Current Medical Research and Opinion

ISSN: 0300-7995 (Print) 1473-4877 (Online) Journal homepage: https://www.tandfonline.com/loi/icmo20

Clinical utility of ADHD symptom thresholds to assess normalization of executive function with lisdexamfetamine dimesylate treatment in adults

Thomas E. Brown, Matthew Brams, Maria Gasior, Ben Adeyi, Thomas Babcock, Bryan Dirks, Brian Scheckner & Timothy Wigal

To cite this article: Thomas E. Brown, Matthew Brams, Maria Gasior, Ben Adeyi, Thomas Babcock, Bryan Dirks, Brian Scheckner & Timothy Wigal (2011) Clinical utility of ADHD symptom thresholds to assess normalization of executive function with lisdexamfetamine dimesylate treatment in adults, Current Medical Research and Opinion, 27:sup2, 23-33, DOI: 10.1185/03007995.2011.605441

To link to this article: https://doi.org/10.1185/03007995.2011.605441

Published online: 05 Oct 2011.

Current Medical Research & Opinion Vol. 27, No. S2, 2011, 23–33

0300-7995
doi:10.1185/03007995.2011.605441

Article ST-0073.R1/605441

Original article

Clinical utility of ADHD symptom thresholds to assess normalization of executive function with lisdexamfetamine dimesylate treatment in adults

Thomas E. Brown
Yale University School of Medicine, New Haven, CT, USA

Matthew Brams
Bayou City Research, Houston, TX, USA

Maria Gasior
Ben Adeyi
Thomas Babcock
Bryan Dirks
Brian Scheckner
Shire Development Inc., Wayne, PA, USA

Timothy Wigal
University of California, Irvine, Child Development Center, Irvine, CA, USA

Address for correspondence:
Thomas E. Brown, PhD, Yale University School of Medicine, 1188 Whitney Avenue, PO Box 6694, Hamden, CT 06517, USA.
Tel.: +1 203-562-5713; Fax: +1 203-562-3465; tebrownyu@aol.com

Key words:
ADHD – BADDS – Executive function – Lisdexamfetamine dimesylate – Receiver operating characteristics – ROC

Accepted: 12 July 2011; published online: 5 October 2011
Citation: Curr Med Res Opin 2011; 27:23–33

Abstract

Objectives:
This analysis assessed the relationship of various cutoff scores of the ADHD Rating Scale IV (ADHD-RS-IV) to levels of improvement in ADHD-related executive function (EF), measured by the Brown ADD Scale for Adults (BADDS), which may provide a measure of clinically meaningful EF improvement after ADHD treatment.

Methods:
Post hoc analysis of a 4-week, open-label, dose-optimization phase in a double-blind, placebo-controlled study of lisdexamfetamine dimesylate (LDX) in adults with ADHD. The BADDS for Adults, a validated, normed, self-report measure of EF in ADHD, provides a qualitative measure to rate treatment progress. The ADHD-RS-IV assesses current symptom status based on *DSM-IV* criteria. Postbaseline ADHD-RS-IV scores were categorized according to four cutoff criteria of symptom remission: (1) ADHD-RS-IV total score $\leq$18; (2) ADHD-RS-IV total score $\leq$10; (3) no ADHD-RS-IV item scored >1; and (4) ADHD-RS-IV total score $\leq$18 and $\leq$2 items per subscale with a score of 2. Sensitivity and specificity of criteria for identifying participants with optimal BADDS scores were assessed using receiver operating characteristics (ROC). Safety evaluation included treatment-emergent adverse events (TEAEs).

Results:
At endpoint, 85/127 participants had optimal BADDS scores. Linear ANOVA indicated limited overlap between BADDS and ADHD-RS-IV scores ($r^2 = 0.20$; $P < 0.0001$). Specificity was similar for criteria 1–4 (0.46, 0.39, 0.39, and 0.42), as were ROC (0.699, 0.776, 0.732, and 0.668). Sensitivity was high for criteria 2 and 3 (0.96, 0.92), lower for criteria 1 and 4 (0.72, 0.75). TEAEs were consistent with those of stimulants.

Conclusion:
Criteria 2 and 3 had satisfactorily high sensitivity, but no criteria had adequate specificity. AUC comparison indicated that criteria 2 and 3 ADHD-RS-IV thresholds may be more accurate assessments of EF normalization as measured by the BADDS. The open-label design, small sample size, and selection criteria limit the applicability of these results to a larger treatment population.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is diagnosed based on *Diagnostic and Statistical Manual of Mental Disorders Fourth Edition, Text Revision* (*DSM-IV-TR*) criteria[1]. Clinicians have recognized problems in applying *DSM-IV-TR* criteria that were originally developed for children to adult patients. The result of using child-centered criteria includes failure to identify adults with too few symptoms but significant functional impairments or those

with executive function (EF)-related symptoms that may be adult-like manifestations but are not recognized in the *DSM-IV-TR*[2–6]. These issues may be addressed, to some degree, when revised diagnostic criteria are adopted in the forthcoming *DSM-V*[7]. Additionally, ADHD symptoms at baseline and during treatment are frequently assessed in research settings with measures such as the ADHD Rating Scale IV (ADHD-RS-IV)[8], based on *DSM-IV-TR* criteria. However, clinicians in both research and community settings find such scales less than ideal for assessing treatment response especially because they provide neither a global assessment of improvement nor a measure of function. Symptomatic remission has been proposed as one clinically relevant treatment goal for patients with ADHD[9,10]. In pediatric investigations, remission has been defined as an ADHD-RS-IV total score $\leq$18[10], but no threshold has been established for adults. To quantify response to treatment in adult patients more reliably, it may be useful to apply the ADHD-RS-IV in concert with another, broader measure that includes EF-related functioning.

Controversy still exists on how to define and measure EF. Generally, EF is understood as a set of cognitive processes that allow self-regulation of attention, emotional expression, and task planning[11–13]. Although laboratory-based neuropsychological tests[14] have traditionally been used to measure EF, their clinical utility and accuracy for identifying EF-related functional impairments have been questioned[15–19]. Alternatively, rating scales that assess EF-related behaviors have been developed[15,20]. The Brown Attention-Deficit Disorder Scale (BADDS) – adolescent/adult version[20] measures EF-dependent behaviors and provides an assessment for clinically meaningful change using a norm-based cutoff score for optimal functioning. When paired with the ADHD-RS-IV, the BADDS may be clinically useful for identifying patients who, upon treatment, exhibit both symptomatic remission and normalization of EF-related functioning.

Lisdexamfetamine dimesylate (LDX; Vyvanse*) is a long-acting prodrug stimulant indicated for ADHD in children aged 6–12 years, adolescents aged 13–17 years, and in adults in the United States[21]. LDX was effective from 2–14 hours following oral administration in adults with ADHD in a randomized, double-blind, placebo-controlled trial that used the setting of the simulated adult workplace environment (AWE)[22]. Using data from this trial, the objective of the current post hoc analysis was to assess the relationship of ADHD-RS-IV-defined symptom severity and BADDS-defined EF behaviors. A secondary objective was to examine the appropriateness of various ADHD-RS-IV remission definitions, using receiver operating characteristics (ROC) analysis[23] (described below) to identify participants with improvement in BADDS-based EF-related behaviors.

