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Open-Label Administration of Lisdexamfetamine Dimesylate Improves Executive Function Impairments and Symptoms of Attention-Deficit/Hyperactivity Disorder in Adults

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Abstract

Introduction/Objective: Executive function (EF) impairment in attention-deficit/hyperactivity disorder (ADHD) may account for behavioral symptoms such as poor concentration, impaired working memory, problems in shifting among tasks, and prioritizing and planning complex sets of tasks or completing long-term projects at work or school. Poor self-regulation and control of emotional behaviors frequently are seen in patients with ADHD. This study assessed EF behaviors in adults with ADHD at baseline and after 4 weeks of treatment with lisdexamfetamine dimesylate (LDX). **Methods:** Executive function behavior was assessed using the Brown Attention-Deficit Disorder Scale (BADDS) during the 4-week open-label dose-optimization phase prior to a 2-period, randomized, double-blind, placebo-controlled crossover study of LDX (30–70 mg/day). The ADHD Rating Scale IV (ADHD-RS-IV) with adult prompts assessed ADHD symptoms. Change in EF behavioral symptoms was evaluated based on week 4 BADDS total and cluster scores; analyses of shifts from baseline among subjects with BADDS scores < 50, 50 to 59, 60 to 69, and ≥ 70; and scores less than or greater than baseline 90% confidence range (eg, reliably improved or worsened, respectively). Treatment-emergent adverse events (TEAEs) were described. **Results:** At week 4, BADDS total and cluster scores were reduced (ie, improved; all $P < 0.0001$ vs baseline [n = 127]). The ADHD-RS-IV with adult prompts scores also improved (all $P < 0.0001$ vs baseline). At week 4, 62.7% of subjects had a BADDS total score of < 50, and 78.9% were reliably improved; 1.4% were reliably worsened. Common TEAEs ($\geq 5\%$) during the dose-optimization phase 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%). **Conclusion:** Clinically optimized doses of LDX (30–70 mg/day) significantly improved EF behaviors in adults with ADHD. Treatment-emergent adverse events with LDX were consistent with those observed with long-term stimulant use.

Keywords: lisdexamfetamine dimesylate; LDX; Vyvanse; ADHD; executive function; Brown Attention-Deficit Disorder Scale

Introduction

Approximately 4.4% of the US adult population has attention-deficit/hyperactivity disorder (ADHD).[1] Impairments seen in patients with ADHD may arise not only from impaired attention or excess of activity, but also from developmental impairments of executive function (EF).[2,3] Theories of EF impairment in ADHD help account for behavioral symptoms such as poor concentration, impaired working memory, problems in shifting among tasks, and prioritizing and planning complex sets of tasks or completing long-term projects at work or school. Executive function impairments can

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also account for poor self-regulation and control of emotional behaviors frequently seen in patients with ADHD, evidenced by outbursts of impatience, frustration, and anger.[4] Executive function comprises a diverse set of cognitive processes that provide mechanisms for self-regulation, enabling individuals to prioritize, integrate, and regulate cognitive and emotional demands.[2,3,5] Brown contends that EF in adults can be conceptualized by 5 general domains: activation, focus, effort, emotion, and memory, each containing related cognitive functions.[2,6,7]

One approach to assessment of impaired EF in ADHD is use of neuropsychological testing.[8] Meta-analyses and literature reviews[8–11] have consistently noted impaired EF task performance among at least a subset of patients with ADHD using several neuropsychological tests. These reports[9,12] have demonstrated that ~30% to 50% of children and adults with ADHD exhibit psychometrically defined EF deficits. From this perspective, EF impairment may not be present in all ADHD cases. It is important, however, to note that the threshold used to define the presence or absence of EF impairments on neuropsychological tests is an important determinant of the proportion of subjects ultimately identified as impaired. In a study by Biederman et al,[9] which identified ~30% of subjects with EF deficits by neuropsychological test, impairment was defined as scores outside 1.5 standard deviation (SD) from the mean of the control group. In a recent study by Brown et al[13] examining neuropsychological test performance in subjects with ADHD and a high intelligence quotient, using a cutoff of 2 SD (defined as severe impairment) from normative mean results identified between 35% and 45% of subjects with impairments, whereas a cutoff of 1 SD (defined as significant impairment) identified between 75% and 87% of subjects with impairments.

Another perspective on the relationship between ADHD and EF contends that EF impairments, viewed over long-term, cross-situation behavior, are near-universal aspects of ADHD.[2,5,14] From this perspective, neuropsychological tests may provide a useful "snapshot" of more extreme EF impairments, but such controlled sets of tasks may be less sensitive to global EF impairment than tests assessing real-world daily task performance.[2,15,16] Neuropsychological tests assess 1 EF aspect at a time (ie, attention) while eliminating or controlling the potential interference by other cognitive processes. Although this approach is scientifically important and valid to identify the role of specific cognitive processes in EF impairments, it has limited utility in accurately assessing how EF impairments influence real-world behavior, where multiple functions are dynamically employed in integrated ways to complete complex tasks or dynamic psychosocial functions over long periods. Moreover, evidence[15,16] suggests that EF deficits may be subject to contextual conditions, such as level of distraction, working memory demands, and variable reward contingencies absent in the laboratory testing. Thus, neuropsychological tests may not capture the full extent of EF deficits in patients with ADHD.

