Clinical Response and Symptomatic Remission in Children Treated With Lisdexamfetamine Dimesylate for Attention-Deficit/Hyperactivity Disorder

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ABSTRACT

Objective: To examine clinical response and symptomatic remission in two studies of lisdexamfetamine dimesylate (LDX) in children with attention-deficit/hyperactivity disorder (ADHD).

Methods: In a 4-week, placebo-controlled, double-blind trial, children 6–12 years of age with ADHD received LDX (30–70 mg/day) or placebo. In an open-label trial, children from previous studies were titrated to optimal dose over 4 weeks and maintained up to 1 year. Primary and secondary efficacy assessments were the ADHD Rating Scale IV (ADHD-RS-IV) and Clinical Global Impressions-Improvement (CGI-I) scale, respectively. Clinical response was defined as ≥30% reduction in ADHD-RS-IV total score with a CGI-I rating of 1 or 2; symptomatic remission was defined by ADHD-RS-IV total score ≤18.

FOCUS POINTS

- Response to treatment with lisdexamfetamine dimesylate (LDX) was evaluated in children with attention-deficit/hyperactivity disorder utilizing criteria for clinical response and symptomatic remission.
- The majority of subjects receiving LDX achieved clinical response and symptomatic remission in both a short-term randomized controlled trial with forced dose-titration, and a long-term, open-label trial with a dose-optimized trial design.
- For nearly half the subjects in the long-term trial, symptomatic remission was maintained throughout the study with continued treatment with LDX.

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Results: In the 4-week study (N=285), at any postdose assessment, 79.3% achieved response (median 13 days) and 67.1% achieved remission (median 22 days) with LDX versus 29.2% and 23.6% with placebo. In the long-term study (N=251), at any postdose assessment, 96.0% responded and 62.7% maintained response; 88.8% achieved remission and 46.4% maintained remission.

Conclusion: Most children treated with LDX achieved clinical response and symptomatic remission at one time point; once achieved, almost half maintained remission.

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INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is among the most commonly diagnosed and treated neurobehavioral disorders in children, with studies indicating that it affects ~4% to 12% of school-aged youths.[1,2] Most ADHD clinical trials evaluate treatment efficacy by comparing change in the mean score of an active medication group with that of a placebo group using a continuous rating scale, such as the ADHD Rating Scale IV (ADHD-RS-IV)[3] or the Swanson, Nolan, and Pelham rating scale (SNAP-IV).[4,5] While mean score change is useful for making comparisons across groups, it provides limited information on clinical response at the individual or subject level. Although ADHD rating scales may be a valuable approach for researchers, for clinicians it may be more meaningful to describe efficacy in terms of the proportion of subjects showing a clinically meaningful response.

Relatively few studies have assessed ADHD clinical trial data using formal criteria for clinical response and symptomatic remission.[6] Clinical response is defined as improvement in symptoms as a result of treatment that is recognizable to clinicians and patients, but subjects may continue to have symptoms of the disorder.[6,7] Remission, in its narrowest sense, has been defined as "sufficient improvement such that the patient no longer displays the diagnostic criteria of the disorder and is virtually asymptomatic."[7] Remission has been associated with decreased relapse rates, restoration of social and occupational functioning, and potentially lower healthcare costs.[6,8-10]

