

Update on the management of attention-deficit/hyperactivity disorder in children and adults: patient considerations and the role of lisdexamfetamine

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Abstract: Attention-deficit/hyperactivity disorder (ADHD) is a behavioral disorder characterized by atypical levels of inattention, hyperactivity, and impulsivity that impair daily living activities. Although commonly associated with children and adolescents, current literature and practice now demonstrate the impairment the disorder may impose on adults as well. Central nervous system (CNS) stimulant medications are the first-line therapy for ADHD. CNS stimulants include methylphenidate and amphetamine derivatives. Longer-acting formulations used once daily are often preferred to avoid medication administration during school or work as well as to avoid side effects associated with rapid fluctuations in serum concentrations associated with multiple daily dosing. Lisdexamfetamine, a new, novel amphetamine product, has been shown to provide efficacy upwards of 12 hours in children and adults with a side effect profile similar to those of other longer-acting amphetamine products. Owing to its unique prodrug composition and the need for oral administration to activate the medication, lisdexamfetamine may offer advantages in clinical situations where stimulant abuse is a concern.

Keywords: lisdexamfetamine, Vyvanse, ADHD, attention-deficit/hyperactivity disorder, stimulants

Introduction

Attention-deficit/hyperactivity disorder (ADHD), a behavioral disorder characterized by impairments in daily living activities by atypical levels of inattention, hyperactivity, and/or impulsivity, affects as many as 7% of American children and 5% of adults.^{1,2} Worldwide, approximately 5% of children have been diagnosed with ADHD.³ Central nervous system (CNS) stimulants are recommended as first-line medication therapy for children⁴ and have demonstrated efficacy in treating adults with ADHD as well.^{5,6} CNS stimulants include formulations of methylphenidate (MPH) and amphetamine-derivatives, and are available in a large variety of immediate- and extended-release preparations. Extended-release preparations are often preferred to limit drug administration during school or work and may help to limit side effects associated with rapid fluctuations in serum concentration. Lisdexamfetamine (Vyvanse®; Shire Pharmaceuticals, Wayne, PA, USA), a prodrug of dextroamphetamine, is approved in the US for the treatment of ADHD in children aged 6 to 12 years and adults aged 18 to 55 years.⁷ The unique pharmacokinetics of the medication resulting from its prodrug design allow for a longer duration of activity and may also help to limit abuse of the agent.

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The characteristics of ADHD across the age spectrum are becoming better understood. Individual symptoms of hyperactivity and inattention, for example, are not necessarily constant, and may decrease with age.^{8,9} That is not to say, however, that children will outgrow a diagnosis of ADHD. According to one review, nearly 75% of children diagnosed with ADHD continue to meet diagnostic criteria into adolescence or young adulthood.¹⁰ Changes in symptomatic behaviors, and the impairment they may present, necessitate continuous review of medication treatment including adjustment or discontinuation when warranted.

Doses of immediate-release formulations of MPH, dextroamphetamine, and mixed-amphetamine salts (MAS) are often administered twice daily: once in the morning and again at lunchtime or early afternoon. Extended-release medications have shown better levels of adherence and improved clinical outcomes in both children and adults.^{11,12} Extended-release formulations administered in the morning help to simplify the adult's medication dosing schedule. Extended-release formulations also eliminate the need for separate prescriptions, medication supply, and reliance on the school nurse for the schoolchild, not to mention potential social stigmatism. Though not a pharmaceutically designed extended-release formulation, once-daily administration of lisdexamfetamine (LDX) does provide efficacy throughout the day for both children and adults.^{13,14} The duration of LDX's clinical effect is comparable to that of osmotically-released MPH and extended-release MAS.

Abuse, misuse, and diversion of stimulant medications may also complicate the treatment of ADHD. Abuse is often considered to describe intentionally using large doses of a medication to achieve a desired effect, eg, euphoria, sedation, hallucinations. Conversely, misuse describes the use of a prescription medication often without a prescription for its intended use. Inconsistencies in terminology can lead to difficulty interpreting abuse and misuse data of stimulant medications. In one sample of 4580 US college students, nearly 2% of those who had never received a prescription for CNS stimulants reported using one illicitly in the past 30 days. This increased to 8% for those who began prescription-stimulant use during high school and to nearly 23% in those who began treatment during college. For those reporting illicit use of a stimulant medication, the odds of having begun legitimate treatment with a prescription stimulant during high school was 3.7; the odds of having begun legitimate treatment during college was 13.¹⁵ One review of misuse and diversion described the rate of high school and college students who sold, traded, or gave away their stimulant medications as

