Atomoxetine (Strattera) for attention deficit hyperactivity disorder

(AT-oh-mox-e-teen)

Summary

- Atomoxetine is a noradrenaline reuptake inhibitor used for treating children, adolescents and adults with attention deficit hyperactivity disorder (ADHD).
- Methylphenidate and dexamphetamine remain first-line drug treatments for ADHD. Atomoxetine is subsidised on the Pharmaceutical Benefits Scheme for people who cannot take psychostimulants.
- Treatment should be based on a comprehensive diagnosis and employ behavioural, psychosocial and educational strategies according to individual needs.
- Atomoxetine is not a psychostimulant and appears to have a low potential for abuse and diversion. It does not require State or Territory department of health permission to prescribe.
- Atomoxetine shares some adverse effects with psychostimulants, including loss of appetite and increased blood pressure, but may cause less sleeplessness. The long-term safety profile of atomoxetine is unknown.
- Atomoxetine may increase the risk of suicidal thoughts and behaviours. Monitor children taking atomoxetine for warning signs.
- Be aware of potential cardiovascular adverse effects; people with symptomatic cardiovascular disease should not use atomoxetine.

PBS listing

Authority required

Initial and continuing treatment of attention deficit hyperactivity disorder (ADHD) diagnosed at age 6–18 years. ADHD must be diagnosed by a paediatrician or psychiatrist according to the *DSM-IV* criteria, and psychostimulants (dexamphetamine and methylphenidate) must pose an unacceptable medical risk for one of the following reasons:

- Contraindications to psychostimulants:
  - a history of substance abuse (other than alcohol), or
  - motor tics or Tourette's syndrome, or
  - severe anxiety (diagnosed according to the *DSM-IV*).
- Psychostimulant treatment has precipitated or worsened a mood disorder (anxiety, obsessive–compulsive disorder or depression) and therefore:
  - the psychostimulant must be discontinued permanently, or
  - another drug is needed to treat the mood disorder and using this other drug with a psychostimulant poses an unacceptable medical risk.
- Both dexamphetamine and methylphenidate have been tried and permanently discontinued because of adverse effects on:
  - growth and weight, or
  - sleep, including insomnia, or
  - appetite, including anorexia

NB: The Pharmaceutical Benefits Scheme (PBS) Safety Net 20-day rule does not apply to atomoxetine. During dose titration in the first month, most patients will need to fill prescriptions for 2 or more strengths of atomoxetine capsules.

Reason for PBS listing

Atomoxetine was approved as treatment for ADHD in people who cannot take psychostimulants on the basis of cost-effectiveness compared with placebo.[1] The PBAC accepted that atomoxetine is significantly more effective than placebo for treating ADHD, and that there is a clinical need for atomoxetine, particularly among people who are unable to take dexamphetamine and methylphenidate.[2]

The manufacturer's submission to the PBAC did not request a listing for patients who fail to respond to, or become tolerant to, psychostimulants.

The PBAC did not accept that atomoxetine has a superior toxicity profile to that of psychostimulants when it was unsuccessfully submitted for a first-line PBS listing in 2005.[3]

Place in therapy

When drugs are required for managing ADHD, the psychostimulants methylphenidate and dexamphetamine are first line, combined with non-drug interventions according to individual needs. The noradrenaline reuptake inhibitor atomoxetine is also effective and may be useful for people who cannot take psychostimulants because of contraindications or adverse reactions, or who do not respond to them. However, the PBS listing of atomoxetine does **not** include treatment for psychostimulant non-responders.

Assess and treat individual needs across multiple domains of functioning

Diagnosis by a paediatrician or psychiatrist is a requirement of the PBS authority for atomoxetine.

Despite a lack of supporting evidence, consensus guidelines recommend that children receive multi-dimensional treatment for ADHD, involving the child, parents and teachers.[4,5] Depending on the child's individual situation, consider options including behavioural management, family education and support (e.g. respite), and developmental or educational interventions, concurrent with medication. Educational support is particularly important because there is little evidence that drug therapy has long-term benefits on academic performance.[5]

Atomoxetine is a noradrenaline reuptake inhibitor used for treating ADHD

Atomoxetine is a noradrenaline reuptake inhibitor that was first approved in 2002 in the USA for treating ADHD. Although it has a similar preclinical pharmacology to the antidepressant reboxetine (Edronax), there is little evidence it has efficacy as an antidepressant.

