A. Jacques

Although ADHD is a common condition, combination drug therapies for children have not been well studied. This clinical review summarizes the current evidence regarding the combined use of atomoxetine and stimulant medications in children and adolescents with ADHD.

Bien que les troubles d'hyperactivité avec déficit de l'attention (THADA) soient des troubles fréquents, les thérapies à médicaments combinés pour les enfants n'ont pas fait l'objet d'études approfondies. Cet examen clinique présente un sommaire des données actuelles relatives à l'utilisation combinée d'atomoxétine et de psychostimulants chez les enfants et les adolescents atteints de THADA.

Atomoxetine and stimulant medications in children and adolescents with persistent symptoms of attention deficit hyperactivity disorder despite monotherapy

Amanda Jacques, BScPharm, RPh, ACPR

Scenario

A 10-year-old, 30-kg boy with attention deficit hyperactivity disorder (ADHD) is taking osmotic-release oral system methylphenidate (Concerta) 36 mg once daily in the morning. Because his ADHD symptoms are only partially controlled with this monotherapy, several attempts have been made to increase the dose. However, each increase has resulted in intolerable gastrointestinal adverse effects. Today, his mother has dropped off a new prescription for atomoxetine 18 mg once daily for 2 weeks, to be followed by 25 mg once daily for an additional 2 weeks. The atomoxetine is to be added to the existing methylphenidate therapy. Is this a safe and effective drug combination? Are there any special precautions related to using this combination? How should the therapy be monitored?

Introduction

Attention deficit hyperactivity disorder (ADHD) is characterized primarily by symptoms of inattention and/or hyperactivity and impulsivity, often leading to behavioural and academic difficulties.¹⁻³ ADHD is the most common neurobehavioural disorder in children and adolescents, affecting up to 8% of this population.¹ Those with ADHD are more likely to experience adverse educational, social, emotional and health outcomes than those without the disorder.^{2,3}

Guidelines for the treatment of children with ADHD recognize the importance of pharmacological intervention, with stimulants recommended as first-line therapy in most cases.^{1,2} Stimulants, such as methylphenidate (MPH), are thought to improve executive functioning by enhancing dopaminergic signalling in the brain.² About 80% of children experience a response to stimulants.^{1,3} The remainder of patients may have no response or only a partial response. Those with only a partial response may be unable to tolerate dosage increases because of common adverse drug effects (ADEs) of stimulants, such as insomnia, mood changes and gastrointestinal (GI) symptoms, including reduced appetite and weight loss.¹⁻³ Atomoxetine (ATMX), a selective norepinephrine-reuptake inhibitor, is a relatively new agent. Because of its novel mechanism of action, the combined use of ATMX and stimulants may represent an interesting therapeutic approach for children lacking a complete response to monotherapy. In general, ATMX and MPH have similar efficacy. However, the extended-release formulation of MPH, known as osmotic-release oral system (OROS) MPH (Concerta), is more effective than immediate-release preparations of this drug.⁴ Long-acting stimulant preparations such as OROS MPH are considered first-line treatments for ADHD, whereas short- and intermediate-acting stimulants

are considered second-line adjunctive treatments.^{2,5} ATMX is currently the only nonstimulant medication considered as a first-line agent for the treatment of ADHD in children.^{2,5}

Clinical issue

Combination drug therapies for children with ADHD have not been well studied. As such, clinicians face an interesting challenge when treating patients with only a partial response to first-line medications. Combining a stimulant (such as MPH) with a nonstimulant medication (such as ATMX) appears rational, given their different mechanisms of action and minimal overlap in terms of ADEs. However, the evidence for this combination is generally limited to case reports and to small, short-term and often open-label studies.

Evidence

Two independent reviewers (including the author) conducted a literature search using OVID MEDLINE, PubMed, Reactions and an internal citation database of pharmacy journals (AskSam) to identify articles related to the use of combination therapy with ATMX and MPH or other stimulants in children with ADHD. The following search terms (Medical Subject Headings and key words) were used: attention deficit disorder with hyperactivity, attention deficit and disruptive behaviour disorders, ADHD, methylphenidate, central nervous system stimulant, stimulant, atomoxetine, adrenergic uptake inhibitor, pediatric and child. Six articles considered relevant by both reviewers (Table 1) were retrieved and are discussed below in chronological order, by date of publication.

