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Authors:

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Maintenance of Efficacy of Lisdexamfetamine Dimesylate in Adults With Attention-Deficit/Hyperactivity Disorder: Randomized Withdrawal Design

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ABSTRACT

Objective: To evaluate lisdexamfetamine dimesylate maintenance of efficacy in adults with attention-deficit/hyperactivity disorder (ADHD).

Method: Adults (aged 18–55 years) who had ADHD meeting *DSM-IV-TR* criteria, baseline ADHD Rating Scale-IV (ADHD-RS-IV) with adult prompts total scores of < 22, and Clinical Global Impressions-Severity of Illness (CGI-S) ratings of 1, 2, or 3 were enrolled. After previously receiving commercially available lisdexamfetamine dimesylate (30, 50, or 70 mg/d) for ≥ 6 months with acceptable tolerability and maintaining response during a 3-week open-label phase at a stable lisdexamfetamine dimesylate dose, the participants entered a 6-week double-blind randomized withdrawal phase on treatment with lisdexamfetamine dimesylate (same dose) or placebo. Data were collected from April 2009 to July 2010. The primary outcome was the proportion of participants having symptom relapse (≥ 50% increase in ADHD-RS-IV score and ≥ 2 rating-point increase in CGI-S score).

Results: A total of 116 participants were randomized (lisdexamfetamine dimesylate n = 56; placebo n = 60). At the randomized withdrawal phase baseline, mean (SD) ADHD-RS-IV scores for lisdexamfetamine dimesylate and placebo were 10.6 (4.96) and 10.6 (4.82), respectively. At endpoint, 8.9% (5/56) of adults taking lisdexamfetamine dimesylate and 75.0% (45/60) taking placebo ($P < .0001$) showed symptom relapse; most showed relapse after 1 and 2 weeks of the randomized withdrawal phase (4 and 0 adults taking lisdexamfetamine dimesylate, 26 and 10 taking placebo, respectively). During the randomized withdrawal phase, treatment-emergent adverse events were reported in 48.2% and 30.0% of participants in the lisdexamfetamine dimesylate and placebo groups, respectively. Treatment-emergent adverse events with incidence ≥ 5% in the lisdexamfetamine dimesylate and placebo groups were headache (14.3% and 5.0%), insomnia (5.4% and 5.0%), and upper respiratory tract infection (8.9% and 0%).

Conclusions: In adults with ADHD on medium- to long-term treatment, lisdexamfetamine dimesylate demonstrated maintenance of efficacy vs placebo upon randomized withdrawal. A majority of patients given placebo showed symptom relapse by 2 weeks. The safety profile of lisdexamfetamine dimesylate was generally consistent with previous lisdexamfetamine dimesylate studies.

Trial Registration: ClinicalTrials.gov identifier: NCT00877487

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Attention-deficit/hyperactivity disorder (ADHD) affects approximately 4.4% of the adult population in the United States.[1] Symptoms of ADHD in adults lead to clinically significant functional impairments that should be observable in 2 or more settings, such as in occupational, social, and personal or home roles.[1–3] For many patients, physicians may consider it necessary to provide ongoing treatment and support for this chronic disorder.[4]

Psychostimulants are a mainstay of treatment for adults with ADHD.[5,6] The prodrug stimulant lisdexamfetamine dimesylate is approved for the treatment of ADHD in children (6–12 years old), adolescents (13–17 years old), and adults.[7] While short-term efficacy of lisdexamfetamine dimesylate and other stimulant formulations has been established for adults in numerous, well-controlled clinical trials,[8–11] the effectiveness of lisdexamfetamine dimesylate for more than 4 weeks has not been established in a randomized controlled trial. To our knowledge, only 2 conventional-design, parallel-group, longer-term studies of stimulant versus placebo treatment of ADHD have been conducted: one 15-month trial in children[12] and one 24-week trial in adults.[13]

