Lisdexamfetamine Dimesylate in Adults With Attention-Deficit/Hyperactivity Disorder Who Report Clinically Significant Impairment in Executive Function: Results From a Randomized, Double-Blind, Placebo-Controlled Study

Lenard A. Adler, MD; Bryan Dirks, MD; Patrick F. Deas, BS; Aparna Raychaudhuri, PhD; Matthew R. Dauphin, MS; Robert A. Lasser, MD; and Richard H. Weisler, MD

ABSTRACT

Objective: Behavioral rating scales that assess impairments in executive function commonly associated with attention-deficit/hyperactivity disorder (ADHD) may offer advantages over neuropsychological testing. The primary objective of this study was to evaluate the efficacy of lisdexamfetamine dimesylate for executive function deficits in adults with ADHD and clinically significant executive function impairment using self-reported Behavior Rating Inventory of Executive Function-Adult version (BRIEF-A) assessments.

Method: This randomized double-blind study, conducted between May 2010 and November 2010, screened at least 1 participant at 35 of 39 registered US clinical research sites. Adults (aged 18–55 years) with a primary ADHD diagnosis (meeting full *DSM-IV-TR* criteria) and executive function deficits (assessed by baseline BRIEF-A Global Executive Composite [GEC] T-scores of at least 65) were randomized to treatment with optimized lisdexamfetamine dimesylate (30 mg/d, 50 mg/d, or 70 mg/d; n = 80) or placebo (n = 81) during a 10-week double-blind treatment period. Outcome measures included the BRIEF-A scales (GEC, index, and clinical subscales).

Results: At week 10 or at early termination, lisdexamfetamine dimesylate was associated with significantly greater reductions from baseline in mean BRIEF-A GEC T-scores than placebo (effect size, 0.74; $P < .0001$) and significantly greater reductions from baseline in mean T-scores for both BRIEF-A index scales (Behavioral Regulation Index and Metacognition Index) and all 9 clinical subscales ($P \leq .0056$ for all). At week 10 or at early termination, mean T-scores for BRIEF-A indexes and clinical subscales were below levels of clinically significant executive function deficits (ie, < 65) with lisdexamfetamine dimesylate treatment. The mean (SD) GEC T-score was 57.2 (14.11) for the lisdexamfetamine dimesylate group and 68.3 (17.12) for the placebo group. The safety profile of lisdexamfetamine dimesylate was consistent with other long-acting psychostimulants.

Conclusion: Among adults with ADHD and clinically significant executive function deficits, lisdexamfetamine dimesylate was associated with significant improvements in self-reported executive function ratings.

Trial Registration: ClinicalTrials.gov identifier: NCT01101022

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Corresponding author: *Lenard A. Adler, MD, New York University School of Medicine, 650 First Ave, 7th Fl, New York, NY 10016 (Lenard.Adler@nyumc.org).*

Attention-deficit/hyperactivity disorder (ADHD) is now recognized to frequently persist into adulthood. A meta-analysis[1] of follow-up studies indicated that approximately two-thirds of children with ADHD remain affected as adults, as defined by full or partial diagnostic status. Overall, approximately 4.4% of adults in the United States have ADHD.[2] Impairments associated with adult ADHD are far-reaching,[3–5] and, although the manifestations of ADHD symptoms may change from childhood through adulthood, they should not be considered any less impactful on the daily lives of patients.[4,6] In fact, the requirements of adult life, such as reliance on self-direction and transition from care receiver to caregiver or provider, may result in increased effects of ADHD impairments on daily life.

Executive function, a collection of cognitive processes, affects goal-directed behavior, plays a role in self-regulation, and controls emotional functioning.[7,8] Executive function is often defined as an array of cognitive processes. These processes allow self-regulation and affect the ability to prioritize and plan multiple tasks, maintain attention and focus, and regulate emotional responses.[9–11] The processes that comprise behavioral executive function and are housed in the active working memory include anticipating, planning and organizing, task shifting, organization by task sequencing, prioritizing, process monitoring, and inhibiting distractions and interference.[7] Moreover, both Barkley[11] and Brown[9] propose that executive dysfunction is a core feature of ADHD. Barkley's behavioral inhibition model[11] defines 4 domains of executive function: nonverbal working memory, verbal working memory (internalization of speech), emotional self-regulation, and planning and problem-solving (reconstitution).

Although not all theories of ADHD posit a primary role of executive function deficits, an association between ADHD and executive dysfunction has been consistently demonstrated.[9,10,12] For example, Kessler and colleagues[13] suggested that executive function impairments were consistent, specific predictors of *DSM-IV*[14] adult ADHD, despite their lack of inclusion in the manual. These authors go further to suggest that the number of executive function symptoms should be increased in the upcoming *DSM-5*, as they are separate and distinct ADHD symptom factors. Moreover, a review[15] that evaluated ADHD diagnostic criteria also proposed that symptoms and characteristics of adult ADHD warrant inclusion of a subtype of executive function deficit in ADHD in the *DSM-5* criteria. Whereas some symptoms of ADHD may decline with

Clinical Points

- Evidence suggests that impairments, beyond core symptoms, may occur in adults with attention-deficit/hyperactivity disorder (ADHD) and may contribute to the negative impact of ADHD.
- Treatment of adults with ADHD and executive function deficits with lisdexamfetamine dimesylate over 4 weeks was efficacious compared with placebo in improving ADHD symptoms, executive behavior dysfunction, and global illness severity.
- Use of multiple outcome assessments may enhance clinicians' ability to monitor treatment progress, manage patients more effectively, and achieve patient-relevant improvement.