Atomoxetine reduced the symptoms of ADHD in several short-term placebo-controlled trials in children and adolescents (age 6–18 years) and adults.[6,7] These results suggest that a clinician can expect to treat 4–5 children or adolescents to see one additional response to that seen with placebo.[8,9] Continuous atomoxetine also reduced the chance of relapse in trials of up to 9 months.[10,11]

Safety and efficacy in children under 6 years have not been established.[9]

In trials of up to 2 years about 15% of 12–18-year-olds[12] and about 25% of 6–7-year-olds[13] withdrew because of a lack of effectiveness. Withdrawals due to adverse events were similar in both age groups, at about 5%.[12,13]

Methylphenidate and dexamphetamine remain first-line drug treatments for ADHD

Methylphenidate and dexamphetamine are first-line drug treatments for ADHD, as their efficacy and safety are well established, based on clinical trials and extensive use (see the *NPS RADAR* article on methylphenidate extended-release for more information on psychostimulant prescribing).[14,15] Without more evidence it is not possible to confirm that atomoxetine is either as effective or well tolerated as psychostimulants.

The PBS listing for atomoxetine covers reimbursement for people with ADHD who cannot take psychostimulants because of a contraindication or adverse reaction. Atomoxetine is also a reasonable second-line choice for non-responders to psychostimulants, but the PBS listing does not cover this situation.

Psychostimulant non-responders may have problems in addition to ADHD, or their primary diagnosis of ADHD may need to be reconsidered before trying second-line drug therapy.[5] Differential diagnoses include anxiety, depression, and learning difficulties.[16]

Atomoxetine may be suitable for people with ADHD who have a history of misusing psychostimulants or other drugs (see Atomoxetine appears to have a low potential for abuse and diversion), who have motor tics or Tourette's syndrome, or who have an anxiety disorder.[9]

If psychostimulant therapy adversely affects weight, appetite or sleep, first consider reducing the dose or changing the time of dosing. Switching between dexamphetamine and methylphenidate may also be helpful.[5] The PBS will only reimburse atomoxetine after both dexamphetamine and methylphenidate have been tried and permanently discontinued because of adverse effects on sleep, growth or appetite. Note that atomoxetine can also cause disturbed sleep or loss of appetite.[9]

Atomoxetine may be less effective than psychostimulants

Few head-to-head trials have been published comparing atomoxetine with methylphenidate or dexamphetamine, and the available data have not established that atomoxetine is similar in efficacy to psychostimulants for ADHD.[17–20] One unpublished trial found that after 6 weeks of treatment 56% of participants responded to methylphenidate while 45% responded to atomoxetine, a response-rate difference of 12% (95% CI 2% to 21%).[21] A smaller, open-label study found no significant difference in response rates between the two drugs.[18]

Evidence for effectiveness in non-responders to psychostimulants is limited

While atomoxetine may be useful for people who have not responded to psychostimulant therapy, there have been no controlled trials specifically in psychostimulant non-responders. One small series of cases found that of 7 methylphenidate non-responders, none subsequently responded to atomoxetine.[22]

Review the ongoing need for drug therapy

Review the management of ADHD at least annually.[5] As part of this review try drug-free periods of 1–2 weeks to assess if medication is still needed, when and if individual circumstances allow it.[5,23] While teachers' reports of behaviour on and off medication are integral to assessing the ongoing need for medication, a trial off medication during school holidays may be easier as a first step.

There is no evidence from controlled trials to indicate how long atomoxetine treatment should be continued.[9] In a randomised trial, children and adolescents who had been stable on atomoxetine for 1 year and who continued therapy had a relapse rate of 2% over 6 months, while those who stopped taking atomoxetine had a relapse rate of 12% (difference in relapse rates 10%, 95% CI 2% to 13%).[11]

Safety issues

As with psychostimulants, atomoxetine increases blood pressure and heart rate and may cause loss of appetite. It may also cause drowsiness and dizziness. Psychiatric adverse events are rare but there may be an increased risk of suicidal thoughts and behaviours. The pressor effects of atomoxetine, as well as a possible propensity to increase QTc interval, are of particular concern for individuals at increased cardiovascular risk. The long-term safety profile of atomoxetine is unknown. Atomoxetine is unlikely to be abused.

