SUPPORTING SCIENTIFIC AND CLINICAL EVIDENCE

KEY ABSTRACTS FROM SELECTED PEER-REVIEW LITERATURE

This section provides abstracts from peer-reviewed papers and poster sessions on the Quotient System.

Please note: the product name has changed over time. The papers refer to MMAT (McLean Motion and Attention Test), OpTax or Quotient depending on the time of the research and the country. Papers cover the following topics:

- Foundational research, including studies on the clinical utility of micro-motion and analysis of shifts in attention state.
- Translational research, including studies on the clinical utility of objective measures during initial assessment (i.e., diagnostic setting) and ongoing management.

The publications are classified according to levels of evidence using guidelines from the University of Cincinnati that classify individual studies by domain, study design and quality.

TABLE OF EVIDENCE LEVELS

DOMAIN OF CLINICAL QUESTION	TYPE OF STUDY / STUDY DESIGN													
	Systematic Review Meta–Analysis	Meta–Synthesis	RCT + CCT +	Psychometric Study	Qualitative Study	Cohort – Prospective	Cohort – Retrospective	Case – Control	Longitudinal (Before/After, Time Series)	Cross – Sectional	Epidemiology Descriptive Study Case Series	Quality Improvement	Economic Analysis Decision Analysis	Expert Opinion Case Reports Guidelines
Treatment / Therapy	1a* 1b*		2a 2b			3a 3b	4a 4b	4a 4b	4a 4b	4a 4b	4a 4b			5a 5b
Diagnosis / Assessment	1a 1b		2a 2b	2a 2b		3a 3b	4a 4b			4a 4b	4a 4b			5a 5b
Prognosis	1a 1b					2a 2b	3a 3b			4a 4b	4a 4b			5a 5b
Etiology / Causation or Prevention or Risk Factors / Harm or Prevalence / Incidence	1a 1b		2a 2b			3a 3b	4a 4b	4a 4b		4a 4b	4a 4b			5a 5b
Economic Analysis or Decision Analysis			2a 2b			3a 3b							1a 1b	5a 5b
Meaning / KAB+		1a 1b			2a 2b	3a 3b				4a 4b				5a 5b
Guidelines														5a 5b

* ***a*** *= good quality study*

* ***b*** *= lesser quality study*

\+ ***CCT*** *= Controlled Clinical Trial;* ***KAB*** *= Knowledge, Attitudes, and Beliefs;* ***RCT*** *= Randomized Controlled Trial*

Shaded boxes indicate study design may not be appropriate or commonly used for the domain of the clinical question.

Development for this table is based on:

1. Phillips, et al: Oxford Centre for Evidence-based Medicine Levels of Evidence, 2001. Last accessed Nov 14, 2007 from http://www.cebm.net/index.aspx?o=1025.
2. Fineout-Overholt and Johnston: Teaching EBP: asking searchable, answerable clinical questions. *Worldviews Evid Based Nurs*, 2(3): 157-60, 2005.

Summary of Publications

Abbreviated title	First Author	Type	Publication	Topic	# Subjects	Domain	Level
Objective Measures of Hyperactivity and Attentional Problems in ADHD	Teicher, 1996	Publication	J Am Acad Child Adol Psych	Controlled Clinical Trial	19	Assessment	2a
Functional Deficits in Basil Ganglia of Children with ADHD with fMRI	Teicher, 2000	Publication	Nature	Controlled Clinical Trial	17	Etiology	2b
Putamen lesions and Development of ADHD Symptomatology	Max, 2002	Publication	J Am Acad Child Adolescent Psych	Controlled Clinical Trial	25	Etiology	2a
Effects of MPH on fMRI of the Cerebellar Vermis in Boys with ADHD	Anderson, 2002	Publication	Am J of Psychiatry	Controlled Clinical Trial	10	Etiology	2b
Discriminating ADHD Through Objective Measures of Motion and Attention	Laptook, Hughes, Emslie, 2003	Abstract	NCDEU proceedings - research poster	Controlled Clinical Trial	38	Assessment	2a
Rate Dependency Revisited: Understanding Effects of MPH in ADHD	Teicher, 2003	Publication	J Child Adol Psychopharm	Randomized Controlled Trial	19	Treatment	2b
Novel Strategy Provides Insight into MPH and Attentional States in ADHD	Teicher, 2004	Publication	J Child Adol Psychopharm	Controlled Clinical Trial	68	Assessment	2a
Objective measurement of hyperkinetic disorders before and after MPH	Heiser, 2004	Publication	Eur Child Adolesc Psychiatry	Controlled Clinical Trial	25	Assessment	4a
MPH Blood Levels and Therapeutic Response in Children with ADHD	Teicher, 2006	Publication	J Child Adol Psychopharm	Randomized Controlled Trial	48	Treatment	2a
Objective Measures in the Differential Diagnosis of Childhood Disorders	Faedda, 2005	Publication	Essential Psychopharm	Case Study	2	Assessment	5a
MPH Effects on Objective Measures Identify Optimal Clinical Response	Teicher, 2006	Abstract	NCDEU proceedings - research poster	Randomized Controlled Trial	13	Treatment	4a
Is OPTAx™ useful for monitoring the effect of stimulants on ADHD?	Tabori-Kraft, 2007	Publication	Eur Child Adolesc Psychiatry	Controlled Clinical Trial	23	Assessment	2a
ADHD Characterized by Spikes in Motor Activity and Impaired Attention	Ohashi, 2007	Abstract	Soc. Bio. Psych proceedings - poster	Controlled Clinical Trial	144	Assessment	2a
Utility of Objective Assessment of Therapeutic Response in ADHD	Teicher, 2008	Publication	J Child Adol Psychopharm	Controlled Clinical Trial	11	Assessment	3a
ADHD Motor Activity and Inattention in Children with Heavy Prenatal Alcohol Exposure	Bazinet, Riley, 2010	Abstract	Res. Soc. Alcohol proceedings - poster	Controlled Clinical Trial	51	Assessment	2a
Objective Measures of Motion and Attention Distinguish Across Diagnoses	Sumner, Amann, Sutton, 2010	Abstract	ISCTM proceedings - research poster	Cohort Prospective	100	Assessment	3a

Abbreviated title	First Author	Type	Publication	Topic	# Subjects	Domain	Level
Unraveling the Nature of Hyperactivity in Children with ADHD	Ohashi, 2010	Publication	Archives General Psychiatry	Controlled Clinical Trial	124	Etiology	2a
Placebo Response Differs Between Objective and Subjective ADHD Measures	Sumner, Sutton, Newcorn, 2010	Publication	Postgrad Medicine	Randomized Controlled Trial	31	Treatment	2a
New Tool for Objective Assessments of ADHD: The Quotient® ADHD System	Sumner, ed. Barkley, 2010	Publication	The ADHD Report	Expert opinion	N/A	Assessment	5a
Examination of Resting State Functional Connectivity Correlates of Motor Activity	Slaughter, DiMartino, Castellanos, 2010	Abstract	AACAP proceedings - research poster	Controlled Clinical Trial	51	Etiology	2a
Attention and Motion in Children with an Oral Language Disorder and ADHD	Bolanos, Hughes, Pickering, 2010	Abstract	AACAP proceedings - research poster	Controlled Clinical Trial	35	Assessment	2b
Hyperactivity Persists In Male and Female Adults with ADHD	Polcari, Fourligas, Navalta, 2010	Abstract	AACAP proceedings - research poster	Controlled Clinical Trial	100	Assessment	2a
Utility of Objective Measures in the Assessment of ADHD Therapeutic Response	Hasson, 2011	Abstract	CNS proceedings - research poster	Case Series	35	Assessment	4a

Summary: There is a consensus in the evidence that benefits clearly outweigh risks and burdens

Levels of Evidence	Total	Etiology	Treatment
1a	0	0	0
1b	0	0	0
2a	12	3	2
2b	4	2	1
3a	2	1	1
3b	0	0	0
4a	3	1	0
4b	0	0	0
5a	2	0	0
5b	0	0	0

Strength of Recommendation for Quotient Assessment in ADHD

Parameter	Finding
1. Grade of the body of Evidence	High grade evidence
2. Safety/Harm	Has minimal adverse effects
3. Health Benefit to Patient	Has significant health benefit
4. Burden on patient to adhere to recommendation	Low burden of adherence
5. Cost-effective to healthcare system	Inconclusive economic effects
6. Directness, evidence directly addresses question	Evidence directly relates to recommendation for this target population
7. Impact on morbidity/mortality or quality of life	Medium-high impact on morbidity/mortality or quality of life