The earliest report, published in 2004, was a case series of 4 patients aged 6 to 17 years.⁶ After insufficient response to single-agent therapy with either extended-release stimulants or ATMX, combination therapy was initiated and continued for up to 5 months. The following combinations were used: OROS MPH 27 mg once daily with ATMX 36 mg once daily (initiated at 18 mg), mixed amphetamines (Adderall XR) 20 mg once daily with ATMX 40 mg once daily (initiated at 18 mg), ATMX 40 mg twice daily with OROS MPH 27 mg once daily (initiated at 18 mg) and ATMX 18 mg twice daily with Adderall XR 5 mg once daily. The combination therapy led to noticeable improvements in a wide range of symptoms. Behaviour in the late afternoon and early evening improved in the 2 cases in which ATMX was added to an extended-release stimulant, whereas improvements in the ability to focus at school were

KNOWLEDGE INTO PRACTICE

- Preliminary short-term data suggest that combination therapy is generally well tolerated and may improve ADHD symptoms in children with inadequate response to stimulant or atomoxetine monotherapy.
- Pharmacists should monitor children initiated on combination therapy regularly and inform patients and/or their caregivers that mild adverse effects are common during the first week of treatment and are likely transient.
- Referral to an ADHD specialist may be preferred in such cases, and children already suffering from significant insomnia, gastrointestinal disturbances, weight loss or cardiovascular effects while taking monotherapy may not be suitable candidates for combination therapy.

observed when an extended-release stimulant was added to ATMX. Reported ADEs included minor GI complaints and somnolence, which dissipated over the first week. The author concluded that the combination of ATMX and stimulants appeared safe and effective in children. The authors also stated that similar positive outcomes had been achieved in 21 other cases, the details of which were not reported.

A single case report, published in 2006, described combination therapy with ATMX and OROS MPH in a 10-year-old boy with ADHD, Tourette syndrome and bipolar disorder who was also taking clonidine.⁷ The child had been taking a stable dose of ATMX 50 mg (1.2 mg/kg) daily, but had displayed only mild improvements in concentration and behaviour at school and at home. OROS MPH was initiated at 18 mg once daily to augment the effects of ATMX. A dramatic improvement in behaviour was reported both at school and at home when the dose of OROS MPH reached 36 mg (0.9 mg/kg) daily and, at the time of publication, the benefits with combination therapy had been maintained for close to 1 year. An expected exacerbation of Tourette syndrome motor tics that occurred with the MPH was managed by increasing the dose of clonidine. No other ADEs were reported.

A 2009 report described the successful use of ATMX 40 mg and MPH 10 mg daily (form unspecified) in an 11-year-old child. The patient had been intolerant of MPH dosage increases because of development of depressed mood and loss of appetite and had retained significant inattention with ATMX alone.⁸

Although positive outcomes were reported in several of these 6 cases, no formal assessments of ADHD symptoms were used to confirm the observations.

TABLE 1 Summary of published evidence describing use of atomoxetine (ATMX) and methylphenidate (MPH) or other stimulants in children and adolescents with ADHD

Study	Design and no. of participants	Patient characteristics	Combination therapy (initial + adjunct)	Duration of combination therapy	Outcome measures
Case reports					
Brown ⁶	Case series (n = 4)	Children aged 6–17 years with insufficient symptom response after monotherapy with stimulant or ATMX	OROS MPH + ATMX Adderall XR + ATMX ATMX + OROS MPH ATMX + Adderall XR	Up to 5 months	Reported improvements in behaviours No formal measures used to evaluate ADHD
Jaworowski et al. ⁷	Case report (n = 1)	10-year-old boy with only mild symptom improvement with ATMX monotherapy (concomitant Tourette syndrome and bipolar disorder)	ATMX + OROS MPH (also receiving clonidine, valproic acid and ziprasidone)	1 year (at time of publication)	Reported improvements in behaviours, adverse effects No formal measures used to evaluate ADHD YGTSS to assess severity and frequency of Tourette tics
Niederhofer ⁸	Case report (n = 1)	11-year-old child unable to tolerate dosage increases of MPH because of adverse effects and with residual symptoms with ATMX monotherapy	ATMX + MPH (form unspecified)	3 months	Reported improvements in behaviours No formal measures used to evaluate ADHD
Experimental studies					
Carlson et al. ⁹	Randomized, double-blind, placebo-controlled study (n = 25)	Children aged 6–12 years with inadequate response to stimulant monotherapy	ATMX + OROS MPH (9 patients randomly assigned to receive combination)	6 weeks	ADHD RS-IV-Parent:Inv, CGI-I, CGI-S, CPRS-R:S, WREMB-R Adverse effects, blood pressure, pulse, weight
Wilens et al. ¹⁰ and Hammerness et al. ¹¹	Open-label trial (effectiveness analysis ¹⁰ and tolerability and pharmacokinetic analysis ¹¹) (n = 82)	Children aged 6–17 years exhibiting partial response to either OROS MPH or ATMX monotherapy	ATMX + OROS MPH (50 patients randomly assigned to receive combination)	3 weeks	ADHD-RS, BRIEF subscales, CGI-I, CGI-S ¹⁰ Adverse effects, blood pressure, pulse, ECG parameters, liver function and hematologic blood tests, ATMX serum levels ¹¹

