

NEW DRUG EVALUATION

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ATOMOXETINE

Atomoxetine is a selective inhibitor of noradrenaline reuptake licensed for the treatment of ADHD in children aged 6 years and older, adolescents and adults. In randomised, placebo-controlled trials lasting 6-12 weeks, atomoxetine significantly improved symptoms. Limited data suggest similar efficacy to methylphenidate. Adverse effects include decreased appetite, weight loss and vomiting, dry mouth, sexual dysfunction, elevated blood pressure and tachycardia. Atomoxetine may offer an alternative to methylphenidate in children but further studies are needed to clarify its efficacy and safety in the longer term; in adults, the role of atomoxetine has not been established.

What is it?

Atomoxetine (Strattera®, Eli Lilly) is a selective inhibitor of noradrenaline reuptake.¹ It is licensed for the treatment of attention-deficit hyperactivity disorder (ADHD) in children aged 6 years and over, adolescents and adults. Unlike methylphenidate, it has no CNS stimulant activity.^{2,3} The recommended maintenance dose is approximately 1.2 mg/kg daily in children and adolescents up to 70 kg body weight.² In adults and adolescents or children weighing > 70 kg, the recommended maintenance dose is 80 mg daily.²

How effective is it?

Four randomised, placebo-controlled trials of atomoxetine in children and adolescents with ADHD have been published in full.^{4,7} In each the primary endpoint was the mean change in ADHD Rating Scale-IV (ADHD-RS), an investigator-administered interview with the parent or caregiver. Secondary endpoints included changes in the hyperactivity/impulsivity and inattention subscales of ADHD-RS, Clinical Global Impressions of Severity scale (CGI-S) and the Conner's Parent Rating Scale (CPRS).

The trials lasted 6 - 12 weeks and involved 759 children and adolescents with an age range of 6 - 18 years. Approximately 55 - 80% had mixed-type ADHD and many of the remainder had inattentive-type ADHD. Doses ranged from 0.5 - 2.0 mg/kg/day, which is more than the recommended maintenance dose (1.2 mg/kg/day).

At doses of 1.2-1.8 mg/kg/day, these trials consistently demonstrated a reduction of approximately 8 - 10 points in ADHD-RS score for atomoxetine compared with placebo, from a baseline of score 35 - 40. There were also improvements in secondary endpoints. Symptom improvement did not vary with age,^{4,5} sex⁶ or prior treatment with a stimulant⁷ and outcomes were similar for the hyperactivity/impulsivity and inattention subscales of ADHD-RS.^{4,5} Defining response as a $\geq 25\%$ reduction in ADHD-RS score, response rates were significantly greater with atomoxetine than with placebo (64% vs. 25% and 59% vs. 40% in two studies⁵ and 60% vs. 31% in a third⁷).

In one study, behaviour assessments by teachers improved more with atomoxetine than with placebo (mean reduction in Conners' Teacher Rating Scale of 5.1 vs 1.6 points, $p=0.02$).⁷

Atomoxetine (0.2 to 2 mg/kg/day) has been compared with immediate-release methylphenidate (5 - 60 mg/day) in one 10-week randomised, non-blinded study in 228 boys (age 7 - 15) and girls with ADHD (age 7 - 9).⁸ This trial was primarily designed to select treatment responders to enter a relapse prevention study rather than to assess treatment efficacy. The primary measure of symptom response was the mean change in the investigator-related total ADHD-RS score. There was no statistically significant difference in the primary endpoint between the methylphenidate and atomoxetine groups (mean reduction of 17.8 vs 19.4 points, $p=ns$). Discontinuation rates of 43% and 36% were reported for the methylphenidate and atomoxetine groups respectively, which are high compared with the placebo-controlled studies.

Atomoxetine has been evaluated in two 10-week randomised, double-blind placebo-controlled trials in 536 adults with ADHD.⁹ The primary endpoint was the sum of the inattention and hyperactivity/impulsivity scales of the Conner's Adult ADHD Rating Scale. Atomoxetine 60 - 120 mg/day (maximum licensed dose is 100mg/day) was associated with significant improvements in ADHD symptoms compared with placebo, including both attention and hyperactivity/impulsivity scales and in patients with mixed or inattentive subtypes of ADHD.

How safe is it?