age, symptoms of executive function deficit remain largely stable.[16,17] Executive function deficits have been associated with reductions in occupational and educational outcomes and in some measures of psychosocial functioning.[18,19] Preliminary data suggest that improvement in executive function may correlate with improvements in quality of life.[20] Swanson and colleagues[21] noted differential effects of psychostimulants on core ADHD symptoms or on cognition and executive function deficits in their recent review of study findings in children with ADHD. Although these agents are very effective for core ADHD symptoms, their beneficial effects on cognition and executive function deficits vary depending on the specific cognitive task or executive function domain being examined. These authors found that, in general, activity-based tasks tend to show greater improvement with psychostimulant therapy than learning or problem-solving tasks.[21]

Measures of executive function are broadly categorized as either neuropsychological tests or behavioral rating scales.[7] Each form of testing may identify discrete subpopulations at risk for distinct sets of functional impairments.[22] However, as reviewed by Barkley et al,[23] neuropsychological executive function testing has limitations, including reliance on multiple areas of cognition and IQ, low ecological validity, and questionable relationship with real-world functioning. Studies[18,19,24,25] using neuropsychological testing to assess executive function suggest the presence of deficits in approximately 25%–50% of patients with ADHD. One study by Biederman and colleagues,[18] using a binary measure of executive function deficits (defined as a score of 1.5 standard deviations [SDs] from the mean and impairment on 2 or more of the 8 neurophysiologic variables tested), demonstrated that 31% of participants with ADHD had executive function deficits. These findings suggest that executive function deficits should be viewed, at least to some degree, as a cognitive comorbidity with ADHD that affects aspects of adaptive behavior and not just as an ADHD diagnostic indicator.[18]

Behavioral rating scales may be advantageous because they rely on ratings of daily, complex tasks in real-world, cross-situational settings over an extended time.[7,9,26] The models formulated by Barkley[11] and Brown[9] for executive function deficits in ADHD were consistent with rating scales that identified executive function deficits in most patients with ADHD.[8,25,27] Behavioral ratings of executive function may also be better predictors of impairment in major life activities and occupational functioning than neuropsychological testing.[23] The Behavior Rating Inventory of Executive Function-Adult version (BRIEF-A)[28] is a validated self-report measure of executive function, with T-scores of 65 and greater indicating clinically significant executive function deficits. Internal consistency of the BRIEF-A is moderate to high, with Cronbach α coefficients ranging from 0.73 to 0.96 for clinical scales and indexes.[28] In general, there is a lack of interrater concordance or agreement between self-reported and informant-reported measures, especially for rating executive function, as indicated by low correlations. On the BRIEF-A, the overall correlations between the self-report and informant-report forms were measured as moderate in a mixed clinical/healthy adult population sample.[28] Overall, the BRIEF-A demonstrated significant correlations with other executive function behavioral scales, including the Frontal Systems Behavior Scale, the Dysexecutive Questionnaire, and the Cognitive Failures Questionnaire, as well as behavioral measures of executive dysfunction in depression, including the Clinical Assessment of Depression and the Beck Depression Inventory II.[28]

In a study by Biederman et al[29] using the aforementioned criteria to assess executive function,[18] investigators reported a comparable proportion of participants (35 of 87; 40.2%) with executive function deficits. However, when they used the BRIEF-A, defining executive function deficit as a T-score of >65 on 2 or more subscales, a much higher proportion of participants met criteria (81 of 87; 93.1%). The Biederman data[29] were consistent with another study[30] that used a behavioral rating scale to assess executive function deficits and also reported a high prevalence (91.5%) in participants with ADHD. Moreover, one adult study[31] that evaluated correlations between ADHD symptoms and impairments in executive function and neurophysiologic tests reported that ADHD symptoms were more severe in adults with executive function deficits versus those without. Overall, data also suggested that various neurophysiologic tests correlated, although differently, with BRIEF-A subscales but not the emotional control subscale, which tracked differently in comparison with other executive function symptoms and neurophysiologic tests.

Lisdexamfetamine dimesylate, a long-acting dextroamphetamine prodrug, is indicated for ADHD in children (aged 6 to 12 years), adolescents (aged 13 to 17 years), and adults.[32] In a randomized, controlled trial[33] in adults, lisdexamfetamine dimesylate demonstrated efficacy in reducing core ADHD symptoms, as assessed by the ADHD Rating Scale IV (ADHD-RS-IV) with adult prompts,[34,35] and was associated with improvement in clinician ratings of global improvement on the Clinical Global Impressions-Improvement scale (CGI-I).[36] During the 4-week open-label phase of an adult workplace environment study[30] of adults with ADHD, lisdexamfetamine dimesylate was associated with significant

improvement from baseline in executive function, as measured by the validated, self-reported Brown Attention-Deficit Disorder Scale (BADDS).[37,38] These results required further study to rule out the contribution of expectancy bias on the part of raters or participants to these observed results.

The primary objective of the present double-blind, placebo-controlled study was to evaluate the efficacy of lisdexamfetamine dimesylate for executive function deficits in adults with ADHD who report clinically significant impairment in executive function behaviors at baseline using self-reported BRIEF-A scores. Clinician-rated ADHD symptom scores, assessed using total scores on the ADHD-RS-IV with adult prompts, and measures of global illness improvement, assessed using the CGI-I, are also reported.

