# Impact of Stimulant Pharmacotherapy on Sleep Quality: Post Hoc Analyses of 2 Large, Double-Blind, Randomized, Placebo-Controlled Trials

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***Background:*** Sleep disturbances may cause distress among individuals with attention-deficit/hyperactivity disorder (ADHD), but few studies have examined the impact of stimulant pharmacotherapy for ADHD on sleep in adults.

***Method:*** These post hoc analyses included sleep data collected with the Pittsburgh Sleep Quality Index (PSQI), a self-rated questionnaire, from 831 adults with *DSM-IV-TR*–defined ADHD in 2 large, randomized, double-blind, placebo-controlled, forced–dose titration studies of lisdexamfetamine (N = 420; conducted from May 25, 2006, to November 16, 2006) and triple-bead mixed amphetamine salts (MAS) (N = 411; conducted from April 25, 2005, to November 4, 2005). Change from baseline to endpoint in PSQI clinically meaningful change categories (ie, "decrease," "no change," or "increase") was analyzed by treatment group in each study using the $\chi^2$ test. The Cochran-Mantel-Haenszel method was used (1) to determine whether there was a statistically significant difference in Clinical Global Impressions-Improvement (CGI-I) score of 1 or 2 (improved) versus > 2 (not improved) relative to a decrease or an increase in PSQI and (2) to analyze shifts from good sleep at baseline (PSQI ≤ 5) to poor sleep at endpoint (PSQI > 5).

***Results:*** Impaired sleep (PSQI score > 5) relative to baseline was demonstrated in 8.3% and 9.7% of the treatment and placebo groups, respectively ($P = .18$), in the MAS study and 7.7% and 8.2%, respectively ($P = .03$), in the lisdexamfetamine study. Clinically meaningful change in baseline to endpoint PSQI was not statistically significantly different between treatment and placebo groups in either study. A significant difference in CGI-I 1 and 2 relative to an increase or decrease in PSQI was found in both the triple-bead MAS ($P < .0001$) and the lisdexamfetamine ($P = .0008$) trials. More subjects with improved CGI-I rating of 1 or 2 had improvement in PSQI than had worsening.

***Conclusions:*** Approximately one-third of subjects receiving treatment or placebo had clinically meaningful sleep improvement, emphasizing that change in sleep quality during treatment may not necessarily be related to stimulant therapy. When managing complaints of sleep difficulties in ADHD subjects, clinicians should undertake a broad assessment and consider underlying conditions that may contribute to sleep disruption.

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Attention-deficit/hyperactivity disorder (ADHD) is a common childhood condition that persists into adulthood. Recent estimates of the prevalence of adult ADHD indicate that the disorder affects 3% to 4% of adults in the United States.[1–3]

Anecdotal reports have emphasized that sleep disruption is common in adults with ADHD. In a controlled study examining self-reported sleep characteristics of adults with and without ADHD,[4] sleep impairment was significantly associated with ADHD, independent of stimulant pharmacotherapy, age at ADHD onset, and comorbidities associated with sleep disturbances. A pilot study of 6 adults with ADHD and sleep complaints showed evidence of sleep-disordered breathing in all patients.[5] Another study comparing adults with ADHD (without comorbidity, substance abuse, or medication) versus healthy controls found that adults with ADHD had a significantly greater incidence of a variety of sleep disorders, including movement disorders, insomnia, and parasomnias.[6]

Stimulant pharmacotherapy is the mainstay of ADHD treatment; however, stimulants may potentially exacerbate sleep disruption in adults with ADHD because of their known wake-promoting effects in healthy individuals. Unfortunately, there have been limited studies examining the impact of pharmacotherapy on sleep in adults with ADHD. Early studies were conducted with methylphenidate only and were limited by small samples or lack of controlled treatment design.[7–9]