To more accurately quantify EF behavioral impairments, self-reported questionnaires have been developed based on extensive clinical interviews of patients. The Brown Attention-Deficit Disorder Scales (BADDS)[7] are clinician-administered, patient self-report, validated, normed, adolescent and adult scales eliciting patient-reported information about EF symptoms during performance of routine tasks and social/emotional functioning. Unlike neuropsychological testing, BADDS may be used clinically to assess EF impairment and change in EF in response to therapy in adolescents and adults with ADHD. While BADDS does not directly measure core ADHD symptoms delineated in the *Diagnostic and Statistical Manual of Mental Disorders*, *Fourth Edition, Text Revision* (DSM-IV-TR), 1 investigation[17] demonstrated that using BADDS to identify patients with clinically significant EF impairment accurately predicted ADHD diagnosis in 84.4% of adult subjects, a rate similar to that seen with the ADHD Rating Scale IV (ADHD-RS-IV) (86.6%). This finding suggests that self-reported EF assessment can reliably identify patients with the disorder, and that more patients with ADHD exhibit EF impairments than has been estimated using neuropsychological tests. It should be noted that these alternative methodologies (ie, neuropsychological tests vs ecological self-report questionnaires) have been developed to measure different behavioral constructs of the same underlying complex cognitive processes subsumed under the umbrella term of EF.

Pharmacotherapy is an important treatment option for adults with ADHD. Guidelines for treatment of adults with ADHD have been published in Canada[18] and the United Kingdom.[19] However, in the United States, there are no recent, widely accepted, evidence-based guidelines that are adult-specific. Furthermore, there are few studies assessing effects of long-acting stimulants on EF behaviors in adults with ADHD.

Lisdexamfetamine dimesylate (LDX) is a long-acting prodrug stimulant indicated for ADHD in children aged 6 to 12 years and in adults in the United States.[20] Lisdexamfetamine dimesylate was effective in a randomized controlled trial of ADHD in adults[21] and in a laboratory Adult Workplace Environment (AWE) study.[22] Patterned after the laboratory

school protocol, the AWE simulates a structured, 14-hour adult workday.[22] Using the AWE, investigators found LDX yielded significant advantages over placebo, based on an objective measure of math performance (effortful task output) from 2 to 14 hours postdose.[22] Lisdexamfetamine dimesylate demonstrated a safety profile consistent with prior LDX studies in adults and children.[21,23,24] The objective of the current study was to assess the impact of LDX on EF and ADHD symptoms in adults with ADHD given open-label LDX over the 1-month dose-optimization phase of the previously reported AWE study.[22]

Materials and Methods

Study Overview

The full methodology of this study was previously reported.[22] This multicenter study began with an open-label, dose-optimization phase that was followed by a randomized, double-blind, placebo-controlled, 2-way crossover phase in a simulated AWE. The study was conducted from July 2008 to December 2008.[22] The study comprised 4 phases: screening and washout, open-label dose optimization (4 weeks), double-blind crossover (2 weeks; AWE sessions 1 and 2), and 7-day safety follow-up (Figure 1).[22] The primary efficacy measure in this study was the Permanent Product Measure of Performance (PERMP), derived from math tests given during 2 sequential Saturdays or Sundays during the double-blind phase of the trial, which has been described previously.[22] Data in the current analysis focus on secondary findings from the 4-week open-label phase during which subjects were titrated over the first 3 weeks to their optimal dose of 30 mg/day, 50 mg/day, or 70 mg/day, and followed for an additional week before randomization. The objective was to assess the impact of LDX on EF during the open-label dose-optimization phase of the investigation.[22]

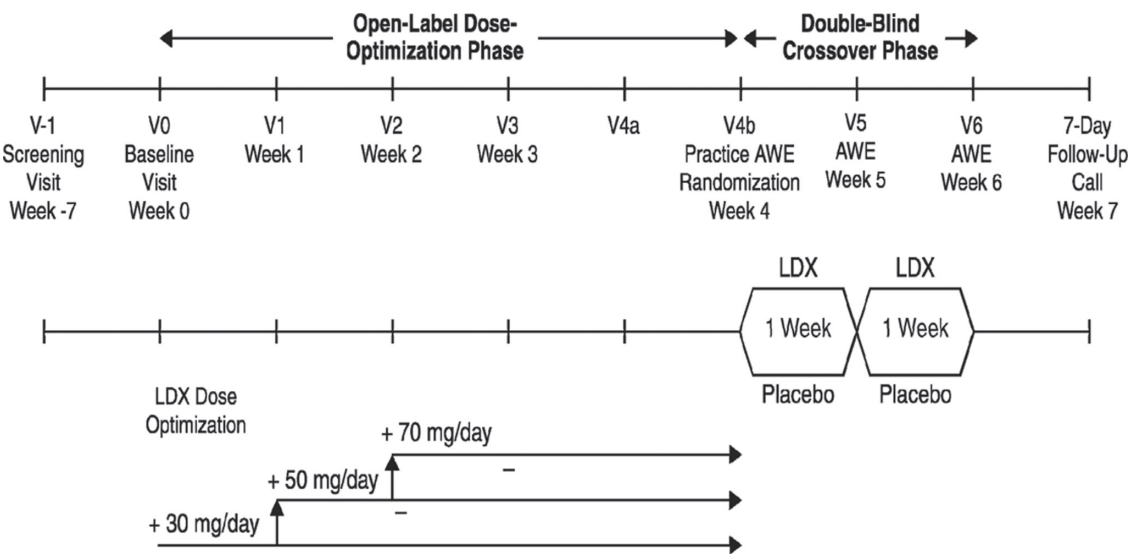
Participants

As described in detail previously,[22] study participants were otherwise healthy adults aged 18 to 55 years who satisfied DSM-IV-TR criteria for a primary diagnosis of ADHD.[25] The participants were also required to have a baseline ADHD-RS-IV with an adult prompts score of ≥ 28.[26,27] Exclusion criteria included comorbid psychiatric diagnoses with significant symptoms that would contraindicate treatment with psychostimulants or compromise assessments; concurrent chronic or acute, significant or unstable illness or medical condition; concurrent use of medications that affected the central nervous system or blood pressure (BP); and a current ADHD medication that was effective and well tolerated or nonresponse to prior amphetamine therapy.