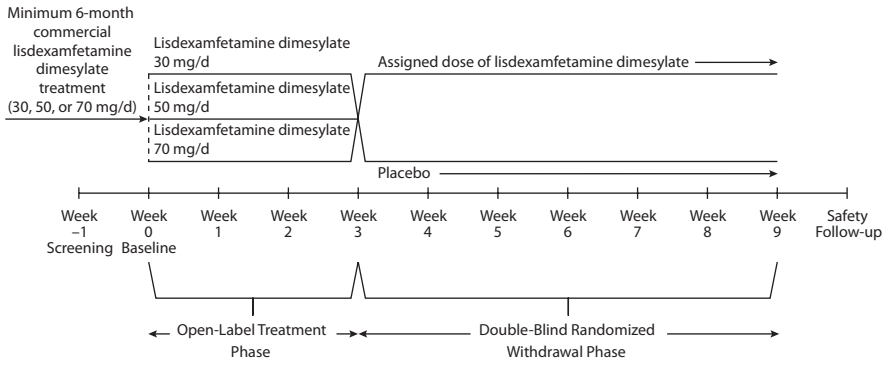
Barriers to the more widespread conduct of medium- to long-term, conventional placebo-controlled studies include existing ethical concerns about withholding a known effective treatment from placebo group participants over time. Such analyses could also be complicated by potentially high dropout rates. Alternatively, it has been proposed[14] that researchers employ a randomized withdrawal design, with symptom relapse as a principal outcome to demonstrate maintenance-of-treatment effect. The advantage of a design constructed with an early-escape endpoint (return of symptoms) is that the period of placebo exposure, with the potential for significant worsening of ADHD symptoms, is relatively short (eg, several weeks), and the return of symptoms is quickly identified so that they can be appropriately managed by clinicians and the adverse impact on functional status limited.

The primary objective was to evaluate maintenance of efficacy in adults with ADHD who previously received treatment with commercially available lisdexamfetamine dimesylate for ≥ 6 months and were randomly assigned to double-blind, continued lisdexamfetamine dimesylate treatment or placebo after open-label lisdexamfetamine dimesylate study medication treatment at a stable dose for 3 weeks. The proportion of lisdexamfetamine dimesylate–versus placebo-group participants showing ADHD symptom relapse during the randomized withdrawal phase was the primary endpoint of interest.

Clinical Points

- While the need for continued treatment of ADHD in adults is acknowledged by experienced clinicians, efficacy of stimulant treatment has not been systematically studied in a well-designed, randomized study beyond 4 to 6 weeks.
- In adults with ADHD, discontinuation of lisdexamfetamine dimesylate after at least 6 months of stable treatment resulted in symptom relapse in 75% of participants randomized to placebo (lisdexamfetamine dimesylate withdrawal) compared with 8.9% of participants randomized to continued lisdexamfetamine dimesylate treatment; most of the relapses occurred within the first 2 weeks.
- Adult patients with ADHD may require continued treatment; understanding the effects of continued treatment and of discontinuation may help clinicians manage patient-specific treatment options.

Figure 1. Study Design



METHOD

Study Design

This double-blind, multicenter (36 sites), placebo-controlled, randomized withdrawal study examining the safety and efficacy of lisdexamfetamine dimesylate consisted of 4 phases (Figure 1). After screening, eligible adults were enrolled for baseline assessments (week 0) and an open-label treatment phase with the participant's stable commercial treatment dose of lisdexamfetamine dimesylate. At the end of the open-label treatment phase (week 3), participants entered a 6-week, double-blind randomized withdrawal phase and were randomly assigned to receive lisdexamfetamine dimesylate (at the participant's open-label treatment phase dose) or placebo, with weekly clinic assessments. Telephone follow-up was conducted 5 to 9 days after the last study medication dose to collect safety information.

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice according to the International Conference on Harmonization guidelines. The study protocol was approved by each center's institutional review board. After complete explanation of the study to participants and prior to conducting any study procedures, voluntary, signed, written informed consent was obtained. The study was conducted from April 2009 to July 2010 and was registered at ClinicalTrials.gov (NCT00877487).

Participants

Adults (aged 18–55 years) who had ADHD meeting *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (*DSM-IV-TR*) criteria[15]; baseline ADHD Rating Scale-IV (ADHD-RS-IV) with adult prompts[16,17] total scores of < 22; and Clinical Global Impressions-Severity of Illness (CGI-S)[18] ratings of 1, 2, or 3 were enrolled. Participants were required to have received commercially available lisdexamfetamine dimesylate (30, 50, or 70 mg/d) for ≥ 6 months with an acceptable safety profile and to have a body mass index of > 18.5 and ≤ 40.

