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Dose Response Effects of Lisdexamfetamine Dimesylate Treatment in Adults With ADHD: An Exploratory Study

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Abstract

Objective—To explore dose–response effects of lisdexamfetamine dimesylate (LDX) treatment for ADHD.

Method—This was a 4-week, randomized, double-blinded, placebo-controlled, parallel-group, forced-dose titration study in adult participants, aged 18 to 55 years, meeting *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., text rev.) criteria for ADHD.

Results—Nearly all participants assigned to an LDX dose achieved their assigned dose with the exception of about 4% of participants assigned to the 50 mg or 14% assigned to the 70 mg doses. Higher doses of LDX led to greater improvements in ADHD-rating scale scores, independent of prior pharmacotherapy. This was evident for both inattentive and hyperactive–impulsive symptoms. The authors found some evidence for an interaction between LDX dose and baseline severity of ADHD symptoms.

Conclusion—For LDX doses between 30 and 70 mg/d, the dose–response efficacy effect for LDX is not affected by prior pharmacotherapy, but patients with a greater severity of illness may benefit more from higher doses, especially for hyperactive–impulsive symptoms. The results do not provide information about doses above 70 mg/d, which is the maximum approved dose of LDX and the highest dose studied in ADHD clinical trials.

Keywords

ADHD; dose–response; lisdexamfetamine dimesylate; amphetamine; stimulants

Introduction

ADHD is a neurocognitive disorder with a high worldwide prevalence (Faraone, Sergeant, Gillberg, & Biederman, 2003). For decades, the stimulant medications methylphenidate, dextroamphetamine, and mixed amphetamine salts have been the most common drugs used in the treatment of ADHD. Therapeutic effects of stimulants include a reduction of the

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hyperactivity, impulsivity, and inattention characteristic of patients with ADHD and improvement of associated behaviors, including on-task behavior, academic performance, and social functioning (Greenhill et al., 2001). Studies demonstrate robust effects in both children and adults (Spencer, Biederman, & Wilens, 2000), and long-acting formulations extend the action of these medications over 8 to 13 hr to allow once-daily dosing (Biederman, Lopez, Boellner, & Chandler, 2002; Greenhill, Findling, & Swanson, 2002; Wolraich et al., 2001).

Lisdexamfetamine dimesylate (LDX) is a long-acting prodrug stimulant, which is indicated for the treatment of ADHD in children aged 6 to 12 years and in adults (Adler et al., 2008; Faraone, 2008). LDX is a therapeutically inactive molecule. Following oral ingestion, it is converted to L-lysine and active D-amphetamine, which is responsible for the therapeutic effect. Data from three double-blinded, placebo-controlled clinical studies show that LDX is well tolerated and effective for the treatment of ADHD in children (Biederman, Boellner, et al., 2007; Biederman, Krishnan, Zhang, McGough, & Findling, 2007) and adults (Adler et al., 2008).

Although the efficacy of LDX and the existence of a dose–response relationship have been well established by this prior literature, little is known about the degree to which potential moderating variables influence the dose–response relationship. The discovery of variables influencing the dose–response relationship would have important implications for clinical care, as they could help clinicians plan treatment regimens or to better interpret the response of their patients to specific doses. To address these issues, this report uses data from Adler et al.'s (2008) double-blinded study of LDX-treated ADHD adults to examine the effects of LDX dose on clinical outcomes. We sought to answer the following study exploratory questions: (a) Does the severity of ADHD at baseline affect dose response? (b) Does a history of prior ADHD pharmacotherapy influence dose response? and (c) Does dose response differ between inattentive and hyperactive–impulsive symptoms? The original study by Adler et al. did not include these exploratory questions as hypotheses. We know of no other studies of LDX or other ADHD medications that have examined these potential moderators of dose response.