METHOD

This randomized, double-blind, multicenter, placebo-controlled study was conducted between May 2010 and November 2010 and screened at least 1 participant at 35 of 39 registered US clinical research sites, with 33 sites enrolling participants. The study protocol was approved by the institutional review board at each study site, and the study was conducted in accordance with the International Conference on Harmonisation Guideline for Good Clinical Practice E6.[39] Following detailed explanation of the study, all participants and informants provided written informed consent. The study was registered on ClinicalTrials.gov (identifier: NCT01101022).

Study Design

Participants underwent a screening and washout period lasting up to 4 weeks. At a baseline study visit (week 0), participants were randomized in a 1:1 ratio to receive lisdexamfetamine dimesylate or placebo. Medication, lisdexamfetamine dimesylate or matching placebo capsules, was to be taken upon awakening (7:00 AM). Following randomization, participants entered a 10-week double-blind treatment phase with weekly study visits. To protect the study blind, the Interactive Voice/Web Response System (Oracle/Phase Forward; Waltham, Massachusetts) was used to randomize participants and for treatment allocation.

During the 4-week dose-optimization period, treatment was initiated at 30 mg/d and titrated in 20-mg/wk increments to optimal dose (up to 70 mg/d). Titration was based on total score on the ADHD-RS-IV with adult prompts, CGI-I score, adverse events, and clinical judgment. An optimal dose was considered to be reached if a participant demonstrated ≥ 30% reduction from baseline in total score on the ADHD-RS-IV with adult prompts and a CGI-I rating of 1 or 2 (very much improved or much improved) in the context of acceptable tolerability. A single dose reduction was permitted during the dose-optimization period. Participants were continued at their optimal dose during the 6-week dose-maintenance period. No dose reductions were permitted during this period. The final visit of the dose-maintenance period occurred at week 10, and participants who did not complete the study were assessed at an early termination visit.

Participants

Adults aged 18–55 years who met full *DSM-IV-TR*[40] criteria for a primary diagnosis of ADHD were eligible. Participants were required to be in a close domicile relationship (eg, spouse or significant other) for ≥ 6 months prior to screening to ensure the availability of an informant who was willing to report on the participant's behavior and symptoms. Additional inclusion criteria included a baseline BRIEF-A Global Executive Composite (GEC) T-score ≥ 65, indicating clinically significant executive function impairment at baseline, and a baseline total score ≥ 28 on the ADHD-RS-IV with adult prompts.

Adults with comorbid psychiatric conditions that were controlled with a prohibited medication or were uncontrolled and associated with significant symptoms, including severe Axis I or II disorders, were excluded from the study. Other key exclusion criteria included cardiovascular disease, which may increase vulnerability to the sympathomimetic effects of a psychostimulant; a history of moderate to severe hypertension; ADHD that was well controlled on current ADHD therapy; and a history of failure to respond to an adequate course of amphetamine therapy.

Assessment Measures

The 75-item BRIEF-A can be administered via participant self-report or by informant report.[28] Items are scored as occurring never, sometimes, or often, on the basis of behavior in the 3 weeks prior to assessment. The items yield 9 clinical subscales, used to calculate 2 indexes: the Behavioral Regulation Index (BRI), which is the sum of the inhibit, shift, emotional control, and self-monitor subscales, and the Metacognition Index (MI), which is the sum of the initiate, working memory, plan/organize, task monitor, and organization of materials subscales. Summation of the BRI and MI indexes yields an overall summary score, the GEC. Raw scores are converted to T-scores, with normative populations having a mean of 50 and an SD of 10. T-scores of ≥ 65 are considered to represent clinically significant behavioral impairment in executive function.

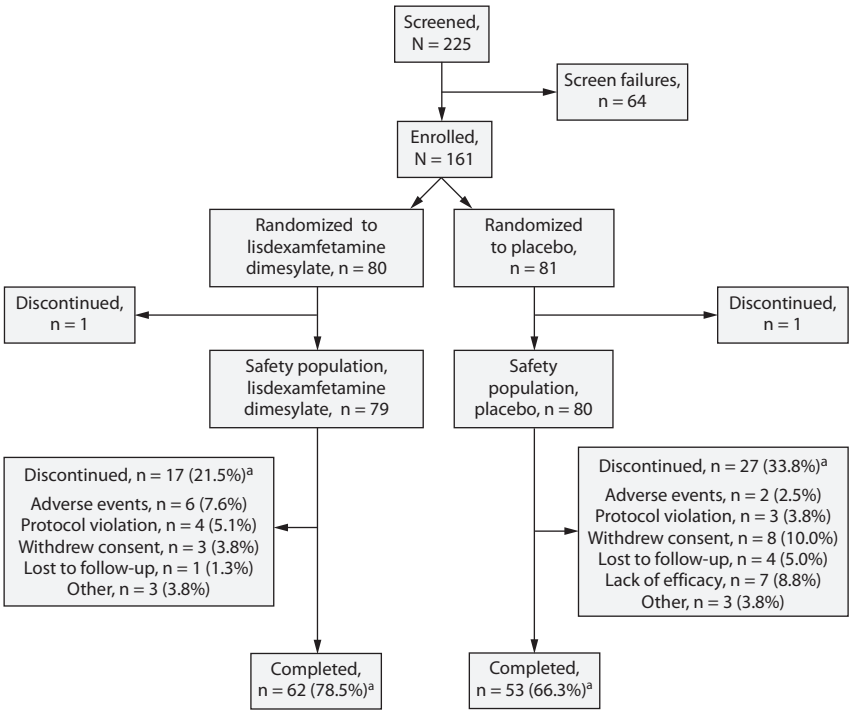
The present study was designed to assess the primary efficacy end point, which was change from baseline at week 10 or at early termination, for the self-reported BRIEF-A GEC T-score. The self-reported BRIEF-A was completed at screening; baseline; and weeks 4, 7, and 10 or at early termination. Secondary efficacy measures included the self-reported BRIEF-A subscales (BRI and MI) and the informant-reported BRIEF-A GEC and subscale T-scores. The informant-reported BRIEF-A was completed at baseline and weeks 4, 7, and 10 or at early termination. Results from informant-rated assessments will be published separately.