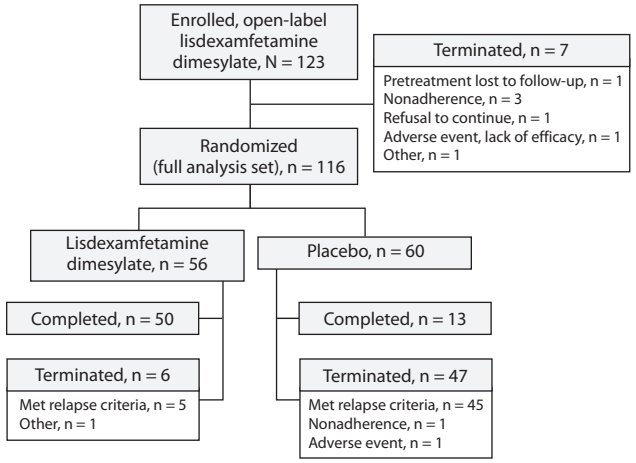
Individuals were excluded if they had a current Axis I or II comorbid psychiatric disorder (as determined by the Structured Clinical Interview for *DSM-IV* Disorders[19]) that was uncontrolled with significant symptoms or controlled with a prohibited medication; current risk or history of suicide attempts; concurrent chronic or acute illness or disability; history of seizures; current diagnosis or history of Tourette disorder; current abnormal thyroid function or glaucoma; family history of sudden cardiac death or ventricular arrhythmias; history of symptomatic cardiovascular disease, stroke, structural cardiac abnormalities, or moderate-severe hypertension (resting systolic blood pressure [SBP] > 139 mm Hg or diastolic blood pressure [DBP] > 89 mm Hg); amphetamine hypersensitivity, allergy, or intolerance; history (≤ 6 months) of suspected substance abuse or dependence disorder; positive urine drug screen (except prescribed amphetamine); or current use of other agents that have central nervous system effects or affect performance.

Efficacy Assessments and Endpoints

Efficacy was assessed at baseline (week 0), then weekly during the open-label treatment phase (weeks 1–3) and randomized withdrawal phase (weeks 4–9) based on the ADHD-RS-IV with adult prompts and the CGI-S. The ADHD-RS-IV consists of 18 items, reflecting *DSM-IV-TR* ADHD symptom criteria, scored from 0 (no symptoms) to 3 (severe symptoms); total scores can range from 0 to 54. Items are also grouped into 2 subscales: inattention and hyperactivity/impulsivity. The CGI-S is a clinician assessment of symptom severity using a 7-point scale (1 = normal, not at all ill to 7 = among the most extremely ill).

The primary efficacy outcome was the proportion of participants in the randomized withdrawal phase who

Figure 2. Participant Disposition



met criteria for ADHD symptom relapse, defined as ≥ 50% increase in ADHD-RS-IV total score and, concurrently, a ≥ 2-point increase in CGI-S rating score compared with randomized withdrawal phase baseline (week 3). Participants who at any weekly randomized withdrawal phase visit met criteria for ADHD symptom relapse were immediately withdrawn from the study. Key secondary efficacy endpoints were ADHD-RS-IV scores and CGI-S ratings at each week of the open-label treatment and randomized withdrawal phases and at endpoint (last randomized withdrawal phase week with a valid score).

Safety Assessments

Medical and medication history was collected and laboratory examinations and a 12-lead electrocardiogram were performed at screening; physical examination was conducted at screening and the final visit (week 9 or endpoint). Weight and vital signs (resting SBP, DBP, and pulse) were measured at screening, baseline, and all treatment visits (weeks 1–9). During the course of the study, the protocol was amended to include the Columbia-Suicide Severity Rating Scale (C-SSRS),[20] which for all newly enrolled and ongoing participants was administered weekly. The C-SSRS, a semi-structured interview assessment of suicidality, was used for ongoing safety monitoring and to determine suitability to continue in the study.