high as 16% to 29%.¹⁶ Setlik et al described a 76% increase in poison control center calls related to adolescents abusing stimulant medications over the period of 1998 to 2005.¹⁷ This was contrasted with a 55% increase in all calls related to adolescents over the same 8-year period. The authors also compared the increase in stimulant-related calls to the increase in stimulant medication prescriptions that increased by 86% over the same time frame. Owing once again to its unique prodrug nature and metabolism, LDX may pose a safer alternative for those concerned with abuse or diversion of stimulant medications.

This review will examine the mechanism of action and unique pharmacology and pharmacokinetics of LDX, discuss the safety and efficacy published to date in children and adults, and describe the potential place in therapy LDX may hold in the treatment of ADHD.

Pharmacology and pharmacokinetics

LDX is a prodrug of dextroamphetamine. It consists of an *l*-lysine moiety covalently bound to the active parent compound. As such, the mechanism of action of LDX is essentially the same as other amphetamine-derivatives. Within the CNS, these noncatecholamine sympathomimetic agents increase the synaptic activity of dopamine and norepinephrine. This is accomplished by increasing the release of the neurotransmitter into the synaptic cleft, decreasing reuptake back into the presynaptic neuron, and inhibiting their catabolism.¹⁸ Potentiating the activity of dopamine and norepinephrine within certain brain structures, eg, the prefrontal cortex, may help to regulate motor and behavioral responses to external stimuli.

The rate-limited metabolism of LDX and subsequent release of the active parent compound dextroamphetamine is the characteristic that sets LDX apart from other amphetamine-derivatives. Following oral administration, the *l*-lysine moiety is cleaved from the parent dextroamphetamine compound via enzymatic biotransformation in the intestine and liver.⁷ In pharmacokinetic studies of both children and adults, this has resulted in higher maximum serum concentrations (C_{max}) of dextroamphetamine as well as greater area-under-the-curve (AUC) profiles when compared to a similar dose of extended-release MAS. In a phase II trial of 52 children aged 6 to 12 years, Biederman et al described the C_{max} of dextroamphetamine administered as 70 mg of LDX as 155 ng/mL and a 12-hour AUC of 1326 ng·h/mL compared to 119 ng/mL and 1019 ng·h/mL when administered as 30 mg extended-release MAS.¹⁹ In adults, the C_{max} following administration of LDX 70 mg was determined

to be 80.3 to 90.1 ng/mL^{20,21} and 24-hour AUC was 1113 ng·h/mL.²¹ Food may slow the time to maximum serum concentrations by 1 hour.²² These pharmacokinetic characteristics are what allow LDX to be utilized as a once-daily medication. Following biotransformation, dextroamphetamine is hepatically metabolized to inactive compounds or renally eliminated unchanged.

Clinical trials

LDX was originally studied in and subsequently approved by the US Food and Drug Administration (FDA) for the treatment of ADHD in children aged 6 to 12 years. In the same phase II study mentioned previously, the efficacy of LDX compared to extended-release MAS was determined.¹⁹ In a blinded, placebo-controlled, crossover manner, Biederman et al compared the effects on classroom ADHD symptoms of a subject-specific effective dose of extended-release MAS to an equivalent dose of LDX. Both extended-release MAS and LDX significantly improved ADHD symptoms compared to baseline assessments. Assessments of symptoms were made frequently on the last day of treatment to determine the effects of treatment over time. At 2 hours, both extended-release MAS and LDX showed significant improvements compared to placebo. This effect peaked at 6 hours before trending back towards the day's baseline value within 10 to 12 hours. A clinically meaningful difference between LDX and extended-release MAS was not demonstrated.

Biederman et al used a placebo-controlled, forced-dose escalation design in their phase III study involving 290 children aged 6 to 12 years.¹⁴ Patients were randomized and titrated to a final dose of 30, 50, or 70 mg LDX/day or placebo over a course of 3 weeks. A clinician-rated ADHD symptom-assessment tool was used to assess the changes in symptom severity from baseline to endpoint at 4 weeks. All three doses of LDX significantly improved symptom scores by the end of the study; the improvement was seen as soon as one week of treatment when all active groups received 30 mg/day. Between-dose comparisons showed a small albeit statistically significant advantage of the 70 mg/day dose compared to 30 mg/day.