Dose-Optimization Study Phase

In the dose-optimization phase, participants began with the lowest LDX dose (30 mg/day). Participants were assessed weekly for tolerability and satisfactory therapeutic response (≥ 30% reduction in ADHD-RS-IV with adult prompts and Clinical Global Impressions–Improvement [CGI-I] scores = 1 or 2). The dose could be increased by 20-mg/day increments

Figure 1. Study design is illustrated in the flow chart.[22]



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Abbreviations: AWE, Adult Workplace Environment study; LDX, lisdexamfetamine dimesylate.

weekly until satisfactory response was observed (maximum dose, 70 mg/day); the dose could also be decreased by 20 mg/day 1 time for lack of tolerability; if lack of tolerability persisted, the subject was discontinued. When the optimal response was obtained, that dose was continued for the rest of the study.

Efficacy Measures

Efficacy assessments administered during the dose-optimization phase included the ADHD-RS-IV with adult prompts and BADDS for adults.[22] The ADHD-RS-IV with adult prompts is an 18-item, investigator-rated scale that assesses current ADHD symptoms, and is more fully described elsewhere.[26,27] Participants were rated at baseline and weekly in the open-label, dose-optimization phase. The total scores and subscale scores for the open-label phase were also reported at the dose-optimization endpoint, defined as the last postbaseline value before the double-blind treatment.

The BADDS was administered at baseline and at the end of the dose-optimization period (week 4). 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 5 clusters of conceptually related symptoms of EF impairment related to ADHD, including[7]: Cluster 1–organizing and activating work with items such as "has difficulty getting organized and started" and "procrastinates excessively;" Cluster 2–sustaining attention and concentration with items such as "tries to pay attention but mind drifts" and "becomes sidetracked easily;" Cluster 3–sustaining energy and effort with items such as "does not work to potential" and "needs reminders of tasks;" Cluster 4–managing affective interference with items such as "is excessively impatient" and "has difficulty expressing anger;" and Cluster 5–using working memory and accessing recall with items such as "intends to do things but forgets" and "makes repeated restarts in writing."[7] BADDS total scores range from 0 to 120, with increasing scores indicating more severe impairment. BADDS total scores of > 50 suggest clinically meaningful impairment in EF and accurately discriminate between normal and ADHD populations. Based on the findings that a score of < 40 indicated that ADHD was not likely and a score of ≥ 55 indicated that impairment was highly likely, a total score of 50 was considered the clinical cutoff in adults for clinically meaningful impairment.[7]

Safety Assessments

Safety assessments used to evaluate LDX safety and tolerability during the study included spontaneously reported treatment-emergent adverse events (TEAEs), physical examination (at screening, baseline, and end-of-study visit), vital signs, weight, and electrocardiogram (at screening, baseline, each crossover week, and end-of-study visit). Treatment-emergent adverse event frequency and severity during the dose-optimization phase were analyzed in the safety population, which included all enrolled subjects who received at least 1 dose of study medication. For the current analysis, TEAEs reported during the dose-optimization phase are described; detailed safety analyses have been previously reported.[22] Treatment-emergent adverse events (referring to events with onset after the first date of treatment, and no later than 3 days following termination of treatment) were recorded separately for the dose-optimization and the double-blind crossover phases of the study. Treatment-emergent adverse events that continued uninterrupted from the dose-optimization to the crossover phase without a change in severity were counted only in the dose-optimization phase category. Treatment-emergent adverse events with a change in severity across phases or that resolved and then restarted in the crossover phase were counted both in the dose-optimization and crossover arms. Treatment-emergent adverse events for which a missing or incomplete start date made it impossible to determine in which phase of the study they started were counted as starting in the dose-optimization phase. Treatment-emergent adverse events were reported as number and percentage of subjects according to system-organ class, preferred term, treatment group, and by last dose received at AE onset. Adverse events were collected at all visits by soliciting subject report with nonleading questions and were coded using the *Medical Dictionary for Regulatory Activities* (MedDRA version 10).

Statistical Analysis

The ADHD-RS-IV with adult prompts total and subscale scores and BADDS were analyzed using the paired *t* test based on data derived from the enrolled efficacy population, defined as all subjects who received at least 1 dose of LDX during the dose-optimization phase and who had at least 1 postbaseline efficacy assessment. For BADDS score analysis, the proportion of subjects who obtained a meaningful level of improvement from their baseline score to the end of open-label dose optimization was evaluated by using the

in-treatment confidence range based on baseline BADDS scores.[7] BADDS total scores below or above the BADDS 90% confidence range were considered reliably improved or reliably worsened, respectively; scores within the 90% confidence range were considered not reliably different from baseline. To further characterize the clinical significance of BADDS EF assessments, BADDS total scores at baseline and week 4 were classified into 4 ranges based on published normative data; an analysis of shift from baseline was also performed.[7] BADDS total score changes from baseline were classified as reliably worsened, unchanged, or, if improved, into 1 of 4 improvement categories. These improvement categories, recommended by Brown[7] to monitor treatment progress, were < 50 (not clinically impaired; optimal); 50 to 59 (very favorable); 60 to 69 (favorable); and ≥ 70 (positive but insufficient). BADDS total scores at baseline were also categorized into 4 ranges: < 50 (not clinically impaired); 50 to 59; 60 to 69; and ≥ 70 (poor).