Abstract

Teicher MH, Ito Y, et al. **Objective Measures of Hyperactivity and Attentional Problems in ADHD**. J Am Acad Child Adolescent Psych, 35(3), 334-342, 1996. (24)

Objective: To precisely describe movement abnormalities in seated children with attention-deficit hyperactivity disorder (ADHD) while they were engaged in a continuous performance test (CPT). **Method:** Diagnoses were made by using structured interviews (Schedule for Affective Disorders and Schizophrenia for School-Age Children-Epidemiologic Version) and *DSM-IV* criteria. Movement patterns of 18 boys with ADHD (9.3±2.4 years) and 11 normal controls (8.6±1.8 years) were recorded using an infrared motion analysis system that tracked the position of four markers 50 times per second to a resolution of 0.04 mm. **Results:** Boys with ADHD moved their head 2.3 times more often than normal children ($p<0.002$), moved 3.4 times as far ($p<0.01$), covered a 3.8-fold greater area ($p<0.001$), and had a more linear and less complex movement pattern ($p<0.00004$). They responded more slowly and with greater variability on the CPT. Complexity of head movement and variability in response latency significantly correlated with teach ratings. A predefined composite of movement and attention discriminated 16 of 18 patients from 11 of 11 controls. **Conclusions:** The relative inability of boys with ADHD to sit still can be objectively verified, and "fidgeting" appears to consist of more frequent, larger amplitude, whole body movements.

Clinical Application

If Quotient ADHD System results correlate strongly with symptom manifestations of ADHD, then results should show marked differences between individuals with ADHD and individuals without ADHD.

The first study of the capacity of infrared motion analysis to quantify fidgeting of children with ADHD during performance of a monotonous attention task revealed robust differences between ADHD subjects and healthy controls. (24) A simple composite of activity and attention results discriminated 16/18 ADHD boys from 11/11 controls.

These findings were replicated in an unpublished study of 62 boys with ADHD (11.0 ± 1.2 years) and a community sample of 82 healthy male controls (10.9 ± 0.9 years). Receiver operating characteristic (ROC) curves showed that variability in correct response latency (most discriminatory standard CPT measure in this sample) had significant capacity to discriminate ADHD subjects from controls (ROC area = 0.716, $p < 10^{-5}$). However, measures of activity, particularly the spatial complexity of the movement pattern (ROC area=0.902, $p < 10^{-16}$), and coefficient of variation (COV) in activity from moment-to-moment (ROC area=0.981, $p < 10^{-38}$), had even greater discriminatory capacity. (Perfect discrimination has ROC area under the curve=1.0).

Abstract

Martin H. Teicher, Carl M. Anderson, Ann Polcari, Carol A. Glod, Luis C. Maas & Perry F. Renshaw**. Functional deficits in basal ganglia of children with attention-deficit/hyperactivity disorder shown with functional magnetic resonance imaging relaxometry**. Nature Medicine, 6(4), 2000 (35)

Attention-deficit/hyperactivity disorder is a highly heritable and prevalent neuropsychiatric disorder estimated to affect 6% of school-age children1–3. Its clinical hallmarks are inattention, hyperactivity and impulsivity4,5, which often respond substantially to treatment with methylphenidate or dextroamphetamine. Etiological theories suggest a deficit in corticostriatal circuits, particularly those components modulated by dopamine. We developed a new functional magnetic resonance imaging procedure (T2 relaxometry) to indirectly assess blood volume in the striatum (caudate and putamen) of boys 6–12 years of age in steady-state conditions. Boys with attention-deficit/hyperactivity disorder had higher T2 relaxation time measures in the putamen bilaterally than healthy control subjects. Relaxation times strongly correlated with the child's capacity to sit still and his accuracy in accomplishing a computerized attention task. Daily treatment with methylphenidate significantly changed the T2 relaxation times in the putamen of children with attention-deficit/hyperactivity disorder, although the magnitude and direction of the effect was strongly dependent on the child's unmedicated activity state. There was a similar but non-significant trend in the right caudate. T2 relaxation time measures in thalamus did not differ significantly between groups, and were not affected by methylphenidate. Attention-deficit/hyperactivity disorder symptoms may be closely tied to functional abnormalities in the putamen, which is mainly involved in the regulation of motor behavior.

Clinical Application

If Quotient ADHD System results are directly related to the underlying neural control state, then the results should correlate with neuroimaging assessments of brain function in the regions of interest.

The test quantitatively assesses the effectiveness of the neurological control processes relevant to the three diagnostic symptom domains of Attention-Deficit Hyperactivity Disorder (ADHD): inattention, hyperactivity, and impulsivity. Research has demonstrated that the quantitative biometric data measured by the Quotient correlates with neuroimaging assessments of brain function and regional blood flow in the brains of patients with ADHD. In one research study demonstrating this correlation, the fMRI technique of T2-Relaxometry was applied to evaluate the striatum of boys with ADHD (n=11; 9.3 ± 1.6 years old) and healthy male controls (n = 6; 10.2 ± 1.5 years old). ADHD subjects were scanned on placebo and on low (0.4 mg/kg), intermediate (0.8 mg/kg) and high (1.5 mg/kg) daily doses of MPH. *Quotient*® was used to provide precise measures of capacity to inhibit motor activity during performance of a monotonous but demanding attention task.

ADHD children and control subjects differed considerably in bilateral putamen T2-RT measures (ADHD: 77.9 ± 1.1 msec;, Control: 76.1 ± 1.1 msec; $F_{1,14} = 9.40$; $P = 0.008$), which was particular apparent on the left side ($F_{1,14} = 14.5$; $P = 0.002$; Fig 10). There were substantial and significant correlations between motor activity and T2-RT for the putamen bilaterally, but not for caudate or thalamus. Temporal scaling and average time spent immobile, two MMAT measures of activity–inactivity, correlated, with r_s values of –0.752 ($P < 0.001$) and –0.730 ($P < 0.001$), respectively, with T2-RT in the putamen. There were also strong correlations between measures of attention performance and T2-RT in the putamen bilaterally. Accuracy on the MMAT continuous performance task correlated with an r_s of –0.807 ($P < 0.0001$), and response latency correlated with an r_s of 0.652 ($P < 0.005$). Further studies have been completed and demonstrate similar correlations in other regions of interest and inter-region connectivity.

Abstract

Becca Laptook, B.A., Markus Glickman, Ph.D., Carroll W. Hughes, Ph.D., Graham Emslie, M.D., Cheryl Silver, Ph.D., Munro Cullum, Ph.D., Beth Kennard, Psy.D., Scott Greenaway, B.A. **Discriminating Attention Deficit Hyperactivity Disorder Through Objective Measures of Motion and Attention**. NCDEU poster session, 2003. (36)

Objective: The present study was designed to test if objective measures of motion and attention in a depressed population could distinguish children and adolescents with Major Depressive Disorder (MDD) from those with a comorbid diagnosis of MDD and Attention Deficit Hyperactivity Disorder (ADHD). Past studies have shown that these objective measures have the ability to discriminate between normal children and those who have ADHD.

Methods: Thirty-four subjects, medication free and ages 7 to 17, meeting DSM-IV criteria for MDD or MDD plus ADHD, as determined by the Kaufman Schedule for Affective Disorders and Schizophrenia – Present and Lifetime (K-SADS-PL), performed a computer-generated continuous performance task called the McLean Motion and Attention Test (MMAT, previously called OPTAx). The SNAP-IV also significantly differentiated the two groups. Objective measures of attention were obtained by performance results while an infrared optical motion sensor obtained objective measures of motion.

Results: Subjects with MDD alone and those with comorbid MDD and ADHD significantly differed on 5 out of the 6 measures of motion tested by the MMAT indicating greater movement, area displaced, temporal scaling and decreased immobility on the task by the comorbid group (all independent t-tests with $p < .05$). In addition, the two groups significantly differed on 5 out of the 6 CPT measures of attention tested by the MMAT (accuracy, omission and commission errors, variability, and response inconsistency – all $p < .05$) with the comorbid group having the most attention-related errors. Both groups had comparable CDRS scores (mean = 72.6 ± 7.4 for MDD and 70.1 ± 7.0 for the comorbid group).