*Vyvanse is a registered trademark of Shire LLC, Wayne, PA, USA.

Patients and methods

Study overview

This was a randomized, double-blind, multicenter, placebo-controlled, two-way crossover AWE study (ClinicalTrials.gov Identifier #NCT00697515) with an open-label dose-optimization phase. This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice according to the International Conference on Harmonisation guidelines. Each center's institutional review board approved the study protocol. Written consent was obtained after the study was explained to the participants. The methodology, results, and analysis from the double-blind crossover phase have been previously reported[22]. For the current analysis, data were derived from the 4-week open-label dose-optimization phase, during which each participant's LDX dosing was individually optimized to 30, 50, or 70 mg/day.

Participants

To be enrolled in the trial, participants were required to be an otherwise healthy adult, aged 18–55 years inclusive, who met *DSM-IV-TR* criteria for a primary diagnosis of ADHD with at least moderate symptom severity, as established by a baseline ADHD-RS-IV with adult prompts score $\geq$28[8,24]. An intelligence quotient score $\geq$80, based on the Kaufman Brief Intelligence Test[25], was also an enrollment requirement of the study. Participants could not take part in the study if any of the following key exclusion criteria were present: a comorbid psychiatric diagnosis with significant symptoms; history of seizures, hypertension, cardiovascular disease symptoms, or structural cardiac abnormality; a current therapy with an ADHD medication that is effective and well tolerated or a history of nonresponse to stimulant therapy; a positive drug result at screening; suspected substance abuse or dependence disorder (except nicotine) within the past 6 months; pregnant or lactating; or a documented allergy or intolerance to amphetamines.

Open-label LDX administration

All participants began open-label treatment with the lowest LDX dose (30 mg/day). At weekly intervals, participants were assessed for therapeutic response and tolerability, and LDX dose could be increased (20-mg/day increments) until satisfactory response ($\geq$30% reduction in ADHD-RS-IV with adult prompts and Clinical Global Impressions–Improvement scores of 1 or 2) was observed,

or if the clinician ascertained that additional benefit could not be achieved by increasing the dose. The maximum permissible LDX dose was 70 mg/day. The dose could be decreased (20-mg/day increment) once for lack of tolerability; if intolerance persisted, the participant was discontinued from the trial. When the optimal response was observed, that dose level was used for the rest of the dose-optimization phase.

Efficacy measures

The primary efficacy measure for the crossover phase was the Permanent Product Measure of Performance (PERMP)[26], a 10-minute, skill-adjusted math test that provides a time-sensitive, objective measure of performance. The average PERMP total score has been reported previously[22]. The ADHD-RS-IV with adult prompts and BADDS for adults were secondary efficacy assessments administered during the dose-optimization phase. The ADHD-RS-IV with adult prompts is an 18-item investigator-rated scale that assesses current ADHD symptoms and has been described elsewhere[8,24]. The ADHD-RS-IV with adult prompts was administered at baseline and each week during the open-label dose-optimization phase and during the double-blind AWE crossover phase. This post hoc analysis will use the ADHD-RS-IV with adult prompts total scores reported at the baseline and at end of the dose-optimization phase.

The BADDS is a 40-item self-report scale administered by the investigator to assess EF; individual items are rated on a scale of 0 (never) to 3 (almost daily). The adult items are grouped into five clusters of related ADHD symptoms (Figure 1)[20,27]. BADDS total scores can range from 0 to 120, with increasing scores indicating more severe impairment. A BADDS total score of 50 is the clinical cutoff in adults and has 4% false negatives and 6% false positives, using a methodology that corrected for an estimated 5% to 8% base rate of ADHD in an adult population[20]. The BADDS scoring includes a 90% confidence interval (CI) around the baseline total score. A clinically meaningful change is defined as a BADDS total score that is either above (worsening) or below (improvement) this baseline CI. A participant with a baseline score <50 still needs to have a change in score in excess of the baseline 90% CI to be considered reliably improved. Such a participant would be considered to have an 'optimal response'. The BADDS was administered at baseline and at the end of the dose-optimization period (visit 4/week 4).

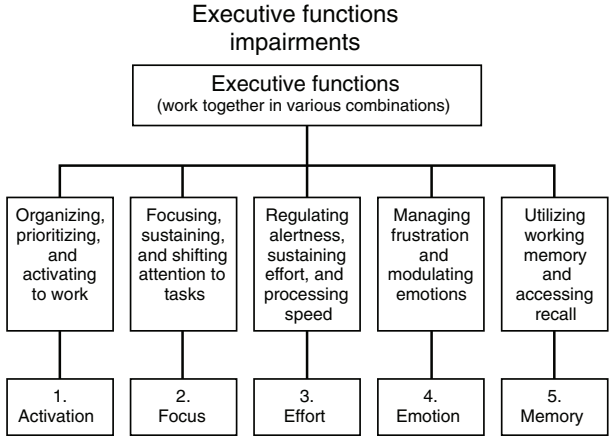

Figure 1. BADDS organizational summary. BADDS, Brown Attention-Deficit Disorder Scale[27].

Symptomatic remission criteria rationale

For this post hoc analysis, an optimal response in BADDS score at the end of the dose-optimization phase (a score that was <50 and that also demonstrated a clinically meaningful change from baseline) was considered one way of understanding symptomatic remission and optimal EF. One objective of this post hoc analysis was to assess how rates of symptomatic remission would vary when based on different ADHD-RS-IV-defined total score thresholds. Participants were categorized as remitters or nonremitters according to four ADHD-RS-IV with adult prompts total score criteria (Table 1). Criterion 1 was set at an ADHD-RS-IV with adult prompts total score of ≤18. A total score ≤18 represents a mean per-item score of ≤1 and is a score at which participants are unlikely to meet current symptomatic criteria for diagnosis of ADHD[10,28]. Criterion 2, an ADHD-RS-IV with adult prompts total score of ≤10, is a stricter cutoff and thereby excludes individuals scoring at least 2 on six items of either the inattention or the hyperactivity/impulsivity subscale. Criterion 3, no ADHD-RS-IV with adult prompts item score of >1, is a stringent cutoff to identify participants who are not suffering from even one *DSM-IV-TR* symptom. Finally, criterion 4 was defined as an ADHD-RS-IV with adult prompts total score ≤18 and ≤2 items per subscale with a score of 2 and no item with a score of 3. This criterion was chosen because participants who responded to LDX treatment may still express some behaviors that are identified as symptoms by *DSM-IV-TR* criteria. At this cutoff, such individuals would not meet standards for diagnosis of ADHD even at a subclinical level.