Recent analyses of the impact of 2 amphetamine-based stimulant medications, lisdexamfetamine dimesylate and a triple-bead formulation of mixed amphetamine salts (MAS), utilized a self-report sleep quality measure, the Pittsburgh Sleep Quality Index (PSQI), to assess sleep at baseline and following 4 weeks of treatment. Roth and colleagues[10] analyzed pooled data from 2 phase 3 studies in adults with ADHD to assess the incidence rate and characteristics of treatment-emergent insomnia reports with triple-bead MAS compared with placebo. Although insomnia was the most common treatment-emergent adverse event reported in the 2 pooled clinical trials (triple-bead MAS, 37.8%; placebo, 10.5%), a similar incidence of insomnia events was reported by subjects with baseline PSQI scores of very good/fairly good compared with subjects who reported very bad/fairly bad sleep. In a 4-week, double-blind, forced–dose escalation study of adults with ADHD, 420 participants received placebo or lisdexamfetamine 30, 50, or 70 mg/d, taken in the morning.[11] Sleep quality was assessed at baseline and

week 4 with the self-rated PSQI. Compared with placebo, lisdexamfetamine was not associated with an overall worsening of sleep.

Proper clinical management of sleep disruption in ADHD subjects with sleep disturbances is important, since sleep impairment is associated with distress and poor daytime function. Because stimulants are a standard therapy for management of ADHD, but have wake-promoting properties that could disrupt sleep, it is important to clarify their impact on sleep to inform clinical treatment decisions.

**Clinical Points**

- Attention-deficit/hyperactivity disorder (ADHD) is often associated with sleep disruption.
- Stimulant therapy may not impair sleep quality in adults with ADHD significantly more often than placebo.
- Comprehensive treatment of ADHD includes evaluation for and therapeutic targeting of sleep disruption.

To clarify the clinical significance of stimulant-related changes in sleep, it is important to understand both the association of ADHD with sleep disruption prior to treatment, which may be inherent to the disorder, and changes in sleep disruption that occur during treatment. Using a validated clinical assessment of overall sleep, this study sought to establish the baseline status of sleep in ADHD prior to initiation of stimulant therapy and to examine how sleep changes with stimulant therapy. Using data on sleep from 2 large, randomized, double-blind, placebo-controlled trials of long-acting amphetamine treatments, we hypothesized that active treatment, relative to placebo, would be associated with significant improvement in sleep for subjects from baseline to study endpoint and that these findings would be replicated across the 2 studies.

## METHOD

Sleep was evaluated in adults participating in 2 large, randomized, double-blind, placebo-controlled trials of long-acting amphetamine treatments: (1) a 4-week, forced–dose titration study of lisdexamfetamine[12] and (2) a 6-week, forced–dose titration study of triple-bead MAS.[10,13] PSQI data were collected from a total of 831 subjects during these trials (triple-bead MAS, N = 411, and lisdexamfetamine, N = 420). The lisdexamfetamine study was conducted from May 25, 2006, to November 16, 2006, and the triple-bead MAS study, from April 25, 2005, to November 4, 2005. The trials were registered with clinicaltrials.gov (NCT00334880 and NCT00152022).

### Subjects

In the lisdexamfetamine study,[12] adults aged 18 to 55 years with moderate to severe ADHD (*Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition, Text Revision [*DSM-IV-TR*] criteria[14]) were treated with lisdexamfetamine 30, 50, or 70 mg/d or placebo. Exclusion criteria were as follows: comorbid psychiatric diagnosis with significant symptoms that might preclude treatment; history of seizures; medications affecting the central nervous system or blood pressure; known cardiac structural abnormality or any condition that could affect cardiac performance; clinically significant electrocardiogram or laboratory abnormality at screening or baseline; history of hypertension or a resting sitting systolic blood pressure > 139 mm Hg or diastolic blood pressure > 89 mm Hg; pregnancy or lactation; and positive urine drug results at screening or baseline. Women of childbearing potential had to comply with contraceptive restrictions.

In the triple-bead MAS study,[10,13] adults aged 18 to 55 years with moderate to severe ADHD (*DSM-IV-TR* criteria) were treated with 25, 50, or 75 mg/d triple-bead MAS or placebo. Subjects were otherwise healthy adult men or nonpregnant, nonlactating women with exclusion criteria similar to those of the lisdexamfetamine study.

Both studies were performed in accordance with the Declaration of Helsinki and Good Clinical Practice according to the International Conference on Harmonization guidelines. Study protocols were approved by the institutional review board of each institution, and all subjects provided written informed consent.