The ADHD-RS-IV with adult prompts (secondary efficacy measure) was administered at screening, baseline, weeks 1 through 4, and week 10 or at early termination. This 18-item, investigator-rated questionnaire assesses ADHD symptoms on the basis of *DSM-IV-TR* criteria. Total scores can range from 0 to 54, with individual items rated as 0 (no symptoms) to 3 (severe symptoms). At all postbaseline

visits, clinicians also rated participants' global improvement relative to baseline ADHD symptoms on the 7-point CGI-I (secondary efficacy measure), rated from 1 (very much improved) to 7 (very much worse).[36]

Safety was assessed by the collection of adverse events at all study visits. Events were coded using the *Medical Dictionary for Regulatory Activities* (MedDRA),[41] Version 11.1. Events beginning or increasing in severity on or after the date of the first dose of study medication and no later than 3 days after the last dose were considered treatment-emergent adverse events (TEAEs). Vital signs, including systolic and diastolic blood pressure and pulse, were also assessed at every study visit. Other safety assessments included physical examination, clinical laboratory evaluations, and electrocardiogram evaluations. Moreover, participant safety was monitored using responses to the investigator-rated Columbia-Suicide Severity Rating Scale[42] (C-SSRS).

Figure 1. Study Participant Disposition



[a]Percentages are based on the safety population.

Statistical Analysis

Efficacy was assessed in the full analysis set, defined as all participants who received ≥ 1 dose of study medication in the double-blind phase and had 1 postrandomization BRIEF-A assessment. Safety was assessed in the safety population, consisting of all participants who received ≥ 1 dose of study medication in the double-blind phase. The primary efficacy outcome was the BRIEF-A GEC T-score change from baseline at week 10 or at early termination; the primary efficacy analysis was performed using an analysis of covariance model, with treatment group as a factor and baseline GEC T-score as a covariate. Analyses were conducted using SAS software, version 9.1 or higher (SAS Institute Inc; Cary, North Carolina).

Secondary efficacy variables were analyzed in a prespecified, sequential order, such that an analysis was performed only if the prior analysis demonstrated significant differences between treatment groups. This "gatekeeping strategy" was intended to control for type 1 error. Of the secondary efficacy end points reported in the present article, the sequential testing order was total score on the ADHD-RS-IV with adult prompts, CGI-I score, self-reported BRIEF-A MI and BRI T-scores, and self-reported BRIEF-A subscale T-scores.

Most secondary efficacy variables were analyzed using an analysis of covariance model. The CGI-I scores were dichotomized with 1 (very much improved) and 2 (much improved) coded as improvement and the remaining items (3–7) as no improvement. The CGI-I scores were analyzed with χ^2 testing. Safety variables were summarized using descriptive statistics.

RESULTS

Participant Disposition and Demographics

Of the 161 adults enrolled, 80 were randomized to receive lisdexamfetamine dimesylate and 81 to receive placebo. The safety population included 79 participants from the lisdexamfetamine dimesylate group and 80 from the placebo group; the full analysis set included 79 participants in the lisdexamfetamine dimesylate group and 75 in the placebo group. Figure 1 summarizes participant disposition in the safety population. At baseline, all but 2 participants (1 in each treatment group) had BRIEF-A self-reported GEC T-scores ≥ 65. The inclusion of these participants in the study was considered a major protocol deviation.

Baseline and demographic characteristics of the treatment groups were generally similar (Table 1). The optimal daily dose among lisdexamfetamine dimesylate–treated participants was 30 mg for 16.5% of participants (n = 13), 50 mg for 38.0% of participants (n = 30), and 70 mg for 45.6% of participants (n = 36). The mean (SD) daily dose of lisdexamfetamine dimesylate received in the lisdexamfetamine dimesylate group during the dose-maintenance period was 56.9 (14.40) mg in this study population with significant executive dysfunction.

Efficacy

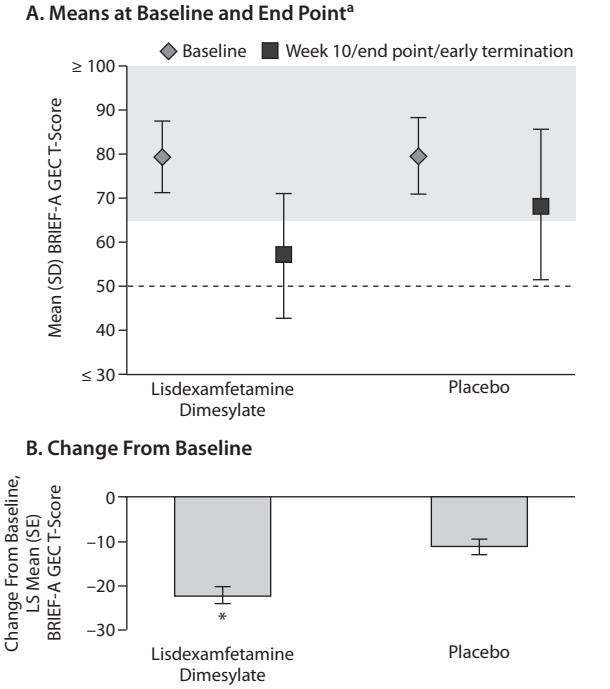
At week 10/early termination, participants receiving lisdexamfetamine dimesylate demonstrated significantly greater reductions from baseline in mean BRIEF-A GEC T-scores than those receiving placebo (Figure 2A and Table 2). The

