Prediction of Placebo Response in 2 Clinical Trials of Lisdexamfetamine Dimesylate for the Treatment of ADHD

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ABSTRACT

Objective: To search for predictors of placebo response in clinical trials of lisdexamfetamine dimesylate for the treatment of *DSM-IV-TR*–defined attention-deficit/hyperactivity disorder (ADHD) in children and adults.

Method: We used data from 2 clinical trials: (1) a 4-week, phase 3, multicenter, randomized, double-blind, forced-dose, parallel-group study of children aged 6 to 12 years with ADHD (n = 290) and (2) a 4-week, randomized, double-blind, placebo-controlled, parallel-group, forced-dose titration study in adult subjects, aged 18–55 years with ADHD (n = 420). Response and remission were defined using the ADHD Rating Scale-IV and the Clinical Global Impressions-Improvement scale.

Results: Symptom remission was inversely correlated with baseline severity in both children and adults (*P* < .001), with less robust effects seen for response. The time to response and remission was delayed in adult subjects prescribed placebo versus lisdexamfetamine dimesylate, while response time in children was also significantly slower with placebo versus lisdexamfetamine dimesylate (*P* < .01). We found little evidence that demographic factors, prior pharmacotherapy, the emergence of adverse events during the trial, or changes in ADHD symptoms from the screening to baseline assessments predicted placebo response. Certain comorbid medical symptoms reduced the response and remission rates to placebo in children (*P* < .001) and adults (*P* < .001).

Conclusions: In both children and adults, baseline symptom severity was the most consistent predictor of remission with placebo while the temporal profile of response reliably differentiated placebo from medication responders. Placebo effects are most likely to be minimized in shorter trials enrolling more severely impaired subjects. The impact of medical and psychiatric comorbidities on placebo response merits further investigation.

Trial Registration: clinicaltrials.gov identifiers NCT00556296 and NCT00334880

A placebo effect can be defined as "…a genuine psychological or physiological effect, in a human or another animal, which is attributable to receiving a substance or undergoing a procedure, but is not due to the inherent powers of that substance"[1(p326)] and conceptualized as the change in a symptom or condition that occurs following the administration of a placebo minus the change that would have occurred naturally had nothing been done.[2–4] The current gold standard for establishing the efficacy of a specific pharmacologic agent is its ability to outperform placebo in controlled studies, and there is a sizable literature documenting the effects of placebos in the field of mental health.[5–9]

Given the robust effects of stimulants in clinical trials of pediatric attention-deficit/hyperactivity disorder (ADHD), relatively little attention has been paid to the role of the placebo in comparison to other disorders, such as major depression, in which active treatments produce smaller incremental benefit over placebo. However, as with most mental health disorders, there are no gold-standard, objective indices of treatment response for ADHD in children or adults. This limitation forces the field to rely on subjective measures such as self-report and collateral report of symptoms.[10] It has been well established that children with ADHD are poor reporters of treatment response, as they are often unaware of their own symptoms.[10,11] Longitudinal studies of children with ADHD followed into adulthood also find that these patients continue to underreport symptoms as young adults, especially those with persistent ADHD.[12,13] Collateral report of treatment response has been found to be more reliable but still has limited correlations with more objective indices such as direct observation.[5,10] For example, it has been observed that subjective measures, such as self-report and collateral symptom reports, produce inflated effect sizes of drug response in comparison to objective indices in pediatric studies.[5,14] Given these complexities in the assessment of treatment effects in mental illness, it may prove valuable to better understand factors influencing response to placebo and active medication. Moreover, examination of placebo responders may help to identify those patients most likely to respond to inert versus active treatments, which would assist in trial design and, more importantly, with tailoring treatments to individual patients. Placebo effects vary across disorders,[6] making it unwise to simply extrapolate results from studies of other psychiatric diseases and necessitating examination of placebo effects specifically in trials of ADHD.

In children, prior work has established the presence of placebo effects in the treatment of ADHD. One review[15] found an effect size of 0.32 for placebo when a 30% improvement rate in symptom scores was used as the definition of response, with almost a third of the children classified as positive responders using this definition. If the definition of positive response is lowered to 20% improvement, then the placebo response rate increases to over 50%.[16] While multiple studies have established the presence of a placebo response in children with ADHD, only 2 studies have examined predictors of this response. First, Sandler and Bodfish[17] found that placebo response was positively correlated with baseline symptom severity as rated by both parents and teachers. However, in this study, placebos were used as an adjunct to stimulant medication treatment—that is, all children were on active medication, but some were on higher doses without placebo and some were

on lower doses with placebo. This is an innovative design but makes interpretation of the findings regarding the prediction of placebo effects difficult to interpret. Second, Newcorn and colleagues[18] examined placebo response in the pediatric trials of atomoxetine and found that subjects more likely to respond to placebo were those with no prior treatment history, the inattentive subtype, a comorbid tic disorder, or nonwhite ethnicity. However, it is not clear if these results generalize to stimulant trials given the significant pharmacodynamic and pharmacokinetic differences between atomoxetine and stimulants.[19]

The rate of placebo response in adolescents and adults with ADHD is similar to or higher than what is found in children, ranging from 17%–40%, depending on the definitions employed.[20–23] Unlike trials in children, for which it is commonplace to obtain collateral ratings, studies in adults rely primarily on self-report for measuring treatment response. It has been theorized that high distress plus high insight predicts a greater response to placebo. For example, placebo response rates are much higher in major depression than in obsessive-compulsive disorder (OCD), presumably because awareness of symptoms in OCD is often very poor.[6] If this interpretation is accurate, it would be expected that adults with ADHD would be more likely than children to respond to placebo because adults are typically self-referred (and thus aware of their own symptoms) while children are brought to treatment by their parents (and most likely unaware of their own symptoms). Consistent with this hypothesis, it has been noted that effect sizes in adult trials are routinely lower than that seen in child trials,[20,22,24] which may be due to a heightened placebo response in adults relative to children. Given the reduced effect sizes seen in adult trials, there may be particular value in examining predictors of placebo response in adults with ADHD, but no studies to date have done so.