Conclusion: Findings suggest that tools, such as the MMAT, which objectively measure motion and attention, are useful instruments in helping to identify ADHD even among children and adolescents with comorbid MDD and ADHD in comparison to MDD alone. Thus, the test's usefulness in detecting ADHD in a normal population can be extended to a depressed population as well. The addition of such tools, which provide independent and objective means of evaluating psychiatric disorders, may be valuable to clinicians who incorporate the instruments into their standard diagnostic batteries. Follow-up work is in the process of assessing the impact of pharmacological intervention on these scores.

Abstract

Teicher MH, Polcari A, et al. **Rate Dependency Revisited: Understanding the Effects of Methylphenidate in Children with Attention Deficit Hyperactivity Disorder.** *J Child Adolescent Psychopharmacology*, 13(1), 41-51 2003. (31)

Although stimulants are widely prescribed for the treatment of attention deficit hyperactivity disorder (ADHD), their calming effects are not easily understood. One hypothesis derived from preclinical studies is that stimulants exert "rate-dependent" effects that are inversely related in magnitude and direction to the baseline rate of activity or distraction. Previously, compelling support for this hypothesis has been lacking. We provide preliminary evidence that methylphenidate exerts rate-dependent behavioral effects in children with ADHD. Activity and attention were quantified in children with ADHD tested on placebo and different doses of methylphenidate using objective measures. Higher doses altered activity and attentiveness in a rate-dependent manner after correction for regression-to-the-mean artifacts. These findings illustrate a clear inverse association between symptom severity and degree of therapeutic response that is crucial for our understanding of stimulant effects and effective clinical treatment of ADHD.

Clinical Application

If Quotient ADHD System results are directly related to the underlying trait of neural control efficiency and not simply the behavioral state of the subject at the time the test is administered, then results should show strong test-retest reliability.

Test-retest reliability of Quotient results was established in two studies. Immediate test-retest was assessed in 15 children (6F/9M, 9.7 ± 5.0 years) with a very wide range of basal activity levels (349 – 4766 microevents) and performance (44-99% accuracy) tested at baseline and retested 1 hour after administration of placebo. Immediate test-retest measures were all very high (e.g., unbiased estimates of reliability [SPSS] were 0.934, 0.973, 0.932 and 0.954 for accuracy, latency, spatial complexity and microevents, respectively).

Delayed test-retest coefficients were established in 17 additional children (9F/8M, 11.9 ± 4 years) with a wide range of basal activity levels (205 – 2456 microevents) and performance scores (65-99% accuracy) retested 5 days after initial assessment. Unbiased estimates of reliability across six activity measures ranged from 0.850 – 0.913, and between six standard attention measures ranged from 0.720 – 0.967.

Abstract

Teicher MH, Lowen SB, et al. **Novel Strategy for the Analysis of CPT Data Provides New Insight into the Effects of Methylphenidate on Attentional States in Children with ADHD**. Journal Child Adolescent Psychopharmacology, Volume 14, Number 2, 2004. (25)

Continuous performance tasks (CPTs) provide a method for studying some components of attention, but do not take into account that attention fluctuates from moment to moment. To address this issue, CPT performance was classified into one of four states (on-task, impulsive, distracted, or randomly responding) every 30 seconds, based on commission and omission error rates. We evaluated this method on 60 boys (10.6 ± 1.1 years) with attention-deficit hyperactivity disorder (ADHD)-Combined subtype, tested before and after a dose of methylphenidate (MPH, 0.4 mg/kg), and 8 unmedicated healthy control boys (11.3 ± 2.0 years of age). Healthy controls were on-task during 82.4% of the 30-second epochs, and made an average of 5.4 attention shifts. In contrast, children with ADHD were only on-task during 42.6% of the epochs (p = 0.0006), and they made an average of 12.8 attention shifts (p = 0.00004). These state measures provided more robust indicators of the difference between children with ADHD and controls than did traditional CPT measures of error rates, latency, and variability. The new state measures were also more significantly affected by MPH. MPH produced a 77% increase in the percent of time children with ADHD spent on-task (p < 1012). Conversely, MPH reduced time spent in the distracted, impulsive, and random response states by 79%, 44.5%, and 69.2%, respectively (all p values < 0.0002). Unlike errors of omission and commission, which are highly correlated (r = 0.722, n = 60, p < 10_11), the percent of epochs spent in impulsive, distracted, and random response states were uncorrelated, and loaded onto discrete independent factors on principal component analysis. The level of activity during the CPT correlated with the degree of distraction, but not with the degree of impulsivity. Children with ADHD could be subtyped according to the nature of their attention performance problems, and these subtypes differed in levels of hyperactivity and degrees of response to MPH.

Clinical Application

If Quotient ADHD System results correlate with efficiency of neural control, Quotient should show strong correlation with the pharmacologic effect of MPH in reducing symptoms of ADHD.

Consonant with the clinical actions of MPH, a probe dose of IR-MPH in usual therapeutic range (0.4 mg/kg single dose, equivalent to 0.8 – 1.2 mg/kg/d) produced a marked improvement in capacity of children with ADHD (n=60) to sit still as measured by infrared motion analysis. Effect sizes for the six different activity parameters ranged from 1.46 to 2.59, which are significantly larger than the effects of MPH found on Parent or Teacher ratings. Similarly, probe-dose IR-MPH produced marked improvement in performance on the attention task. Effect sizes ranged from 1.03 to 2.45.

A 0.4 mg/kg probe dose of IR-MPH, reduced average measures of seated motor activity to at or below normal control levels in children with ADHD (n=60). Similarly, a 0.4 mg/kg probe dose of IR-MPH normalized attentional performance on all measures save for response latency. Prior to treatment these ADHD children responded more rapidly than normal controls but made more errors. After treatment they responded even more rapidly, but now were as accurate and as attentive as controls. Thus, it appears that *Quotient*® measures can show 'normalization' as a potential indicator of outcome. For assessment of normalization we have collected *Quotient*® data and teacher ratings on 687 school children (313M/374F) between 8-12 years of age (proposed age range for these studies).

Heiser P, Frey J, et al. **Objective measurement of hyperactivity, impulsivity, and inattention in children with hyperkinetic disorders before and after treatment with methylphenidate**. European Child & Adolescent Psychiatry 13, 100-104, 2004. (37)

Purpose The purpose of this study was to investigate whether values of the respective parameters of the OPTAx test dependently differ due to the medication methylphenidate (MPH) in children with hyperkinetic disorders (HD) suffering from hyperactivity, impulsivity, and attention deficits. *Methods* The OPTAx test is an infrared motion analysis to record the movement pattern during a continuous performance test. We tested 25 children between 6 and 12 years with HD (ICD-10: F90.0 or F90.1) before and after treatment with MPH. The parameters under investigation were activity (micro-events and spatial scaling), impulsivity (errors of commission), and attentiveness (accuracy and variability). For statistical analysis, a one-tailed matched pairs test (adj. p=0.01) was conducted to discriminate differences found from those occurred at random. A post hoc partial correlation of absolute differences in the respective parameters and the daily dose of MPH (adj. for BMI) was performed if $p<0.01$. *Results* Statistically significant results were found for microevents, spatial scaling, errors of commission, accuracy, and variability. The partial correlation showed significant results for microevents and variability. *Conclusion* The mean pre–post changes found in all parameters investigated consistently correspond with benefits desired from medication with MPH in children with HD. Absolute differences in microevents and variability seem to depend on the daily dose of MPH after adjustment for BMI.

This study demonstrates ecological validity.

