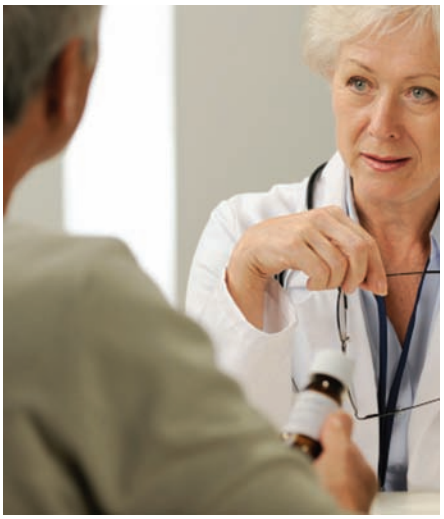

[BRIEF REPORT]

Lisdexamfetamine Dimesylate for the Treatment of Attention Deficit Hyperactivity Disorder in Adults With a History of Depression or History of Substance Use Disorder

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Innov Clin Neurosci. 2011;8(2):28–32

FUNDING: Clinical research was funded by the sponsor, Shire Development Inc.

FINANCIAL DISCLOSURES: Dr. Kollins has received research support and/or consultant fees from Addrenex Pharmaceuticals Inc., CoMentis Inc., Otsuka Pharmaceuticals, Supernus Pharmaceuticals, the Environmental Protection Agency, the National Institute on Drug Abuse, the National Institute of Environmental Health Sciences, the National Institute of Mental Health, the National Institute of Neurological Disorders and Stroke, and Shire Laboratories, Inc.; Dr. Youcha is a Shire employee and owns stocks and/or stock options from Shire; Dr. Lasser is a Shire employee and owns stocks and/or stock options from Shire; and Dr. Thase is/has been a consultant to, received grant/research support from, been on the speakers bureau of, holds equity in, and/or received royalties from American Psychiatric Publishing, Inc., AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Eli Lilly & Co., Forest Laboratories, GlaxoSmithKline, Guilford Publications, Herald House, Janssen Pharmaceutica, MedAvante, Inc., National Institute of Mental Health, Neuronetics, Inc., Novartis Corporation, Schering-Plough, Shire US Inc., Sepracor, Inc., Supernus Pharmaceuticals, Inc., Transcept Pharmaceuticals, Inc., WW Norton & Company, Inc., and Wyeth Pharmaceuticals.

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CLINICALTRIALS.GOV IDENTIFIER: NCT00334880

KEY WORDS: lisdexamfetamine dimesylate, LDX, Vyvanse, ADHD, comorbidities, substance use disorder, depression

ABSTRACT

Objective: To evaluate the efficacy and safety of lisdexamfetamine dimesylate in participants with attention deficit hyperactivity disorder and a history of depression and/or substance use disorder. History of these comorbidities was recorded from medical history forms completed by the study clinicians.

Design/Setting: An exploratory, *post-hoc* analysis was conducted using data from a randomized, double-blind, placebo-controlled, forced-dose titration study of lisdexamfetamine dimesylate.

Participants: Adults with attention deficit hyperactivity disorder.

Measurements: Changes in Attention Deficit Hyperactivity Disorder Rating Scale IV total scores and Clinical Global Impressions-Improvement scale were used to evaluate the efficacy of lisdexamfetamine dimesylate. The incidence of treatment-emergent adverse events was also evaluated.

Results: The intention-to-treat population included 36 participants with a history of depression and 17 participants with a history of substance use disorder. Mean

changes in Attention Deficit Hyperactivity Disorder Rating Scale IV and Clinical Global Impressions-Improvement from baseline to endpoint for these subpopulations were similar to those of participants without a history of depression and/or history of substance use disorder. Lisdexamfetamine dimesylate was generally well tolerated in all subgroups.

Conclusion: The response to lisdexamfetamine dimesylate and the treatment-emergent adverse event profiles of participants with a history of depression and/or a history of substance use disorder were similar to those of participants with no history of these disorders. Larger studies that prospectively enroll participants with attention deficit hyperactivity disorder and these comorbid disorders are needed to more conclusively evaluate the safety and efficacy of stimulant treatment in these populations.