Adderall XR = extended-release preparation of amphetamine mixed salts; ADHD-RS = ADHD Rating Scale; ADHD RS-IV-Parent:Inv = ADHD Rating Scale version IV: Parent Report Investigator Rated Version; BRIEF = Behavioural Rating Inventory of Executive Functioning; CGI-I = Clinical Global Impression–Improvement; CGI-S = Clinical Global Impression–Severity; CPRS-R:S = Conners Parent Rating Scale Revised: Short Form; ECG = electrocardiogram; OROS = osmotic-release oral system; WREMB-R = Weekly Parent Ratings of Evening and Morning Behaviour–Revised; YGTSS: Yale Global Tic Severity Scale.

The first randomized, double-blind, placebo-controlled study investigating the concomitant use of ATMX and OROS MPH was published in 2007.⁹ Its primary objective was to assess the safety of combination therapy. Children with ADHD aged 6 to 12 years (mean 9.6 years; n = 25) who displayed an inadequate response to stimulant monotherapy were recruited from outpatient centres. Children were excluded if they weighed less than 22 kg or more than 60 kg, had another diagnosed Axis I disorder, had contraindications to either medication or had a history of intolerance or nonresponse to ATMX. During the first 4

weeks of the study (phase 1), patients were started on placebo and open-label ATMX titrated to a target dose of 1.2 mg/kg daily. Four patients discontinued treatment during phase 1 of ATMX monotherapy, 2 because of ADEs (mydriasis, vomiting) and 2 because of lack of efficacy or at the physician's discretion. In phase 2 of the study, which began after the initial 4-week period, the patients were classified as "ATMX responders" or, if substantial symptoms remained, as "partial responders," in accordance with the Clinical Global Impression–Improvement (CGI-I) rating. Patients with a response to ATMX monotherapy (n = 4)

remained on ATMX + placebo, whereas the partial responders ($n = 17$) continued taking ATMX and were randomly assigned to the addition of either OROS MPH ($n = 9$) at a target dose of 1.08 mg/kg daily or placebo ($n = 8$) for an additional 6 weeks. Statistical testing for differences in ADEs between groups was not performed because of low enrolment, but this trial revealed fewer ADEs in the group receiving the combination of ATMX and OROS MPH (6 events) than in the ATMX with placebo group (15 events). Adverse effects reported in the ATMX + OROS MPH group included initial insomnia, rash, GI discomfort, vomiting and toothache, whereas the most common ADEs in the ATMX + placebo group were initial insomnia, nausea, vomiting, headache and rhinitis. Two additional patients discontinued treatment during phase 2 because of ADEs: 1 patient in the ATMX + OROS MPH group experienced a cardiovascular ADE (supraventricular extrasystole) and 1 patient in the ATMX + placebo group experienced irritability that was rated as severe. Changes in blood pressure and heart rate were minimal in the group receiving ATMX + OROS MPH and were not considered clinically meaningful (mean changes: +2.1 mm Hg systolic blood pressure, +3.0 mm Hg diastolic blood pressure, pulse +5 beats/min). At the end of the treatment period, a small but statistically significant difference in weight change was observed: weight increased by 0.84 kg among patients in the ATMX + placebo group but decreased by 0.89 kg in the ATMX + OROS MPH group ($p \leq 0.05$). Although the combination was safe and well tolerated, OROS MPH did not appear to enhance the response to ATMX according to structured parental assessments (ADHD Rating Scale Parent Report Investigator Rated Version, Conners Parent Rating Scale, Weekly Parent Ratings of Evening and Morning Behaviour) and clinical disease-severity ratings for ADHD (Clinical Global Impression). However, this small study was not designed to assess the clinical efficacy of this combination.