Abstract

Teicher MH, Polcari A, et al. **Methylphenidate Blood Levels and Therapeutic Response in Children with Attention-Deficit Hyperactivity Disorder I. Effects of Different Dosing Regimens**. J Child Adolescent Psychopharmacology. 16 (4) 414-429, 2006. (26)

Background and purpose: Methylphenidate (MPH) is a drug of choice for treating attention-deficit/hyperactivity disorder (ADHD), although its use has been complicated by its short duration of action. The development of ideal long-acting preparations requires detailed understanding of the pharmacokinetic and pharmacodynamic consequences of complex dosing regimens. The purpose of this study was to ascertain if administration paradigms that produce stable or rising MPH levels alter the rate with which MPH is absorbed, and to determine how effectively long-acting administration paradigms compare with thrice daily administration of immediate-release MPH. *Method:* Forty-eight boys diagnosed with ADHD (mean age 10.6 ± 1.1 year) participated in this double-blind, parallel group study to evaluate the pharmacokinetics and efficacy and of 1 mg/kg/day MPH administered in five different paradigms and placebo. Objective measures of activity and attention (McLean Motion Attention Test; M-MAT™) and plasma measures of *d*- and *l*-MPH were obtained hourly during the course of a 12-hour laboratory session. *Results:* The rate of absorption and elimination of MPH was dependent on the pattern of administration, particularly on the initial bolus concentration. This suggests that MPH may act on the gastrointestinal system to slow absorption of additional MPH. There were significant differences among regimens on time course and degree of therapeutic response. Pulsatile administration produced greater improvement than escalating levels.

Clinical Application

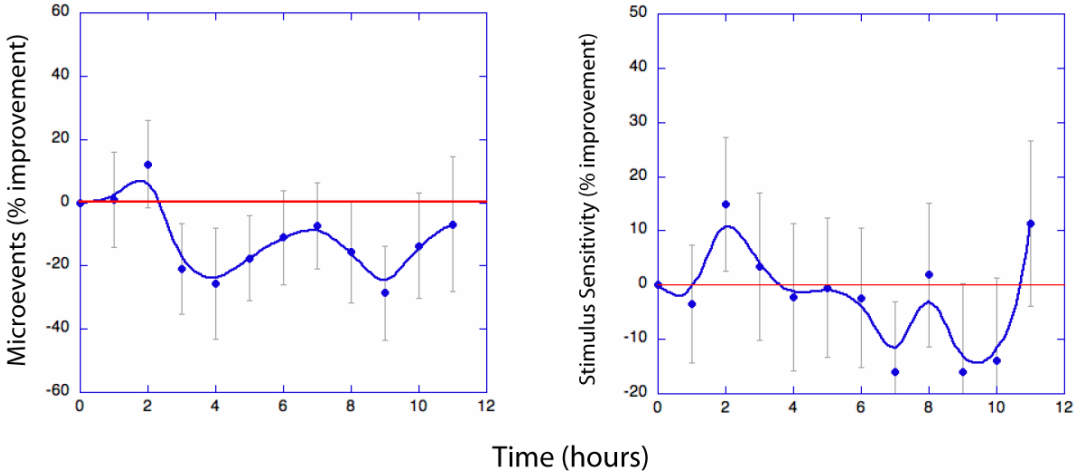
If Quotient ADHD System results correlate with efficiency of neural control, Quotient should show strong coupling between pharmacokinetic (PK) and pharmacodynamic (PD) responses to MPH.

The laboratory school protocol has shown significant within-day coupling between MPH levels and PD response by comparing morning, mid-day, and late afternoon responses on different preparations. Repeated Quotient results should also reveal significant PK-PD relationships. Forty-eight boys diagnosed with ADHD (mean age 10.6 ± 1.1 yr) participated in this double-blind parallel group study to evaluate the pharmacokinetics and efficacy of 1 mg/kg/day MPH administered in 5 different paradigms and placebo. Brief (5-minute) Quotient measures of activity and attention (5 min test) and plasma measures of d- and l-MPH were obtained hourly during the course of a 12-hr laboratory school session. Complete plasma level profiles were obtained on 39 subjects. Correspondence between response and plasma levels are shown for subjects receiving the PD2 pulsatile regimen (n=9), in which they received 0.4 mg/kg IR-MPH at 8 AM, 0.4 mg/kg at 12 PM, and 0.2 mg/kg at 4 PM, as these subjects had the greatest fluctuation in plasma levels during the course of the study (see Fig. 7).

Correlation between average plasma level and average Quotient response was 0.9 for activity (microevents) and 0.8 for attention (stimulus sensitivity) across 12 hours of assessment, revealing a high degree of correspondence between rising and falling plasma levels and degree of improvement in activity and attention. This is the kind of response one would expect from a 'bioassay'. This correspondence shows that brief, repeated, 5-minute *Quotient*® measures were capable of discerning waxing and waning benefits of a short-acting stimulant, and could track an individual's improvement at different times post administration.

In contrast, administration of placebo produced no significant improvement in activity or attention on Quotient measures during the course of the 12-hour laboratory school day. Children were 11.2% more active during hours 1–11 on placebo than when they arrived at the lab and were tested before medication was administered. MPH (1 mg/kg) reduced activity by 34.2-45.5% depending on the dose-administration schedule. Similarly, stimulus sensitivity was 5.6% worse after administration of placebo than it was when they first arrived at the laboratory in an unmedicated state. Methylphenidate (1 mg/kg) enhanced stimulus sensitivity by 23.9% across dose-administration schedules.

Figure 7. Placebo does not affect micro-movements or response accuracy



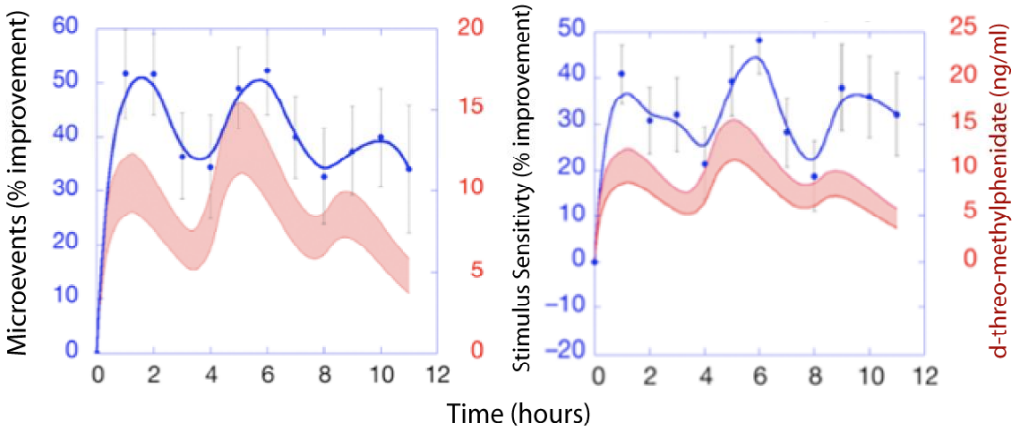
Failure of multiple placebo doses to produce significant improvement in capacity to sit-still (microevents) or to distinguish targets from non-targets (stimulus sensitivity) on QUOTIENT® ADHD SYSTEM during 12-hour laboratory day. From Teicher et al., 2006.

Clinical Application

If Quotient ADHD System results correlate strongly with the pharmacologic effect of ADHD in reducing symptoms of ADHD, then results should indicate onset of action for medications that corresponds to the known onset of action in clinical practice.

The time course of onset of MPH effects on Quotient measures of motor activity and attention parallel reported measures of clinical time reported by Swanson et al and Wolraich and Doffing. Specifically, subjects who received 0.4 mg/kg MPH (n=23) experience maximal initial benefit in capacity to sit-still (reduced microevents) at 1.7±0.9 hours (mean ± S.D.), and maximal initial benefit in improved attention (stimulus sensitivity) at 1.6±1.0 hours.

Figure 8. Quotient results follow drug levels



Temporal relationship between plasma levels of d-threo-methylphenidate (95% confidence intervals – red bands) and percent improvement in QUOTIENT® ADHD SYSTEM activity (microevents) and CPT performance (stimulus sensitivity) in boys with ADHD. From Teicher et al., 2006[163].

Tabori-Kraft J, Sorensen MJ, et al. **Is OPTAx™ [Quotient] useful for monitoring the effect of stimulants on hyperactivity and inattention? A brief report.** *Eur Child Adolesc Psychiatry* May, 571-575, 2007. (38)
Purpose The purpose of this study was to investigate whether OPTAx, an objective measurement of hyperactivity, impulsivity and inattention can be used to measure the positive clinical effect of stimulants found in children with hyperkinetic disorder (HKD) or attention deficit disorder without hyperactivity. *Method*: A total of 22 boys and one girl, with ages ranging between 7-12 years, diagnosed with HKD or attention deficit disorder without hyperactivity and receiving treatment with stimulants were tested with OPTAx, with and without stimulants. The main parameters investigated were: displacement, area, accuracy, variability, errors of commission and errors of omission. *Results* OPTAx showed a significant improvement on all parameters during stimulant treatment compared with no treatment. The improvement measured by OPTAx was supported by clinical assessment, which found that 95% of the children improved much or very much on the Clinical Global Assessment Scale during stimulant treatment. *Conclusions:* The objective parameters of the OPTAx reflected the clinical improvement found in children with HKD or attention deficit disorder without hyperactivity during stimulant treatment. This suggests a greater role for objective measurements such as OPTAx in daily clinical practice.

