when the most stringent response threshold was used (i.e., >40% improvement).
- More subjects met Any or >25% response thresholds based on the ADHD-RS at Week 3 than at Week 1.
- The same number of subjects (8) met the >40% response threshold for ADHD-RS at Week 1 and Week 3.
- Timing of administration of placebo did not affect the number of subjects meeting response thresholds for the Quotient™ Global score.

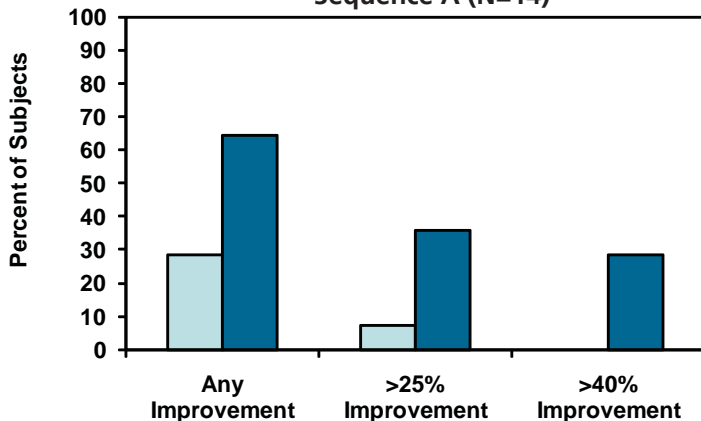
Summary of Placebo Response Rates

Response	Combined (N=30)		Week 1 (N=14)		Week 3 (N=16)	
	Quotient	RS	Quotient	RS	Quotient	RS
Any	8 27%	24 80%	4 29%	9 64%	4 27%	11 80%
>25%	2 7%	14 47%	1 7%	5 36%	1 7%	7 47%
>40%	0 0%	8 27%	0 0%	4 29%	0 0%	4 27%

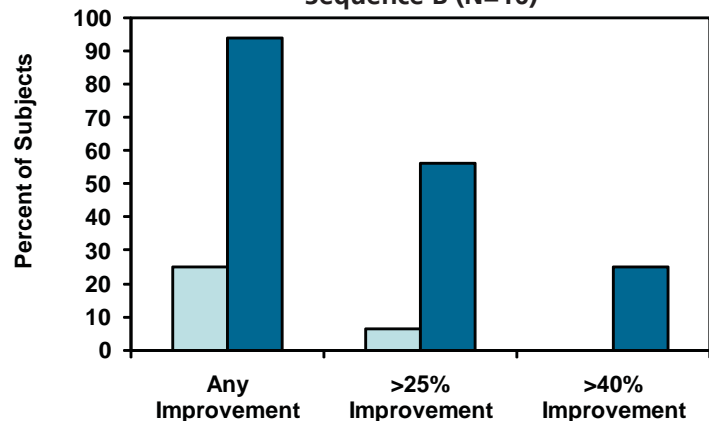
Placebo Response Rate
Weeks 1 & 3 Combined (N=30)



Placebo Response Rate @ Week 1
Sequence A (N=14)

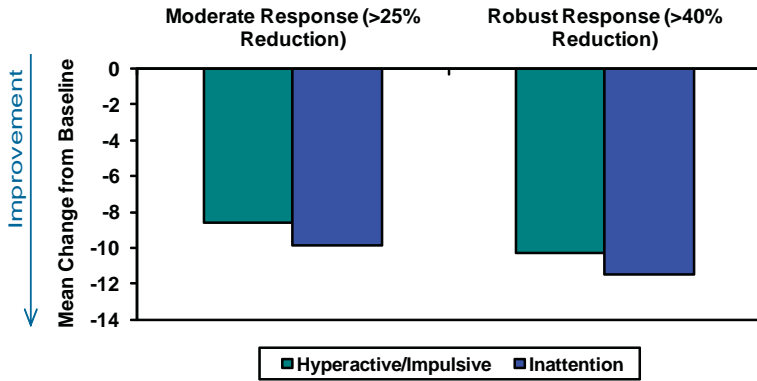


Placebo Response Rate @ Week 3
Sequence B (N=16)

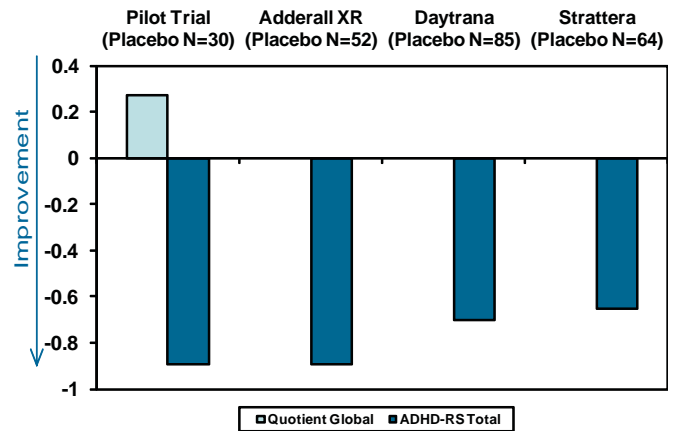


□ Quotient Global Score ■ ADHD-RS Total Score

Hyperactive/Impulsive and Inattention Improvements in Subjects with Placebo Response on ADHD-RS Total