Method

Ascertainment

This was a 4-week, randomized, double-blinded, placebo-controlled, parallel-group, forced-dose titration study to evaluate the efficacy and safety of LDX 30 mg, 50 mg, and 70 mg in adult participants, aged 18 to 55 years, meeting *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., text rev.; *DSM-IV-TR*; American Psychiatric Association, 2000) criteria for a diagnosis of ADHD as determined by a comprehensive psychiatric evaluation and with baseline ADHD-rating scale-IV-Inv estigator rated (ADHD-RS-IV-Inv) score of ≥ 28 using adult prompts. Participants were excluded if significantly underweight (body mass index <18.5) or morbidly obese in judgment of the physician; if they had an active comorbid psychiatric diagnosis with significant symptoms or other concurrent medical illness that could contraindicate treatment with LDX or could interfere with safety or efficacy assessments; had a history of seizures (except infantile febrile seizures), a tic disorder, a family history of Tourette's disorder condition; had structural cardiac abnormalities or other cardiac disorder, including resting systolic blood pressure >139 mmHg or diastolic blood pressure >89 mmHg; had a history of substance abuse within the past 6 months; or a positive urine drug screen (with the exception of current stimulant therapy).

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practices as found in the guidelines of the International Conference on Harmonisation and

was approved by the institutional review board of each study site. Participants provided written informed consent. The study was conducted at 48 centers in the United States between May 25, 2006 and November 16, 2006.

Clinical Assessment

The protocol for this study included a screening visit (Visit 1), a baseline visit at which treatment was assigned (Visit 2), and four weekly treatment visits (Visits 3-6). At baseline, ratings were made on the Clinical Global Impression of Severity (CGI-S) scale, which yields integer scores ranging from 1 = *normal, not at all ill* to 7 = *among the most extremely ill participants*. At each subsequent visit, ratings were made on the CGI of Improvement (CGI-I) scale, which also yields integer scores ranging from 1 = *very much improved* to 7 = *very much worse* indexing the degree of change from the beginning of the study (i.e., prior to the start of study medication) querying the improvement in ADHD symptoms (Guy, 1976). At all visits, each participant was rated on the ADHD-RS-IV-Inv. Two subscales (Inattentive and Hyperactive/Impulsive) can be scored from the sum of 9 items each, and a total score can be determined from the sum of all 18 items.

Statistical Methods

Three dependent measures from the ADHD-RS were evaluated. First was weekly total score on the ADHD-RS, derived as the sum of symptom scores on all 18 items in the scale. The other two dependent measures were weekly scores on two ADHD-RS subscales (Inattentive and the Hyperactive/Impulsive), each of which was derived as the sum of symptom scores on 9 items in the scale. We examined the dose-response relationship of these outcomes from two perspectives. First, we determined if effects of LDX dose on end point scores were moderated by baseline severity, prior pharmacotherapy, and ADHD symptom type. In these analyses, the dependent measures at end point were modeled by linear regression, with predictors including baseline score on the same scale (full or subscale), LDX dose received during the prior week of treatment, and prior ADHD pharmacotherapy (modeled separately to evaluate the effects of prior stimulant therapy and prior ADHD pharmacotherapy of any kind, including stimulants). These end point analyses used each participant's last observation carried forward (LOCF).

In a second set of analyses, we assessed the effects of these potential moderators on the longitudinal change in symptoms during the trial. To account for multiple nonindependent observations from each participant, we modeled weekly symptom scores longitudinally using generalized estimating equations (GEEs). All models were optimized by stepwise removal of nonsignificant terms, beginning with the factor having the highest associated p value and leaving only those factors with $p < .05$. To determine the effects of dropouts, we repeated the analyses utilizing data from only those participants who completed the full 4-week trial. The Type I error rate was fixed at 0.05. All analyses were conducted in Stata SE software, version 9.0 (Stata Corporation; College Station, TX, USA).

