NR9-30

The following information concerns a use that has not been approved by the US Food and Drug Administration.

Lisdexamfetamine Dimesylate in the Treatment of Cognitive Dysfunction in Patients With Partially or Fully Remitted Major Depressive Disorder

Richard Keefe, PhD,[1] Alan Boyd, PharmD,[2] Manisha Madhoo, MD,[3] Robert M. Roth, PhD,[4] Angelo Sambunaris, MD,[5] James Wu, PhD,[3] Madhukar Trivedi, MD,[6] Colleen Anderson, MEd,[3] Robert Lasser, MD[3]

[1]Duke University Medical Center, Durham, NC; [2]CNS Vital Signs, Morrisville, NC; [3]Shire Development LLC, Wayne, PA; [4]Dartmouth Medical School, Lebanon, NH; [5]Atlanta Institute of Medicine & Research, Atlanta, GA; [6]University of Texas Southwestern Medical School, Dallas, TX

ABSTRACT

Objective: A placebo (PBO)-controlled double-blind study in participants with mild major depressive disorder (MDD) on selective serotonin reuptake inhibitor (SSRI) monotherapy examined the effects of lisdexamfetamine dimesylate (LDX) augmentation on executive dysfunction based on subjective ratings from the Behavior Rating Inventory of Executive Function-Adult Version (BRIEF-A). Here, we report the effects of LDX on objective performance-based neurocognitive measures (secondary endpoints) from the same study.

Methods: This study enrolled men and women (18–55 y) with mild MDD (Montgomery-Åsberg Depression Rating Scale total score ≤18) and executive dysfunction (BRIEF-A Global Executive Composite T score [GEC] ≥60) on stable SSRI monotherapy for ≥8 weeks. After a 2-week screening period, participants were randomized to 9 weeks of double-blind LDX (wk 1: 20 mg/d; wks 2–6: maintain or increase LDX in 10-mg increments weekly to 70 mg/d; wks 7–9: maintain optimized LDX dose) or PBO augmentation. Performance-based neurocognitive endpoints were based on 3 indices derived from CNS Vital Signs test battery domains: complex information speed processing index (processing speed, working memory, and executive function), executive function index (executive function and reaction time), and neurocognitive index (memory [verbal, visual, working, composite], sustained and complex attention, cognitive flexibility, executive function, processing speed, and reaction time). Secondary endpoints were assessed in all randomized participants who took ≥1 study drug dose and had ≥1 postbaseline BRIEF-A assessment. The study was not powered for statistical comparisons of secondary endpoints.

Results: Of 143 randomized participants (LDX, 71; PBO, 72), 119 completed double-blind treatment (LDX, 60; PBO, 59). Least squares mean reductions from baseline to week 9/end of study (EOS) in BRIEF-A GEC T scores (primary endpoint) were –21.2 with LDX and –13.2 with PBO (difference: –8.0; P=0.0009). Mean ± SD complex information speed processing index baseline scores were 97.4±14.87 and 98.9±13.12 with LDX and PBO, respectively, and increased by 8.7±10.13 with LDX and 3.7±9.02 with PBO at week 9/EOS. Mean ± SD executive function index baseline scores were 93.4±17.97 and 94.8±17.47 with LDX and PBO, respectively, and increased by 11.0±14.80 with LDX and 6.0±14.43 with PBO at week 9/EOS. Mean ± SD neurocognitive index scores at baseline were 92.7±15.46 and 96.5±12.81 with LDX and PBO, respectively, and increased by 11.5±17.14 with LDX and 2.5±13.74 with PBO at week 9/EOS. For these endpoints, there were no statistically significant treatment differences in median scores at week 9/EOS; however, findings from the computerized performance-based test battery complemented the subjective findings of the BRIEF-A.

Conclusions: These objective secondary endpoints further support subjective reports of improved executive and cognitive function with LDX and serve as a signal for future research.