Table 1. Demographic and Baseline Characteristics by Treatment Group (safety population) (N = 159)

Characteristic	Lisdexamfetamine Dimesylate (n = 79)	Placebo (n = 80)
Age, mean (SD), y	34.2 (10.58)	34.9 (11.02)
Sex, n (%)		
Male	40 (50.6)	43 (53.8)
Female	39 (49.4)	37 (46.3)
Ethnicity, n (%)		
Hispanic or Latino	4 (5.1)	8 (10.0)
Not Hispanic or Latino	75 (94.9)	72 (90.0)
Race, n (%)		
White	65 (82.3)	71 (88.8)
Black or African American	9 (11.4)	7 (8.8)
Asian	2 (2.5)	0 (0.0)
American Indian or Alaska Native	1 (1.3)	1 (1.3)
Other	2 (2.5)	1 (1.3)
Weight, mean (SD), kg	81.8 (16.77)	80.0 (17.62)
ADHD subtype, n (%)		
Inattention	13 (16.5)	16 (20.0)
Hyperactivity-impulsivity	0 (0.0)	1 (1.3)
Combined	66 (83.5)	63 (78.8)
Age at ADHD onset, mean (SD), y	5.4 (0.81)	5.3 (0.66)
Duration of ADHD, mean (SD), y	29.7 (10.51)	30.7 (11.02)
BRIEF-A T-score, mean (SD)		
Global executive composite	79.5 (8.01)	79.6 (8.99)
Behavioral regulation index	72.2 (9.92)	73.8 (11.07)
Metacognition index	81.1 (7.59)	80.2 (8.17)
ADHD-RS-IV with adult prompts, total score, mean (SD)	39.9 (7.37)	39.9 (6.79)

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, ADHD-RS-IV = ADHD Rating Scale-IV, BRIEF-A = Behavior Rating Inventory of Executive Function-Adult version, SD = standard deviation.

Figure 2. (A) Mean (SD) Self-Reported BRIEF-A GEC T-Score at Baseline and Week 10/End Point/Early Termination, and (B) Change From Baseline LS Mean (SE) Self-Reported BRIEF-A GEC T-Score at Week 10/End Point/Early Termination



[a]Shaded area represents range of T-scores considered to represent clinically significant impairments.
*$P < .0001$.
Abbreviations: BRIEF-A = Behavior Rating Inventory of Executive Function-Adult version, GEC = Global Executive Composite, LS = least-squares, SD = standard deviation, SE = standard error.

least-squares (LS) mean (standard error [SE]) change from baseline was greater with lisdexamfetamine dimesylate than placebo (Figure 2B and Table 2). The difference between lisdexamfetamine dimesylate and placebo in LS mean change from baseline at week 10/early termination was −11.2 (95% CI, −15.9 to −6.4; $P < .0001$). Lisdexamfetamine dimesylate was associated with an effect size of 0.74.

Because initial analyses in the prespecified sequential approach demonstrated significant differences between lisdexamfetamine dimesylate and placebo, analyses of the other self-reported BRIEF-A T-scores were performed. At baseline, median BRI T-scores in both the lisdexamfetamine dimesylate and placebo groups were 73.0, indicating that most participants exhibited clinically relevant dysfunction in the ability to regulate behavioral and emotional responses.[28] Least-squares mean (SE) BRI change from baseline at week 10/early termination was greater for lisdexamfetamine dimesylate versus placebo (see Table 2). At week 10/early termination, the difference between placebo and lisdexamfetamine dimesylate in LS mean change from baseline in BRI scores was −8.4 (95% CI, −12.7 to −4.0; $P = .0002$). At baseline, most participants also exhibited clinically relevant dysfunction in their ability to "cognitively manage attention and problem solving,"[28] as demonstrated by median MI T-scores of 81.0 (lisdexamfetamine dimesylate) and 79.0 (placebo). The LS mean (SE) MI change from baseline at week 10/early termination for lisdexamfetamine dimesylate versus placebo was greater (see Table 2). At week 10/early termination, the difference between lisdexamfetamine dimesylate and placebo in LS mean change in MI from baseline was −11.6 (95% CI, −16.3 to −7.0; $P < .0001$).

Baseline mean T-scores on all BRIEF-A self-reported scales, except emotional control in the lisdexamfetamine dimesylate group, were >65 (see Table 2). Compared with placebo, lisdexamfetamine dimesylate was associated with significantly greater improvements from baseline in all the measure's clinical subscales ($P \leq .0056$, based on difference in LS mean [95% CI] for all) (see Table 2). The mean (SD) GEC T-score at week 10/early termination was 57.2 (14.11) for lisdexamfetamine dimesylate, well below the threshold for significant clinical impairment, while for placebo it was 68.3 (17.12), which is above the threshold for significant clinical impairment. The median T-scores at week 10/early termination for participants treated with lisdexamfetamine dimesylate were below levels indicative of clinically significant executive function deficits on all scales (GEC: 56.0; indexes: 55.0 for BRI and 56.0 for MI) and subscales (ranged from 50.0 to 60.0), indicating that the majority of lisdexamfetamine dimesylate–treated participants were well below the threshold for significant clinical impairment. In the placebo group at week 10/early termination, the median GEC T-score was 70; only the emotional control subscale median value was ≤60, with the range of the remaining subscale median T-scores from 63 to 72, and the indexes from 65 to 70.

