ORIGINAL RESEARCH
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Interpreting ADHD Rating *Scale Scores: Linking ADHD Rating Scale Scores and CGI Levels in Two Randomized Controlled Trials of Lisdexamfetamine Dimesylate in ADHD*

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ABSTRACT

Objective: *To provide additional understanding of the clinical significance of Attention-Deficit/Hyperactivity Disorder Rating Scale, Version IV (ADHD-RS-IV) total and change scores in relation to Clinical Global Impressions-Severity or -Improvement (CGI-S/-I) levels.*

Methods: *Using two similarly designed pivotal trials of lisdexamfetamine dimesylate (Vyvanse, Shire US Inc), equipercentile linking was used to identify scores on the ADHD-RS-IV and CGI that have the same percentile rank.*

Results: *As assessed by CGI-S levels, moderately, markedly, severely, and extremely ill adults had mean (SD) baseline ADHD-RS-IV scores of 36.2 (4.9), 42.1 (6.1), 45.4 (5.1), and 53.0, respectively. A similar relationship was observed in children. At endpoint, children categorized as minimally, much, or very much improved by CGI-I demonstrated mean (SD) ADHD-RS-IV changes from baseline of -9.9 (6.8), -25.5 (7.2), and -33.2 (9.3), respectively. Adults demonstrated a similar relationship between ADHD-RS-IV change scores and CGI-I ratings. Based on equipercentile link function, a change from baseline in ADHD-RS-IV total score of ~10–15 points or 25% to 30% corresponded to a change of 1 level in CGI-I score.*

Conclusion: *This analysis makes possible the establishment of a clinical impression of severity of illness from total ADHD-RS-IV scores and may facilitate the clinical interpretation of improvement of ADHD-RS-IV change scores.*

FOCUS POINTS

- Linking the Clinical Global Impressions-Severity (CGI-S) ratings with Attention-Deficit/Hyperactivity Disorder Rating Scale, Version IV (ADHD-RS-IV) scores at baseline, two trials of lisdexamfetamine dimesylate demonstrated that a difference of ~8–10 points in baseline ADHD-RS-IV score is appreciated clinically as a 1-point difference in CGI-S score.
- An improvement in ADHD-RS-IV score of ~50% to 60% is needed to achieve a rating of much improved (2-level improvement) on the CGI-Improvement scale.
- For all three pairs of linkages, the relationship between ADHD-RS-IV scores and CGI levels was consistent across the age groups.

INTRODUCTION

The use of rating scales to quantify subjects' response to treatment for attention-deficit/hyperactivity disorder (ADHD) is commonplace in clinical trials. These scales are less commonly used in clinical practice and, as such, the clinical implications of total or change scores on these scales may not be readily apparent to clinicians. Additionally, the measures of response used in clinical trials may not mimic the standards used by clinicians in practice.

The ADHD Rating Scale, Version IV (ADHD-RS-IV),[1] has been widely used as a measure of efficacy in clinical trials of ADHD treatments in children and adolescents.[2,3] Derived from the 18 inattentive and hyperactive/impulsive diagnostic criteria for ADHD from the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition,[4] the parent

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and teacher versions of the ADHD-RS-IV have a large base of normative data and have demonstrated reliability and discriminant validity in children and adolescents.[1,3] A validated, clinician-administered version of the ADHD-RS-IV using adult prompts was developed at New York University/Massachusetts General Hospital (NYU/MGH) and has been used in adult populations.[5-8] Despite extensive use in clinical trials, the meaning of a reduction (ie, improvement) in ADHD-RS-IV scores in response to treatment, with regard to an overall clinical effect, remains unclear.

Global rating scales of disease severity or improvement such as the Clinical Global Impressions-Improvement (CGI-I) and Severity (CGI-S) scales[9] are typically more intuitive to clinicians,[10] and may better correspond to the global judgments made by clinicians in practice than the item-by-item scores of rating scales. While sometimes adapted for a specific domain of symptoms,[11] these scales typically ask clinicians to make a global assessment of function, symptoms, and adverse events (AEs) to rate a patient's severity of symptoms (ie, CGI-S) and change in symptoms from baseline (ie, CGI-I) based on their experience with the patient population and baseline status, respectively.[9] While the psychometric properties of the CGI have not been fully explored, preliminary studies[12,13] demonstrate that it is sensitive to differences in treatment responses and possesses good internal consistency and concurrent validity. The CGI scales, however, lack well-defined, consistently applied ADHD-specific anchor points and may not yield consistent results across raters as highlighted by a recent study[14] in which clinicians differed considerably in which factors (eg, side effects) they considered when determining a CGI rating.[10,14,15]

Given the widespread use of the CGI in clinical trials and the potential that such a global assessment of patients may be more contextually applicable and generally understandable to clinicians,[10] several analyses have explored the relationship between disorder-specific psychiatric rating scales commonly used in trials (eg, the Positive and Negative Syndrome Scale, the Panic Disorder Severity Scale, and the Brief Psychiatric Rating Scale) and scores on the CGI.[16-19] Such analyses typically use the equipercentile linking technique described by Kolen and Brennan.[20]

The goal of this analysis was to use the equipercentile linking technique to better understand the relationship between scores on the ADHD-RS-IV and scores on the CGI using data from pivotal clinical trials of lisdexamfetamine dimesylate (LDX) in adults and children with ADHD.[21,22] LDX is the first long-acting prodrug stimulant and is indicated in the United States for the treatment of ADHD in children 6–12 years of age and in adults. LDX is a therapeutically inactive molecule. After oral ingestion, LDX is converted to l-lysine and active d-amphetamine, which is responsible for the therapeutic effect.[23,24]