This study demonstrates ecological validity.

Teicher MH, Polcari A, et al. **Utility of Objective Measures of Activity and Attention in the Assessment of Therapeutic Response to Stimulants in Children with Attention-Deficit/Hyperactivity Disorder.** *J OF CHILD ADOLESCENT PSYCHOPHARMACOLOGY*. 18 (3), 265-270, 2008. (30)

Background and purpose: Attention-deficit/hyperactivity disorder (ADHD) is a highly prevalent disorder that can respond dramatically to medication, if dose is appropriately titrated. Studies suggest that computer measures of attention cannot be used for titration as they show improvement on doses too low to produce clinical benefits. We assessed whether measures of motor activity and attention using the McLean Motion Attention Test (M-MAPM) could identify doses associated with optimal clinical response. *Methods:* Eleven boys (9.6 ± 1.8 years), receiving treatment with methylphenidate, and meeting DSM-IV criteria for ADHD, participated in this triple-blind (parent, child, rater), within-subject, efficacy study. Subjects received 1 week each of placebo, low (0.4 mg/kg), medium (0.8 mg/kg), and high (1.5 mg/kg) daily doses of methylphenidate. Parents rated response using an index of clinical global improvement. *Results:* In 9/11 subjects, the dose that produced the best improvement on M-MATTM measures was also the dose that produced the best clinical outcome ($p < 10\text{-}5$). Parents rated response to this dose significantly better than response to previously prescribed treatment. Objective measures of primarily activity and secondarily attention responded to treatment in a manner concordant with clinical ratings, suggesting that these measures have ecological validity, and the potential to facilitate medication management and titration.

Clinical Application

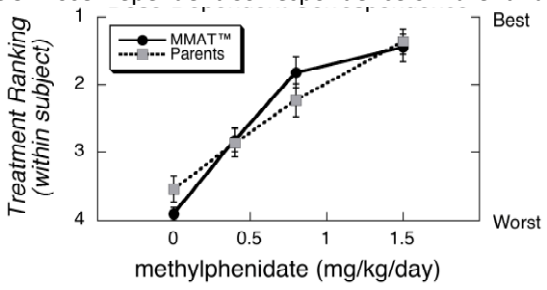
If Quotient ADHD System results correlate strongly with ADHD symptoms at baseline and reflect symptom change in response to treatment, then the results should demonstrate significant concordance with clinical ratings of efficacy.

Children with ADHD were treated for one week each on placebo, low (0.4 mg/kg/d), intermediate (0.8 mg/kg/d) and high (1.5 mg/kg/d) doses of MPH, administered blindly and in randomized order. Each week, on the last day of treatment they were tested using Quotient approximately 2 hours after their most recent dose. Parents evaluated response during each treatment week, which was integrated into the clinician's CGI rating. Subjects included 11 Caucasian boys 6 - 12 years of age (average 9.6 ± 1.8 years) who met DSM-IV criteria for ADHD based on structured diagnostic interviews (K-SADS-E).

In 9 of 11 subjects the dose that produced the best overall improvement on objective measures of activity and attention was also the dose rated best by parents (expected probability: 0.25; observed probability: 0.82; $Z=4.35$, $p < 10^{-5}$). In 7 of 11 subjects the dose that produced the poorest outcome on objective measures of activity and attention was also the dose rated worst by parents (expected probability: 0.25; observed probability: 0.64; $Z = 2.96$, $p < 0.002$).

There was a strong tendency for Quotient measures and parents to rank order response from best to worst as a function of dose (high>medium>low>placebo). Quotient derived rankings had a very strong and somewhat more consistent association to dose ($F_{3,40} = 35.85$, $p < 10^{-10}$; η_p^2 effect size = 0.729) than CGI-derived rankings ($F_{3,40} = 17.27$, $p < 10^{-6}$; $\eta_p^2 = 0.564$). As illustrated in the figure below, there was considerable concordance between Quotient and parental CGI in ranking of response to each dose ($r = 0.655$, $p < 0.001$).

Figure 9. Dose-Dependent Correspondence of Parent Rating Scales and Quotient results



Relationship between Quotient and clinical global impression ratings of response to placebo and low, medium and high doses of methylphenidate (scaled from best = 1 to worst = 4).

This study provides evidence for the **ecological validity of the Quotient as a means of evaluating therapeutic response**.

A.D. Bazinet, A.L. Norman, C.L. McGee, N. Fourligas, E. Riley. **MOTOR ACTIVITY AND INATTENTION DURING A SUSTAINED ATTENTION TASK IN CHILDREN WITH HEAVY PRENATAL ALCOHOL EXPOSURE** Res. Soc. Alcohol poster, San Antonio, 2010. (39)

Background: Previous research has documented a high rate of attention-deficit/hyperactivity disorder (ADHD) in children with heavy prenatal alcohol exposure. Consistent with this finding, alcohol-exposed children demonstrate impairments on laboratory-based sustained attention tasks and increased levels of hyperactivity based on subjective (parent) reports. However, few studies have investigated objective measures of hyperactivity in alcohol-exposed children. The current study aimed to examine hyperactivity in children with heavy prenatal alcohol exposure and their typically developing peers by measuring overt motor movements during a challenging sustained attention task.

Methods: This study used the Quotient ADHD System, a novel technique validated for use in the clinical assessment of ADHD by providing objective measurements of hyperactivity, impulsivity, and inattention. Participants included 51 children between the ages of 6 to 16. Two groups were included: those with known histories of prenatal alcohol exposure (ALC, n=20), and age- and sex-matched controls (CON, n=31). Children completed a 15 or 20 minute continuous performance task in which they were asked to push a button to respond to target shapes while ignoring non-target shapes. While engaged in the task, children's head movements were measured using an infrared motion tracking system and spherical reflectors attached to their foreheads. Measurements of motor activity and attention during the task were obtained, and one-way ANOVA techniques were used to compare differences between groups.

Results: ALC children made more omission errors, had longer response latencies, and greater response variability during the task compared to their CON peers. In addition, they had a greater number of head movements and showed increased frequency of movement. Measures of total task accuracy and commission errors were not statistically different between groups. Groups also did not differ in duration of immobility, or in the total displacement, size/shape, or overall complexity of their movements.

Conclusions: Compared to CON children, ALC participants demonstrated increased hyperactivity and inattention during a sustained attention task. This pattern of performance is consistent with that seen in similar studies of children with ADHD, and suggests that the Quotient ADHD System may be a useful technique for assessing ADHD among the alcohol-exposed population.

Abstract

Calvin R. Sumner, MD; Birgit Amann, MD; Virginia K. Sutton, PhD **Can Objective Measures of Motion and Attention Distinguish Across Diagnoses?** International Society for CNS Clinical Trials and Methodology, Baltimore, Maryland. 2010 (40)

Introduction: The DSM-IV criteria for mood and anxiety disorders and attention-deficit/hyperactivity disorder (ADHD) share common symptoms that can complicate diagnosis, especially when these conditions are comorbid.

Objective: To evaluate the classification utility of the Quotient ADHD System in the assessment of children and adolescents referred to a psychiatric clinical practice for assessment and diagnosis.

Methods: This observational single site study approached patients aged 6 through 14 years old that were referred to the psychiatric clinical practice for evaluation to participate. Rating and assessment scales were administered consistent with the standard practice of the office. The Quotient ADHD Test was administered by designated clinicians who were trained to properly administer the test. It was recommended (but not required) that subjects withhold daily medication on the study visit day until after rating scales, assessments and Quotient testing were completed. The investigator remained blinded to the Quotient ADHD Test results until after a probable diagnosis was made, using the standard rating/assessment scales. Only after the probable diagnosis was documented did the investigator have access to the Quotient Patient Report (test results). ANOVA was used to compare mean scaled Attention and Motion scores and test for differences across diagnostic groups. Individual Quotient variables that contributed to a significant scaled score were tested for a linear trend across diagnostic groups using ANOVA. Tests of hypotheses were adjusted for multiplicity using Holm's step-down procedure.

