

Perspectives in Psychopharmacology: Spotlight on Atomoxetine

Adil Virani, BSc (Pharm), Pharm D^{1,2}

INTRODUCTION

Over the last decade, several advances have been made in the pharmacological treatment of ADHD. Novel medications, longer acting preparations and results from recent clinical trials have broadened the landscape of ADHD management in Canada. Atomoxetine, a novel non-stimulant medication, was approved for use in Canada in December 2004. Unlike methylphenidate and dextroamphetamine, which act primarily by blocking the reuptake of dopamine, atomoxetine selectively inhibits the presynaptic reuptake of norepinephrine (Banaschewski T, et al., 2004). It has been approved for use and indicated in children (6 years of age and older), adolescents, and adults with ADHD. Atomoxetine is not habit forming and is not a controlled substance. Its efficacy and tolerability in children (aged 6 years and older), adolescents, and adults with ADHD has been studied in several RCTs (Banaschewski T, et al., 2004; Biederman J et al., 2002; Kelsey DK et al., 2004; Kratochvil CJ et al., 2002; Michelson D et al., 2003; Michelson D et al., 2002; Michelson D et al., 2001; Spencer T et al., 2002; Weiss M et al., 2005).

ATOMOXETINE: EFFICACY AND DOSING

Results from five double-blind, RCTs of nine weeks or less in youth, suggest that atomoxetine, at doses of 1.2-1.8 mg/kg/day, is more efficacious than placebo at reducing the core symptoms of ADHD (Biederman J et al., 2002; Michelson D et al., 2002; Michelson D et al., 2001; Spencer T et al., 2002). Two short term RCTs in adults with ADHD also found that atomoxetine was more effective than placebo (Michelson D et al., 2003). Kelsey and colleagues (2004) demonstrated that once daily atomoxetine dosing (mean dose of 1.3 mg/kg/day) was significantly more effective than placebo in an 8 week double-blind, RCT. They also observed that once daily atomoxetine had beneficial effects persisting into the evening and the next morning.

However, Atomoxetine's efficacy compared to stimulants as well as its long term effectiveness needs further evaluation. A small head-to-head unblinded trial, where patients were randomized in a 4:1 ratio to atomoxetine or MPH, reported similar efficacy in reduction of core ADHD symptoms, as assessed by parents and investigators (Kratochvil CJ et al., 2002). Issues with the design of this trial limit some of its validity. Some of these issues include it being open label, having a small methylphenidate group (n=40), a high drop out rate and employing a relatively low median methylphenidate dose (27mg; 0.74mg/kg/d) compared to the 1.5mg/kg/d given to the atomoxetine participants (rapid metabolizers).

Unlike the rapid response seen with stimulants, some patients require 3 to 4 weeks of atomoxetine therapy before improvements are seen. Improvements continue to be seen beyond 7 weeks of therapy. Atomoxetine is metabolized in the liver by

the cytochrome P450 isoenzyme 2D6. Though the elimination half-life is approximately 5 hours in most individuals, those taking enzyme inhibitors (e.g., paroxetine, quinidine, fluoxetine) or slow metabolizers (e.g. some Asian populations) may have extended elimination half-lives.

Children should be started at a dose of 0.5 mg/kg. If tolerated, the dose can be increased after at least ten days by 0.3mg/kg intervals to a target daily dose of 1.2 to 1.4 mg/kg. It may be given once a day or in divided doses. Adult patients are started at a daily dose of 40 mg, which, if tolerated, can be increased to 80 mg after a minimum of ten days. Atomoxetine is available in 10mg, 18 mg, 25mg, 40mg and 60 mg capsules. No liquid formulation is available.

Advantages of atomoxetine over stimulants include a lack of abuse potential, decreased risk of rebound hyperactivity and tics, efficacy in the early mornings and evenings. As well, it is not a controlled substance and may be useful in those who do not tolerate stimulants. A recent publication by Kratochvil CJ and colleagues (2005) also reported that atomoxetine may be beneficial (and as effective as the combination of atomoxetine and fluoxetine) when anxiety or mood disorders occur comorbidly with ADHD. Though a recent trial by Michelson D and colleagues (2004) found atomoxetine to be helpful in preventing relapse (defined as a return of 90% of baseline symptoms), there are no trials examining atomoxetine's ability to induce remission of symptoms. Disadvantages over stimulants include a longer onset of action, unclear or a lack of data confirming that it is equally effective to stimulants, and potentially the recent concerns regarding increased suicidality.