METHODS

Data Sources

This analysis was conducted using data from two pivotal trials of LDX, one in adults[21] and one in children[22] with ADHD. Complete descriptions of both studies have been published previously. Briefly, both studies were 4-week, randomized, double-blind, placebo-controlled, forced-dose escalation, parallel-group trials. In the adult trial, subjects were 18–55 years of age, while in the pediatric trial, subjects were 6–12 years of age. In both trials, subjects had to meet *DSM-IV-TR*[25] diagnostic criteria for a primary diagnosis of ADHD and were excluded from the trial if they had a comorbid psychiatric diagnosis with significant symptoms, any medical condition that could interfere with the study or increase risk to the subject, history of seizures (excluding febrile seizures), tic disorder, or Tourette's disorder. Additional exclusion criteria included any cardiac abnormality that may affect cardiac performance, a clinically significant electrocardiogram or laboratory abnormality, hypertension, pregnancy, lactation, and concomitant use of any medication with central nervous system or blood pressure effects (excluding ADHD treatments, which were washed out). Adults were required to have baseline ADHD-RS-IV total scores of at least 28 assessed using NYU/MGH adult prompts, and children were required to have ADHD-RS-IV total scores of at least 28 at baseline.

Each study began with a screening and washout period during which ADHD medications were discontinued. At the baseline visit, adult subjects were randomized to receive once-daily LDX 30, 50, or 70 mg or placebo for 4 weeks in a 2:2:2:1 ratio. In the pediatric trial, subjects were randomized 1:1:1:1 to placebo or once-daily doses of LDX 30, 50, or 70 mg. Subjects followed a forced-dose titration schedule with those randomized to receive 70 mg/day being titrated to that dose over 2 weeks.

Assessments

In the pediatric study,[22] the primary efficacy measure was the ADHD-RS-IV; in the adult study[21] it was the ADHD-RS-IV with adult prompts. In both trials, the ADHD-RS-IV was administered by experienced investigators at each study visit. Whereas the ADHD-RS-IV was originally designed to assess a patient's behavior over a period of 6 months,[1] in these trials it was used to capture behavior over the preceding week. Each item on the 18-item measure is scored on a 4-point scale ranging from 0 (no symptoms) to 3 (severe symptoms), yielding a possible total score of 0–54. Both versions of the scale assess the 18 *DSM-IV* diagnostic criteria for ADHD, but the individual items are phrased slightly

differently. For example, in the pediatric trial, one item asked raters to evaluate if subjects had "difficulty sustaining attention in tasks or play activities." In the adult trial, the analogous item asked whether the subject had "difficulty sustaining attention in tasks or fun activities."

The CGI scale was a secondary efficacy measure in both trials. At the baseline visit, clinicians completed the CGI-S and were asked to evaluate the severity of subjects' illness with respect to ADHD symptoms based on the clinician's experience with this particular population. Possible scores ranged from 1 (normal, not ill at all) to 7 (among the most extremely ill subjects). At all subsequent study visits, clinicians used the CGI-I to rate the subjects' total improvement based on comparison with their baseline assessment from 1 (very much improved) to 7 (very much worse).

Statistical Analysis

The procedure for finding corresponding scores on different measurement instruments is called linking.[26] Equating procedures, originally described as a method intended to provide interchangeable scores, are the strongest form of linking and can be performed on parallel, yet distinct scales, as in the present analysis. When used in such a manner, the results lead to scores that are not necessarily interchangeable but, rather, are concordant.[26,27]

The present trial used the equipercentile linking technique detailed by Kolen and Brennan[20] at two time points (baseline and endpoint) in each LDX clinical trial to derive percentile rankings of baseline scores on the ADHD-RS-IV and CGI-S ratings as well as endpoint change scores on the ADHD-RS-IV and CGI-I ratings, and to identify scores at each time point in each study that had the same percentile rank. The equipercentile linking technique is not a comparison by subject, where the absolute score on the CGI is compared with the absolute score on the ADHD-RS-IV. Rather, equipercentile linking is a technique that identifies scores on two measures that have the same percentile rank (irrespective of which subjects had particular scores on either measure). So, for every score on one scale, there is a corresponding score on the other scale that has the same percentile rank. Percentile rank functions are calculated for both the ADHD-RS-IV and CGI in the present analysis.

Analyses were performed to compare baseline ADHD-RS-IV scores with CGI-S scores as well as the absolute change and percentage change from baseline in ADHD-RS-IV scores with CGI-I scores. The process of equipercentile linking begins with the calculation of percentile rank function for each variable. A graph is then generated using a score on one measure and the score on the other as the X and Y variables for each point, based on each having the same percentile rank.[20] For example, if on Measure 1, 50% of subjects score X or below while on Measure 2, 50% score Y or below; the point X,Y is plotted on a new graph. The X and Y axes are the respective measure scores, not the percentiles. Similar points are generated for each matched percentile ranking, and the resulting line is the equipercentile link function.

Although scores on the CGI scales are discrete, the equipercentile link function is continuous. Therefore, for this analysis, CGI levels are understood to encompass a range. For example, a CGI-S level of markedly ill (a score of 5 on the scale) is equivalent to any score from 4.5–5.5, rather than simply 5. Similarly, CGI-S scores of 2.5–4.5 represent mildly ill (3) to moderately ill (4), 4.5–5.5 represent markedly ill (5), and scores >5.5 represent severely ill (6) to extremely ill (7). On a continuous plot of the CGI-I scale, scores <2.5 represent very much (1) to much (2) improved while scores ranging from 2.5–3.5 represent minimally improved (3), and those >3.5 signify no change (4) or a worsening (5, 6, or 7) compared with the baseline assessment.