Table 2. BRIEF-A Index and Subscale T-Scores: Baseline vs Week 10/Early Termination and Change From Baseline (full analysis set) (N = 154)

	Lisdexamfetamine Dimesylate (n = 79)			Placebo (n = 75)			
Variable	Baseline, Mean (SD)	Week 10/Early Termination, Mean (SD)	Change From Baseline at Week 10/Early Termination, LS Mean (SE)	Baseline, Mean (SD)	Week 10/Early Termination, Mean (SD)	Change From Baseline at Week 10/Early Termination, LS Mean (SE)	Effect Size[a] (lisdexamfetamine dimesylate minus placebo)
Index T-scores							
Global executive composite	79.5 (8.01)	57.2 (14.11)	−22.3 (1.67)[b]	79.4 (8.68)	68.3 (17.12)	−11.1 (1.72)	0.74
Behavioral regulation index	72.2 (9.92)	54.9 (13.23)	−17.5 (1.54)[b]	73.6 (10.64)	64.1 (16.67)	−9.2 (1.58)	0.55
Metacognition index	81.1 (7.59)	58.0 (14.20)	−22.8 (1.63)[b]	79.9 (8.00)	69.0 (15.96)	−11.2 (1.67)	0.83
Subscale T-scores							
Inhibit	74.6 (8.36)	56.7 (13.64)	−17.8 (1.50)[c]	74.2 (10.23)	64.8 (15.37)	−9.5 (1.54)	0.63
Shift	71.9 (11.27)	56.5 (12.45)	−14.5 (1.46)[c]	69.1 (11.34)	62.3 (14.27)	−7.8 (1.50)	0.58
Emotional control	62.2 (11.26)	51.8 (11.43)	−10.9 (1.28)[c]	65.1 (11.56)	58.8 (15.09)	−5.7 (1.31)	0.34
Self-monitor	67.3 (11.77)	51.7 (12.95)	−16.6 (1.44)[c]	71.5 (11.72)	62.0 (14.92)	−8.4 (1.48)	0.44
Initiate	72.6 (8.89)	54.6 (12.18)	−17.9 (1.38)[c]	72.3 (9.72)	63.7 (13.45)	−8.6 (1.41)	0.72
Working memory	83.4 (7.34)	59.9 (14.74)	−23.2 (1.67)[c]	82.4 (8.94)	70.8 (15.64)	−11.9 (1.71)	0.77
Plan/organize	78.7 (8.51)	57.3 (13.54)	−20.8 (1.58)[c]	76.1 (9.19)	66.9 (15.66)	−9.9 (1.62)	0.84
Task monitor	78.2 (9.36)	57.9 (13.82)	−20.1 (1.64)[c]	77.7 (9.94)	67.0 (16.33)	−10.8 (1.68)	0.63
Organization of materials scale	71.6 (9.52)	55.0 (12.98)	−16.5 (1.26)[c]	70.9 (9.84)	63.4 (14.03)	−7.6 (1.30)	0.80

[a]Effect-size values favor lisdexamfetamine dimesylate vs placebo.
[b]$P \leq .0002$, based on difference (lisdexamfetamine dimesylate – placebo) in LS mean (95% CI) for each.
[c]$P \leq .0056$, based on difference (lisdexamfetamine dimesylate – placebo) in LS mean (95% CI) for each.
Abbreviations: BRIEF-A = Behavior Rating Inventory of Executive Function-Adult version, LS = least-squares, SD = standard deviation, SE = standard error.

At baseline, participants had a mean (SD) total score on the ADHD-RS-IV with adult prompts of 39.9 (7.37) for the lisdexamfetamine dimesylate group and 39.9 (6.83) for the placebo group in the full analysis set. At week 10/early termination, LS mean (SE) changes from baseline were −21.4 (1.35) for the lisdexamfetamine dimesylate group and −10.3 (1.38) for the placebo group ($P < .0001$; effect size, 0.94). Similar results were observed in the ADHD-RS-IV inattention and hyperactivity/impulsivity subscales. From mean (SD) baseline scores of 22.6 (3.50) and 22.5 (3.01), ADHD-RS-IV inattention subscale scores decreased by an LS mean (SE) of −12.2 (0.77) and −6.1 (0.79) for lisdexamfetamine dimesylate and placebo groups, respectively ($P < .0001$; effect size, 0.89). From mean (SD) baseline scores of 17.3 (5.19) and 17.4 (5.67), ADHD-RS-IV hyperactivity/impulsivity subscale scores decreased by an LS mean (SE) of −9.2 (0.64) and −4.2 (0.66) for lisdexamfetamine dimesylate and placebo groups, respectively ($P < .0001$; effect size, 0.85).