Because baseline ADHD-RS scores and LDX dosages were both strongly significantly related to ADHD-RS scores at end point, we were interested in further quantifying the ability of these variables to predict outcomes. We used receiver operating characteristic (ROC) curve analysis to determine the potential for making accurate predictions of prodromal symptom status from brain regions significantly associated with the Scale of Prodromal Symptoms (SOPs) scores. ROC analysis assesses the diagnostic efficiency of tests for diagnoses and to adjust cut points for clinical or research purposes (McNeil & Hanley, 1984) and has been widely applied to assessing the accuracy of diagnostic tests (Swets, 1982; Swets, 1986a, 1986b; Swets & Pickett, 1982).

First, we dichotomized the sample based on whether participants achieved a 30% or greater reduction in ADHD symptoms by end point. For each participant, we then computed the predicted values, or logits, from the logistic regression model. For each successive point on the logit scale, we computed a sensitivity and specificity of the logit as a predictor of prodromal status by predicting those higher than the cut point to be prodromal and others not to be prodromal. This was then used to draw the ROC curve. On the ROC graph, the sensitivity (true positive rate) of different cut points on the test are graphed on the y -axis along with 1 minus the specificity (the false positive rate) of the cut points on the x -axis to determine the ability of the test to optimize both measures for each point on the test. The higher the graph extends toward the upper left corner of the graph, the higher the discriminatory power of the test. ROC analysis summarizes diagnostic efficiency with the area under the curve (AUC) statistic. The AUC ranges from 0.5 (for a diagnostically useless test) to 1.0 (for a diagnostic test that is a perfect predictor). The AUC has two useful properties. First, it is equivalent to the Mann-Whitney U statistic computed from a comparison of a continuous score between two groups (Hanley & McNeil, 1982). Second, it equals the probability that a randomly selected prodromal case will have a more extreme logit score than a randomly selected member of the nonprodromal group (Colditz, Miller, & Mosteller, 1988; Hanley & McNeil, 1982).

Results

Achievement of Randomized Doses

Our first objective in these analyses was to determine the degree to which participants achieved their randomized doses. Overall, the rate of attainment of randomized dose was high ($\chi^2_9 = 1100.0$, $p < .001$), with 398 of 420 participants (94.8%) achieving their assigned dose by the end of treatment. All participants assigned to receive placebo ($n = 62$) or the lowest daily LDX dose of 30 mg ($n = 119$) did so; however, fewer participants assigned to receive higher LDX doses attained them. Five of the 117 participants (4.3%) assigned to receive a maximum daily dose of 50 mg did not receive this dosage, instead achieved a maximum of 30 mg/d. Of the 122 participants randomly assigned to receive a maximum daily LDX dose of 70 mg, 7 (5.7%) attained a maximum daily dose of 50 mg and 10 (8.2%) achieved a maximum daily dose of 30 mg.

Effects of LDX Dose on End Point ADHD-RS Total Scores

We next sought to identify the effects of various LDX doses on ADHD symptom scores by examining LOCF end point total scores on the ADHD-RS as a function of the LDX dosage achieved at end point, the participant's baseline total ADHD-RS score, and the interaction of these variables. Baseline total ADHD-RS scores were strong positive predictors of end point total ADHD-RS scores ($\beta = 0.60$, $t_{410} = 6.96$, $p < .001$). LDX dosage was also a strongly significant negative predictor of end point total ADHD-RS scores ($\beta = -0.16$, $t_{410} = 6.53$, $p < .001$). The interaction of baseline total ADHD-RS score and LDX dose was not significant ($\beta = -0.01$, $t_{410} = 1.70$, $p = .090$), suggesting that the effect of various LDX doses on end point total ADHD-RS scores was uniform at all levels of baseline symptom severity. Together, baseline total ADHD-RS scores and LDX dosage accounted for 16.6% of the variance (adjusted r^2) in total ADHD-RS scores at end point. Figure 1 displays the dose response in terms of effect size (Cohen's d) stratified by two quartiles of ADHD-RS baseline severity. It shows that, for all doses, effect sizes were greater for participants showing greater severity at baseline. Participants in both quartiles of ADHD-RS baseline severity show an increasing effect size with increasing dose.