Safety assessments

Treatment-emergent adverse events (TEAEs), vital signs, electrocardiograms, and weight were determined to assess LDX safety. Detailed safety analyses of both the open-label and the double-blind study periods have been previously reported[22]. TEAEs were defined as adverse events that started on or after the first date of study medication administration and no later than 3 days after the last date of study

Table 1. Symptom profile characteristics for remission criteria.

	Criterion 1 Total score ≤18	Criterion 2 Total score ≤10	Criterion 3 No item >1	Criterion 4* Total score ≤18; no item >2; ≤4 items (2 per subscale) =2
Maximum total score	≤18	≤10	≤18	≤18
Maximum number of items with scores ≥2	≤9	≤5	0	≤2 per subscale

*Participants with a score of 3 on any ADHD-RS-IV with adult prompts item were considered to not meet criterion 4 for normalization.

Table 2. Statistical parameters assessment in ROC analysis.

	ADHD-RS-IV remission criteria status	BADDS optimal response criteria status
True positive (TP)	+	+
False positive (FP)	−	+
True negative (TN)	−	−
False negative (FN)	+	−
Sensitivity	TP/(TP + FN)	
Specificity	TN/(TN + FP)	
	TP rate = sensitivity	
	FP rate = 1-specificity	
Positive predictive value (PPV)	TP/(TP + FP)	
Negative predictive value (NPV)	TN/(TN + FN)	

ADHD-RS-IV, Attention-Deficit/Hyperactivity Disorder Rating Scale IV; BADDS, Brown Attention-Deficit Disorder Scale; ROC, receiver operating characteristic.

medication administration. They were classified using the *Medical Dictionary for Regulatory Activities* (MedDRA; Version 10.0) and analyzed according to the LDX dose assigned at the time of TEAE onset.

Statistical analysis

A priori and post hoc analyses of ADHD-RS-IV with adult prompts and BADDS outcomes were based on data derived from the enrolled efficacy population (all participants who took ≥1 dose during the dose-optimization phase and had ≥1 postbaseline efficacy assessment). TEAE frequency and severity were described for the safety population (all participants who entered the dose-optimization phase and took ≥1 dose of open-label study drug).

Change from baseline in ADHD-RS-IV with adult prompts total and subscale and BADDS scores were analyzed using paired *t* tests. A generalized linear effects analysis of variance, using week 4 total scores on the ADHD-RS-IV with adult prompts scale and BADDS, was conducted to determine the proportion of change in BADDS score improvement (dependent variable) that is attributable to the change in ADHD-RS-IV with adult prompts scores.

The threshold for normalization on the BADDS was set at a total score <50, as recommended by Brown to monitor treatment progress[29]. Participants with week 4 scores below the baseline 90% CI and total score <50 were classified as exhibiting an optimal response. To assess the sensitivity and specificity of each ADHD-RS-IV with adult prompts remission criterion, a ROC analysis was performed. For each ADHD-RS-IV with adult prompts criterion described above, participants with or without optimal response as assessed by BADDS were identified, and, as illustrated in Table 2, the following were summarized post hoc: true positives (participants who met the BADDS reliable change and <50 total score thresholds and who met the ADHD-RS-IV with adult prompts remission criterion), false positives (participants who met the BADDS thresholds but who failed to meet the ADHD-RS-IV criterion), true negatives (participants who failed to meet the BADDS thresholds and who failed to meet the ADHD-RS-IV with adult prompts criterion), and false negatives (participants who failed to meet the BADDS thresholds but who met the ADHD-RS-IV with adult prompts criterion). Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were also assessed (Table 2). Using these values, a graphic representation was created with the true-positive rate (sensitivity) on the y-axis as a function of the false-positive rate (1 – specificity) on the x-axis (Figure 2). For this, each point represents a sensitivity/specificity pair corresponding

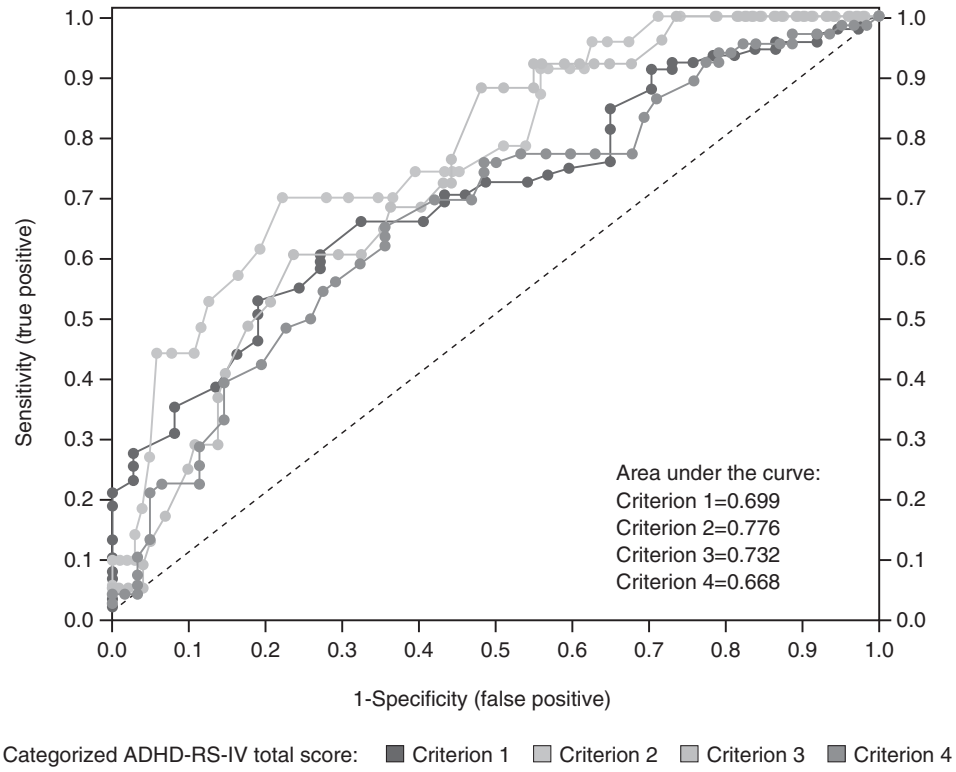

Figure 2. ROC graph of categorized ADHD-RS-IV with adult prompts total scores vs BADDS total scores (enrolled efficacy population). ADHD-RS-IV, Attention-Deficit/Hyperactivity Disorder Rating Scale IV; BADDS, Brown Attention-Deficit Disorder Scale; ROC, receiver operating characteristics.

to a defined therapeutic response threshold; the closer the ROC plot is to the upper left corner, the higher the overall accuracy of the discriminatory thresholds is. The area under the ROC curve (AUC) was also determined. AUC measures how quickly the ROC curve rises to the upper left corner of the graph: the larger the AUC value is, the more accurate the diagnostic threshold is. An AUC value of 1.0 indicates an ideal test (i.e., it achieves both 100% in sensitivity [no false negatives] and specificity [no false positives]). The closer the AUC is to 0.5, the less it is able to discriminate between true positives and false positives or detect a relationship between the conditions tested)[23].