What factors might predict placebo response in children and adults with ADHD? As noted earlier, demographic features, baseline ADHD symptom severity, and prior medication treatment were significant predictors of placebo response in previous research in ADHD.[17,18] These same factors have also been shown to be significant predictors of placebo response in studies of depression in children.[25–27] Thus, further examination of these factors is warranted. In addition, the use of single-blind lead-in phases has been recommended to reduce placebo response rates.[28] Placebo treatments have been used for the management of chronic pain, hypertension, gastrointestinal illnesses, and other medical diseases,[5,29,30] and treatment with placebo has been found to reduce rates of medical complaints in children with ADHD.[31] Therefore, the degree of change in ADHD symptoms between the screening and baseline assessments, comorbid medical symptoms, and the emergence of adverse events during the course of treatment merit investigation as predictors of placebo response.

The present work assesses theorized predictors of placebo response in 2 clinical trials of lisdexamfetamine dimesylate, a long-acting prodrug stimulant used to treat ADHD in children (ages 6–12 years) and in adults.[32–34] In the pediatric study,[33] each lisdexamfetamine dimesylate dose produced significant improvement in ADHD symptoms as measured by the ADHD Rating Scale-IV (ADHD-RS-IV)[35] in the intent-to-treat population of 290 subjects. Compared with placebo, all lisdexamfetamine dimesylate–dose groups had a higher percentage of subjects rated as either "much improved" or "very much improved" on the Clinical Global Impressions-Improvement scale (CGI-I) from baseline to endpoint ($\geq$ 70% vs 18%, P < .001). In the post hoc responder analysis of the study, the proportion of responders (defined as $\geq$ 30% decrease in ADHD-RS-IV total score and a CGI-I score of 1 or 2) at study endpoint for the 30-, 50-, and 70-mg/d cohorts were 66%, 72%, and 80%, respectively. In comparison, the placebo-treated cohorts had a 17% response rate.

A second study showed an analogous level of efficacy in adults.[32] In that trial, 414 adults aged 18 to 55 years with moderate to severe ADHD were randomized to 30, 50, or 70 mg of lisdexamfetamine dimesylate or placebo for 4 weeks following a 7- to 28-day washout period. Significant improvements in ADHD-RS-IV total scores and CGI-I scores were observed as early as 1 week after the start of treatment. The percentage of subjects who improved (CGI-I rating $\leq$ 2) was significantly greater for each lisdexamfetamine dimesylate dose than for placebo at each week and at endpoint (placebo = 29%, 30 mg/d of lisdexamfetamine = 57%, 50 mg/d of lisdexamfetamine = 62%, 70 mg/d of lisdexamfetamine = 61%; all P values < .01).

We used these 2 data sets to evaluate potential predictors of placebo response in children and adults with ADHD, including demographic features, comorbid medical symptoms, baseline ADHD symptom severity, changes in ADHD symptoms between the screening and baseline assessments, prior pharmacotherapy for ADHD, and emergence of adverse events during the course of placebo treatment. We also conducted analyses to compare placebo- and lisdexamfetamine dimesylate–treated subjects in their time to attain our response and remission criteria.

METHOD

Study of Lisdexamfetamine Dimesylate in School-Aged Children

Subjects and design. This phase 3, multicenter, randomized, double-blind, forced-dose, parallel-group study[33] examined children aged 6 to 12 years who met *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (*DSM-IV-TR*)[36] criteria for ADHD. To be eligible, the study required children to have an ADHD Rating Scale-IV[35] score > 28 at baseline. Psychopathology was assessed by a psychiatrist using (1) Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version Diagnostic Interview version 1.0[37] and (2) a semistructured interview based on *DSM-IV-TR* criteria for ADHD. The study is registered at clinicaltrials.gov (identifier NCT00556296).

Subjects with a comorbid psychiatric diagnosis with significant symptoms (eg, psychosis, bipolar disorder); a history of seizures, cardiac abnormalities, or a current diagnosis or family history of Tourette's syndrome; obesity based on

the investigator's opinion; weight < 25 kg (55 lb); positive screening for illicit drug use; and/or current health conditions or use of medications that might confound the results of the study or increase risk to the patient were excluded. All subjects underwent a medical history review and physical examination using a structured assessment form. Any non-exclusionary medical condition or symptom reported by subjects or found during examination was categorized into 1 of the 12 body systems described below in the results section. Similar procedures for coding past medical symptoms were used in the adult trial. After receiving an oral and written description of study requirements, each child's parent or legally authorized guardian provided a signature of informed consent, along with documentation of patient assent, following procedures approved by each participating site's respective institutional review board.

The study had 3 phases and required 6 weeks: 1 week to screen patients (week −2), 1 week to wash out current psychoactive medications (week −1), and 4 weeks for the double-blind treatment (weeks 0–4). Subjects were randomized to receive double-blind, oral (capsules) administration of lisdexamfetamine dimesylate 30 mg (for 4 weeks), 50 mg (30 mg/d for week 1, with forced–dose escalation to 50 mg/d for weeks 2–4), or 70 mg (30 mg/d for week 1, with forced–dose escalation to 50 mg/d for week 2 and 70 mg/d for weeks 3 and 4) or placebo capsules for 4 weeks.