We next evaluated the effect of prior stimulant therapy, including amphetamines ($n = 50$), methylphenidate ($n = 10$), other stimulants ($n = 3$), or a stimulant combination ($n = 3$), by

including in the regression model a dichotomous variable indicating a positive or negative history (1, 0) of exposure. Separately, we evaluated the effect of prior ADHD pharmacotherapy of any kind, including the stimulant regimens described above, plus atomoxetine ($n = 3$), and other nonstimulants ($n = 6$). In each model (evaluating either prior stimulant exposure or prior ADHD pharmacotherapy of any kind), we also evaluated the interactive effects of the exposure indicator variable and the LDX dose achieved at end point.

When controlling for the significant main effects of baseline total ADHD-RS score and LDX dose described above, prior stimulant exposure neither had a significant main effect on end point ADHD-RS total scores ($\beta = 1.09$, $t_{410} = 0.90$, $p = .555$) nor did it interact significantly with LDX dose to influence this measure ($\beta = -0.01$, $t_{409} = 0.06$, $p = .953$). When expanding the classification of prior treatment to include any pharmacotherapy, the results changed little, as evidenced again by a lack of a significant main effect of prior treatment ($\beta = 0.48$, $t_{410} = 0.33$, $p = .744$) and no significant interaction of prior treatment with LDX dose ($\beta = -0.02$, $t_{409} = 0.25$, $p = .806$).

We next sought to determine if the main effect of LDX dose on end point ADHD-RS total scores reported above was different for Inattentive and Hyperactive/Impulsive subscale scores.

Inattentive subscale scores—As with the total ADHD-RS score, end point ADHD-RS Inattentive subscale scores were strongly and positively predicted by the same scores at baseline ($\beta = 0.54$, $t_{411} = 5.99$, $p < .001$). The end point scores significantly decreased with increases in LDX dose ($\beta = -0.09$, $t_{411} = 6.75$, $p < .001$). These effects are seen in Figure 2. As with ADHD-RS total scores, these two factors did not interact to significantly influence end point ADHD-RS Inattentive subscale scores ($\beta = -0.01$, $t_{410} = 1.20$, $p = .232$). End point ADHD-RS Inattentive subscale scores were not influenced by significant main effects of either prior stimulant therapy ($\beta = 0.82$, $t_{410} = 0.94$, $p = 0.350$) or prior ADHD pharmacotherapy of any kind ($\beta = 0.57$, $t_{410} = 0.68$, $p = .496$); furthermore, neither prior stimulant therapy nor prior pharmacotherapy of any kind interacted significantly with LDX dose to influence inattentive symptom scores (stimulant therapy: $\beta = 0.01$, $t_{409} = 0.02$, $p = .987$; any pharmacotherapy: $\beta = -0.01$, $t_{409} = 0.06$, $p = .954$).

Hyperactive/Impulsive subscale scores—End point scores on this symptom subscale were positively related to baseline ADHD-RS scores on the same subscale ($\beta = 0.81$, $t_{410} = 7.46$, $p < .001$). However, unlike total and Inattentive sub-scale scores, end point ADHD-RS Hyperactive/Impulsive subscale scores were not influenced by a main effect of LDX dose ($\beta = 0.04$, $t_{410} = 0.81$, $p = .417$); rather, these scores were influenced by a significant interaction of LDX dose with baseline Hyperactive subscale scores ($\beta = -0.01$, $t_{410} = 2.36$, $p = .019$), indicating that the effect of LDX on scores on this symptom subscale differed according to the level of baseline symptoms (see Figure 3).