A post-hoc analysis of data collected in the phase III trial demonstrated significant improvements in parent-rated ADHD symptom scores measured at 10 AM, 2 PM, and 6 PM during the weekly assessment days in the children receiving LDX compared to those receiving placebo.²³ This analysis further showed significant improvements throughout the day in parent-rated scores of specific behaviors such as hyperactivity and opposition. The continued reductions in

parent-rated symptom scores at 6 PM, approximately 10 hours after administration, reinforce the pharmacokinetically derived extended duration of LDX.

Wigal et al performed a laboratory-classroom study similar to the phase II trial discussed above.²⁴ The purpose of this study was to further describe the onset and duration of LDX effect during the school day. After a 4-week, open-label, dose-optimization period, 117 subjects were randomized into the placebo-controlled crossover phase of the study. Subjects received their randomized medication (best-dose LDX or placebo) daily for 1 week, the end of which culminated in a laboratory classroom session. During this laboratory classroom assessments of ADHD behavior were made by clinical observers 0.5 hour before administration and again 1.5, 2.5, 5, 7.5, 10, 12, and 13 hours post dose. Although LDX demonstrated significantly better improvements in ADHD behavior compared to placebo at all post-dose time points, the assessments made at 12 and 13 hours post dose were not significantly improved compared to the pre-dose assessment. Compared to the pre-dose assessment, LDX demonstrated significant improvement through 10 hours, again reflecting the long-acting nature of the drug.

Findling et al have been the only to date to examine the long-term benefits of LDX in children aged 6 to 12 years.²⁵ After titrating subjects to an effective dose over 4 weeks, subjects continued open-label LDX treatment for an additional 11 months. Clinician-rated ADHD symptom scores decreased significantly from baseline within 1 week of beginning treatment and reached maximum benefit by the fourth week. Scores describing inattention symptoms and hyperactivity symptoms decreased by approximately 60% and 66%, respectively. These improvements were maintained throughout the remaining 11-month study period.

In a study similar in design to Biederman et al's phase III study in children, Adler et al established the efficacy of LDX in treating adults aged 18 to 55 years with ADHD.¹³ Following randomization to placebo, LDX 30 mg/day, 50 mg/day, or 70 mg/day, 414 adults were assessed for improvements in clinician-rated ADHD symptoms. All doses of LDX demonstrated significantly better improvements in ADHD symptom scores compared to placebo. As well, a significantly greater number of subjects receiving LDX showed at least 30% improvement from baseline in clinician-rated ADHD scores compared to placebo.

Safety and tolerability

Side effects reported in studies of both children and adults were similar in incidence to those of other CNS stimulants.

Notable adverse effects that were reported more often in those receiving LDX treatment compared to placebo included decreased appetite, insomnia, irritability, weight decrease, headache, and upper abdominal pain.^{13,14,24} The reported incidences of these are listed in Table 1. The nature of the reported adverse effects and their incidence were generally similar in phase III trials of both children and adults. Out of a total of 28 reports to poison control centers in 8 states, side effects with greater than a 10% incidence included: agitation (43%), tachycardia (39%), insomnia (29%), dystonia (29%), vomiting (18%), chest pain (14%), hallucinations (11%) and jitters (11%).²⁶ These adverse effects tend to be most prevalent during the initiation of treatment with LDX, or following an increase in dose. Although they tended to be transient in nature, side effects of LDX led to discontinuation of 6%–9% of subjects in the phase III trials of children and adults.^{13,14}

Sleep difficulties and insomnia are some of the most frequently reported side effects of LDX. Wigal et al reported an incidence of insomnia of 27% among children treated with LDX.²⁴ A post-hoc analysis of the phase III trial in adults provides more information however regarding the nature of sleep in adults diagnosed with ADHD and the effects of LDX.²⁷ At baseline, subjects randomized to placebo and LDX were both found to have poor sleep quality as demonstrated by a validated self-reported sleep quality questionnaire. This confirms other data describing the sleep habits of individuals with ADHD, regardless of stimulant treatment. Although 19% of the adults randomized to receive LDX reported insomnia compared to approximately 5% of those randomized to placebo, the changes from baseline in the self-reported sleep quality questionnaire were not significantly different between the two.