The primary efficacy measure for this study was the ADHD-RS-IV,[35] an 18-item scale with 1 item for each of the 18 symptoms contained in the *DSM-IV-TR* diagnosis of ADHD. The 18 items were grouped into 2 subscales: (1) hyperactivity/impulsivity and (2) inattentiveness. Each item was scored on a range of 0 to 3 (0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, and 3 = severe symptoms). A total score between 0 and 54 (0 = no symptoms to 54 = the most severe symptoms) was calculated as the sum of the scores on each of the 18 items. The ADHD-RS-IV was used to assess each patient's symptom severity during the previous week, based on an investigator's interview with the parent/guardian and child. At each visit postbaseline, ratings were made on the CGI-I, which yields integer scores ranging from 1 ("very much improved") to 7 ("very much worse"), indexing the degree of change in ADHD symptoms from the beginning of the study (ie, prior to the start of study medication).[38]

Study of Lisdexamfetamine Dimesylate in Adults

Subjects and design. This 4-week, randomized, double-blind, multisite, placebo-controlled, parallel-group, forced–dose titration study[32] evaluated the efficacy and safety of lisdexamfetamine dimesylate 30 mg, 50 mg, and 70 mg in adult subjects aged 18–55 years meeting *DSM-IV-TR* criteria for a diagnosis of ADHD as determined by a comprehensive psychiatric evaluation. Subjects were required to have a baseline ADHD-RS-IV[39] score of ≥ 28 using adult prompts. Subjects were excluded if they were significantly underweight (body mass index < 18.5); were morbidly obese; had a history of substance abuse within the past 6 months; or had a

comorbid psychiatric diagnosis with significant symptoms, cardiac abnormalities, hyperthyroidism, or other concurrent medical illness that could contraindicate treatment with lisdexamfetamine dimesylate or could interfere with safety or efficacy assessments. The study is registered at clinicaltrials.gov (identifier NCT00334880). It was approved by the institutional review board of each study site, and subjects provided written informed consent. Both the child and the adult trial were conducted in accordance with the Declaration of Helsinki.

Definition of Response and Remission

For both studies, treatment response and remission were each defined by 3 criteria. For response, the criteria were (A) a change in ADHD-RS-IV total score from the screening visit of 30% or more; (B) a CGI-I score of 1 ("very much improved") or 2 ("much improved") relative to the screening visit; and (C) an ADHD-RS-IV score change of 30% or more plus a CGI-I score of 1 or 2 relative to the screening visit. For remission, the criteria were (A) an ADHD-RS-IV score of 18 or less; (B) a CGI-I score of 1; and (C) an ADHD-RS-IV score of 18 or less and a CGI-I score of 1. Hereafter, these are referred to as response and remission criteria A, B, and C, respectively.

Statistical Methods

The various response and remission criteria were modeled independently as functions of combinations of potential predictors. In the first 4 sets of analyses, we attempted to identify factors associated with the likelihood of attaining response or remission criteria when subjects were treated with placebo only; thus, these analyses included only placebo-treated subjects. The first set of these analyses was designed to determine if any demographic or baseline clinical factors predicted placebo response or remission in a longitudinal analysis. To reduce the type I error rate without unduly compromising statistical power, we applied the Bonferroni correction for each set of 12 medical systems tested and thus refer to the medical system tests as significant if the *P* value is less than .004. The second set of analyses was designed to determine whether the magnitude and direction of change in ADHD-RS-IV total scores between the screening visit and the baseline visit was related to the likelihood of attaining treatment response or remission criteria during the remaining treatment visits. The third set of analyses was designed to determine whether the receipt of prior pharmacotherapy for ADHD had an effect on the likelihood of attaining any of the response or remission criteria when treated with placebo. The fourth set of analyses was designed to determine whether the emergence of adverse events during the course of placebo treatment influenced the likelihood of attaining any of the response or remission criteria at each study visit. We implemented analyses using generalized estimating equations, with each binomial outcome predicted as a logit function of the set of predictors. All generalized estimating equations employed robust standard errors to account for the nonindependence of observations across study visits.

In addition to these analyses of predictors of placebo response and remission, we also conducted 2 sets of analyses to compare placebo and lisdexamfetamine dimesylate–treated subjects in their rate and time to attain the various response and remission criteria. To compare placebo- and lisdexamfetamine dimesylate–treated groups on their rate of attaining response or remission criteria, we generated Kaplan-Meier survival functions followed by log-rank (χ^2) tests for equality of the survival functions across groups. To better characterize the time course of response or remission in the various treatment groups, we compared successful responders or remitters in the placebo- and lisdexamfetamine dimesylate–treated groups on their time to attain response and remission criteria by 1-tailed t tests. To limit the type I error rate for analyses 2 through 5, we refer to findings as statistically significant if the P value is less than .01, with less than .05 being referred to as marginally significant. All statistical procedures were conducted in Stata/SE software, version 9.2.[40]

RESULTS

Subjects Available for the Analyses

The child study dataset[33] provided treatment response and remission data from 1,626 observations of 297 subjects (an average of 5.5 visits per subject of a possible maximum of 6). Of the 297 subjects with multiple observations in the child study, 72 were treated with placebo throughout the extent of the trial duration, while 218 were titrated to their randomized dose of lisdexamfetamine dimesylate (81 received a maximum of 30 mg/d, 72 received a maximum of 50 mg/d, and 65 received a maximum of 70 mg/d). The remaining 7 subjects in the child study dataset were not treated with either placebo or lisdexamfetamine dimesylate.

The adult study dataset[32] provided data from 2,371 observations of 420 subjects (an average of 5.6 visits per subject of a maximum of 6). Of the 420 subjects with multiple observations in this study, 62 received placebo throughout the entire treatment duration. The remaining 358 subjects were titrated to their maximum lisdexamfetamine dimesylate dosage (134 received 30 mg/d, 119 received 50 mg/d, and 105 received 70 mg/d).