In a pooled analysis of adverse events reported in placebo-controlled clinical trials in children and adolescents with ADHD, atomoxetine was significantly more frequently associated with decreased appetite (14% vs. 6%), vomiting (12% vs. 7%) and dizziness (6% vs 2%).¹⁰ Weight loss of approximately 0.5 - 0.9 kg was reported in short-term clinical trials (compared with weight gain with placebo).^{4,5,7} Growth rates after 2 years of treatment have been reported to be near normal but should be monitored during treatment.²

In children, atomoxetine is associated with reversible increases in blood pressure (2/3 mmHg) and heart rate (8 bpm).¹⁰

In adults, atomoxetine was associated with dry mouth, insomnia, nausea, decreased appetite, constipation, sexual dysfunction, dizziness and sweating.⁹ Blood pressure

increased by 1-2/2-3 mmHg and heart rate increased by 4 - 7 bpm. Discontinuation of atomoxetine was associated with adverse events in 8% - 9% of patients compared with 2% - 4% given placebo.⁹ Withdrawal effects have not been seen in children.¹¹

Both blood pressure and pulse should be monitored periodically in patients on atomoxetine. However, for most patients, the increases in blood pressure and heart rate are not clinically important.²

What other options are there?

Atomoxetine is the only drug licensed for the treatment of ADHD in adults, though stimulants such as methylphenidate and non-stimulants are prescribed. In children, only methylphenidate is licensed specifically to treat ADHD. In 2000, NICE recommended that it may be used as part of a comprehensive treatment programme for children and

adolescents with a diagnosis of severe attention deficit/hyperactivity disorder (ADHD).¹² Dexamphetamine is an alternative for children when methylphenidate is ineffective. Where compliance problems are an issue, sustained-release methylphenidate may be an option.

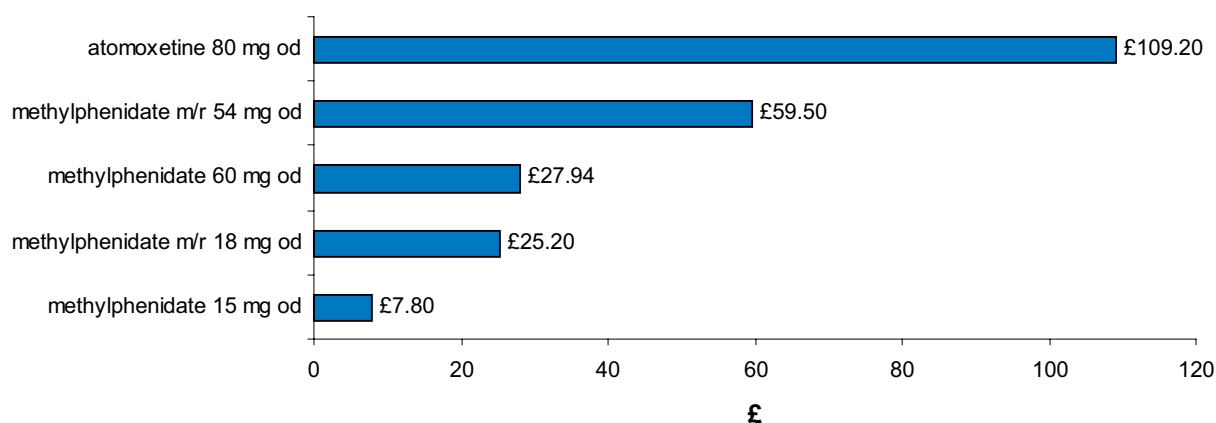
When should it be used?

Treatment with atomoxetine should only be initiated by a physician with experience of treating childhood behavioural disorders or adult ADHD.

Atomoxetine has not been adequately compared with methylphenidate in the treatment of ADHD in children. It offers an alternative when methylphenidate is unsuitable but longer-term trials are needed to establish its relative efficacy and safety. NICE is expected to publish revised guidance on the management of childhood ADHD in August 2005.

How much does it cost?

Cost for 28 days treatment (prices from MIMS/Drug Tariff September 2004)



NB. Doses shown are for general comparison only and do not imply therapeutic equivalence.

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KEY RCT - randomised controlled trial, CT-controlled trial, G-guideline, O-open study, MA-meta analysis, R-review, U-unpublished, Abs- abstract, E-editorial

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