Statistical Analysis

Efficacy analyses were performed on the full analysis set, defined as all randomized participants who received ≥ 1 dose of investigational product and had ≥ 1 ADHD-RS-IV and CGI-S assessment during the randomized withdrawal phase. Safety analyses were performed on the randomized safety population, defined as all randomized participants who were administered study drug in the randomized withdrawal phase.

Primary and secondary efficacy endpoints were summarized for each week by treatment group. The primary efficacy analysis was performed using a 2-sided χ^2 test on combined active doses of lisdexamfetamine dimesylate and placebo. Participants who withdrew and did not provide endpoint efficacy data were classified as treatment failures in the primary efficacy analysis. Two participants who withdrew without providing efficacy data were counted as relapsers at endpoint only. There were no statistical comparisons between treatment groups at each week of the randomized withdrawal phase. Symptom relapse that occurred at early termination was mapped to the week following the participant's last nominal visit.

Statistical analysis of change in ADHD-RS-IV score from baseline of the randomized withdrawal phase to endpoint was performed using an analysis of covariance model, with treatment group (all active lisdexamfetamine dimesylate doses or placebo) as a factor and corresponding baseline score as a covariate. Least squares (LS) mean difference (lisdexamfetamine dimesylate vs placebo) and 95% confidence interval (CI) were calculated; a negative difference in LS mean indicates a positive effect of lisdexamfetamine dimesylate over placebo. ADHD-RS-IV total score change was compared between the 2 treatment groups based on a *t* test and a Cochran Mantel-Haenszel test, respectively. Treatment-emergent adverse events (TEAEs), weight, and vital signs were determined separately for the open-label treatment phase and randomized withdrawal phase. For weight and vital signs at endpoint, the following potentially clinically important criteria were applied: weight, increase or decrease from baseline ≥ 7%; DBP: ≥ 90 mm Hg; SBP: ≥ 140 mm Hg; pulse: ≥ 100 bpm, and ≥ 100 bpm on 2 consecutive occasions.

RESULTS

Participant Disposition

As illustrated in Figure 2, 7 of 123 enrolled participants discontinued the study during the open-label treatment phase. For the 116 participants randomized in the randomized withdrawal phase, 56 received double-blind lisdexamfetamine dimesylate (6, 23, and 27 participants received lisdexamfetamine dimesylate 30, 50, and 70 mg/d, respectively) and 60 received placebo. During the randomized withdrawal phase, 53 (45.7%) of 116 participants discontinued the study; 1 (0.9%) participant receiving placebo due to adverse events, 1 (0.9%) participant receiving placebo due to nonadherence, and 1 (0.9%) participant receiving lisdexamfetamine dimesylate due to "other" causes; 50 (43.1%) due to meeting relapse criteria as detailed in the Efficacy section.

Participant Baseline Demographics and Clinical Characteristics

Table 1 summarizes baseline demographics and clinical characteristics for participants in the open-label treatment phase and randomized withdrawal phase. Across dose and treatment groups, age, sex, race, and ethnicity were similarly distributed. More women than men participated in the study, and most participants were white and non-Hispanic. At baseline of the open-label treatment phase and randomized

Table 1. Baseline Demographics and Clinical Characteristics of Participants in Open-Label and Randomized Withdrawal Phases