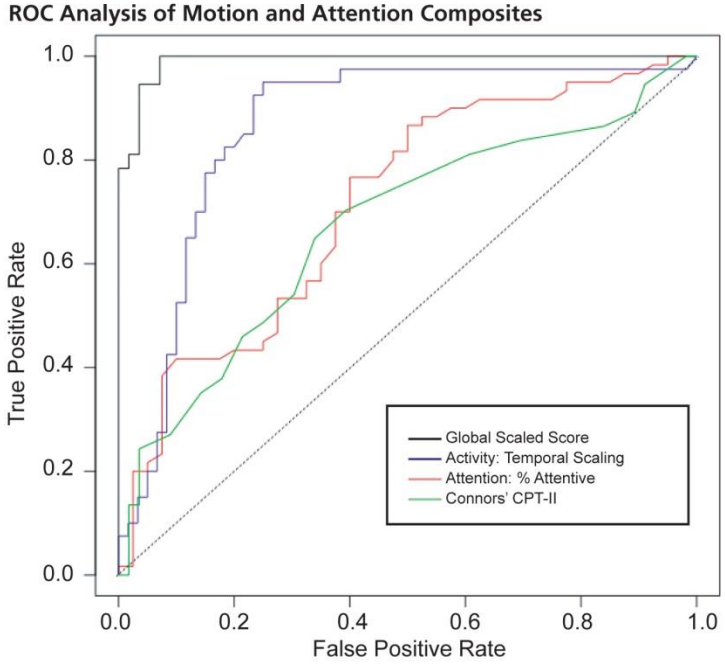
Results: One hundred subjects aged 6 to 14 consented to participate in this single visit study. Eighty-four subjects received a clinical diagnosis; there were 23 subjects with simple ADHD, 14 with a mood, anxiety or learning disorder, and 47 with ADHD and a comorbid mood or anxiety disorder. There was no significant difference in Quotient Attention scores across diagnostic groups; the mean Quotient Motion scores differed significantly across diagnostic groups (simple ADHD=64.0, comorbid ADHD=52.9, and mood/anx/learn=38.5, p=0.017). Diagnostic differences in the Quotient Motion scores were driven by the number of head movements and area of head motion. For both of these parameters, there was a linear trend with ADHD subjects demonstrating the greatest mean number of head movements (3739.65) or movement area (196.57 cm^2) and subjects without ADHD demonstrating the lowest number of movements (1810.64) or movement area (77.21 cm^2). The mean number of movements or movement area for subjects with comorbid ADHD was in between that of simple ADHD subjects and those with a mood, anxiety, or learning disorder but no ADHD diagnosis.

Conclusions: The motion scaled severity score from the Quotient ADHD System applied in a naturalistic clinic setting distinguished between subjects with ADHD and those without, even in the presence of comorbid mood and/or anxiety disorders. The more sensitive of the motion measures were head movements and head movement area which were different for the simple ADHD, comorbid ADHD, and mood/anx/learn groups. This preliminary study suggests that objective measures such as Quotient, which more sensitively measure impairments or deficits in developmental motion control, may be useful in differentiating complex clinical cases. Larger studies with larger samples of patients who have psychiatric conditions other than ADHD are needed to further elucidate these findings.

Abstract

Polcari A, Fourligas N, Navalta C, Teicher MH. **Hyperactivity Persists in Male and Female Adults with ADHD and Remains a Highly Discriminative Feature of the Disorder.** AACAP Poster Session. 2010 (41)

Abstract: Symptoms of hyperactivity are believed to fade with age leaving adults with attention-deficit/hyperactivity disorder (ADHD) mostly inattentive and impulsive. Our aim was to test this assertion using objective measure of hyperactivity, impulsivity and inattention in men and women with ADHD and healthy controls. Participants were 40 subjects with ADHD (23M/17F; 35±10 yrs) and 60 healthy controls (28M/32F; 29±9 yrs) blindly assessed using Wender Utah Interview, Structured Clinical Interviews for DSM-IV Disorders and DSM-IV criteria. A Quotient® ADHD System with modified motion collection for movement of the ankles was used to collect data on micro-motion, attention and shift in attention state. The Adult Quotient attention task requires the subject to press the space bar when any of the three target stimuli appears (i.e., a 5-pointed, 8-pointed or 16-pointed star) and refrain from hitting the space bar when the non-target stimulus appears (i.e., 4-pointed star). Infrared motion capture systems tracked head and leg movements during performance of three different computerized attention tasks. Subjects also completed the Conners' CPT-II. ADHD and control subjects differed significantly in activity and attention. Effect sizes for activity measures (d'= 0.74 – 1.56) were, on average, two-fold larger than differences in attention or impulsivity, and were more discriminatory (Quotient Results: ROC AUC=0.94 for combined activity and attention, 0.87 for activity alone, 0.72 for attention alone; ROC AUC=0.66 for Conner CPT-II). Males and females with ADHD were equally active. However, male controls were more active than female controls, so ADHD/control differences were more marked in females than males. Objectively measured hyperactivity persists in adults with ADHD, and is a highly discriminative feature of the disorder. Women with ADHD, relative to female controls, appear to be even more hyperactive than men with ADHD.



The area under the Receiver Operating Characteristic curve (ROC AUC) was used to assess the discriminative capacity of theses variables, as it provides the best overall index of performance of a diagnostic measure. An ROC AUC of 1.0 indicates perfect discrimination, whereas an ROC AUC of 0.5 indicates performance no better than chance.

- The most discriminative parameter on the Conners' CPT-II (**green line**) had an ROC AUC of only 0.66 (p= 0.014). This is consistent with other reports.
- The most discriminative attention measure for the Quotient ADHD Test was percent time spent in the Attentive state (**red line**, ROC AUC = 0.72).
- All but 2 of the motor activity measures had a greater ROC AUC. The best single motion metric was the mean temporal scaling exponent (**blue line**, ROC AUC = 0.87).
- A combination of activity and the Quotient Adult Attention Test measures yielded an ROC AUC=0.94 (**black line**). This is reported as the Global Scaled Score on the Quotient report.

This study demonstrates the superiority of the Quotient Test to a traditional continuous performance test.

Abstract

Sumner, CR, Haynes, VS, Teicher, MH and Newcorn, JH. **Does Placebo Response Differ Between Objective and Subjective ADHD Measures in Children with Attention-Deficit/Hyperactivity Disorder?** *Postgraduate Medicine.* 122(5), 52-61, 2010 (42)

Background: Placebo response complicates the interpretation of treatment response in both clinical practice and clinical trials in youth with attention-deficit/hyperactivity disorder (ADHD). In a pilot study comparing subjective ADHD symptom rating scales with scores obtained using the Quotient™ ADHD System (an objective computerized technology for the assessment of hyperactivity, inattention and impulsivity in ADHD), it was found that agreement between these 2 measures was not as strong as anticipated. This observation prompted us to evaluate placebo responses associated with subjective and objective assessments. Eligible study participants aged 6-14 years with a *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* ADHD diagnosis based on clinical interviews were randomized to 1 of 2 treatment sequence groups (placebo, low dose, and medium dose; or low dose, medium dose, placebo) using either atomoxitene HCl or osmotic controlled release (OROS) methylphenidate HCl as the active treatment in a 3-week, triple blind (subject, parent, rater) trial. Subjects were exposed to placebo at different medication doses to evaluate the comparative sensitivity of objective and subjective measures in assessing changes in clinical condition. Placebo response was defined using 3 thresholds: any improvement, >25% improvement, or >40% improvement from the baseline on Quotient™ Global Scaled Score (QGSS) or the ADHD Rating Scale (ADHD-RS) Total Score from baseline to the visit when placebo was administered. Lin's concordance correlation coefficient was used to measure agreement between baseline and placebo scores for the objective and subjective assessments. Of 30 subjects with placebo and baseline scores, 80%, 47% and 27% met the 3 response thresholds (i.e., any improvement, >25% improvement, or >40% improvement, respectively) on the ADHD-RS Total score compared with 27%, 7% and 0% on the QGSS. Lin's concordance correlation coefficient was 0.81 and 0.39 for the QGSS and ADHD-RS Total score, respectively. Although larger trials are warranted, we tentatively conclude that using objective measures and higher response thresholds may enhance assay sensitivity in clinical trials and hence limit necessary patient enrollments to rule out type II statistical errors.