Results

Participant demographics

Demographic and baseline characteristics of the safety population ($N = 142$) have been reported previously[22]. Briefly, participants had a mean (SD) age of 30.5 (10.70) years and a mean (SD) weight of 178.1 (37.14) lb, and a majority were men (88/142; 62.0%), were white (127/142; 89.4%), and were between the ages of 18 and 40 years (109/142; 76.8%). More than half the study population (81/142; 57.0%) had prior treatment with ADHD medications and approximately half the study population (73/142; 51.4%) had prior exposure to psychostimulants with the most common prior medications being mixed amphetamine salts (MAS; 45/142; 31.7%) and methylphenidate hydrochloride (40/142; 28.2%). During the dose-optimization phase, 93 (65.5%) participants received concomitant medications; the most commonly taken medications (≥5%) were ibuprofen (37/142; 26.1%), paracetamol (18/142; 12.7%), loratadine (10/142; 7.0%), and a multivitamin (9/142; 6.3%). The majority of participants had the combined ADHD subtype (98/142; 69.0%), followed by the inattentive ADHD subtype (39/142; 27.5%). At the end of the dose-optimization phase, most participants' optimized dose of LDX was 50 mg/day ($n = 70$) or 70 mg/day ($n = 44$); fewer participants received an optimized dose of 30 mg/day ($n = 28$).

LDX efficacy

The mean (SD) ADHD-RS-IV with adult prompts total score (all LDX doses combined) decreased from 37.0 (5.61) at baseline to 15.5 (5.87) at dose-optimization endpoint ($P < 0.0001$). Mean (SD) percentage change in total score from baseline for all LDX doses is illustrated in Figure 3. Significant mean (SD) improvements ($P < 0.0001$) in ADHD-RS-IV mean scores were seen at all postbaseline time points (weeks 1–4) in the dose-optimization phase (−12.3 [8.32], −16.8 [7.83], −20.6 [7.07], and −21.6

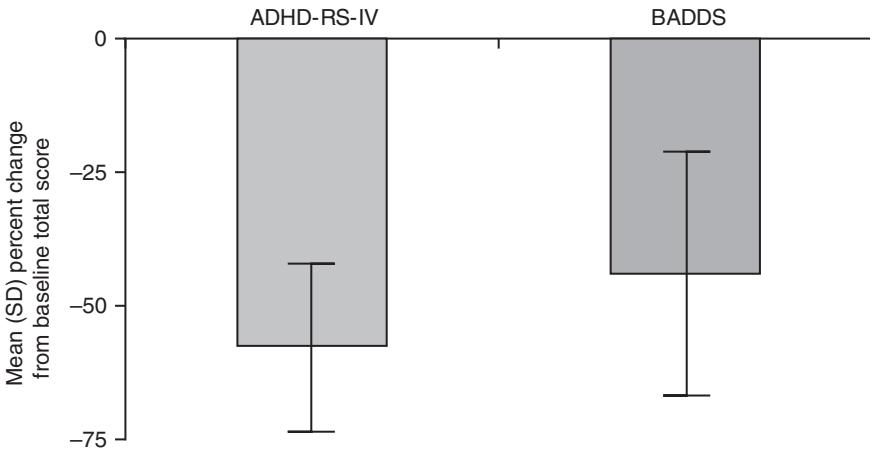

Figure 3. Mean (SD) percentage change from baseline at endpoint in ADHD-RS-IV with adult prompts total scores and BADDS total scores in the LDX open-label dose-optimization phase. Dose-optimization endpoint is last valid assessment through week 4. ADHD-RS-IV, Attention-Deficit/Hyperactivity Disorder Rating Scale IV; BADDS, Brown Attention-Deficit Disorder Scale; LDX, lisdexamfetamine dimesylate.

Table 3. Linear analysis of variance model for change in BADDS total score from baseline to dose-optimization endpoint by change in ADHD-RS-IV with adult prompts total score.

Model Information	Estimate	*t* Statistic	*P* Value*
Intercept	−2.09	−0.31	0.7544
Change from baseline in ADHD-RS-IV total score	1.41	5.01	<0.0001
$r^{2\dagger\ddagger}$	0.20		

ADHD-RS-IV, Attention-Deficit/Hyperactivity Disorder Rating Scale IV; BADDS, Brown Attention-Deficit Disorder Scale.
*P values are for coefficient of linear analysis of variance model with change from baseline to dose-optimization endpoint in ADHD-RS-IV total score as covariate.
†Proportion of change from baseline to dose-optimization endpoint in BADDS total score that is explained by the change in ADHD-RS-IV total score.
‡For this specific model, switching the position of ADHD-RS-IV and BADDS scores resulted in the same r^2 value.

[7.40], respectively). Similar changes in subscale scores were seen (all $P<0.0001$; data not shown).

The mean (SD) BADDS total score (all LDX doses combined) decreased from 74.3 (17.05) at baseline to 40.9 (17.12) at dose-optimization week 4 ($P<0.0001$). Mean (SD) percentage change in BADDS total score from baseline for all LDX doses is illustrated in Figure 3. Optimal response, based on the BADDS, was seen in 85 of 127 (66.9%) participants with valid BADDS scores at week 4.

Post hoc linear analysis of variance model

There is a linear relationship between ADHD-RS-IV with adult prompts and BADDS total scores as the coefficient of estimate is significantly different from zero for change in ADHD-RS-IV with adult prompts score ($P<0.0001$) (Table 3). As shown in Figure 4, a small proportion of the variance in change in BADDS total scores (0.20; i.e., 20%) could be attributed to change in ADHD-RS-IV with adult prompts total scores. Likewise, a small proportion of the variance in change in ADHD-RS-IV with adult prompts total scores (0.20; i.e., 20%) could be attributed to change in BADDS total scores (Table 3). Consequently, the remainder of variance in change (80%) was unique to each scale (Figure 4).

Post hoc ROC analysis

Tables 4 and 5 summarize true-positive, false-positive, true-negative, and false-negative rates and sensitivity/specificity and PPV/NPV analysis outcomes, respectively, with Table 4 showing, for each ADHD remission criterion, the proportion of participants in each of four categories of true-positive, false-positive, false-negative, and true-negative and Table 5 showing calculation of sensitivity, specificity, and PPV/NPV analysis. Sensitivity was

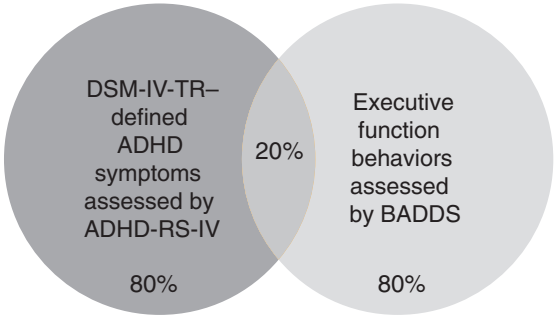

Figure 4. Schematic representation of the overlap between ADHD-RS-IV with adult prompts and BADDS scores variation. ADHD-RS-IV, Attention-Deficit/Hyperactivity Disorder Rating Scale IV; BADDS, Brown Attention-Deficit Disorder Scale; *DSM-IV-TR*, *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition, Text Revision).