Results

Subject Demographics

A summary of the demographic and baseline characteristics in the safety population (N = 142) has been previously reported, along with primary efficacy results and safety results.[22] Briefly, subjects had a mean age (SD) of 30.5 (10.70) years, had a mean (SD) weight of 178.1 (37.14) lb, and were predominantly male (62%) and white (89.4%). The majority of subjects were diagnosed with the combined ADHD subtype (69%); at baseline, mean (SD) ADHD-RS-IV with adult prompts total score was 37.0 (5.61). During the open-label phase, a total of 15 subjects discontinued the study, because of AEs (n = 4), refusal of further participation in the study (n = 5), loss to follow-up (n = 2), and other reasons (n = 4), yielding 127 evaluable subjects.

Efficacy

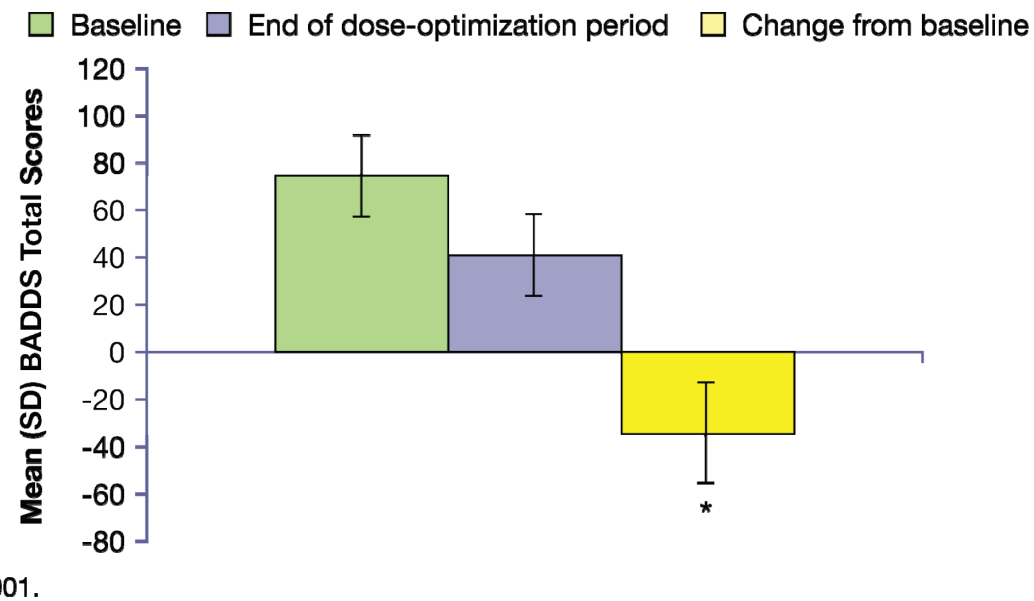
ADHD-RS-IV with Adult Prompts

In the open-label dose-optimization phase, LDX treatment was associated with statistically significant decreases from baseline in ADHD-RS-IV with adult prompts total scores and subscale scores (inattention and hyperactivity/impulsivity) at each week 1 through 4 ($P < 0.0001$). At dose-optimization endpoint, the mean (SD) change from baseline ADHD-RS-IV with adult prompts total score for all LDX dose levels combined was –21.4 (7.31) ($P < 0.0001$); for the inattention and hyperactivity/impulsivity subscales, mean (SD) changes from baseline were –11.6 (4.33) and –9.8 (4.38), respectively (both $P < 0.0001$).