The largest study to date evaluating the efficacy of ATMX in combination with OROS MPH involved children exhibiting a partial response to either drug alone.^{10,11} Children were excluded if they had a history of no response to or intolerable ADEs with either medication, if other psychotropic medications had been prescribed or if any other psychiatric or clinically significant chronic medical conditions had been diagnosed. During the first 4 weeks of this open-label study (phase 1), children aged 6 to 17 years (mean 9.3 years; $n = 82$) were treated with ATMX at a mean dose of 1.1 mg/kg

daily. At the end of phase 1, patients were classified as either “responders” or “partial responders” to ATMX according to CGI-I ratings. Fifty patients with a partial response continued ATMX and began an additional 3-week treatment period (phase 2) during which OROS MPH was initiated at 18 mg daily and titrated by 18 mg increments weekly to a mean dose of 1.0 mg/kg daily. ATMX partial responders whose therapy was augmented with OROS MPH had a significant (40%) reduction in ADHD Rating Scale score (21.1 ± 9.9 at start of phase 2, 12.8 ± 9.7 at end of phase 2; $t = 6.5$, $p < 0.0001$) and a significant reduction in the Clinical Global Impression–Severity rating (from markedly or moderately ill at the start of phase 2 to borderline mentally ill or mildly ill at the end of phase 2; $t = 6.5$, $p < 0.0001$). Six of the 8 patients who discontinued combination treatment because of ADEs did so after the first week. Insomnia, GI upset, loss of appetite and mood changes were the ADEs leading to discontinuation.¹¹ Combination treatment resulted in significantly higher rates of insomnia, irritability and loss of appetite, but lower rates of fatigue, relative to ATMX monotherapy. The mean weight loss of 0.8 kg after 3 weeks of combination treatment was significant compared to no change in weight with ATMX alone ($p < 0.005$). ATMX monotherapy was associated with a significant increase in diastolic blood pressure relative to baseline (+2.2 mm Hg, $p = 0.04$) and combination therapy was associated with further increases (+2.8 mm Hg, $p = 0.05$), totalling an overall increase in diastolic blood pressure of about 5 mm Hg. ATMX was also associated with an increase in heart rate (by 8.6 beats/min, $p = 0.0001$); heart rate was unchanged with the addition of OROS MPH. Changes in electrocardiographic

MISE EN PRATIQUE DES CONNAISSANCES

- Les données préliminaires à court terme suggèrent que la thérapie à médicaments combinés est généralement bien tolérée et peut atténuer les symptômes de THADA chez les enfants ayant une réaction inadéquate aux stimulants ou à l'atomoxétine en monothérapie.
- Les pharmaciens doivent surveiller les enfants suivant une thérapie combinée et doivent aviser les patients ou leur fournisseur de soins que des effets indésirables légers et passagers sont communs au cours de la première semaine du traitement.
- Une orientation à un spécialiste des THADA peut être préférable dans de tels cas. Les enfants souffrant d'insomnie importante, de perturbations gastro-intestinales, de perte de poids ou d'effets cardiovasculaires dans le cadre d'un traitement par monothérapie pourraient ne pas constituer des candidats convenables pour la thérapie à médicaments combinés.

intervals reached statistical significance but were not considered clinically meaningful.

Conclusion

To date, only preliminary data support the combination of ATMX and a stimulant as a therapeutic option in children with ADHD. Combination therapy may further improve the symptoms of ADHD in patients with a partial response to either stimulant or ATMX monotherapy. The available evidence for the combination of ATMX and OROS MPH in a controlled setting involves a total of only 59 children treated for a maximum of 6 weeks and 1-year data are available from only one published case report. Improvements in behaviour with combination therapy were noted for a wide range of symptoms at school and at home in several case reports. Additional benefits included improvements in various parental- and investigator-rated assessments of ADHD symptoms, as well as a reduction in disease severity ratings (Clinical Global Impression). Although preliminary data are encouraging, additional studies are needed to establish the benefits of treatment in a larger population and to confirm the safety of this combination over a longer treatment period. Combination therapy appears to be well tolerated; however, children already suffering from significant insomnia, GI disturbances, weight loss or cardiovascular effects may not be suitable candidates for this therapy.

In cases of inadequate response to first-line treatments, the American Academy of Pediatrics recommended, in its 2011 guidelines, that clinicians re-evaluate the diagnosis of ADHD, attempt to improve medication adherence and consider adjusting medication dosages, switching medications and/or changing behavioural therapy.¹ Extended-release guanfacine and extended-release clonidine, which have been approved by the US Food and Drug Administration, are adjuvant therapies that have been briefly mentioned as treatment options for use with stimulants.¹ Neither preparation is currently available in Canada and other combination treatments are

not recommended.^{1,12} A commonly referenced algorithm from the Texas Health Sciences Centre¹³ includes the option of combined treatment with a stimulant and ATMX after there has been a partial or inadequate response to monotherapy trials of 2 stimulants (methylphenidate and amphetamine medications) and ATMX. Clinicians reported using this combination most often when long-acting stimulant formulations did not adequately improve evening behaviour or when ATMX was inadequate for symptom control in the classroom setting.¹³ In its 2008 clinical guidelines, the UK National Institute for Health and Clinical Excellence recommended referral to specialty services before initiation of combination therapy in patients with inadequate response to monotherapy.⁵ The recently updated guidelines of the Canadian ADHD Resource Alliance (CADDRA), published in 2011, suggest that ATMX may be combined with stimulants in cases of inadequate response, preferably under the supervision of an ADHD specialist.²

