



# THERAPEUTICS INITIATIVE

Evidence Based Drug Therapy

## Atomoxetine for ADHD in children and adolescents

In Letter #69 we summarized the evidence for the CNS stimulants, methylphenidate, dextroamphetamine and mixed amphetamine salts, to treat Attention-Deficit/Hyperactivity Disorder (ADHD) in children and concluded “**Better benefit and harm evidence is necessary before long-term CNS stimulant treatment can be recommended.**”<sup>1</sup> That Letter did not assess atomoxetine (Strattera®) the newest drug indicated for treatment of ADHD. The rate of prescribing of atomoxetine in British Columbia (BC) in 2008 and 2009 is similar to mixed amphetamine salts (Adderall®), about one third of dextroamphetamine (Dexedrine®) and about one sixth of methylphenidate (Ritalin®, Concerta®).

**Approved indications:** ADHD in children aged 6 or older, adolescents, and adults.<sup>2</sup>

**Mechanism of action:** Atomoxetine is a selective inhibitor of the presynaptic norepinephrine transporter mechanism but its mode of action is not known. It is classified as a non-stimulant for regulatory purposes.<sup>2</sup>

**Pharmacokinetics:** Atomoxetine bioavailability is 63% in normal and 94% in poor metabolizers. It is primarily metabolized by cytochrome P450 (CYP) 2D6. The drug half-life in poor metabolizers is 21.6 hours compared to 5.2 hours in normal metabolizers. Seven percent of Caucasians, 2% of African Americans and <1% of Asians have reduced CYP2D6 activity and are poor metabolizers of atomoxetine and other drugs like metoprolol.<sup>3</sup> **In poor metabolizers the overall concentrations of atomoxetine are 10-fold higher and peak concentrations are 5-fold higher than in normal metabolizers.** Despite this the product monograph does not recommend genetic testing and lower doses for poor metabolizers.<sup>2</sup>

### Evidence of Short-term (< 1 year) Efficacy

Population studied: children and adolescents 6-18 years of age with ADHD and no co-morbidity. Eight double-blind RCTs compared atomoxetine to placebo (N = 1472 with a mean duration of 7.3 weeks).<sup>4-10</sup> Three RCTs compared atomoxetine to methylphenidate (N = 942, mean duration of 6.7 weeks)<sup>10-12</sup> and one RCT compared atomoxetine to mixed amphetamine salts (N = 215, mean duration of 2.6 weeks)<sup>13</sup>.

Compared to placebo, atomoxetine (mean dose of 1.43 mg/kg/day) reduced the ADHD Rating Scale (total score range 0 to 54) by 8 (95% CI 7 to 10).<sup>4-10</sup> The clinical significance of this change is unknown.<sup>14</sup>



Atomoxetine increased the Child Health Questionnaire psychosocial summary score (total score range 0 to 100) by 5.6 (WMD, 95% CI 3.71 to 7.48).<sup>6,9,10</sup> However, since this was only reported in 3 of 8 RCTs, it is subject to selective reporting bias. In one trial there was no significant difference in the response for 3 doses of atomoxetine (0.5, 1.2 and 1.8 mg/kg/day) on the ADHD-Rating Scale total score or Child Health Questionnaire.<sup>6</sup> In 4 RCTs comparing atomoxetine to methylphenidate and mixed amphetamine salts, patients receiving comparator drugs did better on ADHD Rating Scales than those receiving atomoxetine (pooled standardized increase in effect size, 0.19 [0.07 to 0.32]).<sup>10-13</sup>

### Risk of Bias

The Cochrane “Risk of Bias” tool identified risk of inadequate blinding, selective reporting and publication bias. All the trials except one included authors that were employees of the manufacturer, Eli Lilly. In the one exception, the trial showing that mixed amphetamine salts were more effective than atomoxetine, the authors included employees of Shire Pharmaceuticals.

### Adverse Effects

**Symptoms:** Compared to placebo, atomoxetine significantly decreased appetite (ARI = 13%, NNH = 8), increased abdominal pain (ARI = 7%, NNH = 14) and somnolence (ARI = 6%, NNH = 17), and increased withdrawals due to adverse effects (ARI = 2.9%, NNH = 35).<sup>2</sup> Withdrawals due to adverse effects were 3.1% higher in poor metabolizers than in normal metabolizers.<sup>2</sup>

Compared to other drugs for ADHD, atomoxetine significantly increased somnolence (ARI = 13%, NNH = 8) and increased vomiting (ARI = 6%, NNH = 17). The one adverse effect that was higher for the other drugs was insomnia (ARI = 11%, NNH = 9).



**Growth:** Among patients treated for at least 1 year, mean weight and height gain were lower than normal growth curves for both poor metabolizers (3.7 kg and 1.5 cm) and for normal metabolizers (1.2 kg and 0.7 cm).<sup>2</sup> In a 6-week dose-ranging trial, 1.3%, 7.1%, 19.3% and 29.1% of patients lost at least 3.5% of body weight in the placebo, 0.5, 1.2 and 1.8 mg/kg/day atomoxetine dose groups, respectively.<sup>6</sup> In the 4 comparative RCTs weight loss was similar for atomoxetine and the other ADHD drugs.<sup>10-13</sup>

**Cardiovascular:** Compared to placebo atomoxetine significantly increased heart rate, 6 beats per minute in normal metabolizers and 10 beats per minute in poor metabolizers.<sup>2</sup> It also increased systolic (2.6 mmHg) and diastolic (2.2 mmHg) blood pressure to a similar extent in both metabolizer groups.<sup>3</sup> Compared to other ADHD drugs, atomoxetine increased heart rate by 4 beats per minute.