To further evaluate the nature of this interaction, we divided participants into four quartiles based on their baseline ADHD-RS hyperactive/impulsive symptom scores and ran regression analyses separately for each group. End point hyperactive/impulsive symptom scores among those participants with the lowest baseline scores on the ADHD-RS Hyperactive/Impulsive subscale were not influenced by a main effect of LDX dose ($\beta = -0.03$, $t_{107} = 2.36$, $p = .092$), whereas participants in the higher quartiles of baseline hyperactive/impulsive symptom scores at baseline exhibited a much stronger influence of LDX dose on their end point scores on this subscale. Participants in the second quartile exhibited a strong main effect of LDX dose on their end point ADHD-RS hyperactive/impulsive symptom scores ($\beta = -0.06$, $t_{129} = 3.17$, $p = .002$), as did participants in the fourth

quartile who had the highest baseline scores ($\beta = -0.11$, $t_{88} = 3.51$, $p = .001$). Participants in the third quartile based on baseline ADHD-RS Hyperactive/Impulsive subscale scores exhibited a marginally significant effect in the same direction ($\beta = -0.06$, $t_{82} = 1.97$, $p = .053$). Of note, the magnitude of the effect of LDX dose was equivalent for those in the second and third quartiles (both $\beta = -0.06$), but the effect of LDX dose did not attain significance in the third quartile due to its relatively smaller sample size ($n = 84$ vs. $n = 131$ in Quartile 2) based on the unavoidable use of a whole number as the cut point for the quartile split.

As with total and inattentive subscale scores, end point scores on the ADHD-RS Hyperactive/Impulsive subscale were not significantly influenced by prior treatment. This included a lack of main effects of prior stimulant therapy ($\beta = 0.09$, $t_{410} = 0.12$, $p = .904$) or any prior ADHD pharmacotherapy ($\beta = -0.07$, $t_{410} = 0.10$, $p = .923$), and no significant interactions with LDX dose (stimulant: $\beta = -0.01$, $t_{409} = 0.10$, $p = 0.922$; any: $\beta = -0.01$, $t_{409} = 0.39$, $p = .700$).

Longitudinal Analyses of Effects of LDX Dose on ADHD-RS Total and Subscale Scores

The linear regression analyses reported above found main effects of LDX dose and baseline ADHD-RS total scores on weekly ADHD-RS total scores, but no significant interaction between the factors. In contrast, longitudinal GEE models of the same data revealed both a main effect of baseline score ($\beta = 0.98$, $z = 14.29$, $p < .001$) and an interaction of baseline score with LDX dose ($\beta = -0.01$, $z = 6.48$, $p < .001$). Similar results were seen for inattentive symptoms, including a main effect of baseline score on the sub-scale ($\beta = 0.93$, $z = 12.78$, $p < .001$) and an interaction with LDX dose ($\beta = -0.01$, $z = 6.46$, $p < .001$).

To understand these interactions, we reran the GEE analyses separately for each quartile of baseline total and baseline inattentive symptoms. Although actual LDX dose was found to have a significant main effect on weekly total and Inattentive subscale scores within each quartile of baseline symptoms (all p s $< .001$), the magnitude of the effect increased with severity of baseline symptoms. Thus, for total symptoms, the main effect of LDX dose on weekly total symptoms was $\beta = -0.25$ in the quartile with the lowest baseline total symptom scores but increased to $\beta = -0.28$ in Quartile 2, to $\beta = -0.33$ in Quartile 3, and again to $\beta = -0.39$ in Quartile 4, which included participants with the highest baseline total symptom scores. For Inattentive subscale scores, the magnitude of the main effect of LDX dose on weekly scores also was smallest in those in the lowest quartile of baseline symptom scores ($\beta = -0.13$), increased in Quartiles 2 ($\beta = -0.18$) and 3 ($\beta = -0.20$), and remained elevated in Quartile 4 ($\beta = -0.20$).

A different pattern of results emerged in the analysis of data from the Hyperactive/Impulsive subscale. For weekly scores on this ADHD-RS subscale, the main effect of baseline score persisted ($\beta = 0.74$, $z = 18.75$, $p < .001$), LDX dose was also found to exert a significant main effect ($\beta = -0.14$, $z = 33.96$, $p < .001$), and the two factors did not interact ($\beta = 0.01$, $z = 1.36$, $p = .175$).