INTRODUCTION

- Of the 9 diagnostic criteria for major depressive disorder (MDD),[1] "diminished concentration or indecisiveness" is the only disturbance that is clearly cognitive. However, affective symptoms (eg, diminished energy, sleep disturbances) can also contribute to cognitive dysfunction.
- Cognitive dysfunction can be represented by several types of deficits involving problem-solving, planning, and information processing.[2]
  - Cognitive deficits can persist in individuals with MDD even after remission of depressive symptoms.[3]
  - Persistent cognitive deficits can impair daily activities and social or vocational functioning.[2,3]
- Monoamines play a key role in cognitive processes[4] and amphetamines raise monoamine levels, which may be low in individuals with MDD.[5]
- Lisdexamfetamine dimesylate (LDX), a prodrug of d-amphetamine, is approved for use in children (≥6 y), adolescents (13–17 y), and adults with attention deficit/hyperactivity disorder (ADHD).[6]
  - In a randomized, double-blind, placebo-controlled study in which effect on executive function was the primary endpoint, LDX augmentation of selective serotonin reuptake inhibitor (SSRI) monotherapy significantly improved executive function as measured by a patient-reported rating scale (Behavior Rating Inventory of Executive Function–Adult Version [BRIEF-A] Self-Report) in individuals with fully or partially remitted MDD and persistent executive dysfunction.[7]
- From the aforementioned study, we report on secondary endpoints relating to the effects of LDX augmentation on performance-based cognitive function.

OBJECTIVE

- To further examine the effects of LDX augmentation of SSRI monotherapy in individuals with mild MDD and persistent cognitive dysfunction using data from the objective performance-based CNS Vital Signs[8] (CNS Vital Signs, Morrisville, NC) test battery.

METHODS

Study Design

- This randomized, double-blind, placebo-controlled, parallel-group, multicenter study was conducted at 27 US sites.

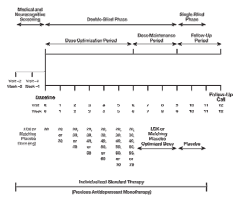
Participants

- Key inclusion criteria
  - Age 18–55 years
  - Diagnosis of recurrent, nonpsychotic MDD (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* [*DSM-IV-TR*] criteria) for ≥2 years before screening
  - ≥8 weeks of SSRI monotherapy before screening
  - Montgomery-Åsberg Depression Rating Scale (MADRS) total score ≤18 at screening and baseline
  - BRIEF-A[9] Self-Report Global Executive Composite (GEC) T score ≥60 at screening and baseline
    - In the BRIEF-A standardization sample, the normative mean is 50 with a standard deviation (SD) of 10; therefore, T scores ≥60 are at least 1 SD above the normative mean.
- Key exclusion criteria
  - Current or comorbid psychiatric disorder controlled with prohibited medications or uncontrolled and symptomatic, LDX contraindication, or previous ADHD diagnosis or fulfillment of *DSM-IV-TR* ADHD criteria before age 7
  - History of psychotic symptoms, nonresponse of depressive symptoms to a stimulant, or hypersensitivity to stimulants; or suicidality (currently at risk or attempt within 3 y)
  - First-degree relative with bipolar I disorder, symptomatic cardiovascular disease history, or serious cardiac problem
  - Recent history of substance abuse (≤6 mo)

Treatment

- Following a 2-week screening period, eligible participants were randomized to LDX or matching placebo (1:1 ratio) for 9 weeks of double-blind augmentation of SSRI monotherapy (**Figure 1**).
  - During week 1, LDX was given at an initial dosage of 20 mg/d.
  - During weeks 2–6, LDX dosage was maintained or increased by 10 mg/d at weekly intervals to optimal dosage (maximum, 70 mg/d).
  - During weeks 7–9, optimal dosage was maintained.
- Treatment during follow-up (weeks 10–12) was single-blind placebo for all participants.

Figure 1. Study Timeline and Dosing Schedule



Medical and Neurocognitive Screening
Double-Blind Phase
Single-Blind Phase
Dose Optimization Period
Dose Maintenance Period
Follow-Up Period
Baseline
Follow-Up Call
Visit
Week
LDX or Matching Placebo Dose (mg)
LDX or Matching Placebo Optimized Dose
Placebo
Individualized Standard Therapy
(Previous Antidepressant Monotherapy)

Endpoints

- Change from baseline to week 9/end of study (EOS) on BRIEF-A Self-Report GEC T score was the primary efficacy endpoint.
- Change from baseline on the CNS Vital Signs battery was a predefined secondary efficacy endpoint. This battery of 7 tests assesses 10 neurocognitive domains, from which 3 indices were constructed (**Table 1**).