BACKGROUND

Adults with attention deficit hyperactivity disorder (ADHD) have higher rates of comorbid psychiatric disorders, including anxiety, impulse control, mood, and substance use disorders (SUDs) compared to the overall population.[1–5]

Because most ADHD clinical trials exclude individuals with concurrent psychiatric disorders, there is little information on treatment outcomes and safety of these individuals. To begin to address this issue, we conducted a *post-hoc* analysis on data from a large four-week, placebo-controlled study[6] comparing the efficacy and safety of lisdexamfetamine dimesylate (LDX; Vyvanse®, Shire US Inc.), a prodrug stimulant,[7] in adults with ADHD and with or without a *history* of depression or SUD. Similar to other stimulants,[8–10] LDX is not indicated for the treatment of ADHD in individuals with comorbid mood disorders or SUDs.[7]

METHODS

The current report describes *post-hoc* analyses of a randomized, double-blind, placebo-controlled, parallel-group, forced-dose titration study of LDX in adults (18–55 years) diagnosed with ADHD and at least mild-to-moderate symptoms at baseline (by ADHD-Rating Scale-IV [ADHD-RS-IV] scores ≥28).[6]

Subject population. Detailed description of participant eligibility and exclusion criteria, study design, and outcomes have been published.[6] Exclusion criteria included a current comorbid Axis I or II diagnosis with significant symptoms contraindicating LDX treatment or confounding efficacy or safety assessments. Current comorbid psychiatric diagnoses were made by a psychiatric evaluation that included the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (*DSM-IV-TR*) disorders (SCID-I)[11] at screening. Exclusion criteria related to SUD included a positive urine drug test (except participant's current stimulant therapy, if any) and drug dependence or SUD (excluding nicotine) within the past six months.

Medical history was used to categorize participants into the following *post-hoc* subgroups: with or without a history of depression (either inactive or currently active but not severe enough to require study exclusion) or with or without a history of SUD, because SCID-I results of historical diagnoses were not captured in the study database and were not available to identify participants in the *post-hoc* analysis. Eight participants had both a history of depression and a history of SUD and were included in both the history of depression and history of SUD subgroups. Participants with a history of depression but no history of SUD were also included in the no history of SUD subgroup, and vice versa for participants with a history of SUD but no history of depression.

Trial design. Following screening and washout of ADHD medications (when necessary), eligible participants were randomized to receive 30, 50, or 70mg/d LDX or placebo. Participants randomized to receive LDX initiated treatment with 30mg/d. For those randomized to 50 or 70mg/d, LDX dose was escalated weekly (by 20mg/week) to the randomized dose.[6]

Efficacy objectives and measures. Efficacy was assessed for all randomized participants having baseline and ≥1 post-randomization ADHD-RS-IV total score.[12,13] Clinical Global Impressions-Improvement (CGI-I) ratings[14] were assessed as the proportion of participants categorized as improved (including ratings of "very much" and "much" improved). Treatment-emergent adverse events (TEAEs), events with onset after the first date of treatment, were monitored in all participants who took one or more doses of study treatment.

Statistical analyses. Standardized effect sizes ±95-percent confidence intervals (CIs) for ADHD-RS-IV for participants with and without a history of depression were reported.

RESULTS

Participant disposition. In the overall study, 36 participants (31 LDX; 5 placebo) reported a history of depression, major depressive disorder, postpartum depression, dysthymia, depressive disorder not otherwise specified, and adjustment disorder with depressed mood; 378 (LDX 321; placebo 57) did not report a history of depression. Discontinuation rates for participants with or without a history of depression receiving LDX were 15.6 and 17.2 percent, respectively, and were similar to the overall study population.[6] Four participants with and 18 without a history of depression discontinued due to TEAEs; 2 out of 4 of those with and 10 out of 18 without a history of depression reported one or more psychiatric adverse event (AE).

