Lisdexamfetamine for ADHD

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Extended-action psychostimulant offers daylong coverage and has comparatively low abuse potential

Lisdexamfetamine—FDA-approved to treat attention-deficit/hyperactivity disorder (ADHD) in children ages 6 to 12 (***Table 1***)—reduces ADHD symptoms during and after school and may be less likely to be abused than other psychostimulants, particularly immediate-release preparations, clinical data suggest.

Clinical implications

Because it is effective for about 12 hours, lisdexamfetamine might improve the child's ability to complete homework and participate in extracurricular activities, which in turn might enhance academic performance and/or socialization skills.

Lisdexamfetamine could help the child with ADHD who shows no contraindications to the drug (***page 105***)—particularly if he or she needs daylong coverage.

How it works

Lisdexamfetamine—a dextroamphetamine derivative—is rapidly absorbed and converted to dextroamphetamine, which is believed to exert therapeutic effect by:

- blocking norepinephrine and dopamine reuptake into presynaptic neurons
- increasing the neurotransmitters' release into the extraneuronal space.

The medication's amphetamine release is highly predictable, which contributes to its therapeutic benefit in ADHD. Amphetamine is released through GI metabolism of lisdexamfetamine, which produces the active d-amphetamine moiety that reaches the bloodstream. The medication is derived from d-amphetamine, with negligible amounts of lysine cleaved.

Table 1

Lisdexamfetamine: Fast facts

Brand name: Vyvanse
Indication: ADHD in children ages 6 to 12
Approval date: February 23, 2007
Manufacturers: New River Pharmaceuticals and Shire
Dosing forms: 30-, 50-, and 70-mg capsules
Recommended dosage: Start at 30 mg/d. If necessary, titrate by 20 mg every 3 to 7 days to a maximum 70 mg/d.

Lisdexamfetamine requires in vivo metabolism (in the GI tract) to its active constituent d-amphetamine. As a result, the medication will not produce high d-amphetamine blood levels—and should not cause euphoria or other reinforcing effects—if injected or snorted. Its abuse potential is lower overall compared with immediate-release psychostimulant formulations.

Pharmacokinetics

Dextroamphetamine's plasma elimination half-life is approximately 9½ hours—which accounts for lisdexamfetamine's extended action. The drug reaches steady-state concentrations in 2 to 3 days.

Food does not affect absorption and delays maximum concentration by 1 hour or less, so taking lisdexamfetamine during breakfast should not slow its therapeutic effect. Because dextroamphet-

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amine reaches maximum concentration in approximately 3½ hours, the medication should take effect by the time the child gets to school. In one randomized, phase-2 trial, children with ADHD who received lisdexamfetamine, 30 to 70 mg/d, showed overall improvement within 2 hours after dosing.[1]

Efficacy

Lisdexamfetamine reduced ADHD symptoms in 2 double-blind studies: a phase-2 crossover study and a phase-3 random-dose trial.

Phase-2 crossover study.[2] Fifty-two children ages 6 to 12 with combined or hyperactive-impulsive type ADHD received extended-release mixed amphetamine salts (MAS) for 3 weeks. Subjects received 10 mg/d or dosages titrated to 20 or 30 mg/d based on response to medication.

The youths then were divided into 3 groups based on optimal MAS dosage and received 3 treatments for 1 week each:

- group 1: placebo; MAS, 10 mg/d; lisdexamfetamine, 30 mg/d
- group 2: placebo; MAS, 20 mg/d; lisdexamfetamine, 50 mg/d
- group 3: placebo; MAS, 30 mg/d; lisdexamfetamine, 70 mg/d.

While taking lisdexamfetamine or MAS, subjects showed similar improvement in behavior, based on Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) scores, and inattention, based on SKAMP and Permanent Product Measure of Performance scores.

Both psychostimulants outperformed placebo in both measures, and both improved behavior more decisively than inattention. Based on post-hoc analysis, improvement 12 hours after dosing was more substantial with lisdexamfetamine than with MAS.

Phase-3 random-dose trial.[3] A total of 290 children ages 6 to 12 with combined or hyperactive-impulsive type ADHD were "washed out" from prior medications over 1 week, then received lisdexamfetamine or placebo for 4 weeks. Treatment-group children were started at 30 mg/d; some received dosages titrated at random to 50 or 70 mg/d in weekly 20-mg increments.

Over 4 weeks, ADHD Rating Scale Version IV (ADHD-RS-IV) scores fell 50% to 59% among the 3 lisdexamfetamine dosage groups, compared with a 15% reduction in the placebo group. Substantial ADHD-RS-IV score improvements after 1 week of lisdexamfetamine were maintained throughout the trial, suggesting the medication sustains ADHD symptom improvement. Controlled trials have not addressed lisdexamfetamine use >4 weeks, however.

Based on parents' and guardians' reports, treatment-group patients' ADHD symptoms were notably less severe at 10 AM, 2 PM, and 6 PM compared with placebo-group children.[3] This suggests that lisdexamfetamine offers a daylong therapeutic effect.

Tolerability

In the phase-3 study,[3] 162 of 218 (74%) children receiving any dosage of lisdexamfetamine reported an adverse event, compared with 34 of 72 (47%) children in the placebo group. Overall, 39% of lisdexamfetamine-group patients reported decreased appetite. Also common were insomnia, headaches, irritability, upper abdominal pain, vomiting, and weight loss (***Table 2, page 98***).