	Open-Label Phase				Randomized Withdrawal Phase		
Characteristic	30 mg/d (n = 14)	50 mg/d (n = 49)	70 mg/d (n = 59)	Overall (n = 122)	Lisdexamfetamine Dimesylate (n = 56)	Placebo (n = 60)	Overall (n = 116)
Age, mean (SD), y	34.1 (13.29)	34.7 (11.74)	36.4 (10.22)	35.4 (11.16)	36.5 (10.95)	35.1 (11.39)	35.8 (11.15)
Sex, n (%)							
Male	5 (35.7)	21 (42.9)	28 (47.5)	54 (44.3)	24 (42.9)	26 (43.3)	50 (43.1)
Female	9 (64.3)	28 (57.1)	31 (52.5)	68 (55.7)	32 (57.1)	34 (56.7)	66 (56.9)
Race, n (%)							
White	12 (85.7)	45 (91.8)	54 (91.5)	111 (91.0)	50 (89.3)	56 (93.3)	106 (91.4)
All others	2 (14.3)	4 (8.2)	5 (8.5)	11 (9.0)	6 (10.7)	4 (6.7)	10 (8.6)
Ethnicity, n (%)							
Hispanic	1 (7.1)	7 (14.3)	1 (1.7)	9 (7.4)	7 (12.5)	2 (3.3)	9 (7.8)
Not Hispanic	13 (92.9)	42 (85.7)	58 (98.3)	113 (92.6)	49 (87.5)	58 (96.7)	107 (92.2)
Height, mean (SD), cm	167.8 (10.93)	169.5 (9.23)	172.8 (10.38)	170.9 (10.10)	169.9 (10.12)	171.5 (10.25)	170.7 (10.18)
Weight, mean (SD), kg	77.6 (24.04)	71.6 (15.67)	79.4 (18.58)	76.1 (18.41)	75.4 (16.81)	76.5 (19.66)	76.0 (18.27)
Baseline[a] ADHD-RS-IV with adult prompts total score, mean (SD)	10.9 (4.67)	11.6 (4.80)	10.9 (5.26)	11.2 (4.98)	10.6 (4.96)	10.6 (4.82)	10.6 (4.87)
Baseline[a] CGI-S rating, mean (SD)	2.2 (0.70)	2.1 (0.71)	2.1 (0.83)	2.1 (0.76)	2.1 (0.80)	2.2 (0.78)	2.1 (0.79)

[a]Baseline scores for the open-label phase are at study baseline (week 0); baseline scores for the randomized withdrawal phase are at randomization baseline (week 3).
Abbreviations: ADHD-RS-IV = ADHD Rating Scale IV, CGI-S = Clinical Global Impressions-Severity of Illness scale.

withdrawal phase, ADHD-RS-IV total scores and CGI-S ratings indicated a low level of ADHD symptom severity, with nearly all participants rated as "not at all," "borderline," or "mildly" ill.

Efficacy

Primary endpoint. At randomized withdrawal phase endpoint, significantly fewer participants showed symptom relapse with lisdexamfetamine dimesylate (5 participants; 8.9%) versus placebo (45 participants; 75.0%) ($P < .0001$) (Figure 3A and 3B). Most participants who met criteria for symptom relapse in either treatment group did so within the first 2 weeks of double-blind randomized withdrawal phase treatment (Figure 3A); thereafter, a plateau near the cumulative total proportion at endpoint was observed (Figure 3B). Median time to treatment failure was not estimable for the lisdexamfetamine dimesylate treatment group due to the small number of treatment failures and was 14 days in the placebo group. Summary statistics of the time to symptom relapse in the randomized withdrawal phase showed a median of 42.0 days for participants taking lisdexamfetamine dimesylate and 13.0 days for those taking placebo.

Key secondary endpoints. At baseline, ADHD-RS-IV scores were similar for participants in the lisdexamfetamine dimesylate and placebo groups (Table 1). Overall, mean (SD) increase in ADHD-RS-IV symptom scores was significantly lower in participants taking lisdexamfetamine dimesylate versus placebo ($P < .0001$), with LS mean (SE) change from baseline of the randomized withdrawal phase to endpoint of 1.6 (1.39) with lisdexamfetamine dimesylate versus 16.8 (1.35) with placebo. LS mean (95% CI) difference (lisdexamfetamine dimesylate vs placebo) in adjusted change from baseline of the randomized withdrawal phase was −15.2 (−19.1 to −11.4), indicating a positive effect of continued lisdexamfetamine dimesylate treatment compared with placebo. Additionally, endpoint ADHD-RS-IV scores ranged from 10 to 50 for participants who met relapse criteria.