Report suspected adverse reactions to the Adverse Drug Reactions Advisory Committee (ADRAC) online or by using the 'Blue Card' distributed with *Australian Prescriber*. For information about reporting adverse reactions, see the Therapeutic Goods Administration website (www.tg.gov.au).

Box 1: Symptoms that may be precursors to suicidality[38]

- Thoughts or talk of death or suicide
- Thoughts or talk of self-harm or harm to others
- Attempts to commit suicide
- New or worsening depression
- New or worsening anxiety
- Feeling very agitated or restless
- Panic attacks
- Difficulty sleeping (insomnia)
- New or worsening irritability
- Acting on dangerous impulses
- An extreme increase in activity and talking
- Other unusual changes in behaviour

Monitor for suicidal thoughts and behaviours

A small number of children (all 12 years old or younger) who took atomoxetine in short-term placebo-controlled trials had suicidal thoughts and behaviours. The incidence of such events was 6/1357 (0.4%) with atomoxetine compared with zero occurrences in the 851 children and adolescents who took placebo.[9] There were no completed suicides. A similar analysis of adult placebo-controlled trials found no increase in suicidal thoughts and behaviours with atomoxetine.[9]

Monitor all children and adolescents treated with atomoxetine for suicidality, clinical worsening, and unusual changes of behaviour, especially during the first few months of treatment or when changing the dose.[9] Consider discontinuing atomoxetine or reducing the dose if there are symptoms that may represent precursors to suicidality (see Box 1), especially if these symptoms are new or severe.

Other psychiatric adverse events, including aggression, mania and psychotic symptoms, have been reported in children and adolescents taking atomoxetine.[9,24,25] There is no conclusive evidence that atomoxetine causes these events, as the incidence in clinical trials was low and not significantly different to that found for placebo.[9,24,26]

Be aware of potential cardiovascular adverse effects

Atomoxetine is contraindicated in symptomatic cardiovascular disease, as it increases heart rate and blood pressure and therefore has the potential to increase the risk of sudden cardiac death.[9,27,28] People who have asymptomatic cardiovascular disease (e.g. hypertension), structural cardiac abnormalities or a family history of sudden cardiac death should only use atomoxetine with caution and should be assessed by a cardiologist.[9]

Obtain a personal and family cardiac history before prescribing atomoxetine. Measure pulse and blood pressure at baseline, after dose increases and periodically. Promptly evaluate any patients who develop exertional chest pain, unexplained syncope or other symptoms of cardiovascular disease.

There have been rare reports of prolonged QTc interval in overdose or in conjunction with cytochrome P450 CYP2D6 inhibitors.[9,29] There has also been 1 case of palpitations and ECG abnormalities after 10 months of standard-dose atomoxetine.[30] Use a reduced atomoxetine dose in people taking a potent CYP2D6 inhibitor (see Dosing issues).

Atomoxetine appears to have a low potential for abuse and diversion

Unlike the psychostimulants, atomoxetine is not a controlled drug and may be prescribed without the permission of State or Territory departments of health. It does not appear to have typical psychostimulant or euphoriant properties. One small, double-blind randomised trial in young adults who had some previous experience of recreational drugs found that atomoxetine's subjective effects differed from those of methylphenidate and that participants judged using atomoxetine as unpleasant.[31]

Atomoxetine shares common adverse effects with the psychostimulants

In the short term, atomoxetine appears to cause adverse effects with similar overall incidence and severity to those of psychostimulants[17]; however, there are some differences in the incidence of individual adverse effects. In a 3-week open-label comparison of atomoxetine and sustained-release methylphenidate, a greater proportion in the atomoxetine group experienced nausea, fatigue, and drowsiness, while insomnia and decreased appetite were more common with methylphenidate.[17]

Common adverse events occurring more frequently with atomoxetine than placebo in children and adolescents include decreased appetite, vomiting, upper abdominal pain and dizziness.[32] Small increases in blood pressure and heart rate are also common[28], while palpitations and tachycardia occur only infrequently.[9] A few children and adolescents in clinical trials discontinued because of aggression, irritability or drowsiness.[9] In adults, urinary retention was reported by 8% of those taking atomoxetine, and dry mouth by 21%.[9]