Back to the scenario

Preliminary evidence and treatment guidelines support a trial of combination ATMX and OROS MPH in this child, who is exhibiting partial symptom response and dose-related ADEs with stimulant monotherapy. Children initiated on combination therapy should be monitored regularly for the emergence of ADEs and should preferably be referred to a specialist. The occurrence of mild ADEs during the first week of combination treatment is common and should be anticipated by clinicians. Patients or their caregivers should be informed that these symptoms are likely transient. ■

From The Ottawa Hospital, General Campus, Ottawa, Ontario. Contact ajacques@toh.on.ca.

Acknowledgements: *The author would like to thank Sangeeta Prasad, BScPharm, of The Ottawa Hospital for her contributions to the literature search and revisions to this article and Mirella Giudice, BScPharm, ACPR, of The Ottawa Hospital for her revisions to this article.*

References

1. American Academy of Pediatrics. ADHD: clinical practice guideline for the diagnosis, evaluation and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics* 2011;128:1-16.
2. CADDRA Canadian ADHD practice guidelines. 3rd ed. Toronto (ON): Canadian Attention Deficit Hyperactivity Disorder Resource Alliance; 2011. Available: www.caddra.ca

(accessed May 6, 2012).

3. Dopheide JA. ASHP therapeutic position statement on the appropriate use of medications in the treatment of attention-deficit/hyperactivity disorder in pediatric patients. *Am J Health Syst Pharm* 2005;62:1502-9.
4. Hanwella R, Senanayake M, de Silva V. Comparative efficacy and acceptability of methylphenidate and atomoxetine in treatment of attention deficit hyperactivity disorder in children

- and adolescents: a meta-analysis. *BMC Psychiatry* 2011;11:176-83.
5. Attention deficit hyperactivity disorder: diagnosis and management of ADHD in children, young people and adults. NICE clinical guideline 72. London (UK): National Institute for Health and Clinical Excellence; 2008. Available: www.nice.org.uk/CG072 (accessed May 6, 2012).
 6. Brown TE. Atomoxetine and stimulants in combination for treatment of attention deficit hyperactivity disorder: four case reports. *J Child Adolesc Psychopharmacol* 2004;14:129-36.
 7. Jaworowski S, Benarroch F, Gross-Tsur V. Concomitant use of atomoxetine and OROS-methylphenidate in a 10-year-old child suffering from attention-deficit/hyperactivity disorder with comorbid bipolar disorder and Tourette syndrome. *J Child Adolesc Psychopharmacol* 2006;16:365-70.
 8. Niederhofer H. Atomoxetine may improve methylphenidates' efficacy in treatment of ADHD? *Psychiatr Danub* 2009;21:330.
 9. Carlson GA, Dunn D, Kelsey D, et al. A pilot study for augmenting atomoxetine with methylphenidate: safety of concomitant therapy in children with attention-deficit/hyperactivity disorder. *Child Adolesc Psychiatry Ment Health* 2007;1:10.
 10. Wilens TE, Hammerness P, Utzinger L, et al. An open study of adjunct OROS-methylphenidate in children and adolescents who are atomoxetine partial responders: I. Effectiveness. *J Child Adolesc Psychopharmacol* 2009;19:485-92.
 11. Hammerness P, Georgiopoulos A, Doyle RL, et al. An open study of adjunct OROS-methylphenidate in children who are atomoxetine partial responders: II. Tolerability and pharmacokinetics. *J Child Adolesc Psychopharmacol* 2009;19:493-9.
 12. Supplemental information: Implementing the key action statements: an algorithm and explanation for process of care for the evaluation, diagnosis, treatment and monitoring of ADHD in children and adolescents. Elk Grove Village (IL): American Academy of Pediatrics; 2011. Available: <http://pediatrics.aappublications.org/content/suppl/2011/10/11/peds.2011-2654.DC1/zpe611117822p.pdf> (accessed May 17, 2012).
 13. Pliszka SR, Crismon ML, Hughes CW, et al.; Texas Consensus Conference Panel on Pharmacotherapy of Childhood Attention Deficit Hyperactivity Disorder. The Texas Children's Medication Algorithm Project: revision of the algorithm for pharmacotherapy of attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 2006;45:642-57.