Analyses were conducted on the intention-to-treat (ITT) populations of both trials, defined as all subjects randomized to receive treatment who had both a baseline and at least one post randomization ADHD-RS-IV total score available. For all analyses, endpoint was defined as the last post randomization treatment week for which a valid ADHD-RS-IV and CGI-I score was obtained. Only subjects with ADHD-RS-IV scores and CGI-I ratings at endpoint were included in the analysis. Additional analyses by gender were conducted to assess whether there were differences between male and female subjects in link analysis of ADHD-RS-IV scores and CGI ratings.

RESULTS

The demographic and baseline characteristics of the pediatric and adult study populations have been detailed in publications by Biederman and colleagues[22] and Adler and colleagues,[21] respectively. The treatment groups within each study were generally well matched at baseline. The ITT populations of the trials consisted of 285 children (213 randomized to receive LDX and 72 randomized to receive placebo) and 414 adults (352 randomized to receive LDX and 62 randomized to receive placebo).

As previously reported, significant treatment effects were observed in the primary efficacy measure, the mean change from baseline to endpoint in ADHD-RS-IV total scores compared with placebo for all LDX doses (adult and pediatric studies, $P<.0001$; Figure 1).[21,22] The proportion of subjects with a CGI-I score of 1 (much improved) or 2 (very much improved) at endpoint was significantly higher in all LDX treatment groups compared with the respective placebo groups (adult study $P<.01$; pediatric study, $P<.0001$). Among patients receiving LDX, AEs were generally mild or moderate in severity and typical of those observed in trials of other amphetamine-

based ADHD treatments. The most common AEs associated with LDX in children included decreased appetite, insomnia, abdominal pain, and irritability, and in adults included dry mouth, decreased appetite, and insomnia.

Linking ADHD-RS-IV Total Scores and CGI-S Levels

The summary statistics for baseline ADHD-RS-IV total scores by baseline CGI-S levels from both studies are presented in Table 1. In the adult study, mean (SD) ADHD-RS-IV scores of 36.2 (4.9), 42.1 (6.1), 45.4 (5.1), and 53.0 corresponded with CGI-S scores of 4 (moderately ill), 5 (markedly ill), 6 (severely ill), and 7 (extremely ill), respectively. It should be noted that these statistics include one subject who had an ADHD-RS-IV total score of 14 (and a CGI-S of markedly ill) at baseline. This subject had an ADHD-RS-IV total score of 35 at screening and 34 after 1 week of treatment. In the pediatric study, mean (SD) ADHD-RS-IV scores of 28.0, 38.7 (6.3), 45.5 (5.8), 48.2 (4.1), and 50.5 (4.0) corresponded with CGI-S scores of 3 (mildly ill), 4 (moderately ill), 5 (markedly ill), 6 (severely ill), and 7 (extremely ill), respectively. Also included in Table 1 are the ADHD-RS-IV quartile scores corresponding to each CGI-S level and the range of ADHD-RS-IV scores corresponding to each CGI-S level that were used in creating the equipercentile link function.

The equipercentile link function for CGI-S and ADHD-RS-IV baseline scores are presented in Figure 2. Data from the adult study demonstrated that a change in the baseline ADHD-RS-IV score of ~8–10 corresponded to a change of 1 in CGI-S level (Figure 2A). Based on the link function from the adult study, baseline ADHD-RS-IV scores ranging from 13.5–37.4 are expected to correspond to CGI-S levels of mildly to moderately ill. Scores ranging from 37.5–48.3 and from 48.4–54.5 corresponded to CGI-S ratings of markedly ill and severely to extremely ill, respectively (Table 2).

Similar to the adult study, the equipercentile link function for CGI-S and ADHD-RS-IV baseline scores derived from the pediatric study also demonstrated that a change in the baseline ADHD-RS-IV score of ~8–10 corresponded to a change of 1 in CGI-S score (Figure 2B). In addition, based on the equipercentile link function, in children a baseline ADHD-RS-IV score of 28.2–41.2 is expected to correspond to a CGI-S level of mildly or moderately ill; an ADHD-RS-IV score of 41.3–50.7 to a CGI-S level of markedly ill; and an ADHD-RS-IV score of 50.8–54.5 corresponded to a CGI-S level of severely to extremely ill (Table 2).

Linking ADHD-RS-IV Total Score Changes From Baseline and CGI-I Levels

The CGI-I levels at endpoint and the corresponding absolute change from baseline to endpoint in ADHD-RS-IV total score are presented in Table 3. In the adult trial, 317 patients were rated improved by CGI-I at endpoint while 97 were rated as no change or worse. Of the 317 adults who improved with treatment, CGI-I scores of 1 (very much improved), 2 (much improved), and 3 (minimally improved) corresponded with mean (SD) changes from baseline in ADHD-RS-IV total scores of -30.4 (7.8), -20.6 (7.2), and -11.2 (5.9), respectively. Adults assessed by CGI-I at endpoint as exhibiting no change demonstrated a mean (SD) change in ADHD-RS-IV total score of -2.1 (3.8).