### Study Design

Both the 4-week lisdexamfetamine[12] and the 6-week triple-bead MAS trials[10,13] were forced–dose titration studies. In the lisdexamfetamine study, after a 7- to 28-day washout, subjects were randomly assigned (2:2:2:1) to 4 weeks of lisdexamfetamine treatment with 30 mg/d, 50 mg/d (30 mg/d for week 1 with forced dose escalation to 50 mg/d for weeks 2 to 4), or 70 mg/d (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, administered orally. In the triple-bead MAS trial, all eligible subjects were randomly assigned (1:1:1:1) to triple-bead MAS treatment with 25, 50, or 75 mg/d or placebo. All subjects assigned to active treatment were started at a triple-bead MAS dose of 25 mg/d. Subjects assigned to doses of 50 mg/d were titrated over 3 weeks, and those assigned to 75 mg/d were titrated over 4 weeks.

### Measures

The PSQI,[15] a 19-item, self-rated questionnaire, assessed various aspects of sleep, sleep quality, and sleep disturbances over the previous month. Psychometric evaluation of the scale supports its internal consistency reliability and construct validity, and the scale is highly sensitive and specific for the identification of sleep disturbances in a variety of clinical populations.[16] The PSQI is composed of 7 components: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The sum of scores for these 7 components yields 1 global score. Total PSQI scores > 5 have yielded a diagnostic sensitivity of 89.6% and a specificity of 86.5% in distinguishing poor sleepers from good sleepers.[15] In the lisdexamfetamine study,[12] internal

consistency reliability for the PSQI total score as measured by Cronbach α was 0.75 for the treatment group and 0.86 for the placebo group. Internal consistency reliability in the triple-bead MAS study[10,13] was low for the treatment group (Cronbach α = 0.56) and acceptable for the placebo group (Cronbach α = 0.69).

Two measures of PSQI scores were used in this study: dichotomized PSQI categories utilizing a score of > 5 as a cutoff, where ≤ 5 indicates better sleep and > 5 indicates poorer sleep, and post hoc–derived PSQI clinical categories of sleep change (referred to as *clinically meaningful change categories*), defined as "increase," where the endpoint assessment is at least 1 modified standard error (SE) distance away from baseline score toward worsening; "no change," where the endpoint assessment is within 1 modified SE distance from baseline; and "decrease," where the endpoint assessment is at least 1 modified SE distance away from baseline toward improvement. The modified SE does not solely rely on sample parameters to determine the significance of a change in a score when reassessed, but considers the reliability or stability of the measure when readministered to establish a level for a clinically meaningful change.[17] The modified SE is defined as the baseline standard deviation × square root of 1 – Cronbach coefficient α of baseline and endpoint.

The Clinical Global Impressions-Improvement scale (CGI-I),[18] an investigator-rated scale, assessed each subject's improvement over time via a 7-point subscale ranging from 1 = very much improved to 7 = very much worse. Prior to analysis, this variable was dichotomized a priori into 2 categories: "improved," which included all subjects regarded as "much improved" and "very much improved" (CGI-I ratings of 1 or 2), or "not improved" (CGI-I rating > 2).

Adverse events during the 2 studies were obtained through close observation and monitoring of subjects during the study[12] and through nonleading questions and spontaneous report by the subjects during clinical interviews.[13] Treatment-emergent insomnia was defined in the triple-bead MAS study as any event with a Medical Dictionary for Regulatory Activities Version 8.1 preferred term of *insomnia, initial insomnia, middle insomnia,* or *early morning awakening* that began or increased in severity on or between the dates of first and last study medication dose.[10,13] For the lisdexamfetamine trial, the Medical Dictionary for Regulatory Activities Version 9.1 was used.[11] In each study, comorbid mental health conditions were assessed at baseline using the Structured Clinical Interview for *DSM-IV-TR* Axis I Disorders during the initial evaluation of subjects to determine eligibility for study enrollment.

### Data Analysis

For purposes of these post hoc analyses, the study populations were all those participants for whom both baseline and endpoint measures of PSQI were available. This is analogous to, but not identical with, the intent-to-treat (ITT) populations, which consisted of all subjects for whom a baseline measure and a subsequent measure were available on the primary study outcome instrument, the Attention-Deficit/Hyperactivity Disorder Rating Scale Version IV. Hypothesis testing was performed at the 5% level. Chi-square statistics were used for the analyses of the change in PSQI clinically meaningful change categories from baseline to endpoint by treatment group in each study. The Cochran-Mantel-Haenszel method with a null hypothesis of no study medication effect across the clinically meaningful change strata was used to answer the question, "Is there a statistically significant difference between CGI-I 1 or 2 versus CGI-I > 2 ratings that depends on whether or not one has a decrease or an increase in PSQI?" and the analysis of shift of categorized sleep quality index (ie, ≤ 5 and > 5).