BADDS Total and Cluster Scores

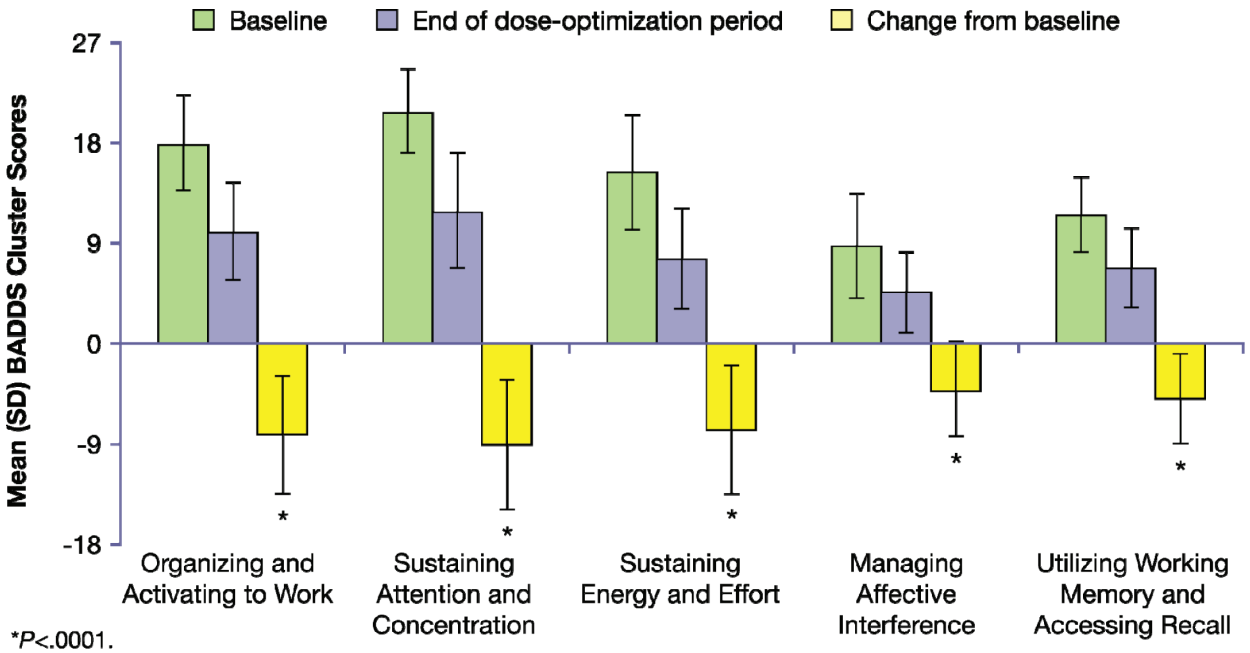
As illustrated in Figure 2, mean (SD) BADDS total score (all LDX doses combined) decreased from 74.3 (17.05) at baseline to 40.9 (17.12) at week 4; mean (SD) change in total score from baseline for all LDX doses was –34.1 (20.99) ($P < 0.0001$). There was also significant ($P < 0.0001$) improvement in each of the 5 BADDS clusters (Figure 3). Improvements from baseline at week 4 were seen in the

Figure 2. BADDS total score improved with LDX.



The total maximum score for all clusters is 120.
Abbreviations: BADDS, Brown Attention-Deficit Disorder Scale; SD, standard deviation.

Figure 3. BADDS cluster scores improved with LDX.



Each item is scored from 0 to 3. Clusters 1, 2, and 3 have 9 items each (maximum score of 27 for each); Cluster 4 has 7 items (maximum score of 21); and Cluster 5 has 6 items (maximum score of 18). The total maximum score for all clusters is 120.[7]
Abbreviations: BADDS, Brown Attention-Deficit Disorder Scale; SD, standard deviation.

mean (SD) change from baseline scores for the organizing and activating to work cluster and the sustaining attention and concentration cluster (−8.1 [5.24] and −9.1 [5.74], respectively). Mean (SD) changes for sustaining energy and effort, managing affective interference, and utilizing working memory and accessing recall were −7.8 (5.69), −4.2 (4.23), and −4.9 (4.04), respectively, also indicating significant improvements in these clusters.

Categorical BADDS Scores

At baseline, 12 subjects had scores of < 50, 17 had scores of 50 to 59, 28 had scores of 60 to 69, and 85 subjects had scores of ≥ 70. At dose-optimization phase week 4, there was a consistent shift toward lower ranges (eg, improvement) (Table 1A). As shown in Table 1A, 89 subjects had scores of < 50, whereas only 10 (7.0%) had scores of ≥ 70; 15 had missing postdose measurements.

Reliable Change in BADDS Score

For each subject, 90% in-treatment confidence ranges were determined based on published guidelines for each baseline BADDS total score. These confidence ranges help to protect against distortions in treatment effects variability caused by regression to the mean or by variability caused by imperfect reliability of the measure. Of the 142 subjects in the analysis population, 112 (78.9%) were considered to be reliably improved, 13 (9.2%) subjects were considered not reliably different, and 2 (1.4%) subjects were reliably worsened (Table 1B). Data were missing for the remaining 15 (10.6%) subjects who discontinued prior to the end of the dose-optimization period and for whom week 4 BADDS total scores were not available.

Frequency and nature of shifts from baseline BADDS categories according to reliable change were also determined. Among the 12 subjects who scored < 50 at baseline, 8 of 10 with week 4 BADDS measurements showed additional improvement that dictated inclusion in the reliable improvement category (Figure 4). For 17 subjects who scored 50 to 59 at baseline, 9 of 14 with week 4 BADDS measurements

Table 1A. Percentages of Subjects with BADDS Total Scores in Specific Ranges at Baseline and with LDX at Week 4

BADDS Total Score Categories	Baseline		Week 4 Dose-Optimization Endpoint	
	Frequency, n N = 142	Subjects, %	Frequency, n Total (N = 142)[a]	Subjects, %
< 50[b]	12	8.5	89	62.7
50–59	17	12.0	21	14.8
60–69	28	19.7	7	4.9
≥ 70	85	59.9	10	7.0

[a]15 subjects had missing BADDS scores at week 4 dose-optimization endpoint.
[b]Scores < 50 were considered not clinically significant.