From the simple definition of response above, other more elaborate definitions have been proposed, mostly in other psychiatric disorders. An early exercise in establishing consensus definitions for major depression posited that response was the treatment-related improvement of sufficient magnitude and the individual was no longer fully symptomatic but continued to have evidence of more than minimal symptoms.[7] This concept has since been operationalized as a reduction of ≥50% on a variety of symptom rating scales including the Hamilton Rating Scale for Depression (HAM-D) or the Montgomery-Åsberg Depression Rating Scale (MADRS).[11] Another recent analysis by Leucht and colleagues[12] suggested that response could be defined for schizophrenia as a ≥50% reduction in symptoms for acutely ill nonrefractory patients, but a 25% reduction in symptoms was more appropriate for refractory patients. For bipolar disorder, response has been further parsed to differentiate bipolar depression and mania and, within each, symptomatic response versus the more expansive and more rigorous syndromal response (≥50% improvement in all core symptoms).[11] In this scheme, symptomatic response can be graded from <25% improvement to 75% to 100% improvement on the HAM-D or MADRS.[11] Because these other psychiatric disorders are generally episodic in nature, the application of these definitions and criteria to ADHD, which is a persistent condition, are not clear-cut. In studies of ADHD, the concept of response has been operationalized as improvement from baseline of 25% to 30% in rating scales such as the ADHD-RS-IV or SNAP-IV.[6]

Three distinct types of remission have been proposed[13] for ADHD: syndromatic, symptomatic, and functional. Syndromatic remission—the loss of full diagnostic status—has been operationalized for ADHD as "failing to meet the full diagnostic criteria for ADHD". Symptomatic remission—defined as the loss of partial diagnostic status—has been described for ADHD as having "fewer than the number of symptoms required for a subthreshold diagnosis". It may be thought of as treatment response that is associated with symptom levels within or near the normal range; in clinical practice, this might represent successful treatment.[5] Finally, functional remission is "the loss of partial diagnostic status plus functional recovery".[13] While there are no widely accepted operational criteria for clinically meaningful response and symptomatic remission, recent studies have sought to test the applicability of scale-based cutoff criteria. In

the Multimodal Treatment Study of Children with ADHD (MTA), this approach defined success or excellent response as a mean per-item score ≤1 (from a composite of parent and teacher ratings on the SNAP-IV) indicating a severity level below symptomatic ADHD.[5] Similarly, an ADHD-RS-IV total score of ≤18 has been proposed as indicating normalization for subjects with combined-type ADHD.[14]

In this study, efficacy data from two clinical trials of lisdexamfetamine dimesylate (LDX) were reassessed. In a short-term (4-week), randomized, placebo-controlled clinical trial, LDX significantly reduced symptoms of ADHD compared with placebo and maintained efficacy throughout the day as measured by parent and clinician ratings.[15] In a 12-month open-label treatment extension with subjects who previously participated in randomized controlled studies of LDX,[15,16] ongoing treatment was also associated with a significant reduction in ADHD symptom scores.[16-18] In this post hoc analysis, the time to clinical response and symptomatic remission in the short-term, parallel-group, randomized, placebo-controlled trial as well as ratings of response and remission by visit in the year-long open-label extension study were examined. Furthermore, the maintenance of response and symptomatic remission during open-label treatment were observed.

METHODS

The methodology of the original clinical trials has been previously described,[15,18] but is briefly summarized here.

Methods Common to Both Clinical Trials

The studies were performed in accordance with the principles of the International Conference on Harmonization Good Clinical Practice, 18th World Medical Assembly (Helsinki, 1964), and amendments of the 29th (Tokyo, 1975), the 35th (Venice, 1983), the 41st (Hong Kong, 1989), and the 48th (South Africa, 1996) World Medical Assemblies. After receiving thorough verbal and written descriptions of all study requirements, and prior to initiation of the study protocol, all subjects and parents/guardians provided written assent/consent following procedures approved by the Institutional Review Board at each participating site.

