Lisdexamfetamine: new second-line treatment option in ADHD

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Lisdexamfetamine is a prodrug of dexamfetamine indicated for the treatment of ADHD. In our New products review, Steve Chaplin presents the clinical data relating to its efficacy and adverse effects, and Dr David Hayward discusses its place in treatment compared with methylphenidate.

The 2008 NICE guideline recommends that drug treatment for school-age children with attention deficit hyperactivity disorder (ADHD) should be reserved ‘for those with severe symptoms and impairment or for those with moderate levels of impairment who have refused nondrug interventions, or whose symptoms have not responded sufficiently to parent-training/education programmes or group psychological treatment’. 1

When drug treatment is appropriate, the choice between methylphenidate, atomoxetine (Strattera) and dexamfetamine depends on co-morbidity, adverse effects, likely adherence, risk of diversion and patient/parental preference.

Stimulants may be associated with severe adverse effects in children. 2 NICE states that ‘dexamfetamine should be considered in children and young people whose ADHD is unresponsive to a maximum tolerated dose of methylphenidate or atomoxetine’. 1

Lisdexamfetamine
Lisdexamfetamine (Elvanse – Shire) is a prodrug of dexamfetamine, undergoing hydrolysis to the active drug primarily in red blood cells. Its duration of efficacy is up to 13 hours. 3

It is licensed as part of a comprehensive treatment programme for ADHD, encompassing psychological, educational and social measures as well as pharmacotherapy, in children aged six and over when the response to previous methylphenidate treatment is considered clinically inadequate. Treatment may continue into adulthood if appropriate.

Treatment must be under the supervision of a specialist in childhood and/or adolescent behavioural disorders. Extensive pretreatment assessment is essential (full details are given in the SPC). The lowest effective dose should be prescribed to minimise the risk of possible overdose.

The recommended dose is initially 30mg in the morning, increased if necessary in weekly increments of 20mg to a maximum of 70mg daily. Treatment must

KEY POINTS
- Lisdexamfetamine (Elvanse) is a prodrug of dexamfetamine for the treatment of ADHD in children and adolescents over six years old who have not responded adequately to methylphenidate
- Dosage is 30mg once daily, increasing if necessary to max. 70mg daily; discontinue if no improvement after one month; cost (28 capsules): £58.24 (30mg), £68.60 (50mg), £83.16 (70mg)
- It must be administered as part of a comprehensive treatment programme after careful pretreatment assessment
- It reduces ADHD severity, with a response rate of about 80 per cent compared with 14–23 per cent with placebo
- Adverse effects are typical of a stimulant and some are potentially serious
- It has a long duration of action that may avoid the need to take the medication during the day
- Lisdexamfetamine may be more effective than methylphenidate and appears to offer a useful option in the treatment of ADHD
be stopped if symptoms have not improved after one month with appropriate dosage adjustment.

No studies have been undertaken on the use of lisdexamfetamine in patients with renal or hepatic impairment but dose reduction may be necessary in patients with renal impairment.

Treatment is contraindicated in patients taking an MAOI or with hyperthyroidism or thyrotoxicosis, an agitated state, symptomatic cardiovascular disease, structural cardiac abnormalities, advanced arteriosclerosis, moderate to severe hypertension or glaucoma.

Clinical trials
The pivotal European study evaluating the efficacy of lisdexamfetamine® randomised 336 children and young people aged 6–17 with at least moderately severe ADHD – baseline ADHD Rating Scale version IV (ADHD-RS-IV) total score ≥28 – to treatment with lisdexamfetamine, modified-release methylphenidate (as a noncomparative reference) or placebo.

Individuals who had previously not responded to treatment with methylphenidate or with risk factors for adverse effects were excluded.

The primary end-point was the change in ADHD-RS-IV total score after seven weeks (including a four-week dose adjustment phase and a three-week maintenance phase).

Fifty-eight per cent of patients completed the study, with a similar rate of discontinuation with lisdexamfetamine and methylphenidate. The most frequent reason for withdrawal was lack of efficacy (lisdexamfetamine 10 per cent, methylphenidate 20 per cent, placebo 49 per cent).

Lisdexamfetamine improved the ADHD-RS-IV total score significantly more than placebo (see Figure 1). Defining response as the percentage reduction in ADHD-RS-IV total score of ≥30 per cent, response rates were 84 per cent with lisdexamfetamine, 68 per cent with methylphenidate and 23 per cent with placebo.2

Lisdexamfetamine also significantly improved scores on the subscales for inattention and hyperactivity/impulsivity compared with placebo.

The proportions of patients rated by investigators as very much or much improved according to the Clinical Global Impressions – Improvement scale were 78 per cent with lisdexamfetamine, 61 per cent with methylphenidate and 14 per cent with placebo.

In a nonblinded extension study, the efficacy of lisdexamfetamine in children and adolescents was maintained for 26 weeks.5

Adverse effects
The adverse effects associated with lisdexamfetamine are typical of stimulants and include decreased appetite and weight loss, insomnia, dry mouth, headache and upper abdominal pain;2 weight loss increases with dose and is evident within four weeks. Lisdexamfetamine slows growth in children and adolescents.2

Potentially serious side-effects include sudden death in patients with pre-existing structural cardiac abnormalities or other serious heart problems, cardiomyopathy with chronic amphetamine use, and exacerbation or emergence of new psychotic or manic illness.

References
1. NICE. Attention deficit hyperactivity disorder. Clinical Guideline 72. September 2008 (mod-

Letters
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Place in therapy

The stimulants used for ADHD are thought to work by compounding the effects of brain dopamine,1 but only dexamfetamine actually increases dopamine release (the other stimulants are dopamine agonists or reuptake inhibitors2). This might explain why dexamfetamine is slightly more effective than methylphenidate: effect size 1.03 vs 0.77, p=0.02; number need to treat (NNT) 2.0 (95% CI 1.7–2.2) vs 2.6 (95% CI 2.4–2.8).3 Lisdexamfetamine is an inactive prodrug of dexamfetamine and l-lysine.

Unique among the ADHD medications, lisdexamfetamine has a sustained plasma concentration but a low peak and these levels are proportional to the dose taken.4 Steady state is achieved after five doses and there is no accumulation.5

In-vitro studies did not demonstrate concentration-dependent inhibition of any of the cytochrome P450 isoforms tested, so lisdexamfetamine should not affect the hepatic metabolism of other drugs.6 Therefore, it ought to have a predictable effect.

The side-effect profile of lisdexamfetamine is similar to that of other stimulant medications. Decreased appetite, insomnia, abdominal pain and irritability are the most commonly reported adverse effects. These are usually mild to moderate but decreased appetite and (to a lesser extent) insomnia can persist.

Prolonged administration is associated with a reduction in expected height, weight and BMI in children (as is the case for other stimulants7). The discontinuation rate caused by adverse events was only 9.2 per cent over 12 months in one study.8

The duration of action is long with simulated classroom studies showing that lisdexamfetamine remains effective for about 13 hours.9 This avoids the need for medication during the day but might cause insomnia.

The contents of the capsules can be dissolved in water and this may aid adherence in those who struggle to swallow tablets or capsules.

Lisdexamfetamine has a similar utility to the slow-release methylphenidate formulations but it may be slightly more effective and predictable. It is marketed as a second-line medication to use when the response to methylphenidate has been inadequate but it appears to be a useful new prescribing option.

References

Declaration of interests

Steve Chaplin has received payments for working on projects for Shire.

Steve Chaplin is a pharmacist who specialises in writing on therapeutics