Atomoxetine is contraindicated for people with narrow-angle glaucoma, as it can cause mydriasis.[9]

Monitor growth during treatment with atomoxetine. Atomoxetine may retard height and weight gain in children and adolescents, probably due to its effect on appetite. The weight and height gain of those treated with atomoxetine lags behind that predicted for about the first 9–12 months of treatment.[24,33] Over 3 years of

monitoring, the height attained was on average 0.4 cm less than that predicted, while weight gain rebounded to slightly greater than predicted.[24,33]

The long-term safety profile of atomoxetine is unknown

Long-term safety data about atomoxetine are limited. About 1000 children and adolescents received atomoxetine for more than 1 year in clinical trials[9] and there are no published studies with longer than 2 years of follow-up. The risk of cardiovascular adverse events or suicide is currently difficult to assess. Five cases of atomoxetine-associated severe acute hepatitis have been reported.[34,35]

Dosing issues

Atomoxetine may be given once or twice daily. Atomoxetine capsules should not be opened to achieve a smaller dose, so most children and adolescents need to be started on one strength then switched to a different one.

Children and adolescents ≤ 70 kg: start with a total daily dose of 0.5 mg/kg; increase after a minimum of 3 days to 1.2 mg/kg.

Children and adolescents > 70 kg, and adults: initiate at a total daily dose of 40 mg; increase after a minimum of 3 days to 80 mg.

After 2–4 additional weeks, if the response is unsatisfactory, the total daily dose may be increased to a maximum of 1.4 mg/kg for children and adolescents ≤ 70 kg (100 mg for others). Note that there are no documented increases in response rates with these higher doses.[36]

Atomoxetine may be given either as a single daily dose in the morning or as evenly divided doses in the morning and late afternoon/early evening. People who have an unsatisfactory response or significant adverse effects when taking atomoxetine as a single daily dose might benefit from taking twice-daily divided doses.[37]

Atomoxetine may be taken before or after food[9], but gastrointestinal distress may be minimised by taking after a meal.[37]

If atomoxetine is co-administered with a potent CYP2D6 inhibitor (e.g. paroxetine or fluoxetine), initiate as usual but do not increase the dose unless there is no improvement after 4 weeks and the initial dose is well tolerated.[9]

The manufacturer states that atomoxetine may be discontinued without tapering the dose.[9] If atomoxetine dosing is interrupted for more than 1 week, it should be restarted at the initiation dose.

Information for patients

Suggest or provide the Strattera consumer medicine information (CMI) leaflet.

Encourage carers to seek urgent medical assistance if children show warning signs of suicidality (Box 1).

Advise patients and carers:

- not to open the capsules
- that nausea and stomach pain can be minimised by taking the medication after a meal
- to avoid over-the-counter decongestants containing phenylephrine or pseudoephedrine, as these might cause a dangerous increase in blood pressure and heart rate
- to talk to the doctor about insomnia or daytime sleepiness, as these may be improved by changing the time of dosing.[37,38]

Inform patients and carers of typical side effects:

- nausea, vomiting, or sore stomach
- decreased appetite and weight
- constipation
- tiredness, early morning waking, difficulty sleeping
- mood swings or irritability
- dry mouth
- difficulty urinating.[9,38]

Also inform patients and carers about the rare but serious risks that may be associated with using atomoxetine:

- suicidal thoughts and behaviours
- heart problems, including sudden cardiac death
- retarded growth
- liver problems.