Both studies enrolled children aged 6–12 years with a primary diagnosis of ADHD,[15,18] based on the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (*DSM-IV-TR*) criteria for the combined or predominantly hyperactive/impulsive subtypes.[19] The primary outcome was the change in ADHD-RS-IV total score from baseline to endpoint.[15,18] The ADHD-RS-IV contains 18 items corresponding to the criteria for an ADHD diagnosis described in the *DSM-IV-TR*.[3,18,19] Each item is scored according to its frequency: 0 (never or rarely), 1 (sometimes), 2 (often), and 3 (very often).[3] Secondary measures included the Clinical Global Impressions-Severity (CGI-S) at baseline and CGI-Improvement (CGI-I) scales at subsequent visits.[15,18,20] The CGI-S is used to rate the severity of symptoms on a 7-point scale ranging from 1 (no symptoms) to 7 (very severe symptoms). At each postbaseline visit, symptom improvement was assessed by the clinician on the CGI-I using a 7-point scale ranging from 1 (very much improved) to 7 (very much worse).[20] Safety assessments for both studies included open-ended elicitation of adverse events (AEs), vital signs, electrocardiogram, routine clinical laboratory monitoring, and physical examinations (eg, height and weight) as previously reported.[15,18]

Short-Term Placebo-Controlled Study

In a 4-week, placebo-controlled, multicenter, double-blind, parallel-group, forced dose-escalation trial, subjects were randomly assigned in a 1:1:1:1 ratio to receive oral LDX (30, 50, or 70 mg/day) or placebo capsules.[15] Subjects assigned the higher doses initiated treatment with 30 mg/day, and the dose was increased, as assigned, at weekly intervals to 50 mg/day and then 70 mg/day. Inclusion and exclusion criteria were previously reported[15] and exclusion criteria included comorbid psychiatric disorders, any current medical condition or history of a medical condition, or current medication use that might confound the results of the study or increase risk to the subject.

Long-Term Open-Label Study

The long-term (12-month), open-label, single-arm study enrolled children aged 6–12 years with ADHD, who were enrolled subsequent to the participation in the short-term trial described above,[15] enrolled in a separate (analog classroom) study,[16] or not enrolled in a previous LDX trial. Inclusion and exclusion criteria were similar to the short-term study and were previously reported.[18] After a 1-week washout (optional for those enrolling directly from

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the short-term study), all subjects were titrated to an optimal dose as previously reported.[18] Treatment was maintained for up to 11 months, during which time the dose could be adjusted to maintain optimal effectiveness and tolerability.

Clinical Response and Symptomatic Remission Analyses

Post hoc analysis criteria for clinical response and symptomatic remission were established based on previous reports,[5,6] and are presented along with other pertinent definitions in Table 1. For symptomatic remission, the mean score on items on the ADHD-RS-IV would be equivalent to an average rating of sometimes (1) or rarely or never (0) on each item; such a score would represent a loss of ADHD symptoms.[3,6] Loss of clinical response or symptomatic remission was defined as failure to meet the criteria for response or remission at a later visit after previously achieving that status among the actively enrolled subjects. Once having failed to meet remission criteria, those subjects were not considered further. In the long-term trial, maintenance of clinical response or symptomatic remission was evaluated among subjects who met response/remission criteria and completed the 4-week dose-optimization phase (optimal dose groups).

TABLE 1.
Definitions/Criteria for Clinical Response and Symptomatic Remission[5,6]

Clinical response	≥30% reduction in ADHD-RS-IV total score* and CGI-I score 1 or 2
Symptomatic remission	ADHD-RS-IV total score ≤18 (average per-item score ≤1)
Time to median response/remission	Time by which half the original sample achieves criteria for response/remission
Loss of response/remission status	Failure to meet criteria for response/remission after having achieved that status at a previous visit
Maintenance of response/remission at endpoint	4-week trial: Subjects meeting criteria for response/remission at postbaseline visits, enrolled at endpoint, and meeting criteria without interruption Long-term trial: Subjects meeting criteria for response/remission at postbaseline visits and meeting the criteria without interruption up to endpoint

*Relative to baseline ADHD-RS-IV total score in the 4-week trial.

ADHD-RS-IV=ADHD Rating Scale, Version IV; CGI-I=Clinical Global Impressions-Improvement.

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Statistical Analysis

Differences among all LDX dose groups in the 4-week study and long-term study for time to clinical response or symptomatic remission were analyzed with a log-rank statistic test. For these analyses, the null hypothesis that there is no difference in events' distribution across the study time among the optimal dose groups was tested; this was a global test of the doses.