Response and Remission Rates

The response and remission rates for each of the studies are reported in Table 1. As shown, the placebo response/remission rates ranged from 5.6% to 26.4% for the child sample and from 8.1% to 34.4% for the adult sample, with the lowest rates produced by the integrative definition of response/remission (definition C). Levels of response and remission to placebo were generally higher in the adult versus child study with the reverse pattern found for active lisdexamfetamine dimesylate. All lisdexamfetamine dimesylate doses separated from placebo except for the 30-mg lisdexamfetamine dimesylate dose in the adult study using remission criteria B (CGI) or C (CGI plus ADHD-RS-IV). This dose did separate from placebo using remission criteria A (ADHD-RS-IV symptoms scores).

Table 1. Rates of Response[a] and Remission[b] as a Function of Placebo and Medication in 2 Clinical Trials of Lisdexamfetamine for ADHD

Treatment	Criterion A	Criterion B	Criterion C
Child sample			
Meeting criterion for response, %			
Placebo	26.4	18.1	16.7
Lisdexamfetamine dimesylate, 30 mg/d	71.8***	69.6***	66.7***
Lisdexamfetamine dimesylate, 50 mg/d	69.9***	71.4***	67.1***
Lisdexamfetamine dimesylate, 70 mg/d	81.7***	77.5***	76.1***
Meeting criterion for remission, %			
Placebo	13.9	5.6	5.6
Lisdexamfetamine dimesylate, 30 mg/d	50.7***	34.8***	31.9***
Lisdexamfetamine dimesylate, 50 mg/d	61.6***	45.7***	45.7***
Lisdexamfetamine dimesylate, 70 mg/d	67.6***	57.8***	52.1***
Adult sample			
Meeting criterion for response, %			
Placebo	34.4	29.0	26.2
Lisdexamfetamine dimesylate, 30 mg/d	55.8**	57.0**	50.9**
Lisdexamfetamine dimesylate, 50 mg/d	65.8***	61.5***	57.0***
Lisdexamfetamine dimesylate, 70 mg/d	65.6***	60.8***	56.4***
Meeting criterion for remission, %			
Placebo	11.3	11.3	8.1
Lisdexamfetamine dimesylate, 30 mg/d	31.1**	19.3	17.5
Lisdexamfetamine dimesylate, 50 mg/d	32.5**	24.8*	23.1*
Lisdexamfetamine dimesylate, 70 mg/d	41.3***	23.3*	22.7**

[a]Response was defined by 3 criteria: criterion A equals change in ADHD-RS-IV total score from the screening visit of 30% or more; criterion B equals CGI-I score of 1 ("very much improved") or 2 ("much improved") relative to the screening visit; and criterion C equals ADHD-RS-IV score change of 30% or more plus a CGI-I score of 1 or 2 relative to the screening visit.
[b]Remission was defined by 3 criteria: criterion A equals an ADHD-RS-IV score of 18 or less; criterion B equals a CGI-I score of 1; and criterion C equals an ADHD-RS-IV score of 18 or less and a CGI-I score of 1.
*P<.01, **P<.001, ***P<.0001, versus placebo.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, ADHD-RS-IV = ADHD Rating Scale-IV, CGI-I = Clinical Global Impressions-Improvement scale.

Demographic and Medical Predictors

Endorsements of medical symptoms at baseline were grouped by body system and numbered from 1 to 12 as follows: (1) general appearance; (2) head, ears, eyes, nose, throat; (3) dermatologic; (4) cardiovascular; (5) respiratory; (6) gastrointestinal; (7) urological/reproductive; (8) musculoskeletal; (9) hemic/lymphatic; (10) endocrine/metabolic; (11) allergic; and (12) neurologic/psychological. In addition, all comorbid medical symptoms were summed into 1 composite category to assess the effects of physical health at baseline on response/remission to placebo. As noted earlier, we applied the Bonferroni correction for each set of 12 medical systems and thus interpret differences as significant if the P value was less than .004.

The child study. In the analysis of demographics, no response or remission criterion was found to be significantly influenced by age, sex, or ethnicity (all P values $\geq$ .16). Likewise, analysis of the composite measure of medical problems reported by subjects was not significantly related to the magnitude of placebo response or remission (all P values $\geq$ .112). Analyses of the results by individual body systems did not yield consistently significant findings except for cardiac and gastrointestinal problems being associated with diminished placebo response and remission rates by all 3 definitions

(β values > −18.97, z values > 14.97, P values < .001; detailed results of analyses of individual medical problems available upon request).

The adult study. In the analysis of demographics, sex and age had no significant influence on the attainment of any of the response or remission criteria (all P values ≥ .02). Patients with Caucasian ethnicity had an increased likelihood of attaining remission criterion B (β = 14.70, z = 22.83, P ≤ .001), but there was no relationship between any ethnicity and remission criteria A or C (both P values ≥ .257) or any of the 3 definitions of response.

Using the composite measure of all past medical symptoms revealed the same general pattern of results that was observed in the child study, in which the composite rating of all medical problems did not significantly influence any of the response or remission criteria (all P values > .265). Analyses of the results by individual body systems did not yield consistently significant findings except for problems in the metabolic/endocrine system being associated with a diminished placebo response and remission rates by all 3 definitions (β values ≥ −25.37, z values ≥ 17.28, P values ≤ .001; detailed results of analyses of individual medical problems available upon request).