## RESULTS

Participants in the lisdexamfetamine study were randomly assigned to lisdexamfetamine 30 (n = 119), 50 (n = 117), or 70 (n = 122) mg/d or placebo (n = 62). Of these, 414 subjects were included in the ITT population (n = 115, 117, 120, and 62, respectively). Of the 420 enrolled subjects, 71 (17%) terminated before study completion. Discontinuation rates in each lisdexamfetamine group (13%–20%) were similar to those among the placebo group (16%). Of the subjects randomly assigned to receive treatment, adverse events were the most common reason for discontinuation (0.5%; 2/358), whereas lack of efficacy was the most common reason in the placebo group (1.6%; 1/62). Sleep-related adverse events leading to discontinuation in the lisdexamfetamine group included insomnia (2.2%; 8/358), hypersomnia (0.3%; 1/358), restlessness (0.3%; 1/358), and sleep disorder not specified (0.3%; 1/358); there were no discontinuations due to sleep-related adverse events in the placebo group.

In the triple-bead MAS trial, all eligible subjects were randomly assigned to triple-bead MAS treatment with 25 (n = 104), 50 (n = 101), or 75 (n = 102) mg/d or placebo (n = 104). Of these, 405 subjects were included in the ITT population (n = 103, 101, 98, and 103, respectively); 120 (29.6%) terminated before study completion. Discontinuation rates in the treatment groups ranged from 22.1% (25 mg/d) to 26.5% (75 mg/d) and 42.3% in the placebo group. Adverse events were the most common reason for discontinuation among subjects who received treatment (11.0%; 34/307), whereas "other" was cited as the most common cause in the placebo group (20.2%; 21/104). Sleep-related adverse events in the triple-bead MAS groups combined included insomnia (3.9%; 12/307) and restlessness (0.7%; 2/307); in the placebo group, these adverse events each led to discontinuation in 1 subject (1.0%).

### Demographic and Baseline Characteristics

Demographic and baseline characteristics of all recruited study participants are summarized in Table 1.[12,13]

### Sleep Outcomes

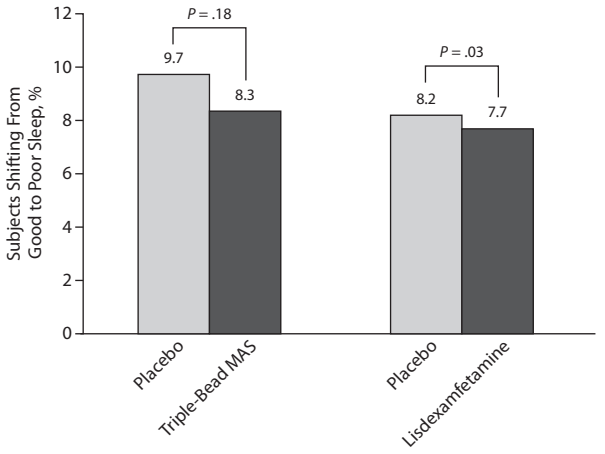
In the triple-bead MAS study, of the 301 treated and 103 placebo subjects, 8.3% of the treatment group and 9.7% of the placebo group demonstrated worse sleep at endpoint

**Table 1. Baseline Demographic and Clinical Characteristics of Enrolled Subjects[a]**

| | Lisdexamfetamine (30, 50, and 70 mg/d combined) | | Triple-Bead MAS (25, 50, and 75 mg/d combined) | |
|---|---|---|---|---|
| Characteristic | Placebo (n = 62) | Lisdexamfetamine (n = 358) | Placebo (n = 104) | Triple-Bead MAS (n = 307) |
| Age, mean ± SD, y | 35.2 ± 10.9 | …[b] | 35.6 ± 9.8 | 37.7 ± 9.7 |
| Men, n (%) | 32 (52) | 196 (55) | 58 (56) | 175 (57) |
| Caucasian, n (%) | 48 (77) | 301 (84) | 89 (86) | 269 (88) |
| Body mass index, mean ± SD | …[b] | …[b] | 27.5 ± 5.2 | 27.9 ± 5.3 |
| Baseline ADHD-RS total score, mean ± SD | 39.4 ± 6.4 | …[b] | 40.0 ± 5.4[c] | 40.3 ± 5.6[d] |

[a]Data from Roth et al[10] and Adler et al.[11]
[b]No group data available.
[c]n = 103.
[d]n = 302.
Abbreviations: ADHD-RS = Attention-Deficit/Hyperactivity Disorder Rating Scale, MAS = mixed amphetamine salts.
Symbol: … = data not available.