Safety

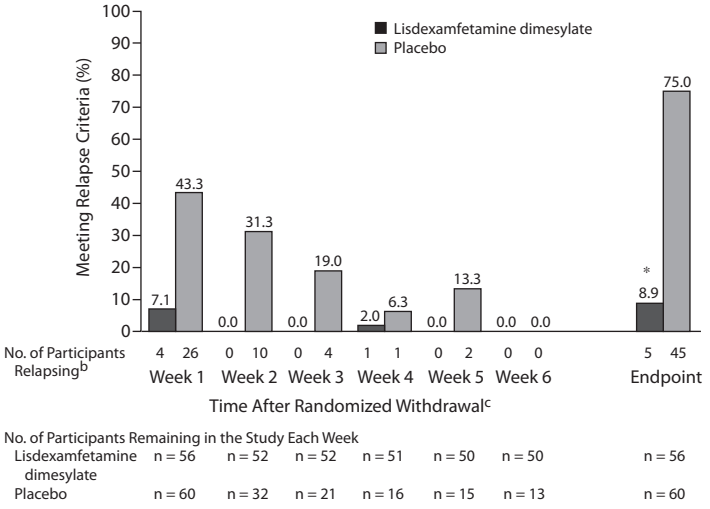
Adverse events. During the open-label treatment phase, 9 (7.4%) of 122 participants reported pretreatment adverse events, and 25 (20.5%) of 122 reported TEAEs. No deaths or serious adverse events (SAEs) were reported during the open-label treatment phase; all adverse events and TEAEs were mild or moderate in severity. One participant (0.8%) taking lisdexamfetamine dimesylate 70 mg/d discontinued due to a TEAE (lack of efficacy). Common TEAEs (reported in ≥ 2% of participants) during the open-label treatment phase (Table 2) were upper respiratory tract infection (2.5%) and headache (2.5%).

During the randomized withdrawal phase, 27 (48.2%) of 56 participants receiving lisdexamfetamine dimesylate and 18 (30.0%) of 60 participants receiving placebo reported TEAEs; common TEAEs are shown in Table 2. One (1.7%) of 60 participants receiving placebo reported posttreatment adverse events. No deaths were reported, and all adverse events and TEAEs were mild or moderate in intensity. One SAE was reported during the randomized withdrawal phase in a male aged 18 years who was randomly assigned to placebo (dose in the open-label treatment phase: lisdexamfetamine dimesylate 70 mg/d). In this participant, suicidal ideation occurred 14 days after randomized treatment was commenced. After a family dispute, he threatened self-harm; he was then hospitalized with discontinuation of study medication. No previous history of suicidal thoughts was reported. The investigator considered this event mild and unrelated to study medication. From weekly clinic C-SSRS assessments, no suicidal ideations or behaviors were identified in any other participants.

Weight and vital signs. Mean weight remained stable throughout the study. During the open-label lisdexamfetamine dimesylate treatment phase, mean (SD) change from baseline to week 3 ranged from −0.3 (1.24) kg to 0.0 (1.06) kg across dose groups. During the randomized withdrawal phase, mean (SD) change from baseline to endpoint was −0.1 (1.73) kg for lisdexamfetamine dimesylate and 0.9 (2.02) kg

Figure 3. Proportion of Participants[a] Randomized to Lisdexamfetamine Dimesylate or Placebo Meeting Criteria for Symptom Relapse During the Randomized Withdrawal Phase

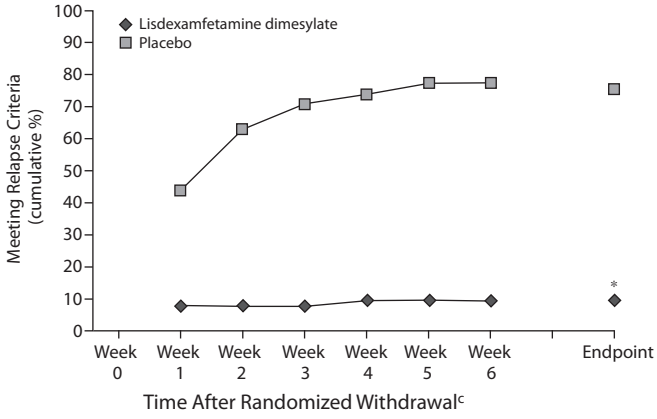
A. Proportion by Treatment Week[a] and at Endpoint



No. of Participants Remaining in the Study Each Week

Lisdexamfetamine dimesylate	n = 56	n = 52	n = 52	n = 51	n = 50	n = 50	n = 56
Placebo	n = 60	n = 32	n = 21	n = 16	n = 15	n = 13	n = 60