TABLE 1
DISTRIBUTION OF BASELINE ADHD-RS-IV SCORES BY BASELINE CGI-S LEVELS

Study	CGI-S	n	Mean (SD)	Quartiles	Min/Max
Adult	4: Moderately ill	139	36.2 (4.9)	(32, 36, 39)	28/50
	5: Markedly ill	218	42.1 (6.1)	(39, 42, 47)	14*/54
	6: Severely ill	56	45.4 (5.1)	(42, 46, 49)	32/54
	7: Extremely ill	1	53.0	53	53
Pediatric	3: Mildly ill	1	28.0	28	28
	4: Moderately ill	101	38.7 (6.3)	(34, 36, 42)	28/54
	5: Markedly ill	134	45.5 (5.8)	(42, 46, 50)	29/54
	6: Severely ill	45	48.2 (4.1)	(45, 49, 51)	38/54
	7: Extremely ill	4	50.5 (4.0)	(48, 52, 54)	45/54

* One subject had a baseline ADHD-RS-IV total score of 14: see text on this page for details.

ADHD-RS-IV=Attention-Deficit/Hyperactivity Disorder Rating Scale, Version IV; CGI-S=Clinical Global Impressions-Severity; Min=minimum; Max=maximum.

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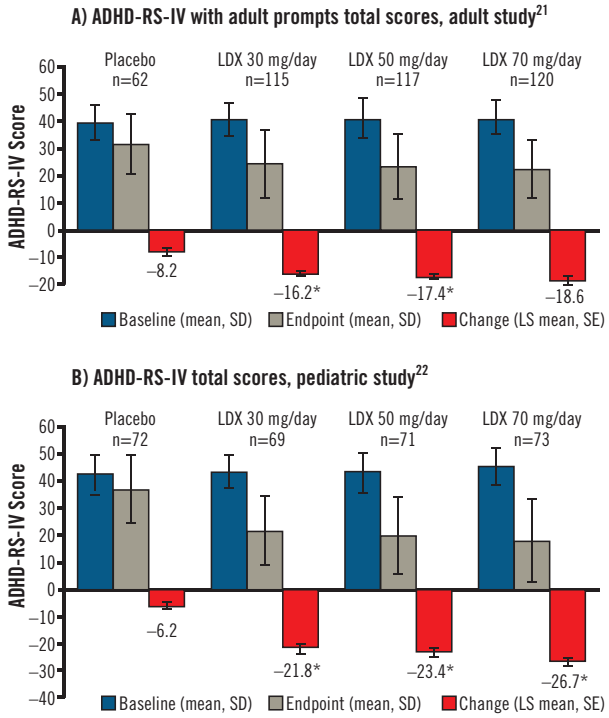
In the pediatric trial, as assessed by the CGI-I, 217 children showed improvement with treatment while 68 showed no change or worse. Of the children demonstrating improvement, the mean (SD) change from baseline in ADHD-RS-IV scores at endpoint were -33.2 (9.3), -25.5 (7.2), and -9.9 (6.8) for subjects with CGI-I scores of 1 (very much improved), 2 (much improved), and 3 (minimally improved), respectively.

FIGURE 1

LDX TREATMENT RESULTED IN SIGNIFICANT IMPROVEMENTS AT ENDPOINT IN ADHD-RS-IV TOTAL SCORES IN A) ADULTS[21] AND B) CHILDREN[22] WITH ADHD



The treatment endpoint of the primary efficacy measure was defined as the last post randomization treatment week for which a valid ADHD-RS-IV score was obtained.

*$P<.0001$ (adjusted Dunnett test compared with placebo following analysis of covariance with baseline score as covariate).

LDX=lisdexamfetamine dimesylate; ADHD-RS-IV=Attention-Deficit/Hyperactivity Disorder Rating Scale, Version IV; LS=least squares.

Adler LA, Goodman DW, Kollins SH, et al. Double-blind, placebo-controlled study of the efficacy and safety of lisdexamfetamine dimesylate in adults with attention-deficit/hyperactivity disorder. *J Clin Psychiatry.* 2008;69(9):1364-1373. Reprinted with permission from Physician's Postgraduate Press. Copyright 2008.

Biederman J, Krishnan S, Zhang Y, McGough JJ, Findling RL. Efficacy and tolerability of lisdexamfetamine dimesylate (NRP-104) in children with attention-deficit/hyperactivity disorder: a phase III, multicenter, randomized, double-blind, forced-dose, parallel-group study. *Clin Ther.* 2007;29(3):450-463. Reprinted with permission from Excerpta Medica, Inc. Copyright 2007.

The graph of the equipercentile link function in Figure 3 shows the relationship between CGI-I levels at endpoint and the *absolute* change from baseline to endpoint in ADHD-RS-IV scores derived from the adult study (Figure 3A) and the pediatric study (Figure 3B). Both graphs indicate that a change from baseline to endpoint in ADHD-RS-IV total score of roughly 10–15 corresponded to a change of 1 in CGI-I score at endpoint.

Based on the above link function, a change from baseline to endpoint in ADHD-RS-IV score of -13.6 to -49.5 corresponded to a CGI-I level at endpoint of much improved or very much improved in adults. Using the link function from the pediatric study, an improvement in ADHD-RS-IV total scores from baseline at endpoint of -17.3 to -50.5 would have been expected to result in a CGI-I score of 2 or 1 (ie, much improved or very much improved) among children. Additional ranges of ADHD-RS-IV scores and their corresponding CGI-I levels are presented in Table 4. In the pivotal trials included in the present analysis, the mean ADHD-RS-IV total score change from baseline at endpoint associated with LDX treatment ranged from -16.2 to -18.6 in the adult study and -21.8 to -26.7 in the pediatric study. According to the link function, these mean scores corresponded to a CGI-I level of much improved.