**Figure 1. Percentage of Subjects Shifting From Good Sleep (PSQI ≤ 5) at Baseline to Poor Sleep (PSQI > 5) at Endpoint, by Study and by Treatment Group**




Abbreviations: MAS = mixed amphetamine salts, PSQI = Pittsburgh Sleep Quality Index.

**Table 2. Change in PSQI Total Score Clinically Meaningful Change Categories From Baseline to Endpoint by Treatment Group and Study**

| | | Clinically Meaningful Change[a] | | | |
|---|---|---|---|---|---|
| Treatment Group | No. of Subjects | Decrease, n (%) | No Change, n (%) | Increase, n (%) | *P* Value[b] |
| Lisdexamfetamine study | | | | | |
| Lisdexamfetamine | 339 | 111 (32.7) | 189 (55.8) | 39 (11.5) | |
| Placebo | 61 | 13 (21.3) | 41 (67.2) | 7 (11.5) | .19 |
| Triple-bead MAS study | | | | | |
| Triple-bead MAS | 301 | 108 (35.9) | 153 (50.8) | 40 (13.3) | |
| Placebo | 103 | 49 (47.6) | 39 (37.9) | 15 (14.6) | .06 |

[a]Clinically meaningful change categories: decrease = at least 1 modified SE distance away from baseline toward improvement; no change = end of study score of assessment is within 1 modified SE distance from baseline; increase = at least 1 modified standard error (SE) distance away from baseline score toward worsening. Modified SE = the baseline standard deviation × square root of 1 – Cronbach coefficient α of baseline and endpoint.
[b]Treatment group vs placebo group; determined by $\chi^2$ test.
Abbreviations: MAS = mixed amphetamine salts, PSQI = Pittsburgh Sleep Quality Index.

(PSQI > 5) than at baseline (PSQI ≤ 5; Figure 1), while 29.2% of the treatment group and 27.2% of the placebo group demonstrated better sleep at endpoint than at baseline. There was no statistically significant difference between treatment groups for shifts from baseline to endpoint PSQI scores ($P = .18$). In the lisdexamfetamine study, of 339 treated and 61 placebo subjects, 7.7% of the treatment group and 8.2% of the placebo group demonstrated worse sleep at endpoint (PSQI > 5) than at baseline (PSQI ≤ 5; Figure 1), while 20.9% of the treatment group and 8.2% of the placebo group demonstrated better sleep at endpoint than at baseline. This relationship between treatment group and endpoint PSQI was significant at $P = .03$.