Minimal increases in pulse and blood pressure are often reported with CNS stimulants. Similar findings were reported in the studies of LDX in children. Wigal et al reported a maximum increase in pulse of approximately 7 beats per

minute (bpm) for all doses of LDX at 12.5 hours after administration; the increase in pulse reported in the 70 mg group was approximately 10 bpm.²⁴ Similarly, those same authors reported increases in systolic (SPB) and diastolic (DBP) blood pressures of approximately 4 and 5 mmHg, respectively, 8 hours after administration of a 70 mg LDX dose. Compared to placebo, Biederman et al's phase II trial reported statistically significant increases in DBP of 4.6 to 4.8 mmHg and in pulse of 6.7 bpm, at 2.5 to 5 hours following administration. There were no differences when compared to comparable doses of extended-release MAS.¹⁹ Findling's long-term open-label study reported an increase in pulse <2 bpm, and <1 mmHg for both SPB and DBP following 12 months of treatment.²⁵ In adults, Adler et al reported significant increases in pulse of approximately 3 to 5 bpm.¹³

Despite some findings of statistically significant changes in electrocardiogram measurements, no clinically significant cardiac conduction changes were described in the phase II and III trials as well as Findling's long-term extension trial.^{13,14,19,25} However, like other amphetamine products, labeling for LDX does include a black box warning describing sudden death associated with misuse of the agent. In addition, although not specifically reported in use of LDX, there are case reports of sudden death associated with the therapeutic use of CNS stimulants. Although a definitive risk relationship between the therapeutic use of CNS stimulants and sudden death has yet to be determined, the American Academy of Pediatrics and the American Heart Association both recommend a thorough family and medical history and physical examination prior to beginning therapy to identify risk factors for sudden cardiac death.^{28,29} The American Heart Association also recommends baseline electrocardiogram tests.²⁸

The long-term effects that stimulant therapy has on growth are still debated. At the end of Findling et al's 12-month extension study, the age- and sex-normalized z-score for height was –0.08; this was statistically significant when compared to baseline.²⁵ The normalized z-score for weight was –0.4, but this was not statistically significant compared to baseline. More data from prolonged use of LDX is necessary to fully understand the effects the agent will have on growth of children.

The unique prodrug design of LDX may also help to limit the abuse potential of the agent. The biotransformation of LDX to active dextroamphetamine occurs following oral administration in the intestine and liver.⁷ Bypassing oral administration, which may occur in cases of abuse or misuse when the formulation is crushed and snorted intranasally or

Table 1 Adverse effects of lisdexamfetamine

Adverse effect	Incidence reported in clinical efficacy trials ^{13,14,24}
Decreased appetite	22%–47%
Insomnia	14%–27%
Headache	12%–17%
Upper abdominal pain	12%–16%
Irritability	10%–16%
Weight decrease	9%

dissolved for intravenous injection, greatly diminishes the subsequent serum concentrations of dextroamphetamine. Jasinski et al demonstrated this by administering comparable doses of LDX and dextroamphetamine intravenously to adult stimulant abusers.³⁰ The maximum dextroamphetamine serum concentration resulting from LDX administration was 20.7 ng/mL compared to a serum concentration of 74.2 ng/mL when administered as the active dextroamphetamine. The subjects also scored the effects of LDX administered intravenously lower than dextroamphetamine on a validated drug-likability scale. In a study of orally administered LDX, adult substance abusers reported a statistically greater preference for control doses of dextroamphetamine and diethylpropion compared to LDX doses < 100 mg; the preference for LDX 150 mg was statistically no different than that of the controls.³¹ Lisdexamfetamine is classified as a schedule-II narcotic by the US Drug Enforcement Agency.³²