As with the regression analyses, we also evaluated the effects of prior pharmacotherapy on the results of our GEE models. When considering any prior pharmacotherapy, no main effect of prior pharmacotherapy was observed for ADHD-RS total ($\beta = -0.17$, $z = 0.17$, $p = .867$), Inattentive subscale ($\beta = 0.06$, $z = 0.10$, $p = .923$), and Hyperactive/Impulsive subscale scores ($\beta = -0.20$, $z = 0.40$, $p = .688$). Furthermore, prior ADHD pharmacotherapy (of any kind) did not interact significantly with actual LDX dose received to influence total ($\beta = -0.02$, $z = 0.85$, $p = .394$), Inattentive subscale ($\beta = -0.01$, $z = 0.38$, $p = .703$), or Hyperactive/Impulsive subscale scores ($\beta = -0.01$, $z = 1.22$, $p = .221$).

Narrowing the focus of prior treatment to stimulants only, the results did not change substantially. Here too, no main effect of prior pharmacotherapy was observed for ADHD-RS total ($\beta = -0.04$, $z = 0.04$, $p = 0.970$), Inattentive subscale ($\beta = 0.08$, $z = 0.14$, $p = .888$), and Hyperactive/Impulsive subscale scores ($\beta = -0.12$, $z = 0.24$, $p = .814$). Furthermore, pharmacotherapy for ADHD did not interact significantly with actual LDX dose received to influence total ($\beta = -0.01$, $z = 0.50$, $p = .614$), Inattentive subscale ($\beta = -0.01$, $z = 0.13$, $p = .893$), or Hyperactive/Impulsive sub-scale scores ($\beta = -0.01$, $z = 0.84$, $p = .399$).

Effect of Dropouts

The analyses reported thus far used each participant's LOCF; however, not all participants completed the full 4-week trial. In fact, some participants contributed as little as one observation to the analyses, whereas others contributed two, three, or four data points. In such instances, the results of analyses may be influenced by factors related to the participants' participation and continuation in the trial rather than the evaluated effects of baseline severity or dose. For example, if participants were more likely to discontinue in the trial because the drug was not effective for their symptoms, then the magnitude of the effect of LDX dose on ADHD-RS symptom scores would be biased upward in the regression analyses due to increased weight (i.e., greater number of observations) given to data from participants for whom the drug was effective. To assess this possibility within our own study, we repeated all analyses described above using only those participants who completed 4 full weeks in the trial ($n = 349$). All results from the analyses of completers were identical in their patterns of significance and directions of effects to the LOCF analyses.

Accuracy of Predictions: ROC Analyses

In a clinical setting, it would be useful to know if baseline data could accurately predict a good response to medication. We tested this using logistic regression to predict the response criterion of a 30% or greater reduction in symptoms by end point from baseline ADHD-RS score and LDX dose. As expected from the prior analyses, this model was significant ($p = .002$). Figure 4 gives the ROC curve. The area under the ROC curve was 0.59, indicating that the two predictors (LDX dosage and baseline ADHD-RS scores) did slightly facilitate the classification of responders and nonresponders beyond chance levels.

Discussion

This was a placebo-controlled, double-blinded, forced-dose, parallel-group study of three doses of LDX treatment for ADHD. Nearly all participants assigned to an LDX dose achieved their assigned dose with the exception of about 4% of participants assigned to the 50 mg dose and 14% assigned to the 70 mg dose. This finding suggests that LDX was well tolerated by the large majority of the treated participants.

Consistent with the prior report from this sample (Adler et al., 2008), higher doses of LDX led to greater improvements in ADHD-RS scores. As indicated by meta-analysis, the efficacy of LDX for adults is comparable with the effects of other stimulant medication (Faraone & Glatt, 2010). The results of the current analyses provide a more detailed analysis of this dose-response relationship from two perspectives. The first analysis determined if the effects of LDX dose on end point scores were moderated by baseline severity, prior pharmacotherapy, and ADHD symptom type. The second analysis assessed the effects of these potential moderators on the longitudinal change in symptoms during the trial.

