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Atomoxetine for Attention Deficit/ Hyperactivity Disorder

Summary

- ✓ **Seven randomized, double-blinded, controlled trials in children, adolescents and adults have shown that atomoxetine improves attention deficit/hyperactivity disorder (ADHD) symptoms compared to placebo.**
- ✓ **There is no evidence that atomoxetine has greater efficacy or a better safety profile than currently used therapy.**
- ✓ **Atomoxetine has been submitted for regulatory approval in Canada and is currently approved in the US. The price of atomoxetine in Canada has not been established.**

The Technology

Atomoxetine (ATX) is designed to selectively inhibit presynaptic norepinephrine reuptake in the nervous system.¹ It is not known how ATX reduces attention deficit/hyperactivity disorder (ADHD) symptoms.¹

Regulatory Status

The US Food and Drug Administration (FDA) approved Atomoxetine (Strattera™) in November 2002 for the treatment of ADHD in children, adolescents and adults. Eli Lilly Inc. has submitted applications for the regulatory approval of ATX in Canada, Australia and New Zealand.²

Patient Group

The diagnosis of ADHD can be difficult and is made according to commonly occurring types of behaviour. Diagnosed individuals exhibit persistent inattention and/or hyperactivity-impulsivity more frequently and severely than their peers.

ADHD is also associated with functional impairment. Some symptoms must be present before age seven; however, the disorder may go unnoticed for several years. Impairment of functioning due to these symptoms must be present in two or more settings (e.g. at school/work and at home) in order to be considered as ADHD.³

The prevalence of ADHD in school children ranges from 1.7 to 17.8% in different countries.^{4,5} In 2001, visits to Canadian physicians (both first and repeat) for ADHD increased by an estimated 20% from 1997. Drug therapy was recommended in 64% of visits.⁶

Current Practice

Methylphenidate (MPH, e.g. Ritalin®) and amphetamine (AMP, e.g. Dexedrine®) products are the most commonly prescribed medications for ADHD in Canada.⁶ However, a minority of individuals (20 to 30%) will not tolerate or respond to these therapies.⁷ Although relatively safe and effective in the short term, some patients do receive these drugs for longer-term treatment. Common adverse events include appetite suppression and sleep disturbance. There is concern surrounding their abuse potential; however, minimal evidence is available.⁷

Tricyclic antidepressants, bupropion, clonidine and guanfacine have also been shown to be efficacious.⁷ None of these agents are approved for the treatment of ADHD in Canada, although they may be used in practice. Behavioural therapy may be recommended to improve target outcomes in children with ADHD.⁸

Changes in behaviour rated by parents or caregivers, and overall health and function, are commonly used to measure response to therapy. Some experts feel teacher rating should also be considered since dysfunction at school is often what prompts medication use.

The Evidence

Children: Four randomized, double blind, placebo-controlled, manufacturer-funded trials were conducted in children and adolescents with ADHD. The ADHD Rating Scale (RS) was used as the primary outcome measure. It is based on the 18 DSM-IV diagnostic criteria, which include a subjective assessment of inattention, hyperactivity and impulsivity. A decrease in ADHD RS represents an improvement in symptoms. In each of these trials, the placebo response using the ADHD RS was high, ranging from 39 to 59% of the ATX response. It is not known whether decreases in ADHD RS scores in these studies signify a clinical benefit.

In the Michelson *et al.* 2001 trial,⁹ a statistically significant decrease in the ADHD RS and the Children's Depression Rating Scale was observed at the two higher doses of ATX compared to placebo. Statistically significant decreases in the Conners' Parent Rating Scale (CPRS) were seen at all ATX doses compared to placebo. The psychosocial summary score of the Children's Health Questionnaire (CHQ), but not all individual components, showed statistically significant decreases at all doses.

In the second trial by Michelson *et al.* (2002)¹⁰ there was a statistically significant decrease in the ADHD RS, the Clinical Global Impression (CGI) severity score, the CPRS and in the Conners' Teacher Rating Scale (mean difference= -3.5, 95% CI: -5.95; -0.05) in the ATX group compared to placebo.

There are two identical trials conducted by Spencer *et al.*,¹¹ where patients with prior exposure to stimulants were randomized to ATX or placebo, and stimulant-naïve patients were randomized to ATX, MPH or placebo. The results of the MPH group were not reported.¹¹ ATX treatment resulted in a greater decrease in ADHD RS compared to placebo, and both studies reported a significant decrease in the CGI ADHD-severity score and CPRS-ADHD index.