Table 1B. Reliable Change in BADDS Total Scores

Category of BADDS Total Score	Total (N = 142)	
	Confidence Range	Subjects, %
Missing		15 (10.6)
Reliably Improved	< 90% confidence range	112 (78.9)
Not Reliably Different	Within 90% confidence range	13 (9.2)
Reliably Worsened	> 90% confidence range	2 (1.4)

showed reliable improvement and a shift in score category to < 50. For 28 subjects who scored 60 to 69 at baseline, 20 of 24 with week 4 BADDS measurements showed reliable improvement, with 19 scoring < 50 and 1 scoring 50 to 59; 2 subjects scored reliably worse at week 4. For 85 subjects who scored ≥ 70 at baseline, 75 of 79 with week 4 BADDS measurements showed reliable improvement, with 49 scoring < 50, 16 scoring 50 to 59, and 6 scoring 60 to 69, with 4 subjects improving within the same category (≥ 70) (Figure 4).

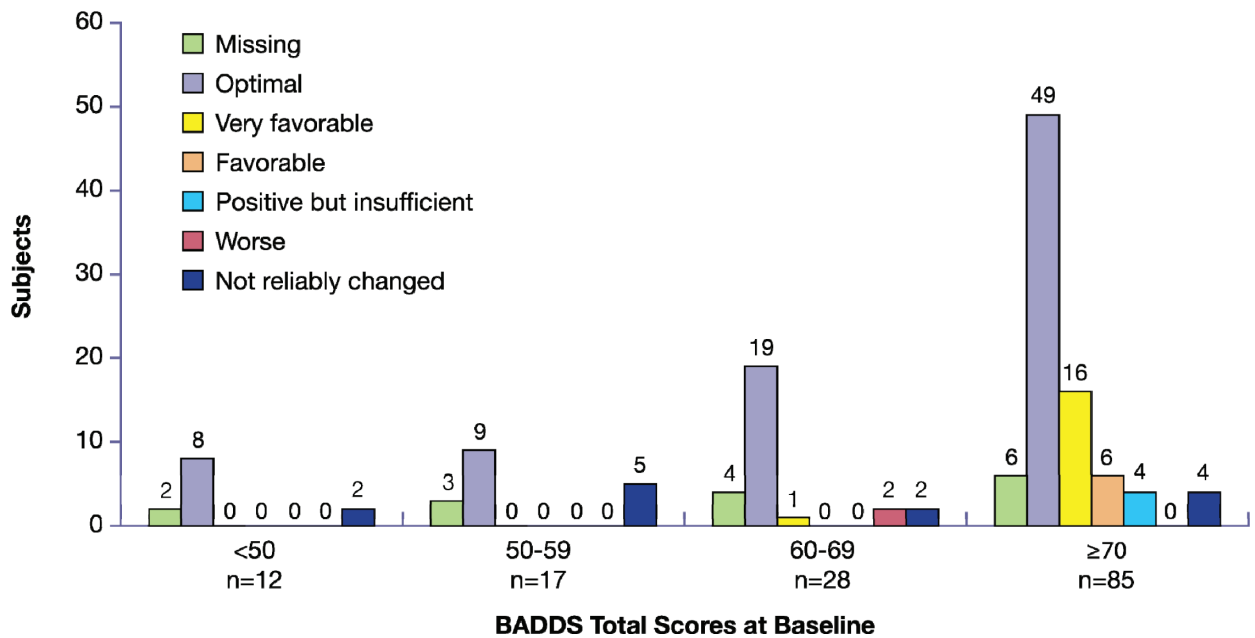
Safety

During the dose-optimization phase, TEAEs reported by ≥ 5% for all LDX doses combined 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%) (Table 2). Treatment-emergent adverse events were also reported by dose (Table 2). Treatment-emergent adverse events were reported according to the dose at which the TEAE started, deteriorated, or restarted > 1 day after it had resolved. The majority of TEAEs were mild or moderate in intensity. Four subjects had severe TEAEs while receiving LDX in the dose-optimization phase; 2 of these (insomnia and initial insomnia) were considered by the investigator to be related to study medication, whereas 2 (headache and bronchial infection) were considered unrelated to study medication. No serious AEs or deaths were reported, and 4 subjects discontinued during the dose-optimization phase because of AEs. Mean (SD) vital sign changes at dose-optimization endpoint included: –0.3 (9.46) mm Hg for systolic BP; –0.2 (6.94) mm Hg for diastolic BP; 3.2 (11.55) bpm for pulse; and –4.04 (4.27) lb for weight.

Discussion

Lisdexamfetamine dimesylate treatment was associated with improvement in EF compared with baseline as measured by the BADDS total score and each of the 5 cluster scores. Approximately 79% of subjects were considered to have shown reliable EF improvement by the end of the 4-week dose-optimization period, as evidenced by a BADDS total score that fell below the baseline 90% confidence range. The majority of subjects also showed DSM-IV–defined ADHD symptom improvement at week 4 with LDX treatment, as measured by the ADHD-RS-IV with adult prompts total and subscale scores. These improvements were observed at week 1 and continued throughout the 4 weeks of assessments. Mean LDX-mediated decreases in

Figure 4. This figure illustrates BADDS shift analysis at endpoint.



Abbreviation: BADDS, Brown Attention-Deficit Disorder Scale.