B. Cumulative Proportion



*$P < .0001$ lisdexamfetamine dimesylate vs placebo.
[a]Weekly proportions based on number relapsing out of total number of participants with data at that week in each group.
[b]Number of participants relapsing at each week in each treatment group.
[c]Weeks after randomized withdrawal, weeks 1–6, are analogous to weeks 4–9 of the overall study scheme.

for placebo groups. At endpoint, 1 participant (lisdexamfetamine dimesylate 50 mg/d during randomized withdrawal phase) met potentially clinically important criteria for weight decrease ≥ 7%, and 1 participant (placebo during the randomized withdrawal phase) met criteria for weight increase ≥ 7%.

Small mean changes in blood pressure and pulse rate from baseline to week 3 in the open-label treatment phase and at endpoint in the randomized withdrawal phase were seen for both lisdexamfetamine dimesylate (across dose groups) and placebo groups. During the open-label phase, mean (SD) change in SBP and DBP ranged from 0.0 (7.11) mm Hg to 1.2 (8.64) mm Hg and 0.8 (5.73) mm Hg to 1.6 (5.55) mm Hg, respectively. During the randomized withdrawal phase, for lisdexamfetamine dimesylate and placebo groups, respectively, mean (SD) change in SBP was −1.9 (8.70) mm Hg and 0.2 (8.73) mm Hg and in DBP was −0.5 (6.58) mm Hg and 0.9 (5.99) mm Hg. At endpoint, 1 participant treated with placebo had elevated SBP ≥ 140 mm Hg and DBP ≥ 90 mm Hg, and another participant treated with placebo had elevated SBP ≥ 140 mm Hg at endpoint. Two participants taking lisdexamfetamine dimesylate had DBP ≥ 90 mm Hg at endpoint. During the open-label phase, mean (SD) changes in pulse rate ranged from 0.2 (9.77) bpm to 8.6 (8.53) bpm. During the randomized withdrawal phase, mean (SD) change in pulse rate was −0.4 (8.97) bpm and −2.6 (10.46) bpm for the lisdexamfetamine dimesylate and placebo groups, respectively. At endpoint, 2 participants, both taking lisdexamfetamine dimesylate, had elevated pulse rate ≥ 100 bpm, 1 of these at 2 consecutive visits.

DISCUSSION

Among adults receiving commercially available lisdexamfetamine dimesylate for ≥ 6 months with adequate therapeutic response at study entry, lisdexamfetamine dimesylate efficacy was maintained in those randomly assigned to continued active treatment, compared with those randomly assigned to placebo. In the group receiving continued lisdexamfetamine dimesylate, < 9% of participants met criteria for ADHD symptom relapse versus 75% of those receiving placebo. Most participants who experienced relapse of ADHD symptoms met criteria within the first 2 weeks of the randomized withdrawal phase.

These efficacy findings for lisdexamfetamine dimesylate versus placebo in the reduction of ADHD symptoms and global illness severity are in line with previous short-term and medium- to long-term studies in adults with ADHD. In a 4-week, randomized, placebo-controlled study,[11] lisdexamfetamine dimesylate treatment given at the same doses of 30, 50, and 70 mg/d as used in the current trial resulted in significant decreases from the first week of treatment versus placebo.

The implemented randomized withdrawal study design has been recommended as a viable alternative[14] to

Table 2. Common (≥ 2%) Treatment-Emergent Adverse Events (TEAEs) During the Open-Label and Randomized Withdrawal Phases (randomized safety population), n (%)

		Randomized Withdrawal Phase	
Adverse Event[a]	Open-Label Phase—Lisdexamfetamine Dimesylate, All Doses (n = 122)	Lisdexamfetamine Dimesylate, All Doses (n = 56)	Placebo (n = 60)
Any TEAE	25 (20.5)	27 (48.2)	18 (30.0)
Fatigue	1 (0.8)	2 (3.6)	1 (1.7)
Headache	3 (2.5)	8 (14.3)	3 (5.0)
Increased appetite	0	1 (1.8)	2 (3.3)
Insomnia	2 (1.6)	3 (5.4)	3 (5.0)
Joint sprain	1 (0.8)	2 (3.6)	0
Upper respiratory tract infection	3 (2.5)	5 (8.9)	0