Baseline Severity of ADHD Symptoms

The child study. Baseline severity of ADHD symptoms (as indexed by ADHD-RS-IV total scores) was not a significant predictor of placebo response according to any of the 3 response criteria (criterion A: β = −0.02, z = 1.15, P = .250; criterion B: β = −0.04, z = 1.74, P = .081; criterion C: β = −0.02, z = 0.88, P = .377). In contrast, greater baseline severity was significantly associated with a lesser likelihood of achieving remission criterion A (β = −0.07, z = 3.79, P < .001), but not criteria B (β = −0.03, z = −1.06, P = .291) or C (β = −0.04, z = 1.43, P = .153).

The adult study. The effects of baseline ADHD symptom severity on placebo response were more pronounced in adult subjects, in whom all 3 remission criteria were significantly negatively associated with baseline ADHD symptom severity (criterion A: β = −0.27, z = 3.65, P < .001; criterion B: β = −0.17, z = 2.96, P = .003; criterion C: β = −0.26, z = 3.97, P < .001). A marginally significant negative relationship was observed for all 3 response criteria, with criteria A and B falling just above Bonferroni-adjusted significance levels (criterion A: β = −0.07, z = 2.37, P = .018; criterion B: β = −0.09, z = 2.56, P = .010; criterion C: β = −0.08, z = 2.20, P = .028).

Change in ADHD Symptoms From Screening to Baseline

The child study. Changes in ADHD-RS-IV total scores from screening to baseline did not significantly predict any of our response or remission criteria (all P values ≥ .01).

The adult study. Changes in ADHD-RS-IV total scores from screening to baseline did not significantly predict any of our response or remission criteria (all P values ≥ .01). Of the 3 response criteria, criterion B (CGI-I) showed a marginally significant association with the change in ADHD-RS-IV

total scores from screening to baseline (β = 0.12, z = 2.07, P = .038). This positive association indicates that increases in total ADHD-RS-IV scores from screening to baseline were linked to an increased likelihood of attaining response criterion B over the remaining weeks of placebo treatment. Consistent with this result, positive screening-to-baseline changes in total ADHD-RS-IV were also marginally associated with an increased likelihood of attaining remission criterion B (β = 0.15, z = 2.50, P = .012) but not remission criteria A or C (both P values ≥ .093).

Prior ADHD Pharmacotherapy

The child study. Of the 72 placebo-treated subjects in this study that had data available for more than 1 visit, 26 had been previously treated for ADHD symptoms, while 46 had not. This prior treatment exposure was not significantly associated with the likelihood of attaining any of the response or remission criteria (all P values ≥ .08).

The adult study. Of the 62 placebo-treated subjects in this study that had data available for more than 1 visit, only 8 had been previously treated for their ADHD symptoms, while the remaining 52 had not. None of the 3 response criteria was associated with prior treatment (all P values ≥ .609). Similarly, attainment of remission criteria was not significantly influenced by prior treatment (all P values ≥ .1).

Emergence of Adverse Events

The child study. Of the 72 placebo-treated subjects in this study who had data available for more than 1 visit, 35 experienced at least 1 adverse event during the trial, while 37 had no such experiences. The presence or absence of adverse events was not significantly related to the likelihood of attaining any of the response or remission criteria by the end of the trial (all P values ≥ .138).

The adult study. Of the 62 placebo-treated subjects in this study who had data available for more than 1 visit, 38 experienced at least 1 adverse event during the trial, while 24 had no such experiences. Similar to the child data, there were no significant relationships between adverse events and attainment of any response or remission criteria (all P values ≥ .188).

Treatment as a Predictor of Time to Response and Remission

The child study. Table 2 shows the mean number of weeks until each of the 4 treatment groups attained the various response and remission criteria. Compared to responders to lisdexamfetamine dimesylate, the responders to placebo were significantly slower to attain each of the response criteria. This was true for all lisdexamfetamine dimesylate dose groups except for the 50-mg and 70-mg lisdexamfetamine dimesylate doses using response criterion C, which just failed to reach significance. The mean difference in time to response between lisdexamfetamine dimesylate and placebo responders was 0.56 weeks or slightly less than 4 days. In contrast to the response data, the results from the placebo group showed no significant delay in attaining any of the

Table 2. Weeks Required to Attain Various Response and Remission Criteria[a] in the Child Study

Treatment Group	Criterion A[b]			Criterion B[b]			Criterion C[b]		
	Mean (SD)	t	P	Mean (SD)	t	P	Mean (SD)	t	P
	Response								
Placebo	2.07 (1.05)	…	…	2.05 (0.86)	…	…	2.15 (0.99)	…	…
Lisdexamfetamine dimesylate, 30 mg/d	1.42 (0.82)	3.12	.001	1.41 (0.73)	3.23	.001	1.44 (0.78)	3.20	.001
Lisdexamfetamine dimesylate, 50 mg/d	1.41 (0.65)	3.54	<.001	1.53 (0.84)	2.40	.009	1.64 (0.86)	2.17	.017
Lisdexamfetamine dimesylate, 70 mg/d	1.55 (0.74)	2.71	.004	1.58 (0.74)	2.36	.010	1.66 (0.78)	2.27	.013
	Remission								
Placebo	2.00 (1.37)	…	…	2.60 (0.89)	…	…	2.75 (0.96)	…	…
Lisdexamfetamine dimesylate, 30 mg/d	2.09 (1.19)	0.261	.603	2.41 (1.02)	0.38	.352	2.37 (1.04)	0.68	.249
Lisdexamfetamine dimesylate, 50 mg/d	1.94 (1.21)	0.177	.430	2.15 (0.93)	1.01	.159	2.36 (1.01)	0.74	.232
Lisdexamfetamine dimesylate, 70 mg/d	2.04 (1.01)	0.125	.549	2.23 (1.06)	0.76	.227	2.33 (1.11)	0.74	.236

[a]Refer to Table 1 for criteria used to define response and remission.
[b]Test statistics and P values are for comparisons with the placebo group, with significance set at P<.01.
Abbreviations: ADHD=attention-deficit/hyperactivity disorder, ADHD-RS-IV=ADHD Rating Scale-IV, CGI-I=Clinical Global Impressions-Improvement scale.