Table 4. True and false positives/negatives observed with tested ADHD-RS-IV with adult prompts criteria for normalization (enrolled efficacy population)*.

		ADHD-RS-IV With Adult Prompts							
		Criterion 1 Total score ≤18		Criterion 2 Total score ≤10		Criterion 3 No item >1		Criterion 4† Total score ≤18; no item >2; ≤4 items (2 per subscale) = 2	
		Yes	No	Yes	No	Yes	No	Yes	No
BADDS	Optimal (TP, FP)	65	20	22	63	23	62	49	36
	Not optimal (FN, TN)	25	17	1	41	2	40	16	26

ADHD-RS-IV, Attention-Deficit/Hyperactivity Disorder Rating Scale IV; BADDS, Brown Attention-Deficit Disorder Scale; FN, false negative (participants failed to meet the BADDS <50 threshold but met the ADHD-RS-IV remission criterion); FP, false positive (participants met the BADDS <50 threshold but failed to meet the ADHD-RS-IV remission criterion); TN, true negative (participants failed to meet the BADDS <50 threshold and failed to meet the ADHD-RS-IV remission criterion); TP, true positive (participants met the BADDS <50 threshold and met the ADHD-RS-IV remission criterion). The term *optimal* denotes BADDS total scores <50 that also demonstrated a clinically meaningful change from baseline; *not optimal* denotes all other BADDS scores.
*Data reflect comparison to criteria for optimal BADDS response (BADDS total score <50).
†Participants with a score of 3 on any ADHD-RS-IV with adult prompts item were considered to not meet criterion 4 for normalization.

Table 5. Sensitivity, specificity, and positive/negative predictive values of tested ADHD-RS-IV with adult prompts criteria for normalization (enrolled efficacy population)*.

	ADHD-RS-IV With Adult Prompts†			
	Criterion 1 Total score ≤18	Criterion 2 Total score ≤10	Criterion 3 No item >1	Criterion 4‡ Total score ≤18; no item >2; ≤4 items (2 per subscale) = 2
Sensitivity	0.72 (65/90)	0.96 (22/23)	0.92 (23/25)	0.75 (49/65)
Specificity	0.46 (17/37)	0.39 (41/104)	0.39 (40/102)	0.42 (26/62)
PPV	0.76 (65/85)	0.26 (22/85)	0.27 (23/85)	0.58 (49/85)
NPV	0.40 (17/42)	0.98 (41/42)	0.95 (40/42)	0.62 (26/42)

ADHD-RS-IV, Attention-Deficit/Hyperactivity Disorder Rating Scale IV; BADDS, Brown Attention-Deficit Disorder Scale; FN, false negative (participants failed to meet the BADDS <50 threshold but met the ADHD-RS-IV remission criterion); FP, false positive (participants met the BADDS <50 threshold but failed to meet the ADHD-RS-IV remission criterion); NPV, negative predictive value; PPV, positive predictive value; TN, true negative (participants failed to meet the BADDS <50 threshold and failed to meet the ADHD-RS-IV remission criterion); TP, true positive (participants met the BADDS <50 threshold and met the ADHD-RS-IV remission criterion).
*Specificity = TN/(TN + FP); false-positive rate = 1 − specificity; sensitivity = TP/(TP + FN); true-positive rate = sensitivity; PPV = TP/(TP + FP); NPV = TN/(FN + TN).
†Data reflect comparison to criteria for optimal BADDS response (BADDS total score <50) and the TP, FP, TN, FN rates.
‡Participants with a score of 3 on any ADHD-RS-IV with adult prompts item were considered to not meet criterion 4 for normalization.

greatest for criteria 2 and 3; these criteria yielded the group of participants with the lowest proportion of false negatives (i.e., fewest participants who met the ADHD remission criterion but failed to meet the BADDS standard for optimal response) (Tables 4 and 5). Specificity was greatest for criterion 1, although no criterion had adequate specificity; criterion 1 contained the lowest proportion of false positives (i.e., participants who failed to meet the ADHD-RS-IV with adult prompts remission criterion but who met the BADDS standard for optimal response) (Tables 4 and 5). As summarized in Table 5, criteria 2 and 3 were associated with the highest NPV but the lowest PPV. Figure 2 illustrates the ROC sensitivity/specificity plots for each of the four remission criteria. AUCs corresponding to the ROCs for remission criteria 1, 2, 3, and 4 were 0.699, 0.776, 0.732, and 0.668, respectively.

TEAEs

During the 4-week open-label LDX dose-optimization phase, TEAEs, reported for all LDX doses combined, occurred in 113 (79.6%) participants. TEAEs reported by ≥5% of participants were decreased appetite (36.6%), dry mouth (30.3%), headache (19.7%), insomnia (18.3%), upper respiratory tract infection (9.9%), irritability (8.5%), nausea (7.7%), anxiety (5.6%), and feeling jittery (5.6%). TEAEs that were mild in intensity were reported by 43.0% of participants (61/142); moderate TEAEs were reported by 33.8% of participants (48/142). A total of four participants had severe TEAEs while receiving LDX in the dose-optimization phase that did not affect dosing or treatment; these occurred in only one participant each and included bronchitis, headache, insomnia,

and initial insomnia. No serious AEs or deaths were reported.

Discussion

LDX treatment was associated with significant improvements in ADHD symptom severity and EF-related behaviors, based on ADHD-RS-IV with adult prompts ($P<0.0001$) and BADDS total scores ($P<0.0001$), respectively. Linear analysis of variance modeling showed that a relatively small but significant proportion (20%) of the improvement in BADDS total scores (EF behaviors) is attributable to improvement in ADHD-RS-IV with adult prompts scores (ADHD symptom severity). Symptomatic remission criteria 2 and 3 were associated with satisfactorily high levels of sensitivity; participants reaching either of these thresholds were likely to also meet criteria for EF normalization based on the BADDS. Criteria 1 and 4 showed lower sensitivity and NPV, but relatively greater specificity (participants not meeting these criteria were also likely to not achieve EF normalization based on BADDS). Even though differences in sensitivity and specificity were observed, ROC analysis yielded AUCs for the criteria that were all generally similar and favorable in terms of ability to relate improvement in EF by BADDS to improvement in symptoms by ADHD-RS-IV.