[a]Preferred term, Medical Dictionary for Regulatory Activities (MedDRA), Version 11.1.

medium- to long-term placebo-controlled trials to provide data on maintenance of efficacy of medium- to long-term treatment versus a placebo condition. This design has been used with some success to examine medium- to long-term efficacy with medication to treat ADHD, including atomoxetine[21] and various methylphenidate preparations.[22,23] The randomized withdrawal design has also been used to assess medium- to long-term efficacy in treating other neuropsychiatric disorders such as major depressive disorder[24,25] and acute mania.[26] These studies share common design features with the current study including (1) an initial open-label treatment period to allow stabilization and assessment of therapeutic response, (2) objective assessments to identify responders eligible for entry into the randomized phase, and (3) defined objective and subjective criteria for assessing maintenance of efficacy versus relapse of symptoms. In the current trial, the open-label treatment phase prospectively confirmed treatment regimen and response to lisdexamfetamine dimesylate.

Despite the recognized advantages, this design approach can be challenging to implement. Recruitment for studies using this design appears to be difficult and time-consuming. This is most likely related to the need to identify participants who are currently adherent with medium- to long-term treatment and are responding well, yet who are willing to be potentially randomly assigned to placebo. In the trial described by Biederman et al,[23] approximately 90% of participants dropped out or were excluded prior to entering the randomized withdrawal phase, limiting interpretability of the final results. The current moderate-sized study with 36 sites enrolling patients required over 15 months to complete. Use of the randomized withdrawal phase design also presented challenges to cross-study effect size comparisons; any resulting effect sizes would not be comparable with effect sizes derived from conventional studies.

TEAEs, weight assessments, and vital signs in the current study were generally in line with results of previous studies of lisdexamfetamine dimesylate in adults[11,27,28] and consistent with findings for other long-acting psychostimulant medications.[8,10,29] The incidence of TEAEs in this study was generally lower than in other lisdexamfetamine dimesylate studies; this was not unexpected given the entry criterion of ≥ 6 months' stable treatment with lisdexamfetamine dimesylate.

Findings of this study should be considered in light of several methodological limitations and factors. Exclusion of participants with active cardiovascular conditions or other unstable medical or psychiatric conditions may limit extrapolation of findings to the general clinical population. The study population comprised mainly white, young adults, potentially limiting generalizing results to other ethnic groups and older adults. Interestingly, unlike many recent clinical trials of long-acting pharmacotherapy agents in adults with ADHD, which enroll more men than women (ranging from 50.0% to 69.7%),[8,10,11,27,29–34] most participants in this study were female. The greater proportion of women raises the possibility that women are more likely to acknowledge the need to be more adherent with, and more responsive to, medium- to long-term care, making them more likely to be recruited into this type of study design. Because only responders to medium- to long-term lisdexamfetamine dimesylate treatment were included, the magnitude of therapeutic response maintenance may be accentuated and the limited occurrence of adverse events and other safety concerns may be minimized, compared with a nonselected population.

CONCLUSIONS

This randomized withdrawal study demonstrates the maintenance of lisdexamfetamine dimesylate efficacy in adults treated for a minimum of 6 months. Most participants treated with placebo and a small proportion of those treated with lisdexamfetamine dimesylate during the randomized withdrawal phase experienced ADHD symptom relapse within 2 weeks of beginning randomized treatment. These study findings suggest the need for practicing clinicians and their patients to be aware of the importance of maintaining lisdexamfetamine dimesylate medication adherence for both optimizing clinical response and decreasing the risks of ADHD symptom relapse. In this study, the safety profile was generally consistent with previous lisdexamfetamine dimesylate studies and with that of long-acting psychostimulants used in the treatment of ADHD. No new clinically relevant safety signals were associated with abrupt discontinuation of lisdexamfetamine dimesylate.

Drug names: atomoxetine (Strattera), lisdexamfetamine dimesylate (Vyvanse), methylphenidate (Focalin, Daytrana, and others).

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