Table 2. TEAEs During the Dose-Optimization Phase that Occurred in ≥ 5% of Subjects in the Safety Population (n = 142)

Preferred Terminology (MedDRA; Version 10.0)	LDX Dose at Onset of Event, n (%)			
	30 mg/day	50 mg/day	70 mg/day	All Doses
	n = 142	n = 119	n = 54	n = 142
Any TEAE	91 (64.1)	50 (42.0)	27 (50.0)	113 (79.6)
Anxiety	7 (4.9)	1 (0.8)	0	8 (5.6)
Decreased appetite	46 (32.4)	5 (4.2)	1 (1.9)	52 (36.6)
Dry mouth	33 (23.2)	10 (8.4)	1 (1.9)	43 (30.3)
Feeling jittery	7 (4.9)	1 (0.8)	0	8 (5.6)
Headache	17 (12.0)	10 (8.4)	2 (3.7)	28 (19.7)
Insomnia	16 (11.3)	10 (8.4)	3 (5.6)	26 (18.3)
Irritability	8 (5.6)	2 (1.7)	3 (5.6)	12 (8.5)
Nausea	9 (6.3)	1 (0.8)	1 (1.9)	11 (7.7)
Upper respiratory tract infection	4 (2.8)	5 (4.2)	5 (9.3)	14 (9.9)

Abbreviations: LDX, lisdexamfetamine dimesylate; TEAE, treatment-emergent adverse event.

ADHD-RS-IV with adult prompts scores at the week 4 endpoint were below ADHD symptom threshold (≤ 18), considered a reasonable criterion for excellent response or symptomatic remission.[28,29]

With respect to the impact of LDX on ADHD symptoms, the current results are consistent with findings in adult subjects both from other trials of LDX[21,30] and from trials with other long-acting stimulant medications.[31–36] An advantage over placebo with LDX similar to that seen currently was observed in a large, randomized, double-blind, placebo-controlled, 4-week trial of LDX conducted in 420 adults.[21] In that short-term trial, there was improvement in ADHD-RS-IV with adult prompts scores for each LDX dose (30, 50, and 70 mg/day) versus placebo, and the benefit was seen as early as week 1.[21] In that trial, mean (SD) changes from baseline at endpoint with LDX were similar in magnitude to that seen currently (−21.4 [7.31]), ranging from −16.2 (1.1) to −18.6 (1.0). Moreover, during a 1-year open-label extension study that enrolled subjects with ≥ 2 weeks of double-blind treatment,[30] therapeutic effects of LDX were found to persist over time. Throughout the 1-year trial, mean ADHD-RS-IV with adult prompts scores were decreased from baseline at all clinic visits as well as at endpoint. The safety profile of LDX in the current study and described in detail in a separate report[22] also generally reflects the AE profile previously described with other long-acting stimulants, marked most frequently by insomnia, dry mouth, and decreased appetite, as well as small and clinically insignificant changes in heart rate and systolic and diastolic blood pressure.[31–36] These and the current findings establish the safety and efficacy of LDX and other long-acting stimulant medications for the treatment of ADHD in adult patients.

In contrast, little is known concerning the impact of stimulant medications on EF outcomes in patients with ADHD, despite widely published and well-developed theories in this field. Executive function defines a broader phenotype of ADHD beyond the currently recognized diagnostic criteria, but EF deficits may have significant negative impact on patients.[2,5] Only a few clinical trials have focused on such theories and reported relevant EF outcomes. The current analysis demonstrated that after 4 weeks of treatment with open-label, optimized doses of LDX (30–70 mg/day), 78.9% of adult subjects with ADHD showed reliable improvement (vs baseline) in EF, as measured by the BADDS total score in relation to baseline 90% confidence range; at week 4, most subjects (59.9%) were in the "optimal" EF (< 50) category. In terms of BADDS cluster scores, clinical improvements in EF after 4 weeks of treatment occurred in all cluster scores: sustaining attention and concentration, organizing and activating to work, sustaining energy and effort, utilizing working memory and accessing recall, and managing affective interference.

The positive EF outcomes seen in this adult trial with LDX are consistent with results from a limited number of existing reports for other stimulant formulations in various populations.[37–41] A recent analysis[37,42] of 2 clinical trials in adults with ADHD receiving an enhanced extended-release formulation of mixed amphetamine salts, triple-bead mixed amphetamine salts, found improvement in EF as measured by BADDS compared with that in subjects receiving placebo. Executive function behaviors were also assessed in a recent 6-month, placebo-controlled trial of the nonstimulant atomoxetine in adults with ADHD.[43] Subjects on atomoxetine demonstrated significant improvement versus placebo in the 5 clusters of BADDS.[43] In an uncontrolled, open-label pilot

study[38] in adults with ADHD, treatment with OROS-MPH resulted in significant improvement in EF measured using traditional neuropsychiatric tasks (eg, Stroop Color-Word, Wechsler Adult Intelligence Scale Working Memory Index, Controlled Oral Word Association Test). Similarly, a small, double-blind, placebo-controlled crossover study[39] conducted in African American children with ADHD indicated improved EF during acute testing following administration of a single dose of short-acting MPH (0.3 mg/kg), as tested by neuropsychological tasks such as the Tower of Hanoi and Paired Associates Learning Task. It should be noted that neuropsychological tests were not developed specifically to assess EF in patients with ADHD, limiting the ability to interpret the results of these studies in relation to EF deficits in ADHD.

A study[40] conducted in children with ADHD showed that subjects who were medicated with stimulants were not impaired (vs non–ADHD-matched controls) on a number of EF tasks, including spatial short-term and working memory, set-shifting, and planning ability, whereas nonmedicated ADHD subjects showed significant EF impairments. Extended-release MPH administered to children in a 4- to 6-week open trial improved global and some individual domain scores of EF,[41] as measured by parent report using the Behavior Rating Inventory of Executive Function (BRIEF) scale.[44] In a 7-week, open-label study of dose-optimized LDX in children with ADHD, improvement from baseline was seen for all global and domain BRIEF scores.[45] It is notable that among the reported studies that assessed the efficacy of stimulants in terms of improving EF, nearly all have been conducted in children, used different study designs, and assessed EF using a wide array of both neuropsychological and parent-reported EF tests. Despite such broad differences, regardless of age group or study design, all of the studies, including the current report, found that stimulants improved EF in subjects with ADHD.