Although most adverse events were mild to moderate, 9.2% of treatment-group children dropped out because of intolerability, compared with 1.4% of the placebo group. The investigators increased dosages quickly, regardless of efficacy or tolerability,[3] which might have increased side-effect incidence among the treatment groups.

Clinical Point

In one study, children with ADHD showed improvement within 2 hours after receiving lisdexamfetamine

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Table 2

Rates of commonly reported adverse effects during phase-3 lisdexamfetamine (LDX) study

Adverse effect	LDX 30 mg/d	LDX 50 mg/d*	LDX 70 mg/d*	LDX all dosages	Placebo
All adverse effects	72%	68%	84%	74%	47%
Decreased appetite	37%	31%	49%	39%	4%
Insomnia	16%	16%	25%	19%	3%
Upper abdominal pain	14%	7%	15%	12%	6%
Headache	10%	10%	16%	12%	10%
Irritability	11%	8%	10%	10%	0%
Vomiting	7%	5%	14%	9%	4%
Weight loss	6%	3%	19%	9%	1%

*Dosages were randomly titrated regardless of efficacy or tolerability.

Source: Reference 3

Clinical Point

ADHD Rating Scale score decreases after 1 and 4 weeks suggest that lisdexamfetamine sustains symptom improvement

In the phase-2 crossover trial,[2] adverse event rates were similar among the lisdexamfetamine, extended-release MAS, and placebo groups (15% to 18%). Among youths receiving lisdexamfetamine, 8% reported insomnia and 6% reported appetite loss, compared with 2% and 4% of the MAS group, respectively.

Safety

Findling et al[4] found a larger change in corrected QT interval with lisdexamfetamine (7 to 14 msec) than with extended-release MAS (5 to 10 msec) 5 and 10 ½ hours after dosing. The authors reasoned that these findings are atypical, and no children suffered serious adverse events during the trial. Nonetheless, more research on whether lisdexamfetamine increases cardiac risk is needed.

In a lethal-dose study in rats,[5] oral lisdexamfetamine doses up to 1,000 mg/kg did not result in death, suggesting the medication might undergo saturation kinetics in the GI tract that may protect against overdose or abuse at higher dosages. By comparison, the median lethal oral dosage of d-amphetamine in rats was 96.8 mg/kg.[5]

Abuse potential

As with other psychostimulants indicated for ADHD, the Drug Enforcement Administration has classified lisdexamfetamine as a schedule II drug, which applies to addictive prescription-only medications with an accepted medical use.

Clinical data suggest, however, that lisdexamfetamine might be less "enjoyable"—and less likely to be abused intravenously, orally, or intranasally—than equipotent d-amphetamine. In an abuse liability study,[6] 12 adults with histories of stimulant abuse received intravenous immediate-release (IR) d-amphetamine, 10 or 20 mg. Two days later, they received a comparable dose of IV lisdexamfetamine, 25 or 50 mg. The researchers found that:

- Plasma d-amphetamine peaked within 5 minutes after injection, compared with 2 to 3 hours after lisdexamfetamine dosing.
- Subjects who received IR d-amphetamine said they felt euphoria within 15 minutes of injection. By contrast, no one reported euphoria or amphetamine-like subjective effects after receiving lisdexamfetamine.

When asked which medication they would try again, 9 of 12 subjects chose IR d-amphetamine and 1 chose lisdexamfetamine.

continued on page 105

continued from page 98

In a double-blind, randomized, placebo-controlled study,[7] oral lisdexamfetamine, 50 or 100 mg, was not more "likeable" than placebo. Subjects reported "liking" effects with 150 mg of lisdexamfetamine, however, suggesting the medication could be misused or abused at higher-than-therapeutic dosages.

Contraindications

As with other psychostimulants, do not give lisdexamfetamine to youths with pre-existing serious structural cardiac abnormalities or other heart problems. Assess patient and family history of heart disease before prescribing this medication.

Do not prescribe lisdexamfetamine to patients taking a monoamine oxidase inhibitor (MAOI). By slowing amphetamine metabolism, these antidepressants intensify amphetamines' effect on monoamine release, which can cause headaches and lead to hypertensive crisis. Before starting lisdexamfetamine, ask if the patient is taking an MAOI or has taken one within 2 weeks of presentation.

Use caution when prescribing lisdexamfetamine to patients with:

- a comorbid eating disorder or sleep disturbance. Determine whether to address the comorbidity before treating ADHD symptoms, and make sure lisdexamfetamine is not worsening the comorbid symptoms.
- untreated hypertension or other cardiovascular conditions, as stimulant medications can increase blood pressure and heart rate. Watch for significant heart rate and blood pressure changes in patients taking lisdexamfetamine, which probably would not cause sustained blood pressure increase in patients taking antihypertensives.[8]

Related Resource

- Lisdexamfetamine Web site. www.vyvanse.com.

Drug Brand Names

Extended-release mixed amphetamine salts • Adderall XR
Lisdexamfetamine • Vyvanse

Disclosure

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Bottom Line

In clinical trials, lisdexamfetamine reduced children's ADHD symptoms and was effective into the evening, suggesting a daylong benefit. Start at 30 mg/d; if necessary, titrate by 20 mg every 3 to 7 days to a maximum 70 mg/d. Monitor response monthly, then less frequently after symptoms are under control.

Clinical Point

Do not prescribe lisdexamfetamine to patients taking an MAOI or who have taken one within 2 weeks of presentation