Clinical Application

If the Quotient ADHD System objectively assesses the efficiency of neural control functions related to ADHD, then the assessment should not be affected by the placebo response when patients are given a non-biologically active pill in a double-blind placebo-controlled clinical trial.

A recent pilot study examined the concordance of the Quotient ADHD Test with clinical ADHD rating scales over 3 medication levels - placebo, low dose, and medium dose. The lack of strong concordance between Quotient and standard rating scales led to an examination of the placebo response in association with each. (42)

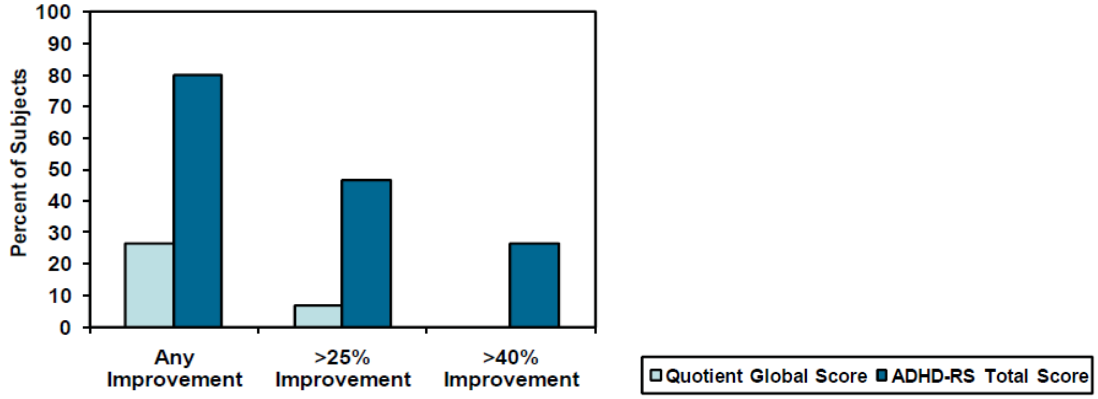
The pilot study was conducted in children aged 6 to 14 with a DSM-IV ADHD diagnosis based on clinician K-SADS-PL interview with the subject and parent were randomized to atomoxetine or extended-release methylphenidate for a 3 week double-blind trial. Subjects in each medication arm were randomized to one of two sequence groups. The order of treatment for the first sequence group was placebo, low dose, and medium dose; the order of treatment for the second sequence group was low dose, medium dose, and placebo. Thus, each subject in this trial received placebo, but the timing of placebo administration was blinded.

To examine 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 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. Secondary analyses computed response rates and concordance coefficients separately for the different treatment sequences.

Thirty-one subjects were entered into Phase II; one subject discontinued prior to the placebo visit and was not included in these analyses. The number of subjects who demonstrated response following placebo treatment is presented in Table 2 (by measure and response threshold). Placebo response rates were numerically lower when

response was determined using Quotient rather than ratings, and when the most stringent response threshold was used. More subjects met any or moderate response thresholds based on the ADHD-RS at Week 3 than reported that response at Week 1. The same number of subjects met the robust 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.

Figure 10. Placebo Response Rate (N=30)



The results of this study clearly demonstrate that the placebo response rate is minimized by using an objective measure of response and higher response thresholds. We therefore tentatively conclude that using objective measures to gauge response in clinical trials enhances assay sensitivity.

Abstract

Henry Hasson, MD, **Utility of Objective Measures of Activity and Analysis of Attention State in the Assessment of Therapeutic Response to Medications in Patients with ADHD: Community Care Perspective.** Child Neurology Society, Savannah, GA, 2011. (43)

Objective: The NIMH Multimodal Treatment of ADHD Study (MTA) of 579 children with ADHD showed routine community care rendered only about 25% of these patients symptom free. This study is to determine the utility of objective measures of hyperactivity, impulsivity and inattention in a community care setting to achieve optimal therapeutic response to ADHD medications rapidly.

Methods: Patients age 6 to 12 years old were evaluated by a board certified child neurologist. Patients with an established diagnosis of ADHD and new patients suspected of having ADHD were tested using the Quotient® ADHD System, a 15-minute computer-based test that combines 6 measures of micro-motion with 13 results from an attention task. Patients meeting the DSM-IV criteria for ADHD were treated and re-assessed in 1-2 weeks.

Results: Thirty-five children with at least 2 Quotient ADHD Tests were included in this series, including 8 children who were on medication for Test #1. 16 (45.7%) achieved normalized motion and attention metrics at the time of the second assessment; 6 (17.1%) achieved normalized motion control, but excessive inattention remained; 4 (11.4%) achieved normalized attention, but excessive hyperactivity remained; and 9 (25.7%) had excessive hyperactivity and inattention. 5 of the 15 patients with normalized motion and attention scores at the time of the second test, were previously treated, but not well controlled at baseline.

Conclusions: It is feasible and practical to implement an objective measurement of hyperactivity and analysis of shifts in attention state using the Quotient ADHD Test in a community care setting. Follow-up studies are needed to determine the time to optimal medication management compared to rating scales, and the impact on compliance, adherence and patient satisfaction.

OTHER KEY PAPERS: BACKGROUND ON ADHD, LANDMARK STUDIES, PROFESSIONAL GUIDELINES

Waschbusch DA, Pelham Jr. WE, et al. **Are There Placebo Effects in the Medication Treatment of Children With Attention-Deficit Hyperactivity Disorder?** *J Dev Behav Pediatr.* 30:158 –168, 2009. (44)
Placebos have been shown to produce significant positive changes in several health and mental health problems, referred to as placebo effects. Although it is well established that stimulant medication is an empirically supported treatment for children with attention-deficit hyperactivity disorder (ADHD), little is known about the role of placebos in the medication treatment of children with ADHD. This article reviews existing studies that evaluate whether placebos produce significant changes in children with ADHD. Published literature and the author's own empirical work were used to evaluate whether placebo effects are present in the medication treatment of children with ADHD. There is little evidence that placebos produce significant changes in the behavior or cognition of elementary school-age children with ADHD. However, there may be significant placebo effects in adults who evaluate children with ADHD. Evidence suggests that parents and teachers tend to evaluate children with ADHD more positively when they believe the child has been administered stimulant medication and they tend to attribute positive changes to medication even when medication has not actually been administered. Several viable mechanisms for these placebo effects are suggested.

Jensen PS, Hinshaw SP, et al. **Findings from the NIMH Multimodal Treatment Study of ADHD (MTA): Implications and Applications for Primary Care Providers.** *Developmental and Behavioral Pediatrics* 22(1), 60-73, 2001. (3)
In 1992, the National Institute of Mental Health and 6 teams of investigators began a multisite clinical trial, the Multimodal Treatment of Attention-Deficit Hyperactivity Disorder (MTA) study. Five hundred seventy-nine children were randomly assigned to either routine community care (CC) or one of three study delivered treatments, all lasting 14 months. The three MTA treatments monthly medication management (usually methylphenidate) following weekly titration (MedMgt), intensive behavioral treatment (Beh), and the combination (Comb) were designed to reflect known best practices within each treatment approach. Children were assessed at four time points in multiple outcome. Results indicated that Comb and MedMgt interventions were substantially superior to Beh and CC interventions for attention-deficit hyperactivity disorder symptoms. For other functioning domains (social skills, academics, parent-child relations, oppositional behavior, anxiety/depression), results suggested slight advantages of Comb over single treatments (MedMgt, Beh) and community care. High quality medication treatment characterized by careful yet adequate dosing, three times daily methylphenidate administration, monthly follow-up visits, and communication with schools conveyed substantial benefits to those children that received it. In contrast to the overall study findings that showed the largest benefits for high quality medication management (regardless of whether given in the MedMgt or Comb group), secondary analyses revealed that Comb had a significant incremental effect over MedMgt (with a small effect size for this comparison) when categorical indicators of excellent response and when composite outcome measures were used. In addition, children with parent-defined comorbid anxiety disorders, particularly those with overlapping disruptive disorder comorbidities, showed preferential benefits to the Beh and Comb interventions. Parental attitudes and disciplinary practices appeared to mediate improved response to the Beh and Comb interventions. J Dev Behav Pediatr 22:60±73, 2001. Index terms: ADHD, stimulants, behavior therapy, attention deficit, treatment, outcomes.