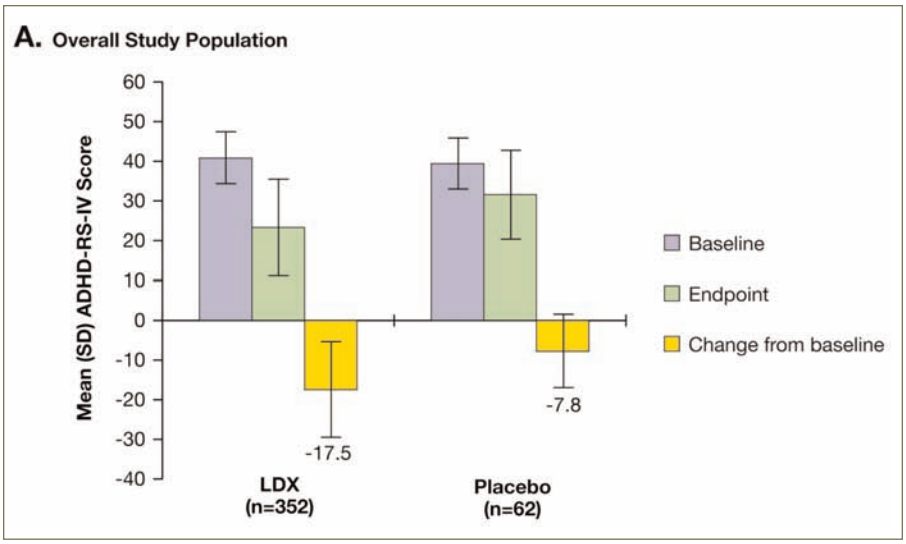
Seventeen participants in the efficacy analysis, all by chance randomized to LDX, reported a history of SUD, including alcohol, marijuana, methamphetamine, or opioid abuse; or alcohol,

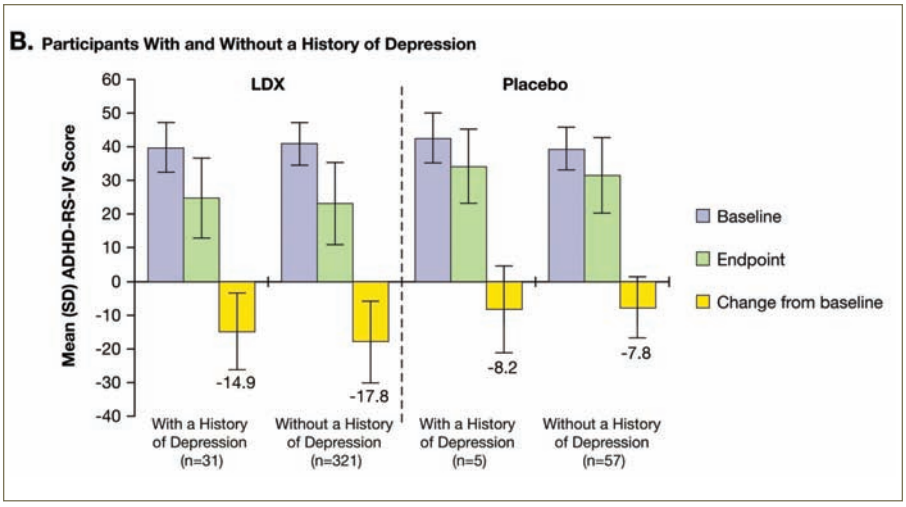
amphetamine, or methamphetamine dependence; as well as less specific disorders including drug dependence, SUD, and a later drug-induced coma, or recreational drug use. Three-hundred ninety-seven participants (LDX 335; placebo 62) did not report a history of SUD. Three participants who did not report a history of SUD were discontinued because of a positive urine screen at baseline. An additional subject with no history of SUD was discontinued at Visit 6 due to positive urine screen for amphetamine/methamphetamine on a random drug screen by the subject's employer, resulting in unblinding of randomization status. No participants who reported a history of SUD were discontinued because of a positive urine drug screen.