Table 1. Summary of CNS Vital Signs Test Battery

Index	Domains	Tests
Neurocognitive Index	Verbal memory	Verbal memory test
	Visual memory	Visual memory test
	Working memory	4-part continuous performance test
	Composite memory	Verbal and visual memory tests
	Sustained attention	4-part continuous performance test
	Complex attention	Stroop test, shifting attention test, continuous performance test
	Cognitive flexibility	Stroop test, shifting attention test
	Executive function	Shifting attention test
	Processing speed	Symbol digit coding test
	Reaction time	Stroop test
Executive Function Index	Executive function	Shifting attention test
	Reaction time	Stroop test
Complex Information Speed Processing Index	Processing speed	Symbol digit coding test
	Working memory	4-part continuous performance test
	Executive function	Shifting attention test

- The CNS Vital Signs battery shows validity comparable to that of similar tests.[8]
- Individuals take the test on computer; completion time is approximately 30 minutes.
- Safety and tolerability measures included adverse events (AEs), vital signs, physical examination including weight and body mass index, laboratory assessments, and electrocardiogram (ECG).

Statistical Analysis

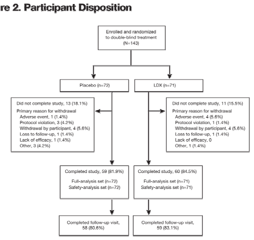
- Analysis of change in BRIEF-A Self-Report GEC T score (primary endpoint) was conducted in the full-analysis set (FAS: randomized participants who took ≥1 study drug dose and had ≥1 postbaseline BRIEF-A assessment).
  - Analysis of covariance was used for the primary endpoint, with treatment as a factor and baseline score as a covariate; last observation carried forward (LOCF) was used to account for missing data.
  - Statistical significance was 2-sided P<0.05.
- CNS Vital Signs data (secondary endpoints) were assessed in the FAS:
  - Median standardized index and domain scores at week 9/EOS between groups were compared using Wilcoxon rank sum tests.
  - Mean standardized index scores at baseline, as well as change from baseline at week 9/EOS, are presented descriptively.
- Safety and tolerability were assessed in the safety-analysis set (all randomized participants who took ≥1 dose of study medication and had ≥1 safety assessment); data are presented descriptively.

RESULTS

Participant Disposition and Demographics

- The enrolled population comprised 143 participants (placebo, n=72; LDX, n=71).
  - All participants were included in the FAS and safety-analysis set.
  - 119 participants completed 9 weeks of treatment (placebo, n=59; LDX, n=60); **Figure 2** shows the participant disposition.

Figure 2. Participant Disposition



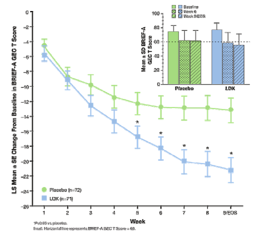
Enrolled and randomized to double-blind treatment (N=143)
Placebo (n=72)
LDX (n=71)
Did not complete study, 13 (18.1%)
Primary reason for withdrawal
Adverse event, 1 (1.4%)
Protocol violation, 3 (4.2%)
Withdrawal by participant, 4 (5.6%)
Loss to follow-up, 1 (1.4%)
Lack of efficacy, 1 (1.4%)
Other, 3 (4.2%)
Did not complete study, 11 (15.5%)
Primary reason for withdrawal
Adverse event, 4 (5.6%)
Protocol violation, 1 (1.4%)
Withdrawal by participant, 4 (5.6%)
Loss to follow-up, 1 (1.4%)
Lack of efficacy, 0
Other, 1 (1.4%)
Completed study, 59 (81.9%)
Full-analysis set (n=72)
Safety-analysis set (n=72)
Completed study, 60 (84.5%)
Full-analysis set (n=71)
Safety-analysis set (n=71)
Completed follow-up visit, 58 (80.6%)
Completed follow-up visit, 59 (83.1%)

- Most participants were white (86.7%) and female (69.2%); mean ± SD age was 40.7±10.23 years.

BRIEF-A Self-Report GEC T Score (Primary Endpoint)

- Least squares (LS) mean ± SE BRIEF-A Self-Report GEC T scores decreased during double-blind augmentation (**Figure 3**).
  - At week 9/EOS, the LS mean (95% CI) treatment difference favored LDX (–8.0 [–12.7 to –3.3], P=0.0009).
- Mean BRIEF-A Self-Report GEC T score was <60 in the LDX group at week 6 and week 9/EOS but not in the placebo group (**Figure 3, inset**).