The results of the current study add to growing literature that provides empirical support for the argument that EF may be a key feature of ADHD in patients with ADHD, and that stimulant therapy can have a positive impact on this aspect of the condition. The relationship between core ADHD symptoms, EF deficits, and their impact on adaptive functioning has not been fully described. However, a 2007 study[46] used factor analysis, maximum likelihood method, and structural equation modeling to assess the relationship of symptom composites, a battery of neuropsychological tests of EF along with concurrent assessments of adaptive functioning (eg, Young Adult Self-Report of global assessment of functioning). Results of this study suggest that inattentive-disorganized symptom domains may mediate important aspects of adaptive functioning and may represent the critical behavioral factors by which EF deficits result in poor adaptive functioning.

There are 2 predominant models that describe EF as the brain's method of self-regulation and interpret ADHD as a disorder characterized by delays in an individual's development of EF.[2,4] To date, EF has been most often assessed using traditional neuropsychological tasks considered sensitive to EF impairments. In direct conflict with prevailing EF theories related to ADHD, some investigators have found these tasks to characterize only a minority of individuals with ADHD as having impaired EF.[9,12] This may be interpreted as an indication that current theories of EF in ADHD are incorrect. It is the belief of the authors of the current report, rather, that the neuropsychological tasks are not sensitive enough to detect clinically observable EF impairments, primarily because they attempt to test just 1 EF variable at a time (eg, are reductionistic)[2,15,47] and, as noted by Rabbit,[47] do not account for the essential nature of EF as encompassing "the simultaneous management of a variety of different functional processes."[47] Several clinical reports in the literature,[15,16,48] in fact, highlight the relative insensitivity of traditional neuropsychological tests of EF to real-world functional EF impairments. These previous reports further detail new, EF-sensitive measures, such as a timed mapping task within a highly distracting/complex environment (a zoo)[16] and a multiple errands test,[15,48] that assess how well an individual can perform complex tasks in situations that more closely reflect daily living situations. Similarly, the BADDS, as a measure of EF, assesses a wider range of complex, self-management functions across 5 distinct domains. These and the current findings provide support for a shift away from neuropsychological tests of EF toward more ecologically based measures that may be more sensitive to EF impairments. Broader use of such measures may help clinicians gain a more accurate understanding of the relationship between EF and ADHD.

Limitations

A number of limitations of the current study deserve mention. The data were derived from the open-label, dose-optimization phase of the trial without proper controls or a comparison arm. Because of the lack of a placebo control group, expectancy bias cannot be ruled out. Additionally, the assessment of ADHD symptoms by ADHD-RS-IV and of EF behaviors by BADDS were performed by the same raters. Future studies investigating the relationship of these assessments and the behavioral domains that they encompass would allow broader

interpretation by the use of more independent assessment schemes. The short duration of the current observation period (4 weeks) precludes evaluation of long-term safety and effectiveness of LDX and its impact on EF. The inclusion and exclusion criteria of the trial may have selected a study sample that may not be representative of patients seen in typical clinical practice. Excluded were individuals with a comorbid psychiatric diagnosis, which may be common among adult individuals with ADHD. Also excluded were individuals with baseline ADHD-RS-IV with adult prompts scores of < 28; indeed, the current sample exhibited an ADHD-RS-IV with adult prompts score of approximately 37.0 at baseline, which is indicative of a severely ill ADHD population, not one with mild or moderate ADHD. Hence, current findings may not generalize to an ADHD population with less severe symptoms. Moreover, the majority of subjects (76.8%) were ≤ 40 years of age, and, thus, the current findings may not be representative of an older adult population. This study was also conducted in a mainly white population (89.4%) so results may not be wholly generalizable to other races.

Conclusion

With 4 weeks of open-label LDX (30–70 mg/day) treatment, adults with ADHD showed significant improvement in EF behaviors compared with baseline, based on assessment using the BADDS. For the large majority of subjects (78.9%), EF was considered reliably improved. Lisdexamfetamine dimesylate demonstrated a safety profile consistent with that observed with long-acting stimulant use.

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http://www.clinicaltrials.gov/ct2/show/NCT00697515?term=NCT00697515&rank=1.

Conflict of Interest Statement

Thomas E. Brown, PhD is a consultant for Abbott, Eli Lilly, Novartis, and Shire Pharmaceuticals. He discloses conflicts of interest with the American Psychiatric Press, Psychological Corporation, and Yale University Press. Matthew Brams, MD discloses conflicts of interest with Cephalon, Eli Lilly and Co., McNeil, Novartis, Pfizer, Shire, and Wyeth. Joseph Gao, PhD and Maria Gasior, MD, PhD are employees of Shire and own stock and/or stock options from Shire. Ann Childress, MD is a consultant for Novartis and Shire; a speaker for Bristol-Myers Squibb, Novartis, and Shire; receives/received research support from Abbott, Bristol-Myers Squibb, Johnson and Johnson Pharmaceutical Research and Development, LLC, Lilly, USA, LLC, NextWave, Novartis, Ortho-McNeil Janssen Scientific Affairs, Shire, and Somerset.

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