Table 3. Weeks Required to Attain Various Response and Remission Criteria[a] in the Adult Study

Treatment Group	Criterion A[b]			Criterion B[b]			Criterion C[b]		
	Mean (SD)	t	P	Mean (SD)	t	P	Mean (SD)	t	P
	Response								
Placebo	2.11 (1.07)	…	…	2.13 (1.06)	…	…	2.32 (0.99)	…	…
Lisdexamfetamine dimesylate, 30 mg/d	1.59 (1.00)	2.36	.010	1.62 (0.89)	2.34	.011	1.75 (0.97)	2.38	.010
Lisdexamfetamine dimesylate, 50 mg/d	1.65 (0.86)	2.30	.012	1.76 (0.92)	1.68	.048	1.82 (0.93)	2.21	.015
Lisdexamfetamine dimesylate, 70 mg/d	1.37 (0.82)	4.33	<.001	1.66 (0.93)	2.17	.016	1.61 (0.82)	3.43	.001
	Remission								
Placebo	2.40 (0.84)	…	…	3.25 (0.71)	…	…	3.33 (0.52)	…	…
Lisdexamfetamine dimesylate, 30 mg/d	1.81 (1.07)	1.65	.052	2.29 (0.90)	2.79	.004	2.37 (0.93)	2.44	.010
Lisdexamfetamine dimesylate, 50 mg/d	1.67 (1.13)	1.93	.029	2.29 (1.01)	2.55	.007	2.30 (0.98)	2.48	.009
Lisdexamfetamine dimesylate, 70 mg/d	1.87 (1.14)	1.40	.084	2.05 (0.96)	3.35	.001	2.15 (1.00)	2.82	.004

[a]Refer to Table 1 for criteria used to define response and remission.
[b]Test statistics and P values are for comparisons with the placebo group, with significance set a P<.01.
Abbreviations: ADHD=attention-deficit/hyperactivity disorder, ADHD-RS-IV=ADHD Rating Scale-IV, CGI-I=Clinical Global Impressions-Improvement scale.

remission criteria relative to any of the lisdexamfetamine dimesylate–dose groups (see Table 2).

The adult study. Table 3 presents a comparison of response and remission times between successful responders in the placebo group and successful responders in each of the lisdexamfetamine dimesylate–dose groups. The placebo responders in the adult study were marginally slower to attain each of the 3 response criteria relative to responders in each of the lisdexamfetamine dimesylate–dose groups, with the 70-mg dose achieving significance on multiple definitions of response. The mean difference in time to response between lisdexamfetamine dimesylate and placebo responders was 0.58 weeks (slightly more than 4 days), which was very similar to the difference observed in the child study. In contrast to the child study, the adult study had higher remission rates overall, and the placebo responders experienced significant delays in attaining remission criteria B and C relative to responders to lisdexamfetamine dimesylate (Table 3).

DISCUSSION

Past research has demonstrated that a substantial portion of children with ADHD show a positive response to placebo, but little work has examined factors that predict this occurrence. There have been no published studies examining the response to placebo in adults with ADHD. This study was designed to address these needs by analyzing data from 2 well-controlled studies that examined the effects of various doses of stimulant medication as compared to placebo for the treatment of ADHD.[32–34]

The placebo response and remission rates in children, as defined by change in symptom scores (ADHD-RS-IV), were lower than those reported in a recent analysis of the pediatric atomoxetine trials in children,[18] which defined response as a 25% reduction (vs 30% here) and remission as a 40% reduction (vs a ADHD-RS-IV total score of 18 or less here). The differential results from these 2 studies, as well as the differences in response/remission rates within this study across the various definitions of these 2 outcomes, suggest that more stringent definitions of response and remission lead to smaller placebo effects, just as they lead to smaller treatment effects. In the child and adult studies, response and remission rates on placebo and lisdexamfetamine dimesylate were typically lower with the CGI-I–based definition versus the one that relied on ADHD symptom counts (as measured by the ADHD-RS-IV). For example, the 30-mg

lisdexamfetamine dimesylate dose separated from placebo on the ADHD-RS-IV definition of remission but not by the CGI-I–based definition in the adult study, primarily due to a lower remission rate for lisdexamfetamine dimesylate using the CGI-I versus the ADHD-RS-IV. The relationship with predictors also varied depending on the definitions employed. In adults, the majority of significant associations were found with the CGI-I–based definition, whereas in children there was little difference in the correlation with predictors between the ADHD-RS-IV and CGI-I definitions of response/ remission. These mixed results suggest that a definition of response integrating symptom reports (ADHD-RS-IV) with clinician assessment (CGI-I) may be preferable and that sole reliance on any 1 measure of response is not ideal in clinical practice or research trials. In addition, consistent use of the same outcome measures at the same threshold of response across studies would enhance generalizability of findings.

Greater baseline symptom severity of ADHD predicted a reduced rate of remission in children and adults as well as a trend toward reduced response to placebo in adults. The greater association of baseline severity with remission versus response is likely due to the differential symptom thresholds for these 2 outcomes (an ADHD-RS-IV score < 18 for remission vs a 30% score reduction for response). Our findings on baseline symptom severity are consistent with results from adult and child depression trials showing that greater symptom severity is associated with reduced placebo response.[7,25,27,41] The combined results suggest that baseline symptom severity merits more study as a predictor of remission on placebo, especially in adults in whom a stronger association was found for both response and remission. If these findings are replicated, it would suggest that individuals with milder symptoms of ADHD may be amenable to placebo interventions, whereas the same approach is unlikely to lead to significant improvement in patients with more severe symptoms. It is also possible that milder cases of ADHD enrolled in clinical trials represent false-positive diagnoses, which would explain their apparent "remission" during treatment. In clinical practice, these findings suggest that seriously impairing ADHD symptoms are unlikely to remit without active treatment.