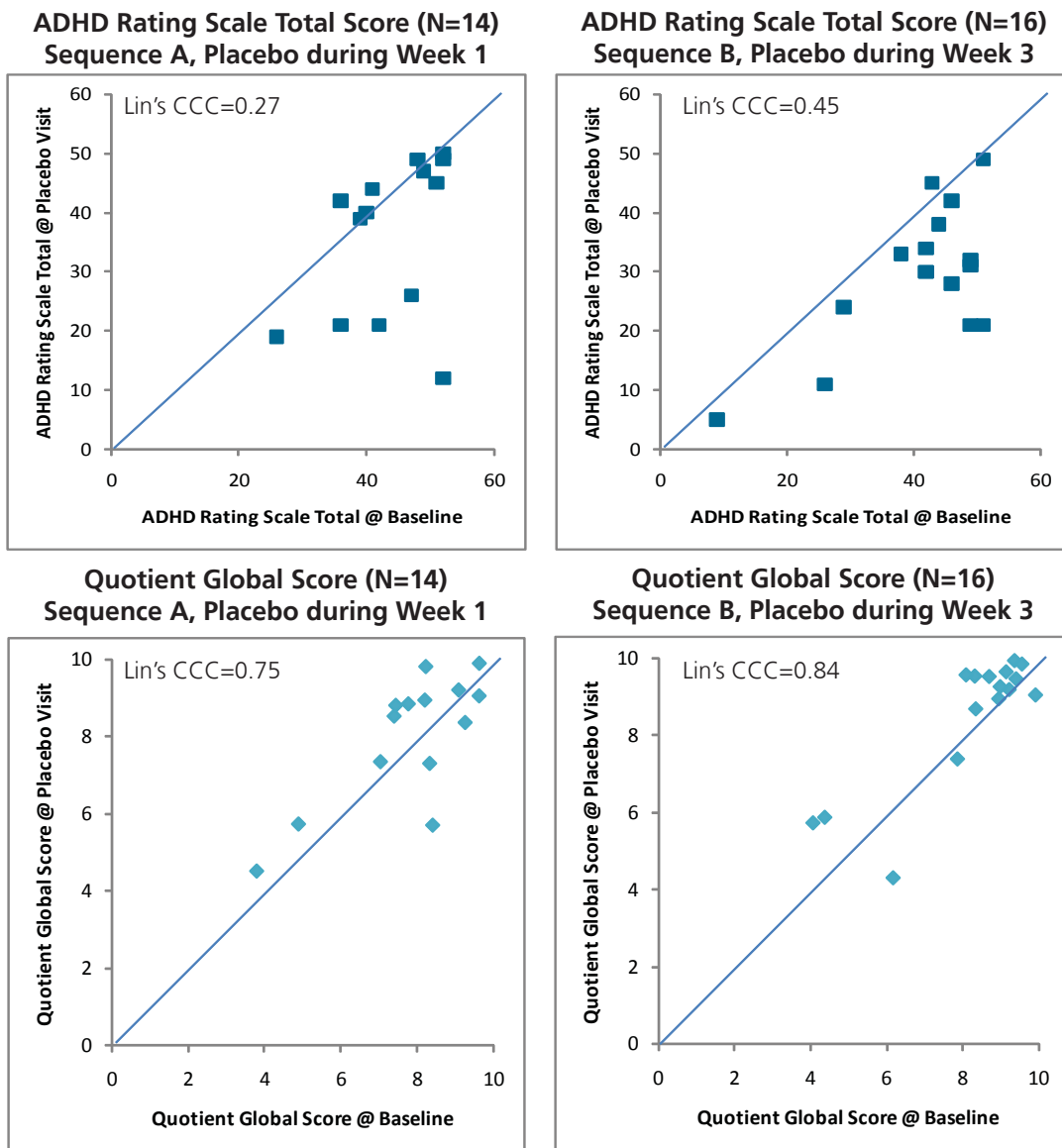
Placebo Effect Results in Pilot Study Mirror ADHD-RS Results from Other ADHD Trials



Source: www.clinicalstudyresults.org and Kelsey et al, 2004²

Correlation of Baseline and Placebo Visit Assessments

- Baseline and placebo response scores by the Quotient™ ADHD System were better correlated than response scores ADHD-RS.
 - Week 1 Lin's CCC: Quotient™ Global Score=0.75, ADHD-RS=0.27
 - Week 3 Lin's CCC: Quotient™ Global Score=0.84, ADHD-RS=0.45



Conclusions

- Using higher response thresholds and an objective measure (e.g. the Quotient™ ADHD System) together eliminated placebo response. This suggests that cost savings may be realized in ADHD drug clinical trials by implementing these protocol additions.
 - The Quotient™ ADHD Test performed considerably better than rating scales at detecting placebo effect.
 - The response threshold of >40% better distinguished placebo effect than a response threshold of >25%.
 - Larger trials are warranted to better evaluate and understand this methodology.
- Among placebo responders, there was greater perceived improvement in inattention than hyperactivity/impulsivity (similar to Newcorn et al., In Press).
- Clinical relevance:
 - In clinical practice, objective measures provided by the Quotient™ ADHD System could aid in distinguishing placebo effect from a true early drug response that will be maintained through the trial.
 - Findings may also have relevance for protecting against Type II errors in clinical trials.
- These findings were based on the Quotient™ ADHD System, and may be unique to this system or common to other objective measures. This requires further investigation.
- Given the potentially important consequences of the data reported here, it is curious that objective measures have fallen out of favor in clinical research - especially considering the high cost associated with placebo response.

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