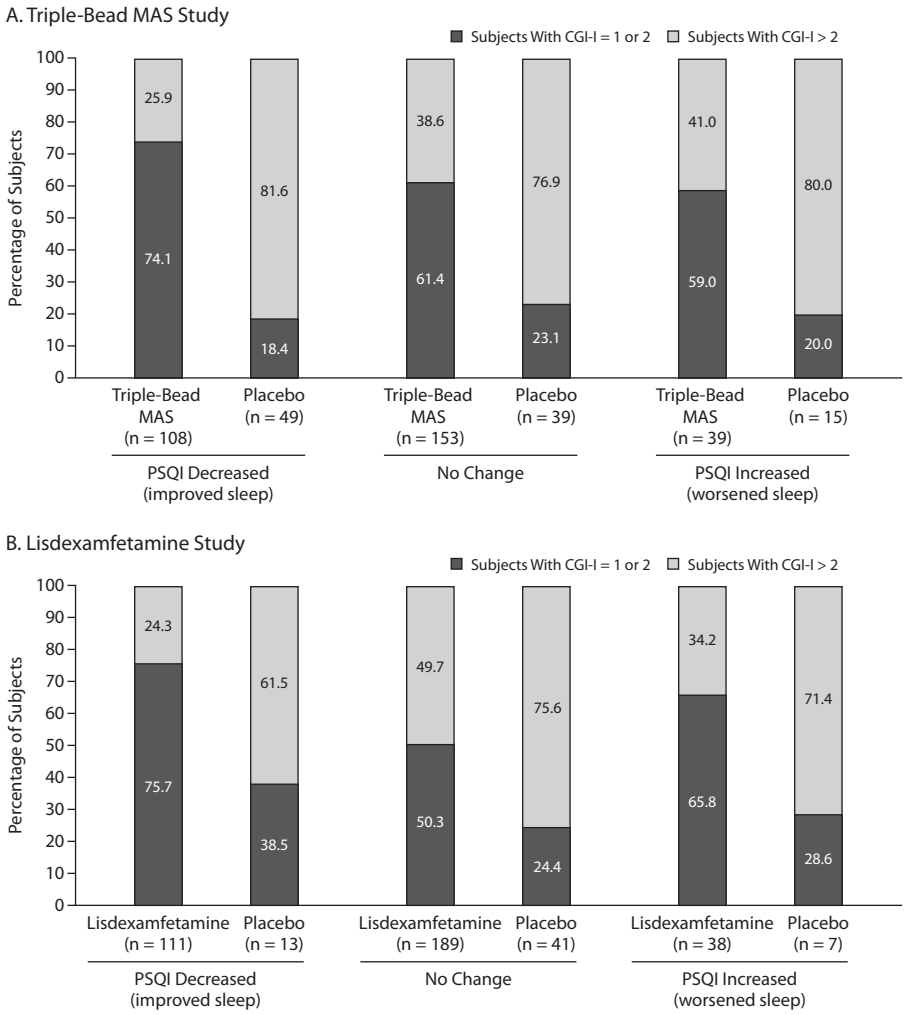
In both trials, generally more study subjects were in the PSQI no change category than either the increase or decrease categories. In both the lisdexamfetamine and the triple-bead MAS trials, there were no statistically significant differences in the proportion of subjects in these PSQI change categories between treatment and placebo groups ($P = .19$ and .06, respectively; Table 2).

When the data were examined for subjects showing a clinically meaningful change in sleep quality, 108 MAS subjects had clinically meaningful improvement, of whom 80 (74.1%) were classified as having a CGI-I rating of 1 or 2. In placebo subjects, 49 had clinically meaningful improved sleep, of whom 9 (18.4%) showed improvement by the CGI-I. Of 39 MAS subjects who had clinically meaningful worsening of sleep, 23 (59.0%) showed improvement on the CGI-I, while 3 of 15 (20.0%) placebo subjects with worsened sleep had improvement on the CGI-I (Figure 2A). For lisdexamfetamine subjects, 111 had clinically meaningful improvement in sleep, of whom 84 (75.7%) had a CGI-I rating of 1 or 2. In placebo subjects, 13 had improvement in sleep, of whom 5 (38.5%) showed improvement on the CGI-I. There were 38 lisdexamfetamine subjects with clinically meaningful worsening of sleep, of whom 25 (65.8%) had improvement on the CGI-I, compared to 2 of 7 (28.6%) placebo subjects with worsened sleep (Figure 2B). The Cochran-Mantel-Haenszel method was used to test for a statistically significant difference in CGI-I rating of 1 or 2 (improved; vs CGI-I > 2) relative to an increased or decreased PSQI. A significant difference was found in both the triple-bead MAS ($P < .0001$) and the lisdexamfetamine ($P = .0008$) trials.

## DISCUSSION

We conducted an assessment of change in sleep among 2 large groups of adults with ADHD participating in double-blind, placebo-controlled trials of amphetamine treatment to test the relationship between quality of sleep and ADHD treatment. In both studies, only a small percentage of the treated subjects experienced worsening of sleep (8.3%,

**Figure 2. Percentage of Subjects With Endpoint CGI-I Category 1 or 2 (improved) or >2 (not improved) by PSQI Clinically Meaningful Change Category, by Treatment Group**




Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, MAS = mixed amphetamine salts, PSQI = Pittsburgh Sleep Quality Index.

triple-bead MAS; 7.7%, lisdexamfetamine), and this was comparable to or significantly less than that experienced by the subjects given placebo (9.7%, triple-bead MAS; 8.2%, lisdexamfetamine). No significant differences in the proportion of patients in each PSQI clinically meaningful change category were observed between treatment and placebo groups in both trials. In addition, 11.5% of subjects treated with lisdexamfetamine and 13.3% of those receiving triple-bead MAS experienced a clinically meaningful increase in PSQI (ie, poorer sleep) from baseline to endpoint, while 32.7% and 35.9%, respectively, reported a clinically meaningful decrease in PSQI (ie, improved sleep). This finding supports the hypothesis that, in some ADHD subjects, sleep quality improves with stimulant treatment. These observations may be attributed, at least in part, to changes in daytime functioning, as daytime functioning is a component of the PSQI.