RESULTS

The predefined outcome measures from the two clinical trials have been previously reported.[15,18] Data from the current post hoc analysis are reported herein.

Short-Term Study

Of the 297 subjects enrolled in the short-term double-blind study, 290 were randomized, efficacy was assessed in 285 subjects (72 received placebo, 213 received LDX), and 230 completed the study (54 received placebo, 176 received LDX).[15] Across the four treatment groups, subjects had a mean age range of 8.7–9.4 years at baseline. Males comprised approximately two-thirds of the sample population and >77% of subjects were identified as Caucasian or African American. Moreover, ~96% of the subjects were diagnosed with combined-subtype ADHD.

Among subjects who responded to LDX treatment and completed the study (n=158), 135 (85.4%) continued to meet criteria for clinical response at all subsequent study visits. Similarly, of the patients who achieved symptomatic remission with LDX treatment and completed the study (n=121), 100 (82.6%) continued to meet criteria for symptomatic remission at all subsequent visits. Table 2 summarizes the proportion of subjects who met criteria for clinical response and symptomatic remission at any time during the study and the median clinical response time and median symptomatic remission time from baseline (also depicted in the Kaplan-Meier analyses). Time to median clinical response or median symptomatic remission was when half the population is considered to have had the event in question.

Of the 213 subjects treated with LDX, 169 (79.3%) responded to treatment and 143 (67.1%) achieved remission, compared with 21 (29.2%)

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and 17 (23.6%) of the 72 subjects in the placebo group, respectively (Table 2). In the Kaplan-Meier analysis, time to median clinical response was 13 days and to median symptomatic remission was 22 days for all LDX groups combined (Table 2; Figures 1 and 2). For these global analyses, the null hypothesis of events' distribution across the study time among the optimal dose groups was statistically significant but no pairwise comparisons were tested among the optimal doses.

Long-Term Open-Label Study

The long-term open-label study enrolled 274 children: 272 subjects received LDX treatment and 2 subjects discontinued the study prior to receiving treatment. Effectiveness was assessed in 270 subjects and 147 completed the study. Of the 274 enrolled subjects, 273 participated in one of two prior short-term studies of LDX,[15,16] and one had not previously participated in a study of LDX.

Of the 270 children assessed for effectiveness, 195 (72.2%) met protocol-defined criteria for prior LDX exposure (ie, were randomized to and received LDX treatment in the short-term study) while 75 (27.8%) did not. However, a complicating factor was the inclusion of an *optional* washout period prior to initiating participation in the long-term study, resulting in variable initial treatment conditions at the outset of the optimization period of the long-term study. Since baseline measures were not obtained in the long-term study, it was not possible to determine whether

TABLE 2.
Clinical Response and Symptomatic Remission Outcomes in the Short-Term Study by Treatment Group (N=285)

	Placebo	*30 mg/day LDX*	*50 mg/day LDX*	*70 mg/day LDX*	*All LDX Doses*
Clinical response, n (%)	21 (29.2)	54 (78.3)	55 (77.5)	60 (82.2)	169 (79.3)
Time to median clinical response (days)		9.0	14.0	15.0	13.0
Symptomatic remission, n (%)	17 (23.6)	43 (62.3)	48 (67.6)	52 (71.2)	143 (67.1)
Time to median symptomatic remission (days)		23.0	22.0	21.0	22.0

LDX=lisdexamfetamine dimesylate.