In only one trial report is the comparative efficacy of ATX and MPH in children reported (10-week duration, n_{ATX} =184 and n_{placebo} = 44).¹² No statistically significant differences were observed between ATX and MPH in the ADHD RS (p=0.66)¹² It is unclear whether this trial had sufficient power to detect statistical differences in efficacy. Both drugs demonstrated improvement

Table 1: Placebo-controlled trials of atomoxetine in children and adolescents

Author, Year	Intervention and duration of study	Number of patients	Outcome measure ADHD RS in ATX compared to placebo Mean difference (95% CI)*
Michelson <i>et al.</i> , 2001	ATX 0.5 mg/kg/bid, ATX 1.2 mg/kg/bid, ATX 1.8 mg/kg/bid, or placebo for 8 weeks	44	-4.1 (-9.0, 0.8)
		84	-7.8 (-11.6, -4.0)
		85	-7.7 (-11.6, -3.8)
		84	
		Total: 297	
Michelson <i>et al.</i> , 2002	ATX 1.0 mg/kg/daily [†] or placebo for 6 weeks	85	-7.8 (-11.2, -4.4)
		85	
		Total: 171 [‡]	
Spencer <i>et al.</i> , 2002	ATX 1.5 mg/kg/bid, MPH 1.5 mg/kg/bid, or placebo for 9 weeks	65	-10.10 (-14.5, -5.7)
		20	
		62	
		Total: 147	
Spencer <i>et al.</i> , 2002	ATX 1.5 mg/kg/bid, MPH 1.5 mg/kg/bid, or placebo for 9 weeks	64	-8.5 (-13.0, -4.0)
		18	
		62	
		Total: 144	

bid = twice daily; ATX = atomoxetine; MPH = methylphenidate

* mean difference between ATX and placebo, calculated using Cochrane Review Manager 4.1 software and ITT data where possible

[†] Mean dose = 1.3 mg/kg/day

[‡] One patient did not receive any study medication and was not included in the analysis

in inattentive and hyperactive/impulsive symptoms. The types and rates of adverse events were similar.

Adults: Three randomized, double blind, placebo controlled trials have been conducted in adults with ADHD. One trial (n=22) demonstrated a statistically significant decrease in ADHD RS in the ATX group compared to placebo.¹³ Two identical 10-week trials (n=280 and n=256) demonstrated a statistically significant decrease in the Conners' Adult ADHD RS in the ATX group compared to placebo.¹⁴

Adverse Effects

In the studies involving children, symptoms such as dizziness,⁹ a decreased appetite, vomiting, nausea, asthenia and dyspepsia¹⁰ were significantly more frequent in the ATX group compared to placebo. The Spencer *et al.* study combined the adverse events of the two studies and found that significantly more patients treated with ATX reported a decreased appetite compared to placebo.¹¹

Among the studies involving adults, appetite suppression was experienced significantly more frequently in the ATX group ($p < 0.05$).¹³ In the Michelson *et al.* studies, the adverse events from the two identical studies were pooled.¹⁴ Dry mouth, insomnia, nausea, decreased appetite, constipation, dizziness and sweating occurred significantly more frequently in the patients receiving ATX compared to those receiving placebo. Patients receiving ATX also experienced decreased libido and difficulty attaining or maintaining an erection significantly more often than patients receiving placebo.

ATX is metabolized via the CYP 2D6 system of the liver; thus, poor metabolizers may experience high concentrations of the drug due to slower elimination.¹ Physicians will need to take liver function and potential drug interactions (e.g. with paroxetine and fluoxetine) into consideration before prescribing ATX.¹

Administration and Cost

The manufacturer recommends a dose of 1.2 mg/kg/day for those below 70 kg and 80 mg/day for those above 70 kg. Strattera™ capsules are supplied in 5, 10, 18, 25, 40 and 60 mg strengths and can be administered once in the morning or in divided doses.¹

In the US, the average wholesale price of ATX is US\$90 for 30 capsules, regardless of strength.¹⁵ The potential price of ATX in Canada is unknown.

Concurrent Developments

New formulations of methylphenidate or amphetamine (e.g. MPH - Concerta® and Methypatch®, AMP - Focalin™) and trials of previously existing therapies (e.g. Modafinil, approved for use in narcolepsy) have been the focus of ADHD research. None are approved for use in Canada.¹⁶

Rate of Technology Diffusion

There is much debate over the diagnosis and medication of children with ADHD. Parents or clinicians who have rejected the use of stimulants to treat ADHD might be more accepting of a new drug such as ATX.

There is currently no evidence that ATX reduces symptoms of ADHD more effectively, or that it is safer than the currently used therapy. Therefore, its use may be limited to patients who are unresponsive or intolerant to the commonly prescribed medications. The efficacy of ATX in these patients, however, is not known.

Implementation Issues

ATX is chemically different than currently used stimulant therapy. Whether this translates into a clinical advantage is still unknown. The long-term effects of ADHD are also uncertain, even though treatment of the disorder may continue into adulthood.¹⁷ Furthermore, it is uncertain whether ATX improves a child's performance in the classroom, since only one randomized controlled trial included a teacher rating. Although

specific Canadian pricing is unknown, it is likely to be more expensive than currently used stimulant medications, which are available in generic form.

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