JENSEN PS, ARNOLD EL, et al. **3-Year Follow-up of the NIMH MTA Study.** *J AM. ACAD. CHILD ADOLESC. PSYCHIATRY.* 46(8) 989-1002, 2007. (45)
Objective: In the intent-to-treat analysis of the Multimodal Treatment Study of Children With ADHD (MTA), the effects of medication management (MedMgt), behavior therapy (Beh), their combination (Comb), and usual community care (CC) differed at 14 and 24 months due to superiority of treatments that used the MTA medication algorithm (Comb+MedMgt) over those that did not (Beh+CC). This report examines 36-month outcomes, 2 years after treatment by the study ended. Method: For primary outcome measures (attention-deficit/hyperactivity disorder [ADHD] and oppositional defiant disorder [ODD] symptoms, social skills, reading scores, impairment, and diagnostic status), mixed-effects regression models and orthogonal contrasts examined 36-month outcomes. Results: At 3 years, 485 of the original 579 subjects (83.8%) participated in the follow-up, now at ages 10 to 13 years, (mean 11.9 years). In contrast to the significant advantage of MedMgt+Comb over Beh+CC for ADHD

symptoms at 14 and 24 months, treatment groups did not differ significantly on any measure at 36 months. The percentage of children taking medication 950% of the time changed between 14 and 36 months across the initial treatment groups: Beh significantly increased (14% to 45%), MedMed+Comb significantly decreased (91% to 71%), and CC remained constant (60%Y62%). Regardless of their treatment use changes, all of the groups showed symptom improvement over baseline. Notably, initial symptom severity, sex (male), co-morbidity, public assistance, and parental psychopathology (ADHD) did not moderate children's 36-month treatment responses, but these factors predicted worse outcomes over 36 months, regardless of original treatment assignment. Conclusions: By 36 months, the earlier advantage of having had 14 months of the medication algorithm was no longer apparent, possibly dueto age-related decline in ADHD symptoms, changes in medication management intensity, starting or stopping medications altogether, or other factors not yet evaluated. J. Am. Acad. Child Adolesc. Psychiatry, 2007;46(8):989Y1002. Key Words: attention-deficit/hyperactivity disorder, clinical trial, stimulant, behavior therapy, multimodal treatment.

Sanchez RJ, Crismon ML, et al. **Assessment of Adherence Measures with Different Stimulants Among Children and Adolescents.** *Pharmacotherapy*, 25 (7), 909-917, 2005. (9)
Study Objective: To examine adherence measures with different stimulants in children and adolescents. **Design**: Retrospective analysis. **Data Source:** Texas Medicaid prescription claims database. **Patients**: A total of 9549 patients aged 5–18 years with attention deficit–hyperactivity disorder. **Measurements and Main Results**: Paid prescription claims for newly started stimulants during the 2001–2002 school year were extracted from a database; 28,344 prescriptions (9549 patients) were available for analysis. Adherence was evaluated based on the drug therapy prescribed (i.e., mixed amphetamine salts, immediate-release methylphenidate, and extended release methylphenidate–OROS [oral-osmotic formulation]) and the age and sex of the patient. Adherence measures were persistence and medication possession ratio (MPR). Persistence was higher for extended-release methylphenidate–OROS (0.50 ± 0.33) than for mixed amphetamine salts (0.42 ± 0.29) or immediate-release methylphenidate (0.37 ± 0.26; $p<0.001$). The MPR was also higher for extended-release methylphenidate–OROS (0.76 ± 0.37) than for mixed amphetamine salts (0.73 ± 0.37) or immediate-release methylphenidate (0.69 ± 0.37; $p<0.001$). Patients aged 5–9 years had equal or better persistence and MPR than those aged 10–14 and 15–18 years ($p<0.001$). No sex-related differences in adherence were observed. **Conclusion**: Adherence measures in our study were low. Although they were significantly better for extended-release methylphenidate–OROS than the other stimulants, the clinical significance of these differences are unclear. Further research should be conducted regarding pharmaceutical products, administration methods, and clinical interventions that may enhance adherence. Key Words: adherence, stimulants, methylphenidate, extended-release methylphenidate–OROS, children, adolescents, attention-deficit–hyperactivity disorder

Leslie LK, Weckerly J, et. al. **Implementing the American Academy of Pediatrics Attention- Deficit/Hyperactivity Disorder Diagnostic Guidelines in Primary Care Settings**. *Pediatrics* 114 (1) 129-140, 2004. (46)
Objectives. To evaluate the feasibility of the San Diego Attention-Deficit/Hyperactivity Disorder Project (SANDAP) protocol, a pediatric community-initiated quality improvement effort to foster implementation of the American Academy of Pediatrics (AAP) attention-deficit/hyperactivity disorder (ADHD) diagnostic guidelines, and to identify any additional barriers to providing evidence-based ADHD evaluative care. ***Methods***. Seven research-naive primary care offices in the San Diego area were recruited to participate. Offices were trained in the SANDAP protocol, which included 1) physician education, 2) a standardized assessment packet for parents and teachers, 3) an ADHD coordinator to assist in collection and collation of the assessment packet components, 4) educational materials for clinicians, parents, and teachers, in the form of handouts and a website, and 5) flowcharts delineating local paths for referral to medical subspecialists, mental health practitioners, and school-based professionals. The assessment packet included the parent and teacher versions of the Vanderbilt ADHD Diagnostic Rating Scales. In this study, we chose a conservative interpretation of the AAP ADHD guidelines for diagnosing ADHD, requiring that a child met criteria for ADHD on both the parent and teacher rating scales. A mixed-method analytic strategy was used to address feasibility and barriers, including quantitative surveys with parents and teachers and qualitative debriefing sessions conducted an average of 3 times per year with pediatricians and office staff members. ***Results***. Between December 2000 and April 2003, 159 children were consecutively enrolled for evaluation of school and/or behavioral problems. Clinically, only 44% of the children met criteria for ADHD on both the parent and teacher scales, and 73.5% of those children were categorized as having the combined subtype. More than 40% of the

subjects demonstrated discrepant results on the Vanderbilt scales, with only the parent or teacher endorsing sufficient symptoms to meet the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. Other mental health and learning problems were common in the sample; 58.5% of subjects met screening criteria for oppositional defiant disorder/conduct disorder, 32.7% met screening criteria for anxiety/depression, and approximately one-third had an active individualized education program in place or had received an individualized education program in the past. On evaluation, the SANDAP protocol was acceptable and feasible for all stakeholders. However, additional barriers to implementing the AAP ADHD guidelines were identified, including 1) limited information in the guidelines regarding the use of specific ADHD rating scales, the evaluation and treatment of children with discrepant and/or negative results, and the indications for psychologic evaluation of learning problems, 2) families' need for education regarding ADHD and support, 3) characteristics of physical health and mental health plans that limited care for children with ADHD, and 4) limited knowledge and use of potential community resources. *Conclusions.* Our results indicate that children presenting for evaluation of possible ADHD in primary care offices have complex clinical characteristics. Providers need mechanisms for implementing the ADHD diagnostic guidelines that address the physician education and delivery system design aspects of care that were developed in the SANDAP protocol. Additional barriers were also identified. Careful attention to these factors will be necessary to ensure the sustained provision of quality care for children with ADHD in primary care settings.

Gibbins C, Weiss M. **Clinical Recommendations in Current Practice Guidelines for Diagnosis and Treatment of ADHD in Adults**. *Current Psychiatry Reports*, 9, 420–426, 2007. (47)

Attention-deficit/hyperactivity disorder (ADHD) is a lifelong neurodevelopmental disorder in which approximately two thirds of patients experience impairment in adulthood. Although some adults with ADHD were diagnosed as children, many are first diagnosed as adults. This poses particular challenges given the limited familiarity with ADHD of many adult mental health services. As a result, several organizations, including the Canadian ADHD Resource Alliance, the American Academy of Child and Adolescent Psychiatry, the National Institutes of Health, and the British Association for Psychopharmacology, have developed practice guidelines for the assessment and treatment of adults with ADHD. This article reviews those guidelines in order to examine current best practices in adult ADHD. There is considerable agreement among these guidelines, which should be a critical part of moving from emerging knowledge to patient care, although both empirical evaluation and ongoing updates as new knowledge emerges will be important for their future development.