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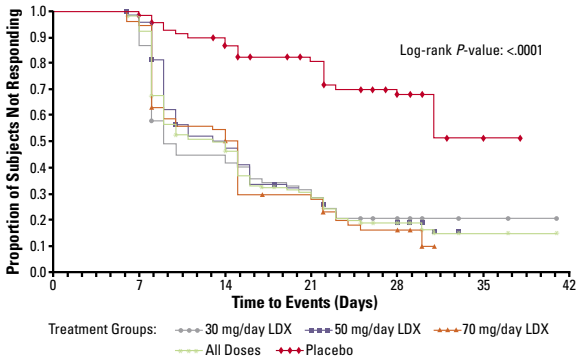
FIGURE 1.
Kaplan-Meier plot time to clinical response from baseline in the short-term study by LDX treatment group (N=285)



Statistically significant differences globally among the doses – not specifically tested between any particular doses; LDX=lisdexamfetamine dimesylate.

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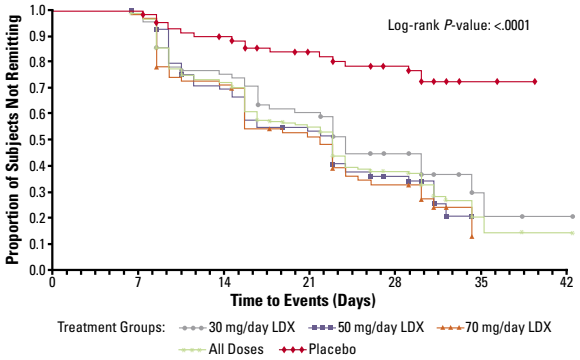
FIGURE 2.
Kaplan-Meier plot time to symptomatic remission from baseline in the short-term study by LDX treatment group (N=285)



Statistically significant differences globally among the doses – not specifically tested between any particular doses; LDX=lisdexamfetamine dimesylate.

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TABLE 3.
Clinical Response and Symptomatic Remission Outcomes in the Long-Term Study Among Subjects Who Completed Dose Optimization by Optimized Dose (n=251)

	30 mg/day LDX	*50 mg/day LDX*	*70 mg/day LDX*	*All LDX Doses*
Clinical response, n (%)	67 (98.5)	99 (98.0)	75 (91.5)	241 (96.0*)
Symptomatic remission, n (%)	62 (91.2)	92 (91.1)	69 (84.1)	223 (88.8†)

* See Figure 3.

† See Figure 4.

LDX=lisdexamfetamine dimesylate.

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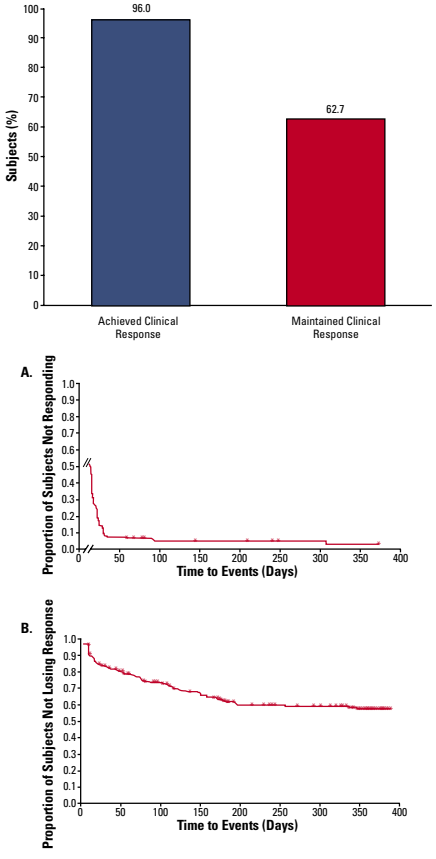
FIGURE 3.
Percentage of subjects that achieved clinical response and maintained clinical response and Kaplan-Meier time-course (inset) of attainment (A) and loss (B) of clinical response from baseline in the long-term study for all lisdexamfetamine dimesylate treatment groups



No day 0 for time to clinical response analysis was defined since response status at the start of the long-term study was not determined. Day 0 for time to loss of clinical response analysis was the beginning of the maintenance phase after the dose-optimization period.