The current results are consistent with data from a large, randomized, double-blind, placebo-controlled 4-week trial in adults and a 1-year open-label extension study that showed improvement in ADHD-RS-IV with adult prompts scores with LDX[30,31]. As in the current trial, studies of other long-acting stimulants (e.g., osmotic-release oral system methylphenidate [OROS*MPH], d-MPH extended release, and MAS) conducted in adults have also shown improved ADHD symptoms throughout active treatment[32–37]. Such results provide substantial support for the clinical use of psychostimulants as first-line agents for the management of *DSM*-defined ADHD symptoms in adult patients.

By contrast, there is a relative paucity of information from controlled clinical trials regarding the impact of psychostimulants on EF-related behaviors and functioning in patients with ADHD. This may, in part, reflect the current lack of consensus regarding the role of EF in ADHD symptoms, whether all patients with ADHD exhibit EF deficits, and how to properly measure EF in clinical trial settings. Some investigators argue that beyond the core symptoms of ADHD as defined in the *DSM-IV-TR*, EF impairment such as poor emotional regulation, motivational dysfunction, and impaired task planning[13,27] may be integral to the description of the disorder[11–13], especially in adults. However, consensus on this has yet to be found[12,38].

EF impairment, as measured using traditional neuropsychological tests[14], however, has been found to occur in approximately 30% to 50% of children and adults with ADHD, particularly on tasks that assess response inhibition and set shifting[14,18,19,38–41]. Nevertheless, the clinical utility and accuracy of such tasks for identifying patients with EF-related functional impairments appear rather limited[15–17]. Further, it has been argued that because each such task has been carefully designed to assess only a single aspect of EF, task performance does not yield information about daily functioning in complex real-world situations, which demand integrative executive processing[15]. By contrast, clinic-based assessments designed to assess EF behaviors appear to more readily detect real-world impairments[15–17,20]. When applied in patients with ADHD, such instruments have detected significant dysfunction. Barkley and Murphy[15] found that 89%–94% of adults with ADHD fell within the clinically impaired range on the Deficits in EF Scale. Similarly, in the current trial, adults with ADHD exhibited significant EF-related behavioral impairments at baseline, marked by a mean BADDS total score that was well above the cutoff score of <50, which is indicative of 'optimal' EF-related behavior and is consistent with an assessment of lack of impairment.

A limited number of studies have examined the impact of pharmacotherapy on EF. Fallu *et al.*[42] described significant improvement in EF, based on neuropsychological measures (e.g., Stroop Color–Word, working memory tasks, interference/response inhibition), among adults with ADHD given open-label OROS-MPH. Similarly, Biederman *et al.*[43] found that, in adolescents and young adults with ADHD, those who took their prescribed stimulant medication performed significantly better on measures of sustained attention ($P=0.04$) and verbal learning ($P=0.03$) than did participants with ADHD not taking their medication; both ADHD groups, however, performed significantly more poorly than did normal controls (all $P\leq0.003$). In a previously published analysis of the current study[44], there was clinically meaningful improvement in EF-related behaviors based on BADDS total scores after 4 weeks of open-label LDX; most participants were in one of the two highest categorical improvement ranges, 'optimal' or 'very favorable', relative to pretreatment as defined by Brown[20]. This is in agreement with a 7-week placebo-controlled study of adults with ADHD treated with dose-optimized triple-bead MAS that showed significant improvement vs placebo in EF behaviors, as measured by BADDS ($P<0.0001$), and in ADHD symptoms using the ADHD-RS-IV with adult prompts ($P<0.0001$ for total scores; $P<0.01$ for inattention and hyperactivity–impulsivity subscale scores)[45]. A controlled trial with the nonstimulant atomoxetine in adult participants with ADHD that employed BADDS also showed significant

*OROS is a registered trademark of the ALZA Corporation.

improvement in BADDS cluster scores vs placebo ($P \leq 0.008$ for all clusters)[46]. In summary, the available literature suggests that EF impairments are present in adults with ADHD and improvements in EF behaviors during pharmacotherapy may be robust; such improvements are detectable based on both neuropsychological task performance and clinician-administered questionnaires such as the BADDS. To more rigorously characterize EF benefits of pharmacotherapy, additional randomized, placebo-controlled trials that describe EF-related functioning are needed; these should be conducted in broader pediatric and adult patient populations and with a variety of treatment regimens.

Given the currently observed improvements in both ADHD-RS-IV and BADDS scores with LDX therapy, it was of interest to determine to what degree these two scales may assess similar domains of impairment (i.e., overlap). The finding here that 20% of the improvement in BADDS total scores was accounted for by improvements in ADHD-RS-IV with adult prompts total scores and vice versa indicates that, indeed, there is some modest degree of overlap between the ADHD-RS-IV scale measuring ADHD symptom expression and severity and the BADDS measuring expression of EF-related functional impairment. This overlap may be partially attributable to the measures of inattention, but not hyperactivity, in the BADDS assessment. However, the finding that the remaining majority (80%) of score variation is unique to each scale indicates that the ADHD-RS-IV and BADDS assess largely distinct domains of ADHD impairments. Moreover, EF-related functional impairments and improvements with treatment are not well captured by the ADHD-RS-IV. The additional use of the BADDS can also provide clinically important and more detailed information than can the ADHD-RS-IV. BADDS clusters, activation, focus, effort, emotion, and memory, are interrelated with items that follow with each other (e.g., the effort cluster includes regulating alertness, sustaining effort, and processing speed); by examining cluster scores, clinicians can have a sense of how patients are doing in specific domains. The clinical use of these two scales in concert thus provides a broader picture of patient symptoms and functioning than can either scale used alone.

The current findings also support the growing consensus that current *DSM-IV-TR* symptom criteria do not adequately account for the range of ADHD impairments that include executive dysfunction marked by emotional volatility, poor time management, memory disturbance, and poor regulation of motivation and goal-directed behavior[3,5,13]. Using current symptom definitions, clinicians may fail to recognize that patients' behaviors may be attributable to ADHD, thereby excluding from treatment those adult patients with ADHD who experience these EF-related symptoms and functional impairments. Likewise, among those adults with ADHD who receive treatment, outcome assessment by *DSM-IV-TR*-defined symptoms based on rating scales such as the ADHD-RS-IV alone may not fully characterize clinically meaningful improvements in EF-related behaviors and fail to allow for normalized functioning.

Clearly defined, rating scale-based ADHD remission criteria would be highly useful to clinicians and researchers alike, allowing clear-cut differentiation of patients with 'normalized' behavior vs those with suboptimal therapeutic response. There is currently no consensus among experts with regard to criteria for clinical response or remission in ADHD. In children, researchers have applied an ADHD-RS-IV total score of $\leq$18 as the criterion for symptomatic remission[10,47]. No criteria have been examined in adults. Using ROC analysis, four different ADHD-RS-IV-based symptomatic remission criteria yielded relatively similar AUC values, indicating similar levels of sensitivity and specificity. Participants who met symptomatic remission criterion 2 or 3 were very likely to also meet the criterion for optimal EF. The other remission definitions captured more participants with nonoptimal EF functioning, based on the BADDS; even though ADHD-RS-IV scores were relatively low (ADHD-RS-IV total score $\leq$18), these participants likely continued to show a small number of significant ADHD symptoms and impaired EF-related behaviors. Future research should continue to elucidate rating scale-based thresholds for normalization of ADHD symptoms. Such cutoffs may differ according to the intended goal (e.g., screening, diagnosis, and evaluation of treatment response) and may serve as useful guides for making crucial diagnostic and treatment decisions.