### Warnings

**“Rigorous clinical monitoring for suicidal ideation or other indicators of potential for suicidal behaviour is advised for patients of all ages (risk 0.4% for atomoxetine vs 0% for placebo). This includes monitoring for agitation-type of emotional and behavioural changes and clinical worsening.”<sup>2</sup>**

**“Atomoxetine can cause severe liver injury in rare cases.”<sup>2</sup>**

The draft of this Therapeutics Letter was submitted for review to 45 experts and primary care physicians in order to correct any inaccuracies and to ensure that the information is concise and relevant to clinicians.

### References

1. Therapeutics Initiative. *What is the evidence for using CNS stimulants to treat ADHD in children?* Therapeutics Letter 2008; 69:1-2. <http://ti.ubc.ca/letter69>
2. Strattera Product Monograph, Eli-Lilly, December 2007.
3. Trzepacz PT, Williams DW, Feldman PD et al. *CYP2D6 metabolizer status and atomoxetine dosing in children and adolescents with ADHD.* European Neuropsychopharmacology 2008; 18(2):79-86.
4. Gau SSF, Huang Y-S, Soong W-T, Chou M-C et al. *A randomized, double-blind, placebo-controlled clinical trial on once-daily atomoxetine hydrochloride in Taiwanese children and adolescents with attention-deficit/hyperactivity disorder.* Journal of Child and Adolescent Psychopharmacology 2007; 17(4):447-460.
5. Kelsey DK, Sumner CR, Casat CD et al. *Once-daily atomoxetine treatment for children with attention-deficit/hyperactivity disorder, including an assessment of evening and morning behavior: a double-blind, placebo-controlled trial.* Pediatrics 2004; 114(1):e1-e8.
6. Michelson D, Faries D, Wernicke J et al. *Atomoxetine in the treatment of children and adolescents with attention-deficit/hyperactivity disorder: a randomized, placebo-controlled, dose-response study.* Pediatrics 2001; 108(5):e83-e91.
7. Michelson D, Allen AJ, Busner J et al. *Once-daily atomoxetine treatment for children and adolescents with attention deficit hyperactivity disorder: a randomized, placebo-controlled study.* American Journal of Psychiatry 2002; 159:1896-1901.
8. Spencer T, Heiligenstein JH, Biederman J et al. *Results from 2 proof-of-concept, placebo-controlled studies of atomoxetine in children with attention-deficit/hyperactivity disorder.* The Journal of Clinical Psychiatry 2002; 63(12):1140-1147.

### Dosing and Cost

Initiate at a total daily dose of 0.5 mg/kg and maintain for a minimum of 10 days. If tolerated, increase to 0.8 mg/kg per day and maintain for a minimum of 10 days and then increase again to 1.2 mg/kg per day if no clinical benefits are seen by week 3. **The total daily dose should not exceed 1.4 mg/kg or 100 mg, whichever is less.<sup>2</sup>**

Average daily cost of atomoxetine in BC is \$4.20 to \$8.40.

### Conclusions

- **Short-term use (< 1 year):** Based on RCTs < 8 weeks, atomoxetine reduces teacher and parent ratings of hyperactive/impulsive disruptive behaviour but the effect is less than that seen with methylphenidate and mixed amphetamine salts. Atomoxetine causes the following adverse effects in 5 to 15% of patients: decreased appetite, abdominal pain, vomiting and somnolence.
- **Intermediate- to long-term use (>1 year):** No RCTs are available. Effects on educational achievement are unknown. Atomoxetine adversely affects growth (weight and height) compared to national norms. Adverse consequences of the increased heart rate and blood pressure caused by atomoxetine are expected based on epidemiologic data.<sup>15</sup>

### Recommendation

**Without large, long-term RCTs demonstrating a benefit of atomoxetine on educational achievement, school completion, employment and future health and in view of the risk of serious harm, use of atomoxetine should be limited to exceptional cases intolerant to other ADHD drugs.**

WMD = weighted mean difference

CI = confidence interval

ARI = absolute risk increase

NNH = number needed to treat to cause one harmful event

9. Weiss M, Tannock R, Kratochvil C et al. *A randomized, placebo-controlled study of once-daily atomoxetine in the school setting in children with ADHD.* Journal of the American Academy of Child and Adolescent Psychiatry 2005; 44(7):647-655.
10. Newcorn JH, Kratochvil CJ, Allen AJ et al. *Atomoxetine and osmotically released methylphenidate for the treatment of attention deficit hyperactivity disorder: acute comparison and differential response.* American Journal of Psychiatry 2008; 165(6):721-730.
11. Sangal RB, Owens J, Allen AJ et al. *Effects of atomoxetine and methylphenidate on sleep in children with ADHD.* Sleep 2006; 29(12):1573-1585.
12. Wang Y, Zheng Y, Du Y et al. *Atomoxetine versus methylphenidate in paediatric outpatients with attention deficit hyperactivity disorder: a randomized, double-blind comparison trial.* Australian and New Zealand Journal of Psychiatry 2007; 41(3):222-230.
13. Wigal SB, Wigal TL, McGough JJ et al. *A laboratory school comparison of mixed amphetamine salts extended release (Adderall XR) and atomoxetine (Strattera) in school-aged children with attention deficit/hyperactivity disorder.* Journal of Attention Disorders 2005; 9(1):275-289.
14. Sangal RB and Sangal JM. *What is a significant response in drug studies of attention-deficit/hyperactivity disorder: statistical significance is necessary, but is it sufficient?* Psychopharmacology Bulletin 2003; 37(2):50-58.
15. Greenland P, Daviglius ML, Dyer AR et al. *Resting heart rate is a risk factor for cardiovascular and non-cardiovascular mortality: the Chicago Heart Association Detection Project in Industry.* Am J Epidemiol 1999; 149(9):853-862.