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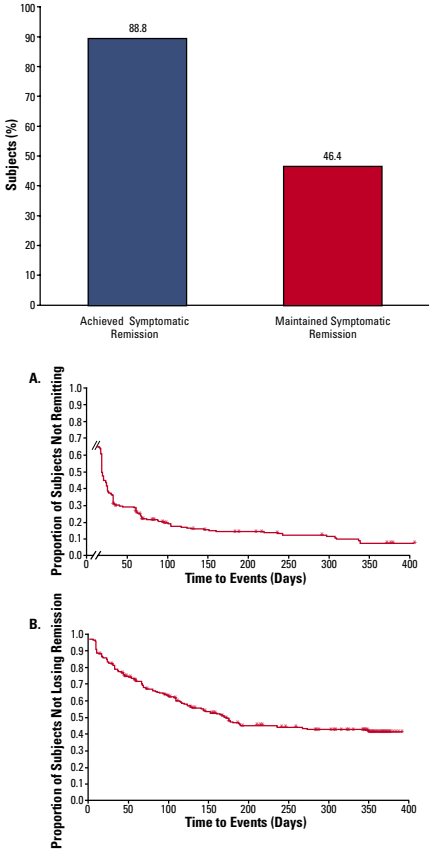
FIGURE 4.
Percentage of subjects that achieved symptomatic remission and maintained symptomatic remission and Kaplan-Meier time-course (inset) of attainment (A) and loss (B) of symptomatic remission in the long-term study for all lisdexamfetamine dimesylate treatment groups



No day 0 for time to symptomatic remission analysis was defined since remission status at the start of the long-term study was not determined. Day 0 for time to loss of symptomatic remission analysis was the beginning of the maintenance phase after the dose-optimization period.

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enrolling subjects had already achieved clinical response or symptomatic remission prior to initiating treatment. Therefore, because the effect of prior LDX exposure on time to clinical response or symptomatic remission in the long-term study could not be determined, time to median clinical response and symptomatic remission was not determined and Kaplan-Meier graphic representation for the long-term study begins with the week 1 assessment.

Of the 270 subjects assessed in the open-label study, 253 (93.7%) met criteria for clinical response at one or more contiguous time points during the study. Moreover, 230 (85.2%) subjects met criteria for remission at one or more contiguous study visits. Of the 251 subjects who completed the 4-week dose-optimization phase, 241 (96.0%) met criteria for clinical response (Table 3 and Figure 3) at one or more contiguous time points during participation in the open-label trial. Of these 241 subjects who responded to treatment, 151 subjects (62.7%) once having achieved response remained responders at each subsequent visit (Figure 3).

Criteria for symptomatic remission were met by 223 (88.8%) of the 251 subjects completing dose optimization (Table 3 and Figure 4) at one or more contiguous study visits. Of these 223 subjects, 220 met criteria for symptomatic remission and continued participation into the maintenance phase (month 2 through month 12 visits). Of these, 102 (46.4%) of the 220 continued to meet criteria for symptomatic remission at each subsequent visit of the 12-month study (Figure 4).

Nineteen subjects were excluded from the time to events analysis in the maintenance phase due to discontinuations before the first maintenance phase visit: 5 withdrew due to adverse events, 7 were lost to follow-up, 5 withdrew consent, 1 withdrew due to lack of efficacy, and 1 did not meet inclusion/exclusion criteria. Time of exposure for these subjects was: 1 week for 1 subject, 2 weeks for 3 subjects, 3 weeks for 8 subjects, 4 weeks for 4 subjects, 5 weeks for 1 subject, and 6 weeks for 2 subjects. Before discontinuing, 6 of the 19 met criteria for clinical response only, 1 subject met criteria for symptomatic remission only, and 6 met criteria for both clinical response and symptomatic remission.