It seems reasonable to assume that given the fairly instantaneous and robust effects of stimulants for improving ADHD symptoms, parents or adult patients who have witnessed the beneficial effects of stimulants in themselves or their child may be better at differentiating medication effects from the normal daily variations in their child's behavior. These past medication experiences should translate to lower rates of placebo response. However, no such association was found, possibly due in part to the low rates of prior pharmacotherapy.

Placebo responders/remitters did not significantly differ from medication responders in the degree of symptom change between screening and baseline, suggesting that the probability of responding to a placebo cannot be reliably detected during a lead-in phase to treatment. Therefore, single-blind lead-in phases do not appear to be necessary in stimulant trials. Their utility has been questioned in depression trials as well.[9,28]

Consistent with the results of Sandler and Bodfish,[17] demographic factors were not reliable predictors of placebo response, with the only exception being that Caucasian ethnicity had an increased likelihood of attaining remission criterion B in the adult study. However, ethnicity did not predict outcome using any other definition of placebo response or remission in either the child or the adult lisdexamfetamine dimesylate trial. Similarly negative results for socioeconomic status and ethnicity as a predictor of response to active treatment were found in the Multimodal Treatment Study of Children with ADHD.[42,43] Children with ADHD and other psychiatric illness have been found to express higher rates of physical complaints than children without a mental health diagnosis.[44,45] In a trial of methylphenidate for pediatric ADHD, Rapport and colleagues[31] found that both placebo and active medication decreased the frequency of physical complaints by children and their parents. These combined results suggest a possible relationship between medical health and placebo response in ADHD trials. No association was found between our summary measure of comorbid medical symptoms and placebo response or study-emergent adverse events and placebo response. However, when body systems were individually analyzed, children with a past history of cardiac and gastrointestinal symptoms had reduced response and remission rates to placebo across all definitions. The most common symptoms reported in these 2 categories were stomachaches and palpitations. Stomachaches and loss of appetite are common side effects of stimulants,[46,47] and there has been ongoing concern about the cardiac effects of stimulants in children[48]; therefore, it is likely that study clinicians would have reviewed these issues with parents and subjects ahead of time. Parents of children with preexisting health issues in these areas may have been sensitized to expect them to worsen, creating a negative expectancy effect. In adults, metabolic/ endocrine issues were similarly predictive of a reduced rate of remission and response. The most common health issue in this category was hypothyroidism, which was not exclusionary. Decreased thyroid function can lead to difficulties with attention that could resemble ADHD.[49] It would be reasonable to assume that the attentional difficulties associated with hypothyroid states would be less amenable to placebo interventions than those due solely to ADHD. However, these explanations are speculative, and findings must be replicated before any definitive connections can be made between specific comorbid medical conditions and the response to inert or active ADHD treatments.

The prior work examining predictors of placebo response in children with ADHD produced some contrasting results in comparison to this study. Most notably, our study found that severity of ADHD symptoms at baseline was negatively correlated with remission rates on placebo as measured by symptom scores, whereas previous ADHD research found no association[18] or the opposite pattern.[17] In addition, the atomoxetine analyses also found an association between lack of prior stimulant usage and nonwhite ethnicity with enhanced response to placebo, neither of which were

significant associations in this analysis.[18] The conflicting ethnicity findings across the lifespan from this trial and differential effect of ethnicity in the pediatric subjects from this study versus those from the atomoxetine analysis suggest that ethnicity merits further exploration as a predictor of placebo response. The data on the effects of ethnicity in pediatric trials of depression and anxiety are similarly mixed.[25,27]

There were several methodological differences between the studies that may have contributed to these different results. The atomoxetine analyses[18] employed a different measure of response and remission (25% or 40% improvement in ADHD-RS-IV score vs 30% and an ADHD-RS-IV score < 18 used in this study) and enrolled a sizable number of children with the inattentive type, whereas almost 100% of the pediatric subjects in this study met criteria for the combined subtype. Subjects with the inattentive subtype were more likely to respond to placebo in the atomoxetine analyses, even though baseline symptom severity was not associated with placebo response. This result is surprising because large-scale twin studies have found that the ADHD subtypes represent differential severities of the same disease rather than distinct entities.[50,51] Therefore, if subtype is predictive of response, one would also expect an association with baseline symptom severity, which was not found. The type of medication used also differed across the study and may account for the contrasting results. Atomoxetine has a significantly different pharmacokinetic profile than stimulants, with full effects often not seen for 3–6 weeks,[19] possibly impacting a subject's expectation of medication relative to placebo. Lastly, the atomoxetine analyses merged 7 separate studies with variable methodologies and entry criteria, while all the child subjects in this lisdexamfetamine dimesylate analysis came from a single trial.

The Sandler and Bodfish[17] study examined the effects of substituting placebo for active medication among children who had already demonstrated a positive response to medication. In contrast, medication response was not a selection criterion for the lisdexamfetamine dimesylate pediatric trial analyzed in this article, suggesting that the 2 samples may have differed in important ways. Moreover, in the Sandler and Bodfish[17] study, all informants (parents, children, clinicians) were aware of the true nature of all prescribed treatments that subjects were taking—in essence creating an open-label study of placebo. In the lisdexamfetamine dimesylate child study, subjects and raters were blind to medication status. In addition, all subjects in the Sandler and Bodfish[17] study remained on active medication for the duration of the trial, but 50% had half of their dose replaced by placebo. Thus, placebo effects may have been influenced by the fact that placebo was always paired with active medication. In contrast, placebos were administered as a separate treatment condition in the lisdexamfetamine dimesylate study. Lastly, their study[17] was a pilot study with a small sample size (n = 26), whereas the child study[33] in the present work was a multisite trial with a sample size that was more than 10 times larger (n = 290).