Limitations

The current analysis was based on the open-label study phase of a controlled trial in a relatively small sample of adults with ADHD, so conclusions regarding the impact of treatment on ADHD symptoms and EF-related daily functioning must be made with caution. Participants were selected based on narrowly defined inclusion/exclusion criteria, which may have resulted in a sample not representative of clinical practice. Only those individuals with moderate to severe ADHD symptoms were included; this may not reflect an ADHD population with less severe symptoms who may experience less robust improvements from baseline. Moreover, participants with comorbid medical or psychiatric diagnoses were excluded; this likely does not reflect the majority of adult patients with ADHD. Participants were mainly white and between ages 18 and 40 years; the current findings may not be representative of patients in other demographic groups. ROC analysis does not address aspects of time to event and right censoring, and may, therefore, produce results that differ from those

provided by survival analyses such as Kaplan–Meier or Cox regression analyses.

Conclusions

After 4 weeks of open-label, dose-optimized LDX treatment, adult participants with ADHD showed significant improvement in both *DSM-IV-TR*-defined ADHD symptoms and EF behaviors compared with pretreatment baseline. Although there is a small degree of overlap in assessments between the two scales, these instruments measure, for the most part, distinct domains of ADHD-related impairment, namely EF behaviors and *DSM*-defined ADHD symptoms. ROC analysis showed that ADHD-RS-IV-defined remission, as total score ≤10 or as ≤1 on each item, identified participants with normalized EF behaviors based on the BADDS. Our findings support the notion that comprehensive management of adults with ADHD would be better served by employing such complementary tools, both of which can be readily conducted in a clinical setting. A clinician- or patient-administered ADHD symptom scale can be supplemented with a brief, uncomplicated, readily administered measure of EF impairments for a more complete understanding of patient response to therapy.

Transparency

Declaration of funding
Clinical research was funded by the sponsor, Shire Development Inc.

Declaration of financial/other relationships
T.E.B. is a consultant for Abbott, Eli Lilly, Novartis, and Shire; receives research grants from Eli Lilly; receives royalties for publications from American Psychiatric Press, Psychological Corporation, and Yale University Press. M.B. serves as a speaker for Cephalon, Eli Lilly, McNeil, Novartis, Pfizer, Shire, and Wyeth. M.G. is an employee of Shire and holds stock and/or stock options in Shire. B.A., T.B., B.D. and B.S. are employees of Shire and hold stock and/or stock options in Shire. T.W. is a consultant/has consulted for Eli Lilly, McNeil, Otsuka, and Shire; receives/received honoraria from Eli Lilly, McNeil, Otsuka, and Shire; received research funding from NICHD, NIDA, and NIMH; receives/received research support from Eli Lilly, McNeil, Otsuka, and Shire; serves/served as a speaker for Celltech, Cephalon, Eli Lilly, Janssen, McNeil, Novartis, Otsuka, and Shire.

Acknowledgment
Under the direction of the authors, Karen Dougherty, PhD, and Michael Pucci, PhD, employees of Ogilvy CommonHealth Scientific Communications (OCHSC), provided writing assistance for this publication. Editorial assistance in formatting, proofreading, copy editing, and fact checking was also provided by OCHSC. Gary Chen, PhD, from Shire Development Inc. provided support in programming for statistical analyses. Shire Development Inc. provided funding to OCHSC for support in writing and editing this manuscript. Although the sponsor was involved in the design, collection, analysis, interpretation, and fact checking of information, the content of this manuscript, the ultimate interpretation, and the decision to submit it for publication in *Current Medical Research and Opinion* were made by the authors independently.

These data were previously presented at the 163rd Annual Meeting of the American Psychiatric Association, May 22–26, 2010, in New Orleans, LA, USA.

References

1. American Psychiatric Association. Attention-deficit and disruptive behavior disorders. In: Diagnostic and Statistical Manual of Mental Disorders DSM-IV-TR, 4th Edn, Text Revision. Washington, DC: American Psychiatric Association, 2000:85-93
2. Stefanatos GA, Baron IS. Attention-deficit/hyperactivity disorder: a neuropsychological perspective towards DSM-V. Neuropsychol Rev 2007;21:5-38
3. Brown TE. DSM-IV: ADHD and executive function impairments. Adv Stud Med 2002;2:910-14
4. Faraone SV, Biederman J, Spencer T, et al. Diagnosing adult attention deficit hyperactivity disorder: are late onset and subthreshold diagnoses valid? Am J Psychiatry 2006;163:1720-9
5. Spencer TJ, Biederman J, Mick E. Attention-deficit/hyperactivity disorder: diagnosis, lifespan, comorbidities, and neurobiology. J Pediatr Psychol 2007;32:631-42
6. McGough JJ, Barkley RA. Diagnostic controversies in adult attention deficit hyperactivity disorder. Am J Psychiatry 2004;161:1948-56
7. American Psychiatric Association. Attention Deficit/Hyperactivity Disorder. 314.0x. Summary of changes under consideration for ADHD. Available at: http://www.dsm5.org/ProposedRevisions/Pages/proposedrevision.aspx?rid = 383 [Last accessed 17 March 2010]
8. DuPaul GJ, Power TJ, Anastopoulos AD, et al. ADHD Rating Scale-IV: Checklists, Norms, and Clinical Interpretation. New York, NY: Guilford Press, 1998
9. Biederman J, Mick E, Faraone SV. Age-dependent decline of symptoms of attention deficit hyperactivity disorder: impact of remission definition and symptom type. Am J Psychiatry 2000;157:816-18
10. Steele M, Jensen PS, Quinn DMP. Remission versus response as the goal of therapy in ADHD: a new standard for the field? Clin Ther 2006;28:1892-908
11. Brown TE. Executive functions and attention deficit hyperactivity disorder: implications of two conflicting views. Int J Disability Develop Educ 2006;53:35-46
12. Castellanos FX, Sonuga-Barke EJ, Milham MP, et al. Characterizing cognition in ADHD: beyond executive dysfunction. Trends Cogn Sci 2006;10:117-23
13. Barkley RA. Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. Psychol Bull 1997;121:65-94
14. Hervey AS, Epstein JN, Curry JF. Neuropsychology of adults with attention-deficit/hyperactivity disorder: a meta-analytic review. Neuropsychology 2004;18:485-503
15. Barkley RA, Murphy KR. Impairment in occupational functioning and adult ADHD: the predictive utility of executive function (EF) ratings versus EF tests. Arch Clin Neuropsychol 2010;25:157-73
16. Shallice T, Burgess PW. Deficits in strategy application following frontal lobe damage in man. Brain 1991;114:727-41
17. Alderman N, Burgess PW, Knight C, et al. Ecological validity of a simplified version of the multiple errands shopping test. J Int Neuropsychol Soc 2003;9:31-44