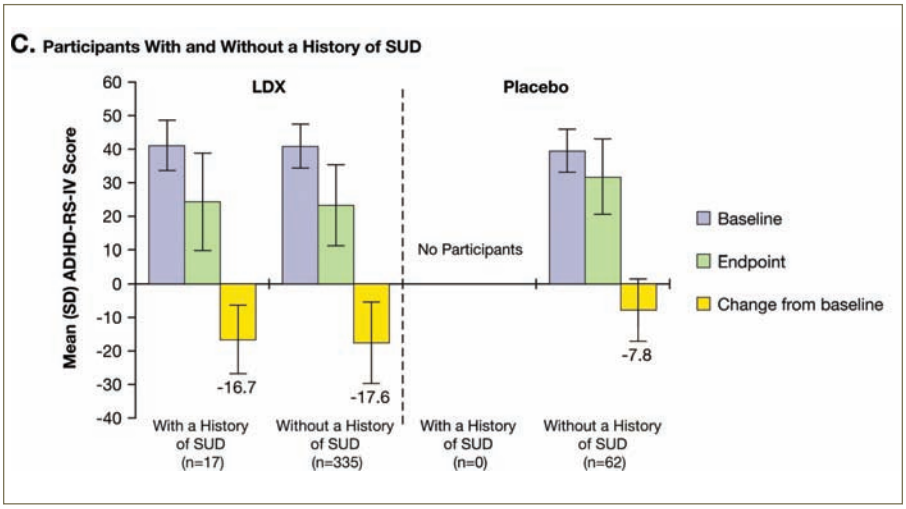
Discontinuation rates were 16.7 and 17.1 percent for the participants with and without a history of SUD receiving LDX, respectively, and were similar to the overall study population. Two participants with a history of SUD discontinued due to TEAEs (both reported psychiatric TEAEs); 19 participants without a history of SUD and treated with LDX discontinued due to TEAEs; 12 of these participants reported psychiatric AEs. The discontinuation rates in each subgroup were similar to that of the overall study population.

EFFICACY

Participants with and without a history of depression had similar baseline ADHD-RS-IV scores (Figures 1A and B). Mean (standard deviation [SD]) change in ADHD-RS-IV scores from baseline to endpoint for participants in the overall study, with and without a history of depression, were -17.5 (12.07), -14.9 (11.38), and -17.8 (12.12), respectively, for LDX, and -7.8 (9.28), -8.2 (12.91), and -7.8 (9.05), respectively, for placebo. The effect sizes (95% CI) for LDX in subgroups with and without a history of depression were d=0.58 (CI -0.37, 1.53) and d=0.86 (CI 0.57, 1.14), respectively. Although direct







FIGURES 1A–C. ADHD-RS-IV total scores at baseline and endpoint and mean change from baseline.

ADHD-RS-IV= Attention Deficit Hyperactivity Disorder Rating Scale IV
LDX= lisdexamfetamine dimesylate
SUD= substance use disorder

statistical analysis was not warranted, the CIs of the effect size values for subgroups with or without a history of depression were broad and overlapping.

Participants with and without a history of SUD had similar baseline ADHD-RS-IV scores (Figure 1C). Mean (SD) changes in ADHD-RS-IV scores for participants receiving LDX with or without a history of SUD were -16.7 (10.25) versus -17.6 (12.16), respectively, and for participants without a history of SUD receiving placebo was -7.8 (9.28). Because no subject with a history of SUD was randomly assigned to the placebo group, effect size could not be calculated.

The percentage of participants who were categorized as improved on the CGI-I at study endpoint among the overall study and those with and without a history of depression receiving LDX were 60, 52, and 60 percent, respectively, and for those receiving placebo were 29, 20, and 30 percent, respectively. Also, the percentage of participants who were categorized as improved at study endpoint using the CGI-I scale among those with and without a history of SUD receiving LDX were 65 and 59 percent, respectively. For participants without a history of SUD receiving placebo, 29 percent were categorized as improved.