In addition to examining predictors of placebo response/remission, we examined the temporal differences in the rate of response between active medication and placebo. Compared to responders to lisdexamfetamine dimesylate, responders to placebo took significantly longer to attain each of the response criteria in the child study and all but criterion B in the adult study. Likewise, in the adult study, it took longer to achieve remission with placebo versus all the doses of lisdexamfetamine dimesylate. Given the forced-dose design of these studies, it is difficult to definitively separate dose from time effects. However, lisdexamfetamine dimesylate and placebo were always administered as a single dose per day, and subjects were not aware of the titration schedule, which suggests that increased rates of response/remission on placebo over time were not primarily due to subjects believing that they were on a higher dose as time progressed. A slower onset of response for placebo is not surprising given the rapid onset of effect with stimulant medications. In contrast to findings with antidepressants in which the majority of placebo response occurs early in the course of treatment,[9,52] subjects responding to placebo appear to have a delayed response to treatment in comparison to those responding to active medication, which suggests that placebo effects appear to play a larger role in prolonged versus early response. Other studies have also found a positive correlation between trial length and placebo response.[53,54] Hence, shorter trial durations may lead to a reduced placebo response rate, and a delayed therapeutic response may suggest the presence of other mechanisms beyond medication driving the response to treatment. Significant differences in time to remission were seen only in adults, which may in part be due to the higher remission rates in the adult versus child subjects.

Our findings should be viewed in the context of several limitations. Due to our exclusion criteria, our results may not generalize to patients having complex clinical presentations, such as those with psychiatric comorbidities, serious medical comorbidities, or impaired cognitive functioning. Typically, comorbid subjects are excluded from clinical trials such as this one, so there are limited data on the impact of comorbidities on placebo response. However, the atomoxetine analyses also found no associations between psychiatric comorbidity and placebo response, except for a weak association with tics on 1 of 2 measures of response.[18] While results may not generalize to those with exclusionary medical conditions such as hypertension, positive associations were found with several common medical symptoms that merit further investigation. No prior work has specifically assessed socioeconomic status or cognitive functioning as a predictor of placebo response in children with psychiatric illness, in part because these variables are typically not systematically reported in industry-sponsored trials. If socioeconomic status was a robust predictor of placebo response, then related factors such as ethnicity and conduct problems should also predict the response to placebo. However, neither oppositional defiant disorder nor conduct disorder was found to influence placebo rates in the atomoxetine analyses,[18] and the association between ethnicity and placebo response is inconsistent across studies. Nonetheless, future analyses should directly assess the impact of socioeconomic status,

psychiatric comorbidities, and intellectual functioning on placebo response in ADHD trials.

Almost 100% of the pediatric subjects had the combined subtype while subtype was not coded in the adult lisdexamfetamine dimesylate trial, precluding any meaningful analysis of it as a predictor. Subtype of ADHD has not been found to be stable over time,[55,56] limiting its utility as a predictor of response. The raters trained in this protocol had prior expertise in the clinical evaluation and treatment of ADHD, so the generalizability of these findings to less experienced clinicians cannot be assumed. However, the placebo rates observed in these trials are consistent with those found in other pediatric[57,58] and adult trials of stimulants[20–22] despite variable definitions of response and remission used across the studies.

Both trials in this study used a fixed-dosing design, which may limit the generalizability of findings and could have impacted the placebo response rate. Fixed-dosing designs are often employed in clinical trials to examine the relationship between dose and response but are not consistent with "real world" dosing practices because medication dose is disconnected from the patient's symptom level and initial response. Depression trials using fixed-dosing designs have produced elevated rates of placebo response versus those using flexible-dosing designs in which the clinician is allowed to adjust the dose based on patient response.[59] Future work should specifically examine placebo response rates in flexible-dosing studies of ADHD as well as other designs, such as within-subject crossover trials.

Both trials lasted only 4 weeks, so results are not applicable to sustained response to placebo. While Khan[9] found that 79% of responders to placebo in depression trials maintained their response for more than 3 months, it is unknown whether these results would generalize to ADHD.

A sizable minority of ADHD subjects respond to placebo, particularly in trials of adults. As long as the benchmark for US Food and Drug Administration approval remains the ability of a drug to outperform placebo under controlled settings, it is important to examine predictors of placebo response. This statement is particularly germane for mental health disorders, such as ADHD, which typically employ subjective ratings of symptoms as their primary outcome measure. Baseline symptom severity was the most robust predictor of remission in both children and adults, with other demographic and clinical factors having little effect. It also influenced placebo response rates in the adult trial. Response and remission with placebo are slower to occur than with active medication. These results suggest that placebo response rates in stimulant trials of ADHD may be minimized by enrolling subjects with more severe symptomatology and using short trial durations. Future research should focus on the impact of socioeconomic status, cognitive, medical, and psychiatric comorbidities as well as aspects of trial design on response to placebo, especially in studies of adults in which placebo rates tend to be higher than those seen in pediatric trials.

Clinically, these findings clearly suggest the need for multiple indices of treatment response, as improvement on one measure does not guarantee comparable results on a different measure. They also demonstrate that impairing ADHD symptoms are stable over the short term and unlikely to resolve without active treatment. In contrast, remission occurring several weeks after the initiation of a therapeutic dose of a stimulant medication is uncommon and may suggest the presence of other factors besides medication influencing treatment response.

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