DISCUSSION

These analyses of data from a short-term study and a long-term study of LDX in children with ADHD have shown that, in the 4-week study, a majority of subjects met post hoc criteria for clinical response and symptomatic remission during the trial; in the 12-month study, nearly all optimized subjects (96.0%) met criteria for clinical response and almost as many (88.8%) met criteria for symptomatic remission at least once during the trial. Of the subjects who met clinical response criteria, 62.7% continued to meet criteria at every subsequent visit and of those who met symptomatic remission criteria, almost half (46.4%) continued to meet remission criteria at every subsequent visit.

Time to clinical response and symptomatic remission informs clinicians of the time after which they could expect to see substantial therapeutic effects in their patients. This information may be helpful for clinicians to provide better care for their patients, so that they may better manage dose changes or switching to other medications to achieve the desired therapeutic effect. The two studies in this post hoc analysis of clinical response and symptomatic remission were included to provide a balanced appraisal of time to onset of response or remission and persistence over a long-term period. The short-term study allowed assessment of the time to response or remission in a placebo-controlled fashion. However, that trial had insufficient duration to adequately assess the maintenance of initial response. The long-term trial, then, provided data on the persistence of response with continuing treatment. In the short-term study, time to clinical response with LDX was achieved in ~2 weeks when subjects randomized to receive 50 mg/day or 70 mg/day were receiving the intermediate dose (50 mg/day) while those randomized to receive 30 mg/day remained at this lowest dose. It is possible in clinical practice that both achieving optimal dose and time on treatment are important factors in time to clinical response and symptomatic remission. However, due to the design limitations of these studies (discussed below), it is not possible to differentiate the relative contributions of dose level versus time on treatment in determining the time to achievement of clinical response or symptomatic remission. Overall, based on time to median clinical response in the short-term study, the majority of subjects responded either by the time of the 50-mg/day dose (for those randomized to 50 or 70 mg/day of LDX) or by 2 weeks of treatment (for those randomized to continue on 30 mg/day). Similarly, half the subject group achieved symptomatic remis-

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sion by 3 weeks of treatment in the short-term study, irrespective of the actual dose received.

Some prior studies have reported response rates and remission rates for stimulant and nonstimulant pharmacotherapy in children with ADHD. Typically, clinical response has been defined either as a 25% to 30% decline from baseline in symptom scores on the ADHD-RS-IV or other measures of symptom severity or as a global rating, such as CGI-I of very much improved or much improved at endpoint[14,21-27]; symptomatic remission is sometimes reported as well.[5,6,14,27-29] However, these studies vary widely in design, outcome measures, medication dosage and use, as well as study length. Due to these between-study differences, it may not be surprising that differences in response and remission rates have been reported.[5,6,14,21-33] As such, because few of these studies investigate medications head-to-head (none compares long-acting stimulants with each other) and because of the diverse methodological approaches, meaningful comparisons between medications are not possible. However, this does not preclude the usefulness of these data on clinical response and symptomatic remission rates as a further indication of efficacy data expression.

There are no established guidelines or consensus for appropriate criteria to operationalize proposed definitions of clinical response or symptomatic remission. Definitions of response typically rely on a single measure.[6,22-26,33] The choice of a cutoff value for clinical response is somewhat arbitrary, but others have proposed a 25% or 30% reduction in the ADHD-RS-IV score and/or a CGI-I rating of 1 or 2.[6,24] The criteria for clinical response used in the current study were conservative, requiring improvement as assessed by ADHD-RS-IV and CGI. Several factors argue against a single cutoff criterion. First, a percentage reduction in ADHD-RS-IV alone is not sufficient as a standard because a reduction in the ADHD-RS-IV total score of that size may leave the most severely ill with significant symptoms. Second, depending on the level of baseline severity, a 30% change will have different meaning to those who are severely ill compared with those who are mildly ill; thus, a composite score is required to ascribe further meaning to percentage improvement. Finally, the findings in a recent study using the equipercentile linking technique showed[34] that a percent change from baseline to endpoint in ADHD-RS-IV score of ~25% to 30% or an absolute change of ~10–15 points both corresponded to a change of 1 level in CGI-I ratings at endpoint. This suggests that robust improvements (eg, achieving a CGI-I rating of very much or much improved) would require a larger magnitude (or percentage) of change in ADHD-RS-IV score. With regard to the criteria for symptomatic remission applied in the current study, the definition of symptomatic remission, which indicates improvement to the point that the subject is virtually asymptomatic, is consistent with some definitions previously proposed for symptomatic remission[5,14,28] and represents a treatment-associated loss of symptoms sufficient for a diagnosis of ADHD. This should be considered an additional strength of the design.