When the equipercentile link function was carried out for CGI-I scores at endpoint and the *percent* change from baseline at endpoint in ADHD-RS-IV, CGI-I scores of 1, 2, and 3 (very much improved, much improved, and minimally improved) roughly corresponded to percent changes in ADHD-RS-IV scores of -80% and -80%, -48%, and -52%, and -25% and -27% (adult and pediatric studies, respectively; Figure 4). A percent change from baseline to endpoint in

TABLE 2

CORRESPONDING RANGES OF ADHD-RS-IV TOTAL SCORES AND CGI-S LEVELS DERIVED FROM THE LINK FUNCTION

CGI-S	ADHD-RS-IV
Adult Study	
Mildly to moderately ill	13.5 to 37.4
Markedly ill	37.5 to 48.3
Severely to extremely ill	48.4 to 54.5
Pediatric Study	
Mildly to moderately ill	28.2 to 41.2
Markedly ill	41.3 to 50.7
Severely to extremely ill	50.8 to 54.5

ADHD-RS-IV=Attention-Deficit/Hyperactivity Disorder Rating Scale, Version IV; CGI-S=Clinical Global Impressions-Severity.

ADHD-RS-IV total score of ~25% to 30% corresponded to a change of 1 in CGI-I score at endpoint. Therefore, an improvement in ADHD-RS-IV score of ~50% to 60% and >75% is needed to achieve a rating of much improved and very much improved, respectively.

Post hoc analyses found no gender differences in linking ADHD-RS-IV and CGI in relation to either baseline severity or change from baseline at endpoint.

DISCUSSION

In this analysis, the linking between CGI levels and ADHD-RS-IV scores was established using the equipercentile link function and was based on LDX trial data from adults and children with ADHD. To the authors' knowledge, this is the first time a reliable and valid ADHD-specific rating scale,[7,8] the ADHD-RS-IV, has been linked to a clinically meaningful global assessment such as the CGI. This analysis generated three sets of link functions, each containing one linkage for adult subjects and one for pediatric subjects with ADHD. For all three pairs of linkages, the relationship between ADHD-RS-IV scores and CGI levels were consistent across the age groups. This is noteworthy because ADHD symptoms are often variable across the life span and the goals of treatment may be distinct in adults compared with children.[28] Such a consistent relationship between the ADHD-RS-IV and CGI across age groups, however, should allow for a valid and consistent means of treatment titration even as children grow into adulthood.

The ability to link ADHD-RS-IV score changes to global improvements as assessed by the CGI-I has several implications for the interpretation of clinical trial results. For example, absolute changes in ADHD-RS-IV scores associated with a given treatment should be interpreted with the understanding that an absolute change of ~10–15 is required to be detected as a change of 1 level on the CGI-I. Clinicians may find such global assessments more clinically useful than reports of mean changes in rating scale scores compared with placebo, the measure usually reported in clinical trials, to understand the likely impact of a treatment on their patients. Furthermore, given that clinicians may not routinely use rating scales such as the ADHD-RS-IV, these results facilitate interpretation of the results of trials of ADHD treatments by healthcare providers and patients because more widely used and readily understood clinical terms may be applied to ADHD-RS-IV scores.

Based on this analysis, a clinically detectable response to treatment, that is, a change in CGI-I score of at least 1 level, requires at least a 25% to 30% change in ADHD-RS-IV score. Historically, clinical trials have often used a 25% to 30% reduction in symptoms as assessed by the ADHD-RS-IV as a threshold for response.[29] Interestingly, this threshold has not been fully substantiated by statistical support for the adequacy of this cutoff. Clinical trials have also defined response as a global rating of much or very much improved. The results of this analysis suggest that these two definitions of response are not concordant and that the benchmark of a 25% to 30% reduction in symptoms as a barometer of

TABLE 3

DISTRIBUTION OF ABSOLUTE ADHD-RS-IV TOTAL SCORE CHANGES FROM BASELINE AT ENDPOINT BY CGI-I LEVELS AT ENDPOINT

Study	*CGI-I*	*n*	*Mean (SD)*	*Quartiles*	*Min/Max*
Adult	1: Very much improved	86	-30.4 (7.8)	(-37, -31, -25)	-46/-14
	2: Much improved	142	-20.6 (7.2)	(-25, -20, -16)	-49/4
	3: Minimally improved	89	-11.2 (5.9)	(-14, -11, -8)	-41/0
	4: No change	86	-2.1 (3.8)	(-4, -2, 1)	-12/13
	5: Minimally worse	9	4.8 (5.5)	(4, 7, 8)	-8/10
	6: Much worse	2	6.0 (1.4)	(5, 6, 7)	5/7
Pediatric	1: Very much improved	102	-33.2 (9.3)	(-41, -34, -26)	-50/-16
	2: Much improved	65	-25.5 (7.2)	(-31, -25, -20)	-42/-11
	3: Minimally improved	50	-9.9 (6.8)	(-15, -10, -5)	-24/6
	4: No change	47	-1.1 (5.2)	(-3, -1, 2)	-24/13
	5: Minimally worse	15	-0.1 (9.8)	(-4, 2, 7)	-21/13
	6: Much worse	4	5.3 (5.1)	(1, 5, 10)	0/11
	7: Very much worse	2	-10.5 (2.1)	(-12, -11, -9)	-12/-9

ADHD-RS-IV=Attention-Deficit/Hyperactivity Disorder Rating Scale, Version IV; CGI-I=Clinical Global Impressions-Improvement.