ATOMOXETINE SAFETY AND SUICIDALITY

Several RCTs conducted in over 4,000 children and adolescents have found atomoxetine to be relatively well-tolerated. Common adverse effects associated with atomoxetine include somnolence, decreased appetite, headaches, upper abdominal pain, nausea, vomiting, weight loss, dizziness, fatigue, emotional lability, and small, clinically insignificant (in healthy patients) increases in heart rate and blood pressure. To date, at least 2 cases (one possible and one probable) of reversible liver dysfunction have been reported (FDA, 2004). Giving atomoxetine with meals may increase tolerability. Side effects sometimes differ between adults and children. In adult trials side effects included dry mouth, constipation, decreased libido and erectile dysfunction (Michelson D et al 2003).

On September 28, 2005, Eli Lilly and Health Canada released a warning to Canadians after the manufacturer conducted a meta analysis to evaluate the association between atomoxetine and suicide related events. All the short-term, randomized, placebo-controlled, double-blind atomoxetine clinical trials that

¹Medication Management Coordinator, Fraser Health Authority, Vancouver, British Columbia

²Clinical Consultant in Child and Adolescent Psychiatry and Assistant Professor (Part-Time),
UBC Faculty of Pharmaceutical Sciences, Vancouver, British Columbia

enrolled 20 patients per arm were included to reach a total of 4,998 patients: 2,208 (1357 atomoxetine, 851 placebo) children and adolescents, and 2,790 (1,718 atomoxetine, 1,072 placebo) adults. In the adult patients, 1,844 were enrolled in depression trials and 946 were from ADHD trials. The search was limited to adverse events occurring in the double-blind treatment phase or those that occurred within 24 hours of stopping randomized treatment. Researchers used similar techniques as those employed in the recent evaluations of suicide related events in pediatric depression trial. There were no completed suicides in any of the clinical trials.

Six suicide-related events were identified in 1357 pediatric ADHD patients (0.44%) receiving atomoxetine while no events were seen in the 851 patients taking placebo. One event was observed in an adult ADHD patient (out of 405) given placebo and none observed in the 541 adults taking atomoxetine. When a second analysis was conducted, two additional pediatric patients (1 atomoxetine-treated and 1 placebo-treated) who had self injurious behaviour were identified. The statistical results from each method of analysis were similar and did not impact the final conclusions made. Note that the six events reported here, based on data Eli Lilly has on file (2005) differ from the 5/1357 reported in the Health Canada Endorsed warning.

All of the six events in pediatric patients occurred in patients between the ages of 7 – 12 years. Only 25% of the meta analysis study population incorporated data from those over 12 years of age. It is also important to recognize that five of the six events observed were categorized as “suicidal ideation” and that the six patients were considered to be moderately – severely ill (as defined by baseline Conners’ Global Index – Severity scores of 4 – 6). These six patients were prescribed atomoxetine doses ranging from 0.48 to 1.40 mg/kg/day and did not appear to take concomitant medications or have other comorbid illnesses. Interestingly, as observed with the antidepressants used in pediatric depression trials, the average time to onset of suicide-related events occurred somewhat recently after initiation of atomoxetine and averaged approximately 20 days. At the time of suicide-related event, 50% (3 of the 6 patients) had not had a response (defined as a 25% or more reduction from baseline ADHD-Rating Scale score).

Though a prospective, controlled trial is the best way to identify adverse events, it often does not have the statistical power to identify rare events, such as suicide related occurrences. Furthermore, unlike the pediatric depression trials, it is not common practice to discuss suicide feelings in all pediatric patients with ADHD.

Since evaluating suicide-related behavior was not an a priori objective of the atomoxetine ADHD studies, documentation of these events and characteristics that support these events was lacking during the clinical trials. For example, in those patients who had a suicide related event, the documentation regarding a family history of suicide, depression or even ADHD was not collected or known.

In addition, many atomoxetine clinical trials excluded or did not enroll those patients with substance abuse, depression and/or anxiety. Though this may be helpful in learning about the efficacy and safety of a product in patients who only have

ADHD, it is problematic when attempting to generalize the data to those patients seen in the general population who suffer from these (or other) comorbid illnesses often associated with suicide related behavior. Furthermore, where the incidence of suicidal behaviour increases in adolescence and this data has not been adequately collected nor studied, it is difficult to gage the impact of this potentially serious side effect in adolescents with ADHD given atomoxetine.