Patient considerations

The benefits of LDX for the treatment of ADHD in children and adults include clinical improvement comparable to that of extended-release MAS and once-daily administration. For young children unable to swallow tablets, the capsule of LDX may be opened and the contents dissolved in a glass of water for administration.⁷ This unique advantage allows for a long-acting formulation that does not need to be swallowed whole. The formulations of the primary comparators of LDX, extended-release MAS and osmotically-released MPH, do not allow for this point-of-care extemporaneous solution. Food may slow the time needed to achieve the maximum serum concentration for the dose by approximately one hour.²² Similar to other long-acting CNS stimulants, LDX may be administered only on school or workdays if preferred. Longer drug holidays are possible too if the patient chooses. Although no cost-benefit analysis of LDX has yet been performed, the average wholesale price of Vyvanse® (LDX, Shire Pharmaceuticals, Wayne, PA, USA) is less than that of Adderall XR® (extended-release MAS, Shire Pharmaceuticals, Wayne, PA, USA) and Teva USA's generically available extended-release MAS formulation: \$4.89/Vyvanse® capsule vs \$7.49/Adderall XR® capsule vs \$6.13/generic extended-release MAS capsule.³³

A significant disadvantage currently is the lack of data demonstrating efficacy and safety of LDX in adolescents aged 13 to 17 years. Clinical trials of LDX within this population are ongoing however. LDX also has not distanced itself from other long-acting CNS stimulants in terms of efficacy and

side effects. Future prospective, head-to-head comparisons may help to describe the place in therapy of LDX relative to its primary comparators, extended-release MAS and osmotically-released MPH.

Summary and conclusions

LDX is the latest CNS stimulant to be approved by the FDA for the treatment of ADHD. Its unique pharmacokinetic profile and long duration of activity result from the rate-limited biotransformation of the prodrug compound to the active agent, dextroamphetamine. As such, the mechanism of action, efficacy, and side effect profile of LDX are similar to those of other amphetamine derivatives. LDX has been demonstrated to attenuate symptoms of ADHD in children and adults for as long as 10 hours. Common side effects include decreased appetite, insomnia, headache, and irritability.

In conclusion, LDX does offer another effective and long-acting option for the treatment of ADHD in both children and adults and can be considered an appropriate choice for first-line treatment of those populations. LDX may be a preferred agent in clinical situations where there is a concern by the patient, parent, or clinician of abuse or diversion, or in individuals unable to swallow an extended-release formulation.

Disclosure

The author declares no conflicts of interest.

References

1. Bloom B, Cohen RA, Freeman G. Summary health statistics for US children: National Health Interview Survey, 2007. *Vital Health Stat.* 2009;10:1–80.
2. Kessler RC, Adler L, Barkley R, et al. The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. *Am J Psychiatry.* 2006;163:716–723.
3. Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: a systematic review and meta-regression analysis. *Am J Psychiatry.* 2007;164:942–948.
4. Pliszka S. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry.* 2007;46:894–921.
5. Medori R, Ramos-Quiroga JA, Casas M, et al. A randomized, placebo-controlled trial of three fixed dosages of prolonged-release OROS methylphenidate in adults with attention-deficit/hyperactivity disorder. *Biol Psychiatry.* 2008;63:981–989.
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;11:625–639.
7. Vyvanse (lisdexamfetamine dimesylate) [Package insert]. Wayne, PA: Shire Pharmaceuticals, April 2008.
8. Biederman J, Mick E, Faraone SV. Age-dependent decline of symptoms of attention deficit hyperactivity disorder: impact of remission definition and symptom type. *Am J Psychiatry.* 2000;157:816–818.
9. Hart EL, Lahey BB, Loeber R, Applegate B, Frick PJ. Developmental change in attention-deficit hyperactivity disorder in boys: a four-year longitudinal study. *J Abnorm Child Psychol.* 1995;23:729–749.