Figure 3. BRIEF-A Self-Report GEC T Scores, FAS (LOCF)



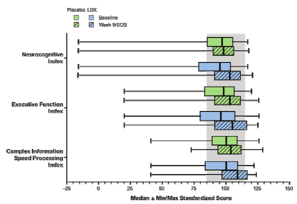
*P≤0.05 vs placebo.
Inset: Horizontal line represents BRIEF-A GEC T Score = 60.

CNS Vital Signs (Secondary Endpoint)

Index Assessments

- At week 9/EOS, there were no significant treatment differences in the median index scores.
- From baseline to week 9/EOS, median standardized scores for CNS Vital Signs indices generally increased, with the magnitude generally being more pronounced with LDX (**Figure 4**).

Figure 4. Median CNS Vital Signs Index Standardized Scores, FAS (LOCF)*



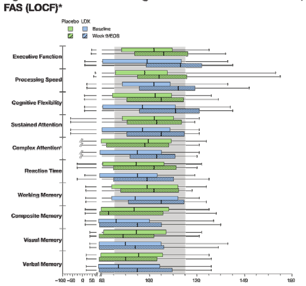
*Based on comparisons of median index scores between treatments using Wilcoxon rank sum tests: Neurocognitive Index (P=0.0738), Executive Function Index (P=0.4930), Complex Information Speed Processing Index (P=0.0882).
The vertical line within each box plot represents the median; the left and right ends of each box represent the first and third quartiles, respectively; the left and right error bars represent the minimum and maximum values, respectively. Grey area represents normal range (mean ± SD standardized score of 100±15).

- Mean ± SD baseline index scores for placebo and LDX groups were: neurocognitive, 96.5±12.81 and 92.7±15.46, respectively (increased by 2.5±13.74 and 11.5±17.14, respectively, at week 9/EOS); executive function, 94.8±17.47 and 93.4±17.97 (increased by 6.0±14.43 and 11.0±14.80 at week 9/EOS); complex information speed processing, 98.9±13.12 and 97.4±14.87 (increased by 3.7±9.02 and 8.7±10.13 at week 9/EOS).

Domain Assessments

- At week 9/EOS, there were no significant treatment differences in median domain scores.
- From baseline to week 9/EOS, median standardized scores for CNS Vital Signs domains generally increased with LDX; in contrast, scores for complex attention and memory (verbal, visual, and composite) tended to decrease with placebo (**Figure 5**).

Figure 5. Median CNS Vital Signs Domain Standardized Scores, FAS (LOCF)*



Placebo LDX
Baseline
Week 9/EOS
Executive Function
Processing Speed
Cognitive Flexibility
Sustained Attention
Complex Attention†
Reaction Time
Working Memory
Composite Memory
Visual Memory
Verbal Memory
Median ± Min/Max Standardized Score

*Based on comparisons of median domain scores between treatments using Wilcoxon rank sum tests: Executive Function (P=0.0941); Processing Speed (P=0.1548); Cognitive Flexibility (P=0.1301); Sustained Attention (P=0.6807); Complex Attention (P=0.1107); Reaction Time (P=0.0914); Working Memory (P=0.3369); Composite Memory (P=0.1746); Visual Memory (P=0.1967); Verbal Memory (P=0.1906).
†Minimum values (error bars) for all Complex Attention Domain assessments were –807.
The vertical line within each box plot represents the median; the left and right ends of each box represent the first and third quartiles, respectively; the left and right error bars represent the minimum and maximum values, respectively. Grey area represents normal range (mean ± SD standardized score of 100±15).

Safety and Tolerability

- The overall incidence of treatment-emergent AEs (TEAEs) and the most commonly reported TEAEs are summarized in **Table 2**.