Compared with adults receiving placebo, a significantly greater proportion of participants receiving lisdexamfetamine dimesylate were rated as improved on the CGI-I beginning at week 1 and continuing through week 9 ($P \leq .0125$ for all weeks). At week 4, the end of dose optimization, 69.6% (55 of 79) of the participants taking lisdexamfetamine dimesylate were improved versus 29.3% (22 of 75) of the participants taking placebo. At week 10/early termination, 78.5% (62 of 79) of lisdexamfetamine dimesylate–treated adults were rated as improved, compared with 34.7% (26 of 75) of placebo-treated adults ($P < .0001$).

Safety

The proportion of participants who reported TEAEs in the lisdexamfetamine dimesylate and placebo groups was 78.5% (62 of 79) and 58.8% (47 of 80), respectively. Common TEAEs (≥ 5% in either group) are presented in Table 3. There were no deaths or serious adverse events during the trial. Most participants reported TEAEs that were mild or moderate in severity. Severe TEAEs were reported in 3 participants (3.8%) receiving lisdexamfetamine dimesylate (diarrhea, food poisoning, and insomnia in 1 participant each) and 3 participants (3.8%) receiving placebo (fall, radius fracture, skin laceration, and upper limb fracture in 1 participant, and migraine and mood swings each in 1 participant). Five of 79 participants (6.3%) who were randomized to receive

Table 3. Treatment-Emergent Adverse Event Incidence ≥ 5% in Either Treatment Group (safety population) (N = 159)

Adverse Event, Preferred Terminology (MedDRA Version 11.1)	Lisdexamfetamine Dimesylate Group (n = 79), n (%)	Placebo Group (n = 80), n (%)
Any event	62 (78.5)	47 (58.8)
Decreased appetite	26 (32.9)	5 (6.3)
Dry mouth	25 (31.6)	6 (7.5)
Headache	20 (25.3)	2 (2.5)
Feeling jittery	10 (12.7)	0 (0.0)
Insomnia	10 (12.7)	3 (3.8)
Initial insomnia	8 (10.1)	5 (6.3)
Irritability	8 (10.1)	3 (3.8)
Weight decreased	8 (10.1)	0 (0.0)
Diarrhea	6 (7.6)	2 (2.5)
Fatigue	6 (7.6)	3 (3.8)
Hyperhidrosis	5 (6.3)	0 (0.0)
Upper respiratory tract infection	5 (6.3)	1 (1.3)
Anorexia	4 (5.1)	0 (0.0)
Heart rate increased	4 (5.1)	2 (2.5)
Libido decreased	4 (5.1)	0 (0.0)
Nasopharyngitis	4 (5.1)	4 (5.0)
Nausea	2 (2.5)	5 (6.3)

Abbreviation: MedDRA = *Medical Dictionary for Regulatory Activities*.

lisdexamfetamine dimesylate discontinued as a result of the following TEAEs: rectal fissure, fatigue, irritability, and influenza, each reported by 1 participant, and decreased libido and erectile dysfunction reported by 1 participant. In the placebo group, 2 of 80 participants (2.5%) discontinued as a result of TEAEs: 1 reported irritability and agitation, and 1 reported an upper limb fracture.

Mean changes in vital signs from baseline at week 10/early termination were not clinically meaningful. In the lisdexamfetamine dimesylate and placebo groups at week 10/early termination, mean (SD) increases from baseline in systolic blood pressure were 2.6 (8.39) and 1.7 (9.22) mm Hg, respectively. Mean (SD) increases from baseline in diastolic blood pressure of 1.7 (7.60) and 1.5 (8.85) mm Hg were observed at week 10/early termination for the lisdexamfetamine dimesylate and placebo groups, respectively. Participants in the lisdexamfetamine dimesylate group demonstrated mean (SD) increases in pulse rate from baseline of 5.4 (10.79) bpm at week 10/early termination compared with 3.3 (8.35) bpm for the placebo group. No changes in mean laboratory parameters were of clinical concern. On the C-SSRS, 1 participant in the placebo group reported at week 10/end point/early termination a "wish to be dead," but this response was considered by the investigator not to constitute an adverse event, and the issue was resolved at the follow-up call. The investigator determined that the response was due to frustration with not improving. There were no other postscreening positive responses on the C-SSRS.

DISCUSSION

In this trial among adults with ADHD and significant executive function impairment at baseline, lisdexamfetamine dimesylate was associated with significant improvements versus placebo in all self-reported ratings of executive function domains. Moreover, at end point, most adults treated with lisdexamfetamine dimesylate in this study had median BRIEF-A GEC, index, and subscale T-scores below the level considered indicative of clinically significant impairment (ie, < 65). The effect of lisdexamfetamine dimesylate on BRIEF-A GEC T-scores was estimated to be moderate to large (effect size, 0.74),[43] with similar effects observed for most other BRIEF-A T-scores. Data suggested that, at week 10, the majority of lisdexamfetamine dimesylate participants, compared with placebo participants, were improved below the T-score cutoff (< 65) for clinically significant executive function deficits and approached normative T-scores. The association of lisdexamfetamine dimesylate treatment with improvements in executive function was consistent with findings of prior trials.[30,44] Study results from the present double-blind, placebo-controlled trial were consistent with those of a prior open-label pediatric lisdexamfetamine dimesylate study[44] that demonstrated efficacy in the management of ADHD symptoms and executive function deficits and of an open-label adult lisdexamfetamine dimesylate study[30] that demonstrated improvements on the BADDS. Moreover, in the previous trial in children,[44,45] lisdexamfetamine dimesylate demonstrated small but significant effects on emotional lability and the emotional control domain of the BRIEF. These effects were generally consistent with the results of the present trial. The interpretation of previous trials, however, was limited by their use of an open-label design, lack of comparator arms, use of different rating scales, and lack of inclusion criteria to ensure enrollment of only those participants demonstrating executive function impairment.