The end point analyses found a significant effect of baseline total ADHD-RS scores on the end point scores, which indicates that the degree of symptom reduction afforded by LDX was not influenced by baseline severity (i.e., on average, the patients who were the most ill

at baseline were also the most ill at follow-up, despite showing significant improvement with treatment). This finding would likely be different in a study that used titration to optimal dose. Although higher LDX doses were associated with increased efficacy, this effect did not interact with baseline severity. This finding indicates that the LDX dose–response effect was uniform at all levels of baseline symptom severity for the total ADHD-RS score. Thus, for the total ADHD-RS score, we found no evidence that patients with a greater severity of baseline illness require higher doses or that patients with lower levels of severity required lower doses. Notably, baseline total ADHD-RS scores and LDX dosage accounted for only 16.6% of the variance in total ADHD-RS scores at end point. Because much of the variance in outcome scores is not explained by either dose or baseline severity, it suggests that future research should search for sources of this unexplained variance. For example, error in measurement likely accounts for some unexplained variance. Thus, improving the reliability of outcome measures should increase the amount of variance explained. It is also likely that pharmacogenetic factors account for some variability in response (McGough et al., 2006; Mick & Faraone, 2008; Mick, Neale, Middleton, McGough, & Faraone, 2008). Although history of prior pharmacotherapy could possibly influence treatment outcome, we found no main effect of prior stimulant therapy or prior therapy with any ADHD medication. Moreover, prior pharmacotherapy did not influence the LDX dose–response relationship. Although having had a history of prior pharmacotherapy did not affect response, we did not have sufficient data to determine if response to prior pharmacotherapy would have moderated the dose–response relationship.

The results for end point Inattentive and end point Hyperactive–Impulsive subscales were identical to the results for the ADHD-RS total score with one exception. For hyperactive–impulsive symptoms only, we found a significant interaction between baseline ADHD-RS severity and LDX dose. This indicated that the LDX dose–response effect for this symptom class differed according to the level of baseline symptoms. We found no dose–response effect among patients in the lowest quartile of baseline scores on the ADHD-RS Hyperactive/Impulsive subscale, whereas participants in the higher quartiles of baseline hyperactive/impulsive symptoms exhibited a stronger and significant LDX dose–response effect on their end point hyperactive/impulsive scores. This cannot be due to a “floor effect” because, to be enrolled in the study, patients were required to have an ADHD-RS score greater than 28.

Our longitudinal analyses assessed the effects of potential moderators on the longitudinal change in symptoms during the trial. Whereas the first analysis examined the effect of final achieved LDX dose on end point scores, these analyses examined the effects of increasing dose during the trial. Due to the nature of dose titration in which doses are increased from one visit to the next, it is not possible to disentangle the effects of dose from the effects of time. Despite this limitation, the results from the longitudinal analyses were mostly consistent with what we found for the end point analyses. There was, however, one notable difference: In the longitudinal analyses, we found a significant interaction between baseline ADHD-RS severity and weekly ADHD-RS scores for the total ADHD-RS and for the Inattentive subscale. For both these scores, the magnitude of the dose–response effect increased with increasing severity of baseline symptoms. We did not find a significant interaction for the Hyperactive–Impulsive subscale.

Regarding interaction of LDX dose with baseline ADHD-RS scores, the results of the longitudinal GEE analyses contrast with the results of the end point linear regression analyses. In the linear regression analyses, total and Inattentive sub-scale scores on the ADHD-RS were influenced by main effects of LDX dose that did not vary across different levels of baseline symptom severity (i.e., LDX dose did not interact with baseline symptom scores); however, Hyperactive/Impulsive subscale scores were influenced by such an

interaction. Yet, in the GEE analyses, total and Inattentive sub-scale scores were influenced by the interaction of baseline scores and LDX dose, whereas Hyperactive/Impulsive sub-scale scores were not.