Table 2. Treatment-Emergent Adverse Events (TEAEs), Safety-Analysis Set

	Placebo (n=72)	LDX (n=71)
Participants with any TEAE, n (%)	53 (73.6)	56 (78.9)
TEAEs in ≥5% of participants in either treatment group, n (%)		
Decreased appetite	3 (4.2)	16 (22.5)
Headache	11 (15.3)	16 (22.5)
Dry mouth	6 (8.3)	11 (15.5)
Insomnia	2 (2.8)	10 (14.1)
Irritability	5 (6.9)	9 (12.7)
Urinary tract infection	3 (4.2)	7 (9.9)
Anxiety	4 (5.6)	6 (8.5)
Upper respiratory tract infection	4 (5.6)	6 (8.5)
Nausea	4 (5.6)	5 (7.0)
Fatigue	4 (5.6)	4 (5.6)
Hyperhidrosis	0	4 (5.6)
Somnolence	2 (2.8)	4 (5.6)
Diarrhea	4 (5.6)	2 (2.8)
Sinusitis	4 (5.6)	1 (1.4)

- There were 6 serious AEs during the study.
  - 5 serious TEAEs (placebo: viral gastroenteritis, salmonellosis, and rhabdomyolysis; LDX: loss of consciousness and suicidal ideation) occurred during double-blind treatment.
  - 1 serious AE (pelvic inflammatory disease) occurred during the single-blind phase (follow-up period; participant receiving placebo).
- TEAEs leading to discontinuation included headache with placebo (n=1) and 1 case each of loss of consciousness, depression, rash, and suicidal ideation in the LDX group (n=4).
- There were no remarkable changes in vital signs, physical examinations, laboratory values, or ECG assessments with either treatment (**Table 3**).

Table 3. Vital Signs Changes From Baseline at Week 9/EOS, Safety-Analysis Set

	Placebo (n=72)		LDX (n=71)	
	n	Mean ± SD	n	Mean ± SD
Systolic blood pressure, mmHg	59	1.0±10.39	63	1.2±9.40
Diastolic blood pressure, mmHg	59	0.8±7.76	63	2.2±7.91
Pulse rate, beats/minute	59	–1.4±6.99	63	4.2±10.25
Weight, kg	59	0.5±1.57	63	–2.3±2.42
Body mass index, kg/m²	59	0.2±0.53	63	–0.9±0.88

CONCLUSIONS

- **Standardized CNS Vital Signs index and domain scores did not demonstrate improvement in participants receiving LDX augmentation compared with those receiving placebo. There were trends for LDX to demonstrate benefit on individual domains compared to placebo, but none were statistically significant.**
  - **These findings are partially consistent with those reported for BRIEF-A Self-Report GEC T score (primary endpoint),[7] which suggested that LDX augmentation mitigated cognitive dysfunction in individuals with fully or partially remitted MDD and persistent cognitive dysfunction.**
- **The safety profile of LDX was consistent with prior LDX ADHD studies and long-acting stimulant use.[10,11]**
- **Study limitations**
  - **The study was not powered to assess changes on the cognitive performance measures assessed by the CNS Vital Signs test battery; further work should explore this area of research with larger sample sizes.**
  - **Future research should further elucidate which aspects of cognitive function are impaired in MDD and which of the many objective test batteries that are currently available are most appropriate to assess these processes.**

References

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision*. Washington DC: American Psychiatric Association; 2000.
2. Gualtieri CT, et al. *J Neuropsychiatry Clin Neurosci*. 2006;18(2):217-225.
3. Reppermund S, et al. *Psychol Med*. 2009;39(4):603-614.
4. van Waarde A, et al. *Behav Brain Res*. 2011;221(2):543-554.
5. Hirschfeld RM. *J Clin Psychiatry*. 2000;6161(suppl 6):4-6.
6. Vyvanse (lisdexamfetamine dimesylate). Full Prescribing Information, Shire US Inc., Wayne, PA, 2012.
7. Madhoo M, et al. Efficacy and safety of lisdexamfetamine dimesylate in adults with executive dysfunction and partial or full remission of major depressive disorder. Presented at: the Annual Meeting of the College of Psychiatric & Neurologic Pharmacists; April 29-May 2, 2012; Tampa, FL.
8. Gualtieri CT and Johnson LG. *Arch Clin Neuropsychol*. 2006;21(7):623-643.
9. Roth RM, et al. *Behavior Rating Inventory of Executive Function-Adult Version (BRIEF-A) Professional Manual*. Lutz, FL: Psychological Assessment Resources; 2005.
10. Weisler R, et al. *CNS Spectr*. 2009;14(10):573-585.
11. Wigal T, et al. *Behav Brain Funct*. 2010;6:34.

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