Studies of other ADHD treatments have shown mixed results regarding their effects on executive function. In a placebo-controlled study[29] of osmotic-release oral system methylphenidate, approximately 50% of those adults receiving active therapy continued to demonstrate impairment in executive function (as defined by ≥ 2 BRIEF-A scales with T-scores > 65). In an analysis of data[46] from a pair of longitudinal studies among adolescents and young adults with ADHD, psychostimulant therapy was associated with significantly improved performance on neuropsychological tests of sustained attention and verbal learning (vs no psychostimulant treatment; effect sizes were approximately 0.5). However, no significant difference was observed with psychostimulant therapy for working memory, interference control, set shifting, visuospatial organization, or processing speed.[46] In a recent, double-blind, placebo-controlled trial[47] of adults with ADHD, the nonstimulant atomoxetine was associated with significant improvement in executive function as assessed by BADDS total and cluster scores.

As in a previous trial of lisdexamfetamine dimesylate for the treatment of ADHD in adults,[33] significant improvements in ADHD symptoms were observed. The effect size observed in the present study pertaining to core ADHD symptoms (as measured by the total score on the ADHD-RS-IV with adult prompts) is consistent with prior trials of lisdexamfetamine dimesylate and other long-acting psychostimulants among adults with ADHD.[33,48] Moreover, the dose-optimization trial design of the current study may have underestimated the potential effect sizes as compared with fixed-dose trials since participants are not dose-titrated once they obtain minimal response criteria.[49]

Additionally, global assessment of improvement, as quantified by CGI-I ratings, indicated that lisdexamfetamine dimesylate was efficacious early in treatment; 69.6% of lisdexamfetamine dimesylate–treated participants (n = 55) were assessed as improved at the end of the dose-optimization period (week 4). Although the data gathered in this study do not allow in-depth assessment, the parallel temporal improvement in ADHD symptoms and executive function deficits, as well as global illness improvement, suggests that these assessments may be interrelated and that global improvement may be linked to more specific improvements in symptoms and executive function deficits.

Most participants reported TEAEs that were mild to moderate in severity and infrequently associated with treatment discontinuation. Consistent with the known effects of psychostimulants, vital-sign changes were generally small. No participant discontinued from the trial secondary to changes in pulse or blood pressure. Even though design features such as optimized dosing limit the ability to assess

the potential for dose effects on safety outcomes, overall, the observed safety profile of lisdexamfetamine dimesylate was similar to that seen in previous lisdexamfetamine dimesylate clinical trials among adults with ADHD[33,50,51] and was consistent with that of other long-acting psychostimulant formulations.[52,53]

The results of the present study should be viewed in light of several limitations. Adults with comorbid psychiatric disease and significant cardiovascular disease were excluded from the current study, potentially limiting the ability to generalize these results to the broader adult population with ADHD. Study limitations also included a predominantly white and non-Hispanic/non-Latino population, limiting extrapolation of the results to other races and ethnicities. Although optimized dosing may provide an advantage as a more clinically relevant approach to dosing, it limits the ability to assess the balance between beneficial and potentially limiting efficacy and safety effects. Study data may not be representative of adults with ADHD who have less significant executive function impairments (BRIEF-A GEC T-scores < 65) and/or who are less severely ill. Additionally, although behavioral ratings of executive function appear to be somehow predictive of future outcomes, these ratings of executive function are actually predictors of impairments in life activities, not of future outcomes.[23] However, the subjective nature of such ratings should be considered when interpreting data. The retrospective, self-reported assessment of executive function behaviors may result in inherent biases related to underestimation or overestimation of impairments. The relationship of self-reports to informant reports will be more closely examined in a subsequent report. In the current study, similar to previous work,[31] improvements in emotional control did not track as closely with other executive function domains or ADHD symptoms. This finding suggests that emotional control may have a unique relationship to other ADHD deficits, which may warrant further study. The short-term design of the present trial prevents characterization of the long-term effects of lisdexamfetamine dimesylate on executive function and whether these effects are associated with improvements in educational and occupational functioning, quality of life, and interpersonal relationships. Future trials should aim to examine the long-term effects of lisdexamfetamine dimesylate on executive function and associated outcomes.

Despite such limitations, the present trial demonstrated that lisdexamfetamine dimesylate treatment of adults with ADHD and clinically significant impairment in executive function is associated with significant improvements in self-reported executive function ratings, clinician ratings of core ADHD symptoms, and global ratings of improvement. In conjunction with prior data, this study supports the effectiveness of lisdexamfetamine dimesylate for the treatment of core symptoms of ADHD and associated executive function deficits in adults.

Drug names: atomoxetine (Strattera), lisdexamfetamine dimesylate (Vyvanse), osmotic-release oral system methylphenidate (Concerta).

Author affiliations: Departments of Psychiatry and Child and Adolescent Psychiatry, New York University School of Medicine, and Psychiatry Service, New York Veterans Affairs Harbor Healthcare System, New York, New York (Dr Adler); Clinical Development and Medical Affairs, Shire Development LLC, Wayne, Pennsylvania (Drs Dirks, Raychaudhuri, and Lasser and Messrs Deas and Dauphin); and Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, North Carolina, and Department of Psychiatry, University of North Carolina at Chapel Hill (Dr Weisler). Dr Lasser is currently employed by inVentiv Health Clinical, Princeton, New Jersey.

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