IMPACT ON THE CLINICIAN

Though the magnitude of these suicide related events are at a substantially lower level than those seen with antidepressants used in pediatric depression, some lessons learned from depression trials may be helpful here. First, when presenting the data regarding the benefits and risks of atomoxetine to patients and their caregivers, it is important to provide accurate details regarding the low risk of potential suicidal ideation and the actions that should be taken if this occurs. Second, clinicians should document that this discussion has occurred. Third, clinicians should monitor for this side effect (in addition to assessing the efficacy and other side effects) especially in the first month after starting atomoxetine. The first month is especially important; given the average time to onset of suicidal ideation in the atomoxetine trials was 3 weeks. Lastly, since history has shown us that rare events, such as this one and liver toxicity, are not likely to be detected in clinical trials, it is difficult to get an accurate sense of the incidence of these events. Hence, if clinicians suspect an unusual or rare side effect may be occurring to this, or any other agent, they are encouraged to report these findings to the Adverse Drug Reaction group at Health Canada.

REFERENCES

- Banaschewski T., Roessner V., Dittman R. W., Santosh P. J., Rothenberger A. (2004). Non-stimulant medication in the treatment of ADHD. *European Child and Adolescent Psychiatry*, 13 (Suppl 1), 102-116.
- Biederman J., Heiligenstein J. H., Faries D., Galil N., Dittmann R., Emslie G. J., et al. (2002). Efficacy of atomoxetine versus placebo in school-age girls with attention-deficit/hyperactivity disorder. *Pediatrics*, 110, e75.
- Data on File, Eli Lilly Inc. Retrieved October 14, 2005.
- FDA Talk Paper. Safety information on Strattera. (2004). Retrieved October 14, 2005 from <http://www.fda.gov/bbs/topics/ANSWERS/2004/ANS01335.html>.
- Health Canada Endorsed Important Safety Information Strattera. (2005). Retrieved October 14, 2005 from http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/strattera_hpc-cps_e.pdf.
- Kelsey D. K., Sumner C. R., Casat C. D., Coury D. L., Quintana H., Saylor K. E., et al. (2004). 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*, 114(1), e1-8.
- Kratochvil C. J., Newcorn J. H., Arnold L. E., Duesenberg D., Emslie G. J., Quintana H., et al. (2005). Atomoxetine alone or combined with fluoxetine for treating ADHD with comorbid depressive or anxiety symptoms. *Journal of the American Academy of Child and Adolescent Psychiatry*, 44(9), 915-24.
- Kratochvil C. J., Heiligenstein J. H., Dittmann R., Spencer T., Biederman J., Wernicke J., et al. (2002) Atomoxetine and methylphenidate treatment in children with ADHD: a prospective, randomized, open-label trial. *Journal of the American Academy of Child and Adolescent Psychiatry*, 41, 776-784.

Michelson D., Buitelaar J. K., Danckaerts M., Gillberg C., Spencer T. J., Zuddas A., et al. (2004). Relapse prevention in pediatric patients with ADHD treated with atomoxetine: a randomized, double-blind, placebo-controlled study. *Journal of the American Academy of Child and Adolescent Psychiatry*, 43(7), 896-904.

Michelson D., Adler L., Spencer T., Reimherr F. W., West S. A., Allen A. J., et al. (2003). Atomoxetine in adults with ADHD: two randomized, placebo-controlled studies. *Biological Psychiatry*, 53, 112-120.

Michelson D., Allen A. J., Busner J., Casat C., Dunn D., Kratochvil C., et al. (2002). Once-daily atomoxetine treatment for children and adolescents with attention deficit hyperactivity disorder: a randomized, placebo-controlled study. *American Journal of Psychiatry*, 159, 1896-1901.

Michelson D., Faries D., Wernicke J., Kelsey D., Kendrick K., Sallee F. R., et al. (2001). Atomoxetine in the treatment of

children and adolescents with attention-deficit/hyperactivity disorder: a randomized, placebo-controlled, dose-response study. *Pediatrics*, 108(5), 83.

Spencer T., Heiligenstein J. H., Biederman J., Faries D. E., Kratochvil C. J., Conners C. K., et al. (2002). Results from 2 proof-of-concept, placebo-controlled studies of atomoxetine in children with attention-deficit/hyperactivity disorder. *Journal of Clinical Psychiatry*, 63, 1140-1147.

Weiss M., Tannock R., Kratochvil C., Dunn D., Velez-Borras J., Thomason C., et al. (2005). 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*, 44(7), 647-655.