SAFETY

For participants with and without a history of depression, 78.1 versus 78.8 percent receiving LDX reported any TEAE and 37.5 versus 37.1 percent reported psychiatric TEAEs. Common TEAEs were generally similar for participants with and without a history of depression and receiving LDX; these included decreased appetite (25.0% vs. 26.7%), insomnia (18.8% vs. 19.3%), and headache (15.6% vs. 21.2%). TEAEs with incidence of five percent or greater and a 50-percent or greater difference between participants with and without a history of depression were anxiety (9.4% vs. 5.5%), diarrhea (3.1% vs. 7.1%), dry mouth (37.5% vs. 24.5%), irritability (0% vs. 6.1%), and upper respiratory tract infection (URTI) (0% vs. 5.8%).

For participants with and without a history of SUD receiving LDX, 83.3 versus 78.5 percent reported any TEAE. Common TEAEs were generally similar for participants with and without a history of SUD and receiving LDX; these included decreased appetite (22.2% vs. 26.8%), dry mouth (33.3% vs. 25.3%), and insomnia (22.2% vs. 19.1%). TEAEs with incidence of five percent or greater and a 50-percent or greater difference between participants with and without a history of SUD and receiving LDX were anorexia (11.1% vs. 4.5%), anxiety (16.7% vs. 5.0%), diarrhea (0% vs. 6.7%), headache (44.4% vs. 18.4%), initial insomnia (0% vs. 5.0%), nausea (11.1% vs. 6.4%), and URTI (0% vs. 5.6%).

DISCUSSION

Similar to the overall study population,[6] LDX was effective in these *post-hoc* analyses in participants with ADHD with a history of depression or SUD. Other stimulants and nonstimulants used to treat ADHD have also been shown to relieve ADHD symptoms in participants with comorbid mood disorders[15–17] and SUD.[18–25] The TEAE profiles for participants with a history of depression and SUD were similar to that reported for the overall study population.[6]

Although preliminary, these findings suggest that LDX may be effective in patients with ADHD and a history of these comorbid conditions. However, no conclusions can be drawn regarding effects of LDX for the treatment of ADHD and *current* comorbid conditions. LDX and other stimulants are not approved for ADHD with concurrent depression or SUD. Additionally, a history of drug abuse is a contraindication of stimulant use in the United States.

Aspects of this study limit extrapolation of these findings to the range of adults with ADHD seen in clinical practice, including the following: exclusion of participants with current comorbid psychiatric disorders and SUD; the exploratory nature of this *post-hoc* analysis with small sample size across groups; diagnoses of history of comorbid disorders derived from the medical history; and the lack of quantitative measures, such as depression or substance use inventories.

CONCLUSIONS

This exploratory analysis suggests that short-term treatment with LDX may be effective for adults with ADHD and a history of depression or SUD with a safety profile consistent with that seen in the broader population of ADHD patients. Based on the results of this analysis, large, well-designed, and controlled studies should be performed to fully assess the efficacy and safety of LDX in treating symptoms of ADHD in these patients.

ACKNOWLEDGMENT

Clinical research was funded by the sponsor, Shire Development Inc. Under the direction of the authors, Michael Pucci, PhD, employee of Ogilvy CommonHealth Scientific Communications (OCHSC), provided writing assistance for this publication. Editorial assistance in formatting, proofreading, copy editing, and fact checking was also provided by OCHSC. Brian Scheckner, PharmD, Thomas Babcock, DO, Bryan Dirks, MD, and Ben Adeyi, MS, from Shire Development Inc. also reviewed and edited the manuscript for scientific accuracy. Shire Development Inc. provided funding to OCHSC for support in writing and editing this manuscript. Although the sponsor was involved in the design, collection, analysis, interpretation, and fact checking of information, the content of this manuscript, the ultimate interpretation, and the decision to submit it for publication in *Innovations in Clinical Neuroscience* were made by the authors independently.

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