10. Spencer TJ, Biederman J, Mick E. Attention-deficit/hyperactivity disorder: diagnosis, lifespan, comorbidities, and neurobiology. *J Psychiatr Psychol.* 2007;32:631–642.
11. Ramos-Quiroga JA, Bosch R, Castells X, et al. Effect of switching drug formulations from immediate-release to extended-release OROS methylphenidate: a chart review of Spanish adults with attention-deficit hyperactivity disorder. *CNS Drugs.* 2008;22:603–611.
12. Sanchez RJ, Crismon ML, Barner JC, Bettinger T, Wilson JP. Assessment of adherence measures with different stimulants among children and adolescents. *Pharmacotherapy.* 2005;25:909–917.
13. 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;69:1364–1373.
14. 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;29:450–463.
15. Kaloyanides KB, McCabe SE, Cranford JA, Teter CJ. Prevalence of illicit use and abuse of prescription stimulants, alcohol, and other drugs among college students: relationship with age at initiation of prescription stimulants. *Pharmacotherapy.* 2007;27:666–674.
16. Wilens TE, Adler LA, Adams J, et al. Misuse and diversion of stimulants prescribed for ADHD: a systematic review of the literature. *J Am Acad Child Adolesc Psychiatry.* 2008;47:21–31.
17. Setlik J, Bond GR, Ho M. Adolescent Prescription ADHD medication abuse is rising along with prescriptions for these medications. *Pediatrics.* 2009 Aug 24. [Epub ahead of print].
18. Solanto MV. Neuropsychopharmacological mechanisms of stimulant drug action in attention-deficit hyperactivity disorder: a review and integration. *Behav Brain Res.* 1998;94:127–152.
19. Biederman J, Boellner SW, Childress A, Lopez FA, Krishnan S, Zhang Y. Lisdexamfetamine dimesylate and mixed amphetamine salts extended-release in children with ADHD: a double-blind, placebo-controlled, crossover analog classroom study. *Biol Psychiatry.* 2007;62:970–976.
20. Krishnan SM, Pennick M, Stark JG. Metabolism, distribution and elimination of lisdexamfetamine dimesylate: open-label, single-centre, phase I study in healthy adult volunteers. *Clin Drug Investig.* 2008;28:745–755.
21. Krishnan SM, Stark JG. Multiple daily-dose pharmacokinetics of lisdexamfetamine dimesylate in healthy adult volunteers. *Curr Med Res Opin.* 2008;24:33–40.
22. Krishnan S, Zhang Y. Relative bioavailability of lisdexamfetamine 70-mg capsules in fasted and fed healthy adult volunteers and in solution: a single-dose, crossover pharmacokinetic study. *J Clin Pharmacol.* 2008;48:293–302.
23. Lopez FA, Ginsberg LD, Arnold V. Effect of lisdexamfetamine dimesylate on parent-rated measures in children aged 6 to 12 years with attention-deficit/hyperactivity disorder: a secondary analysis. *Postgrad Med.* 2008;120:89–102.
24. Wigal SB, Kollins SH, Childress AC, Squires L. A 13-hour laboratory school study of lisdexamfetamine dimesylate in school-aged children with attention-deficit/hyperactivity disorder. *Child Adolesc Psychiatry Ment Health.* 2009;3:17.
25. Findling RL, Childress AC, Krishnan S, McGough JJ. Long-term effectiveness and safety of lisdexamfetamine dimesylate in school-aged children with attention-deficit/hyperactivity disorder. *CNS Spectr.* 2008;13:614–620.
26. Spiller HA, Griffith JR, Anderson DL, Weber JA, Aleguas A. Poison centers detect an unexpectedly frequent number of adverse drug reactions to lisdexamfetamine. *Ann Pharmacother.* 2008;42:1142–1143.
27. Adler LA, Goodman D, Weisler R, Hamdani M, Roth T. Effect of lisdexamfetamine dimesylate on sleep in adults with attention-deficit/hyperactivity disorder. *Behav Brain Funct.* 2009;5:34.
28. Vetter VL, Elia J, Erickson C, et al. Cardiovascular monitoring of children and adolescents with heart disease receiving medications for attention deficit/hyperactivity disorder [corrected]: a scientific statement from the American Heart Association Council on Cardiovascular Disease in the Young Congenital Cardiac Defects Committee and the Council on Cardiovascular Nursing. *Circulation.* 2008;117:2407–2423.
29. Perrin JM, Friedman RA, Knilans TK. Cardiovascular monitoring and stimulant drugs for attention-deficit/hyperactivity disorder. *Pediatrics.* 2008;122:451–453.
30. Jasinski D, Krishnan S. Human pharmacology of intravenous lisdexamfetamine dimesylate: abuse liability in adult stimulant abusers. *J Psychopharmacol.* 2009;23:410–418.
31. Jasinski D, Krishnan S. Abuse liability and safety of oral lisdexamfetamine dimesylate in individuals with a history of stimulant abuse. *J Psychopharmacol.* 2009;23:419–427.
32. Schedules of controlled substances: placement of lisdexamfetamine into schedule II. Final rule. *Fed Reg.* 2007;72:24532–24534.
33. Vermont Disclosure Act. Shire Pharmaceuticals, 2009. URL: <http://www.shirepricing.com/Documents/VYVANSE-long-form.pdf>. Accessed Nov 12, 2009.

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