18. Biederman J, Petty CR, Fried R, et al. Stability of executive function deficits into young adult years: a prospective longitudinal follow-up study of grown up males with ADHD. Acta Psychiatr Scand 2007;116:129-36
19. Boonstra AM, Kooij JJ, Oosterlaan J, et al. To act or not to act, that's the problem: primarily inhibition difficulties in adult ADHD. Neuropsychology 2010;24:209-21
20. Brown TE. Brown Attention-Deficit Hyperactivity Disorder Scales for Adolescents and Adults. San Antonio, TX: The Psychological Corporation, 1996
21. Vyvanse [package insert]. Wayne, PA, USA: Shire US Inc., 2010
22. Wigal T, Brams M, Gasior M, et al. on behalf of the 316 Study Group. Randomized, double-blind, placebo-controlled, crossover study of the efficacy and safety of lisdexamfetamine dimesylate in adults with attention-deficit/hyperactivity disorder: novel findings using the adult workplace environment design. Behav Brain Funct 2010;6:34
23. Lasko TA, Bhagwat JG, Zou KH, et al. The use of receiver operating characteristic curves in biomedical informatics. J Biomed Inform 2005;38:404-15
24. Faries DE, Yalcin I, Harder D, et al. Validation of the ADHD Rating Scale as a clinician administered and scored instrument. J Atten Disord 2001;5:107-15
25. Kaufman AS, Kaufman NL. KBIT-2: Kaufman Brief Intelligence Test, 2nd Upper Saddle River, NJ: Pearson Education, Inc., 2004
26. Swanson J, Wigal S, Greenhill L, et al. Objective and subjective measures of the pharmacodynamic effects of Adderall® in the treatment of children with ADHD in a controlled laboratory classroom setting. Psychopharmacol Bull 1998;34:55-60
27. Brown T. Attention Deficit Disorder: The Unfocused Mind in Children and Adults. New Haven, CT: Yale University Press, 2005
28. Swanson JM, Kraemer HC, Hinshaw SP, et al. Clinical relevance of the primary findings of the MTA: success rates based on severity of ADHD and ODD symptoms at the end of treatment. J Am Acad Child Adolesc Psychiatry 2001;40:168-79
29. Brown TE. Brown Attention-Deficit Disorder Scales for Children and Adolescents. San Antonio, TX: The Psychological Corp., 2001:1-149
30. Adler LA, Goodman DW, Kollins SH, et al. on behalf of the 303 Study Group. Double-blind, placebo-controlled study of the efficacy and safety of lisdexamfetamine dimesylate in adults with attention-deficit/hyperactivity disorder. J Clin Psychiatry 2008;69:1364-73
31. Weisler R, Young J, Mattingly G, et al. on behalf of the 304 Study Group. Long-term safety and effectiveness of lisdexamfetamine dimesylate in adults with attention-deficit/hyperactivity disorder. CNS Spectr 2009;14:573-85
32. Biederman J, Mick E, Surman C, et al. A randomized, placebo-controlled trial of OROS methylphenidate in adults with attention-deficit/hyperactivity disorder. Biol Psychiatry 2006;59:829-35
33. Medori R, Ramos-Quiroga JA, Casas M, et al. A randomized, placebo-controlled trial of three fixed dosages of prolonged-release OROS methylphenidate in adults with attention-deficit/hyperactivity disorder. Biol Psychiatry 2008;63:981-9
34. Reimherr FW, Williams ED, Strong RE, et al. A double-blind, placebo-controlled, crossover study of osmotic release oral system methylphenidate in adults with ADHD with assessment of oppositional and emotional dimensions of the disorder. J Clin Psychiatry 2007;68:93-101
35. Weisler RH, Biederman J, Spencer TJ, et al. Mixed amphetamine salts extended-release in the treatment of adult ADHD: a randomized, controlled trial. CNS Spectr 2006;11:625-39
36. Biederman J, Spencer TJ, Wilens TE, et al. on behalf of the SLI 381.304 Study Group. Long-term safety and effectiveness of mixed amphetamine salts extended release in adults with ADHD. CNS Spectr 2005;10:16-25
37. Spencer TJ, Adler LA, McGough JJ, et al. the Adult ADHD Research Group. Efficacy and safety of dexmethylphenidate extended-release capsules in adults with attention-deficit/hyperactivity disorder. Biol Psychiatry 2007;61:1380-7
38. Willcutt EG, Doyle AE, Nigg JT, et al. Validity of the executive function theory of attention-deficit/hyperactivity disorder: A meta-analytic review. Biol Psychiatry 2005;57:1336-46
39. Loo SK, Humphrey LA, Tapio T, et al. Executive functioning among Finnish adolescents with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 2007;46:1594-604
40. Nigg JT, Willcutt EG, Doyle AE, et al. Causal heterogeneity in attention-deficit/hyperactivity disorder: do we need neuropsychologically impaired subtypes? Biol Psychiatry 2005;57:1224-30
41. Biederman J, Petty C, Fried R, et al. Impact of psychometrically defined deficits of executive functioning in adults with attention deficit hyperactivity disorder. Am J Psychiatry 2006;163:1730-8
42. Fallu A, Richard C, Prinzo R, et al. Does OROS-methylphenidate improve core symptoms and deficits in executive function? Results of an open-label trial in adults with attention deficit hyperactivity disorder. Curr Med Res Opin 2006;22:2557-66
43. Biederman J, Seidman LJ, Petty CR, et al. Effects of stimulant medication on neuropsychological functioning in young adults with attention-deficit/hyperactivity disorder. J Clin Psychiatry 2008;69:1150-6
44. Brown TE, Brams M, Gao J, et al. Open-label administration of lisdexamfetamine dimesylate improves executive function impairments and symptoms of attention-deficit/hyperactivity disorder in adults. Postgrad Med 2010;122:7-17
45. Spencer TJ, Adler LA, Weisler RH, et al. Triple-bead mixed amphetamine salts (SPD465), a novel, enhanced extended-release amphetamine formulation for the treatment of adults with ADHD: a randomized, double-blind, multicenter, placebo-controlled study. J Clin Psychiatry 2008;69:1437-48
46. Brown TE, Holdnack J, Saylor K, et al. Effect of atomoxetine on executive function impairments in adults with ADHD. J Atten Disord 2011;15:130-8
47. Findling RL, Adeyi B, Chen G, et al. Clinical response and symptomatic remission in children treated with lisdexamfetamine dimesylate for attention-deficit/hyperactivity disorder. CNS Spectrums 2010;15:559-68