In both studies, more subjects on active ADHD treatment than those on placebo had improved CGI-I scores of 1 or 2. This relation was observed regardless of whether there was an increase or decrease in endpoint PSQI clinical categories of sleep change, although treated subjects who reported clinically meaningful change of improved sleep were more likely to be rated clinically improved (CGI-I 1 or 2) than were those who reported worsened sleep quality (74.1%, triple-bead MAS and 75.7%, lisdexamfetamine vs 59.0%, triple-bead MAS and 65.8%, lisdexamfetamine, respectively). Clinical rating of improvement or no improvement in ADHD was significantly correlated with increase or decrease in PSQI in both trials (MAS, $P < .0001$; lisdexamfetamine, $P = .0008$). This finding suggests that ADHD improvement may correlate with improved sleep quality. However, because of the overwhelming improvement in ADHD symptoms, which makes the direction of influence unclear, further study is needed to appreciate the potential clinical relevance of this finding.

Because similar proportions of subjects in the placebo and treatment groups experienced either improvement or deterioration of sleep and because the magnitude of improvement in each group exceeded that of worsening, our replication analysis suggests that sleep impairment may be a function of ADHD, independent of stimulant pharmacotherapy. This is consistent with the findings of a large, controlled study of adults in a community setting, in which sleep impairments were significantly associated with ADHD, independent of ADHD pharmacotherapy.[4] Our findings are also consistent with those from a retrospective study by Dodson and Zhang,[8] who found that stimulant treatment was associated with significant reductions in insomnia and sleep disruption.

The findings of this study should be viewed within the context of its methodological limitations. Low rates of comorbidity at baseline, as are typical in clinical trials, limit the generalization of our findings to typical ADHD subjects, who are likely to have more comorbidities.[4] However, low rates of comorbid mental health conditions in our study minimize the possibility that reported changes in sleep are attributable to improvement in comorbid conditions. It is also unlikely that PSQI findings were related to baseline demographic

differences, since these characteristics of treatment groups were similar. The examination of changes in PSQI clinically meaningful change categories from baseline to endpoint was a post hoc analysis and should be replicated in a prospective design. The internal consistency reliability of the PSQI in the triple-bead MAS treatment group was low. In addition, self-report measures have inherent limitations, including recall bias, and future replications should consider physiologic parameters such as actigraphy as a measure of sleep quality.

Despite these methodological considerations, this study offers the first replicated evidence of sleep changes in 2 large, placebo-controlled trials of amphetamine treatment. Findings consistently support the hypothesis that sleep quality in subjects taking ADHD medication is similar to that in subjects given placebo. Only a small percentage of treated subjects experienced worsened sleep, and this was comparable to or less than the sleep deterioration experienced by the subjects given placebo. In addition, approximately one-third of treated subjects in both studies reported improved sleep, supporting the conclusion that, in some subjects, ADHD treatment improves sleep quality. Our replication analyses thus suggest that clinicians should not assume that stimulants will have a negative impact on sleep quality in adults with ADHD. The analyses also provide some evidence for association between ADHD and sleep disruption through evidence of sleep benefit from treatment for ADHD, as statistically more subjects had improvement on PSQI ratings of sleep quality on active lisdexamfetamine treatment than on placebo, although this finding was not replicated in the MAS study. Further study of individuals with ADHD and sleep impairment can clarify the association of sleep impairment with ADHD. Treatment studies of adults with ADHD and sleep impairment might clarify which presenting clinical characteristics or pharmacotherapy mechanisms elicit resolution of sleep impairment.

***Drug names:*** lisdexamfetamine (Vyvanse), methylphenidate (Focalin, Daytrana, and others), mixed amphetamine salts (Adderall and others).

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