The difference between the end point and longitudinal analyses is likely due to the fact that, in the longitudinal analyses, dose and time are confounded. Thus, the pattern of interactions found in the end point and longitudinal analyses suggests that patients with more severe levels of inattentive ADHD require more time to respond than do milder patients; they do not necessarily need greater doses. In contrast, patients with more severe levels of hyperactive-impulsive ADHD do not have a slower time to response than other patients, but they may need greater doses. These findings illustrate that both LOCF and GEE analyses have limitations and, although GEE is superior to LOCF methodology in many cases, it cannot overcome limitations imposed at the level of research design. This pattern of findings would require replication before definitive clinical recommendations could be made. The design of future studies should consider that time in treatment may have effects that are independent of the dose increases due to time-dependent titration.

Although we found some significant predictors of ADHD-RS ratings at end point, the ROC analyses show that the degree of prediction is not large. Figure 4 shows that to have a high level of sensitivity (e.g., .75), one would have to tolerate a high false-positive rate (e.g., .60). Thus, it is unlikely that these results will be useful in clinical practice.

Our findings should be viewed in the context of several limitations. The raters trained in this protocol had prior expertise in the clinical evaluation and treatment of ADHD. The generalizability of these findings to less experienced clinicians cannot be established. In our longitudinal analyses, dose and time are confounded, which makes it difficult to draw firm conclusions. Study designs that avoid such confounding should be considered for future work.

We found no evidence that patients with a greater severity of baseline illness require higher doses based on our finding that the dose effect on symptom reduction was uniform for all levels of severity. This result may have been different if we had used a design in which doses were titrated to optimal levels of efficacy. We attempted to disentangle time effects from dose effects but must be cautious about these inferences due to the confounding of time and titration during the protocol.

Another limitation of our work is that we had few outcome measures, which were highly correlated measures of ADHD symptoms. Future work should address additional domains, such as quality of life, social functioning, and neuropsychological functioning. Also, we did not collect symptom information from informants, so we cannot determine if our results would generalize to other informants.

In summary, our analysis of LDX's efficacy dose-response relationship confirms the dose-response findings reported by Adler et al. (2008), which shows that it is independent of prior pharmacotherapy and that it is evident for both inattentive and hyperactive-impulsive symptoms. We found some evidence for an interaction between LDX dose and baseline severity of hyperactive-impulsive symptoms. This latter finding suggests that patients with a greater severity of illness may benefit more from higher doses, especially for hyperactive-impulsive symptoms. However, more work is needed to address this issue using research designs that unconfound dose and time in the trial. In addition, our results do not provide information about doses above 70 mg/d, which is the maximum approved dose of LDX and the highest dose studied in ADHD clinical trials.

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Figure 1. Effect size of LDX relative to placebo by baseline severity quartile: ADHD-RS total scores at end point

Note: LDX = lisdexamfetamine dimesylate; ADHD-RS = ADHD-rating scale. Baseline severity quartiles based on median split of ADHD-RS.

Figure 2. Effect size of LDX relative to placebo by baseline severity quartile: ADHDRS inattentive scores at end point

Note: LDX = lisdexamfetamine dimesylate; ADHD-RS = ADHD-rating scale. Baseline severity quartiles based on median split of ADHD-RS.

Figure 3. Effect size of LDX relative to placebo by baseline severity quartile: ADHD-RS hyperactive/impulsive scores at end point

Note: LDX = lisdexamfetamine dimesylate; ADHD-RS = ADHD-rating scale. Baseline severity quartiles based on median split of ADHD-RS.

Figure 4. ROC curve for LDX dose and baseline ADHD-RS as predictors of a 30% or greater reduction in symptoms by end point

Note: ROC= receiver operating characteristic; LDX = lisdexamfetamine dimesylate; ADHD-RS = ADHD-rating scale.