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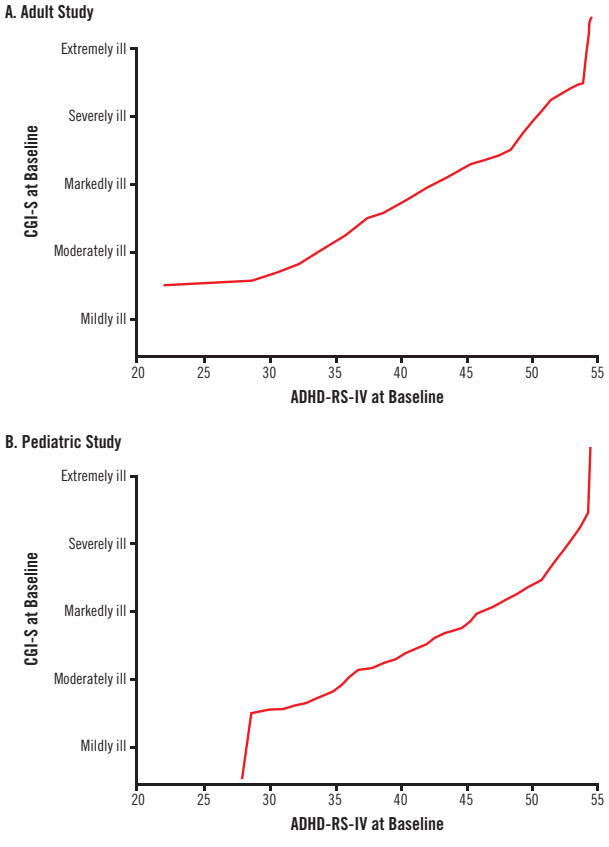
efficacy, while satisfactory, may not be optimal for future development of useful treatments for ADHD. This also raises the possibility that more stringent criteria, perhaps a 50% reduction in ADHD-RS-IV total score, might be considered as a new standard for response in clinical trials.

The results of the present analysis should be viewed in light of several limitations. Although the results obtained from the adult and pediatric trial were similar, it should be noted that the versions of the ADHD-RS-IV used in these trials were not identical. In the adult study, the ADHD-RS-IV was a semistructured scale and used adult ADHD prompts,[5] whereas the pediatric scale was a more structured assessment. In both trials, the scoring of the CGI and ADHD-RS-IV were not independent since they were completed by the same investigator based on behavior observed and reported during the same study visit. Because neither trial included adolescent patients, relationship between ADHD-RS-IV scores and CGI levels in that population remains unknown.

The present analysis contains both potential ceiling and floor effects. The CGI-S was only assessed at baseline, at which point subjects were required to have ADHD-RS-IV scores of ≥28. The lack of CGI-S scores available at endpoint precludes the establishment of a threshold for normalization. Relatively few subjects represented the low and high ends of the ADHD-RS-IV and CGI scales, which likely accounts for the abrupt changes observed in the slopes of the equipercentile link function showing the relationship between ADHD-RS-IV scores at baseline and CGI-S levels (Figures 2A and 2B). For example, only one patient in the adult study had a CGI-S score of 7 and none had a CGI-S score of 3; in the pediatric trial, only one subject was assessed as mildly ill (ie, CGI-S score of 3) and four were assessed as being extremely ill (ie, CGI-S score of 7).

FIGURE 2

LINK FUNCTION OF ADHD-RS-IV AND CGI-S BASELINE VALUES DERIVED FROM A) ADULT AND B) PEDIATRIC PIVOTAL TRIALS OF LDX



LDX=lisdexamfetamine dimesylate; ADHD-RS-IV=Attention-Deficit/Hyperactivity Disorder Rating Scale, Version IV; CGI-S=Clinical Global Impressions-Severity.

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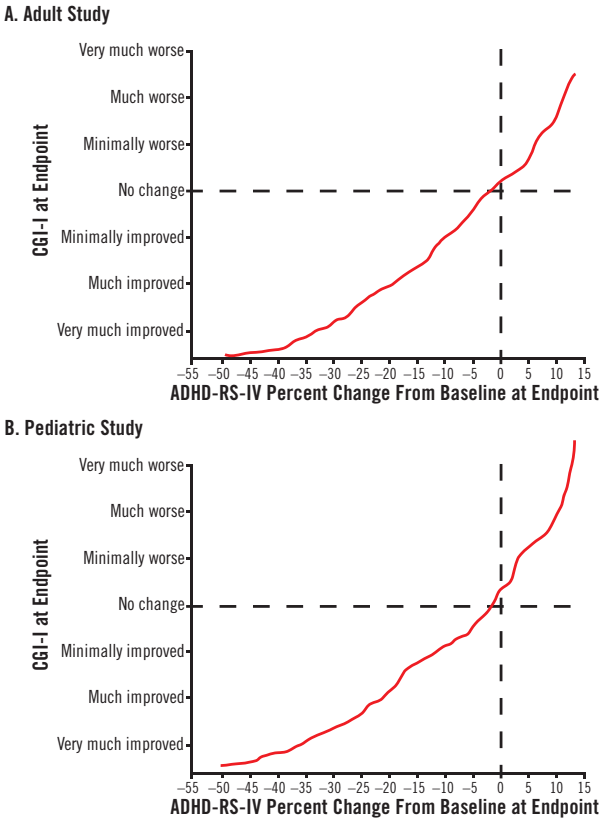
FIGURE 3

LINK FUNCTION FOR THE ABSOLUTE CHANGE FROM BASELINE TO ENDPOINT IN ADHD-RS-IV TOTAL SCORES AND CGI-I SCORES AT ENDPOINT DERIVED FROM A) ADULT AND B) PEDIATRIC TRIALS OF LDX



LDX=lisdexamfetamine dimesylate; ADHD-RS-IV=Attention-Deficit/Hyperactivity Disorder Rating Scale, Version IV; CGI-I=Clinical Global Impressions-Improvement.