References

1. Australian Government Department of Health and Ageing. November 2006 PBAC outcomes: positive recommendations. http://www.health.gov.au/internet/wcms/publishing.nsf/Content/pbacrec-nov06-positive (accessed 20 December 2006).
2. Australian Government Department of Health and Ageing. Public summary document for atomoxetine hydrochloride, capsules, 10 mg, 18 mg, 25 mg, 40 mg and 60 mg, Strattera November 2006. http://www.health.gov.au/internet/wcms/publishing.nsf/Content/pbac-psd-atomoxetine-nov06 (accessed 13 April 2007).
3. Australian Government Department of Health and Ageing. March 2005 PBAC outcomes: "subsequent" decisions not to recommend. http://www.health.gov.au/internet/wcms/publishing.nsf/Content/pbacrec-mar05-neg2 (accessed 2 January 2006).
4. Brown RT, et al. Pediatrics 2005;115:e749–57.
5. Therapeutic Guidelines: Psychotropic. Version 5, 2003.
6. King S, et al. Health Technol Assess 2006;10:1–146.
7. Michelson D, et al. Biol Psychiatry 2003;53:112–20.
8. Michelson D, et al. Am J Psychiatry 2002;159:1896–901.
9. Eli Lilly Australia. Strattera product information. 20 September 2006
10. Michelson D, et al. J Am Acad Child Adolesc Psychiatry 2004;43:896–904.
11. Buitelaar JK, et al. Biol Psychiatry 2006.
12. Wilens TE, et al. J Pediatr 2006;149:112–9.
13. Kratochvil CJ, et al. J Am Acad Child Adolesc Psychiatry 2006;45:919–27.
14. Australian Medicines Handbook, 2007.
15. National Institute for Health and Clinical Excellence. Methylphenidate, atomoxetine and dexamfetamine for attention deficit hyperactivity disorder (ADHD) in children and adolescents. Review of Technology Appraisal 12. Technology Appraisal 98. 2006. http://www.nice.org.uk/guidance/TA98 (accessed 2 January 2006).
16. Hutchins P, et al. Attention deficit hyperactivity disorder (ADHD). Ch 15. in: The Clinician's Guide to Psychotropic Prescribing in Children & Adolescents. Child and Adolescent Mental Health Statewide Network, 2004. http://www.camhsnet.org/editLevel3.asp?subsectionID=28&SectionID=7&SectionName=Publications&SubSectionTitle=Reference+Materials (accessed 1 February 2007).
17. Kemner JE, et al. Adv Ther 2005;22:498–512.
18. Kratochvil CJ, et al. J Am Acad Child Adolesc Psychiatry 2002;41:776–84.
19. Gibson AP, et al. Ann Pharmacother 2006;40:1134–42.
20. Wigal SB, et al. J Atten Disord 2005;9:275–89.
21. Michelson D. Results from a double-blind study of atomoxetine, OROS methylphenidate and placebo. American Academy of Child and Adolescent Psychiatry 51st annual meeting (October 19–23, 2004).
22. Velcea G ,Winsberg BG. Am J Psychiatry 2004;161:1718–9.
23. Scottish Intercollegiate Guidelines Network. Attention deficit and hyperkinetic disorders in children and young people. http://www.sign.ac.uk/pdf/sign52.pdf (accessed 31 January 2007).
24. Eli Lilly and Company [USA]. Strattera (atomoxetine) Prescribing Information. http://www.fda.gov/cder/foi/label/2006/021411s018lbl.pdf (accessed 20 December 2006).
25. Henderson TA ,Hartman K. Pediatrics 2004;114:895–6.
26. Polzer J, et al. Biol Psychiatry 2006.
27. Dworkin N. J Am Acad Child Adolesc Psychiatry 2005;44:510.
28. Wernicke JF, et al. Drug Saf 2003;26:729–40.
29. LoVecchio F, Kashani J. J Emerg Med 2006;31:267–8.
30. Rajesh AS, et al. Arch Dis Child 2006;91:1023–4.
31. Heil SH, et al. Drug Alcohol Depend 2002;67:149–56.
32. Wernicke JF, Kratochvil CJ. J Clin Psychiatry 2002;63[Suppl.]12:50–5.
33. Spencer TJ, et al. Pediatrics 2005;116:e74–80.
34. Lim JR, et al. J Pediatr 2006;148:831–4.
35. Stojanovski SD, et al. Clin Toxicol (Phila) 2007;45:51–5.
36. Strattera (Atomoxetine) Approval Package. Company: Eli Lilly and Company, Application No.: 21-411, Approval Date: 11/26/2002. http://www.fda.gov/cder/foi/nda/2002/21-411_Strattera.htm (accessed 20 December 2006).
37. Pliszka SR, et al. J Am Acad Child Adolesc Psychiatry 2006;45:642–57.
38. Eli Lilly Australia. Strattera consumer medicine information. July 2006.

Date prepared: May 2007.

The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence.
Any treatment decisions based on this information should be made in the context of the clinical circumstances of each patient.