There were several general limitations in these studies and analyses. First, the long-term study or extension phase was open-label, in which both the clinician and the subject knew what treatment subjects were receiving. It also has to be taken into consideration that study populations were different from those seen in clinical practice, so it may not be possible to generalize results. Also, different criteria for defining response and remission could lead to different results. Of particular note, this publication is derived from post hoc analyses rather than predefined study endpoints and, as such, these studies were not powered for rigorous analysis of response and remission endpoints.

It is also important to point out other more specific limitations of these studies related to the analysis of time to clinical response and symptomatic remission. While the dose-optimizing design of the long-term study for analysis of time to response or remission may relate more closely to real-world clinical practice, this long-term study presents other limitations in this respect. The entry conditions of the long-term study were variable with some subjects entering from a short-term classroom analog study where all subjects were treated with two different long-acting stimulants and also were alternately receiving LDX and placebo treatment,[16] and other subjects entering from a short-term longitudinal study and variably received LDX or placebo treatment.[15] In addition, most subjects entering the long-term study did not undergo the optional washout period. The long-term study did not include a baseline assessment of ADHD-RS-IV scores. Since it is not possible to determine whether subjects entered the long-term study having already achieved response or remission due to carryover effects from prior LDX treatment

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in the short-term studies, the impact of such prior treatment with LDX on time to response or remission in the long-term study is unclear.

It should be stressed that these analyses focused on response and remission of ADHD symptoms and did not address effects on functional impairments. Additionally, these analyses assessed impact of treatment on symptoms over a 1-year period; it is unknown whether response or remission would continue over longer periods. It is not clear whether the long-term benefits of pharmacotherapy on symptom reduction are paralleled by similar lasting benefits on functional impairments. While recent analyses of data from the MTA[35] and from a year-long study of children in community-practice settings[36] suggest that long-term symptom reduction and functional improvements may not be closely linked, other evidence suggests distinct benefits in terms of comorbid psychiatric disorders and academic achievement into adolescence with continued stimulant treatment.[37]

Most children achieved significant improvement in ADHD symptoms, clinical response, and symptomatic remission with short- and long-term treatment with LDX. Almost half the treated subjects maintained continuous symptomatic remission during the 11-month follow-up. Assessments of clinical response and symptomatic remission provide clinicians with additional measures of treatment efficacy that are more closely related to clinical approaches than assessments of group average scores.[5] Further studies are required to validate this concept of symptomatic remission—what does it predict in the future and how does it impact functionality. Additionally, further carefully designed prospective studies should be able to provide insight into the relative impact of optimal dose achievement versus time on treatment in determining at what point clinicians and patients might expect to see measureable clinical response and symptomatic remission.

CONCLUSION

The post hoc analysis used in these two studies applied previously proposed criteria for ADHD symptom response (reduction in ADHD-RS-IV total score of ≥30% and a CGI-I rating of 1 or 2) and symptomatic remission (ADHD-RS-IV total score of ≤18) to evaluate clinically meaningful symptom improvement among children with ADHD who received LDX treatment.[5,6,14] The majority of subjects receiving LDX achieved clinical response and symptomatic remission in both the short-term randomized controlled trial with forced-dose titration and the long-term open-label trial with a dose-optimized trial design. For approximately half of those in the long-term trial, symptomatic remission was maintained during continued treatment with LDX. Further study using prospective evaluation of response and remission endpoints is needed to confirm these results. ***CNS***

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