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The data from the present analysis originated from two studies with very similar methodologies and included data from ~700 subjects with ADHD. As pivotal trials, both studies had rigorous inclusion and exclusion criteria such as the exclusion of subjects with most medical and psychiatric comorbidities. Such limitations result in a patient population distinct from that seen in clinical practice and may limit generalization of the present results to broader patient populations. Additional analyses using similar methods across other data sets should attempt to confirm and extend these findings, perhaps providing data at the ends of the scales or demonstrating that these findings are similar in other patient populations.

CONCLUSION

Clinical studies of ADHD often employ rating scales to assess symptom improvement associated with a given treatment. Such measures, while psychometrically sound, are less intuitive and may be assessed by clinicians less frequently than global assessments of improvement since it is often unclear how much of a change in symptom-based scores corresponds to a change that can be observed clinically. In this preliminary analysis, ADHD-RS-IV scores were linked to CGI ratings using the equipercentile linking technique and produced results that were consistent between children and adults. A change of ~10–15 points in ADHD-RS-IV score corresponded to a change of 1 level in CGI-I rating. When analyzed by percent change, each change of ~25% to 30% in ADHD-RS-IV score resulted in a 1 level change in CGI-I. These results may further the clinical understanding of severity levels and change scores on the ADHD-RS-IV and suggest new thresholds for defining clinical response when evaluating ADHD treatments. ***PP***

TABLE 4

CORRESPONDING RANGES OF ADHD-RS-IV TOTAL SCORE CHANGES FROM BASELINE AND CGI-I LEVELS DERIVED FROM THE LINK FUNCTION

Study	*CGI-I Level*	*ADHD-RS-IV Score Change From Baseline*
Adult	Very much to much improved	-13.6 to -49.5
	Minimally improved	-5.6 to -13.4
	No change or worse	13.5 to -5.4
Pediatric	Very much to much improved	-17.3 to -50.5
	Minimally improved	-4.9 to -17.2
	No change or worse	13.5 to -4.8

ADHD-RS-IV=Attention-Deficit/Hyperactivity Disorder Rating Scale, Version IV; CGI-I=Clinical Global Impressions-Improvement.

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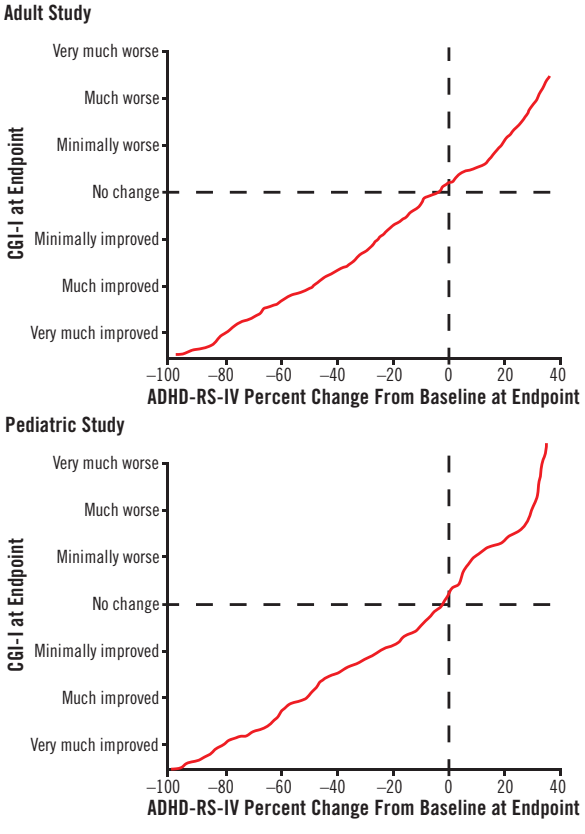
REFERENCES

1. DuPaul GJ, Power TJ, Anastopoulos AD, Reid R. *ADHD Rating Scale–IV: Checklists, Norms, and Clinical Interpretation.* New York, NY; Guilford Press; 1998.
2. Spencer TJ, Wilens TE, Biederman J, Weisler RH, Read SC, Pratt R. Efficacy and safety of mixed amphetamine salts extended release (Adderall XR) in the management of attention-deficit/hyperactivity disorder in adolescent patients: a 4-week, randomized, double-blind, placebo-controlled, parallel-group study. *Clin Ther.* 2006;28(2):266-279.
3. Collett BR, Ohan JL, Myers KM. Ten-year review of rating scales. V: scales assessing attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry.* 2003;42(9):1015-1037.
4. *Diagnostic and Statistical Manual of Mental Disorders.* 4th ed. Washington, DC: American Psychiatric Association; 1994.
5. Adler L, Cohen J. Diagnosis and evaluation of adults with attention-deficit/hyperactivity disorder. *Psychiatr Clin North Am.* 2004;27(2):187-201.
6. Weisler RH, Biederman J, Spencer TJ, et al. Mixed amphetamine salts extended-release in the treatment of adult ADHD: a randomized, controlled trial. *CNS Spectr.* 2006;11(8):625-639.
7. Spencer TJ, Adler LA, Qiao M, et al. Validation of the Adult ADHD Investigator Symptom Rating Scale (AISRS). *J Atten Disord.* 2009 Sep 30. [Epub ahead of print].
8. Adler LA, Spencer TJ, Biederman J, et al. The internal consistency and validity of the Attention-Deficit/Hyperactivity Disorder Rating Scale (ADHD-RS) with adult ADHD prompts as assessed during a clinical treatment trial. *J ADHD Relate Disord.* 2009;1(1):14-24.
9. Guy W. Clinical global impressions. In: *ECDEU Assessment Manual for Psychopharmacology.* Rockville, MD: US Department of Health, Education, and Welfare; Public Health Service, Alcohol, Drug Abuse and Mental Health Administration, NIMH Psychopharmacology Research Branch; 1976;218-222.
10. Nierenberg AA, DeCecco LM. Definitions of antidepressant treatment response, remission, nonresponse,

FIGURE 4

LINK FUNCTION FOR PERCENT CHANGE FROM BASELINE TO ENDPOINT IN ADHD-RS-IV TOTAL SCORES AND CGI-I SCORES AT ENDPOINT DERIVED FROM A) ADULT AND B) PEDIATRIC TRIALS OF LDX



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partial response, and other relevant outcomes: a focus on treatment-resistant depression. *J Clin Psychiatry.* 2001;62(suppl 16):5-9.

11. Huber CG, Lambert M, Naber D, et al. Validation of a Clinical Global Impression Scale for Aggression (CGI-A) in a sample of 558 psychiatric patients. *Schizophr Res.* 2008;100(1-3):342-348.
12. Leon AC, Shear MK, Klerman GL, Portera L, Rosenbaum JF, Goldenberg I. A comparison of symptom determinants of patient and clinician global ratings in patients with panic disorder and depression. *J Clin Psychopharmacol.* 1993;13(5):327-331.
13. Leucht S, Engel RR. The relative sensitivity of the Clinical Global Impressions Scale and the Brief Psychiatric Rating Scale in antipsychotic drug trials. *Neuropsychopharmacology.* 2006;31(2):406-412.
14. Busner J, Targum SD, Miller DS. The Clinical Global Impressions scale: errors in understanding and use. *Compr Psychiatry.* 2009;50(3):257-262.
15. Kadouri A, Corruble E, Falissard B. The improved Clinical Global Impression Scale (iCGI): development and validation in depression. *BMC Psychiatry.* 2007;7:7.
16. Leucht S, Kane JM, Kissling W, Hamann J, Etschel E, Engel R. Clinical implications of Brief Psychiatric Rating Scale scores. *Br J Psychiatry.* 2005;187:366-371.
17. Leucht S, Kane JM, Etschel E, Kissling W, Hamann J, Engel RR. Linking the PANSS, BPRS, and CGI: clinical implications. *Neuropsychopharmacology.* 2006;31(10):2318-2325.
18. Leucht S, Kane JM, Kissling W, Hamann J, Etschel E, Engel RR. What does the PANSS mean? *Schizophr Res.* 2005;79(2-3):231-238.
19. Furukawa TA, Shear KM, Barlow DH, et al. Evidence-based guidelines for interpretation of the Panic Disorder Severity Scale. *Depress Anxiety.* 2009;26(10):922-929.
20. Kolen MJ, Brennan RL. Observed score equating using the random groups design. In: Kolen MJ, Brennan RL. *Test Equating Methods and Practices.* New York, NY: Springer Verlag New York, Inc.; 1995.
21. Adler LA, Goodman DW, Kollins SH, et al. Double-blind, placebo-controlled study of the efficacy and safety of lisdexamfetamine dimesylate in adults with attention-deficit/hyperactivity disorder. *J Clin Psychiatry.* 2008;69(9):1364-1373.
22. Biederman J, Krishnan S, Zhang Y, McGough JJ, Findling RL. Efficacy and tolerability of lisdexamfetamine dimesylate (NRP-104) in children with attention-deficit/hyperactivity disorder: a phase III, multicenter, randomized, double-blind, forced-dose, parallel-group study. *Clin Ther.* 2007;29(3):450-463.
23. Pennick M. Hydrolytic conversion of lisdexamfetamine dimesylate to the active moiety, d-amphetamine. Poster presented at: the 64th Annual Scientific Convention and Meeting of the Society of Biological Psychiatry; May 14-16, 2009; Vancouver, British Columbia, Canada.
24. Pennick M. Absorption of lisdexamfetamine dimesylate and hydrolysis to form the active moiety, d-amphetamine. Poster presented at: the 49th Annual Meeting of the New Clinical Drug Evaluation Unit; June 29-July 2, 2009; Hollywood, FL.
25. *Diagnostic and Statistical Manual of Mental Disorders.* 4th ed, text rev. Washington, DC: American Psychiatric Association; 2000.
26. Lim RL. Linking results of distinct assessments. *J Applied Measure Ed.* 1993;6(1):83-102.
27. Pommerich M, Hanson BA, Harris DJ, Sconing JA. Issues in creating and reporting concordance results based on equipercentile methods. ACT Research Report Series 2000-1. Iowa City, IA: ACT, Inc.; 2000.
28. Weiss MD, Weiss JR. A guide to the treatment of adults with ADHD. *J Clin Psychiatry.* 2004;65(suppl 3):27-37.
29. Steele M, Jensen PS, Quinn DMP. Remission versus response as the goal of therapy in ADHD: a new standard for the field? *Clin Ther.* 2006;28(11):1892-1908.

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