Taking the stress out of individualizing ADHD drug therapy

Melanie McLeod ACPR Tessa Laubscher MB ChB CCFP FCFP Loren Regier Brent Jensen

Attention deficit hyperactivity disorder (ADHD) is characterized by 3 core symptoms: inattention, hyperactivity, and impulsivity.[1,2] The presence and severity of these symptoms vary and characterize the 3 subtypes of ADHD: predominantly inattentive (10% to 20%), predominantly hyperactive or impulsive (5% to 10%), and combined inattentive and hyperactive (70% to 80%).[3,4] Children with ADHD might experience substantial functional problems, such as academic underachievement, troublesome interpersonal relationships, and low self-esteem.[3,5] Ultimately, the goals of treatment are to substantially reduce the core symptoms, improve behavioural and academic performance, and improve self-esteem and social functioning.

Evidence supports the use of psychostimulant medication, particularly in school-aged children.[6-8] Controlled trials demonstrate that approximately 70% of patients given stimulant medication will have clinically significant decreases in the core symptoms of ADHD.[9-11] The Multimodal Treatment Study of ADHD established that combining pharmacologic and nonpharmacologic therapy (eg, behaviour modification programs) is an effective treatment strategy.[12,13] Stimulant medications and atomoxetine are effective therapies for the core symptoms, while behavioural therapies play an important role in improving social interactions, self-esteem, and the common behaviour seen.[3,9] Overall, the effect size for psychostimulants on ADHD core symptom control is larger compared with nonstimulant therapies, and some patients might respond better to one agent than another.[14-16] Potential benefits must be weighed against concerns such as drug abuse or diversion, side effects, growth retardation, and cardiovascular risk.

Case

Fred is a 9-year-old boy who has been your patient since he was born. Last year, after failing the fourth grade, Fred was diagnosed with ADHD, inattentive subtype. Over the past year, Fred's ADHD symptoms have responded extremely well to methylphenidate (MPH). His dose was titrated to optimize control of his symptoms, and his current dosage is 10 mg, 3 times daily (8 AM, noon, and 4 PM). He receives his morning and late-afternoon doses at home, and his noon dose is administered at school by the school nurse. He is doing much better academically, has developed many good friends, and has had no problems tolerating the medication so far. He has a healthy appetite, is an average weight and height for his age, and sleeps well at night. Fred's parents also believe that the behavioural therapy training workshops they attended have improved their ability to understand Fred's behaviour and provide more structure in his home environment.

Fred will soon be moving to a new school that has a policy that prevents school personnel from administering MPH or other medications. Fred's parents are concerned that Fred will forget to take his noon dose at school. They come to see you at the clinic to discuss the possibility of changing Fred to one of the newer ADHD medications that will work for the whole school day. They also ask if they need to worry about warnings they have read about ADHD medications causing "problems with the heart."

In an effort to enhance the individualized approach to ADHD management, and to ultimately improve tolerability and adherence to therapy, an increasing number of products with novel delivery systems have become available in Canada. **Table 1**[3,9,17,18] lists available products and differentiates them according to whether they are short-acting, intermediate-acting, or long-acting preparations. Generally, all psychostimulants are considered equally efficacious and they do not differ considerably with respect to tolerability.[9] The differences among the psychostimulant delivery systems often guide prescribers' choices. These differences relate to onset of action, duration of effect, cost, convenience of administration, and dosage form (capsules that can be opened vs tablets that must be swallowed whole).

While short-acting agents are less expensive, are more easily titrated, and can be timed to correspond to certain activities (eg, homework in the evening), long-acting medications also offer advantages. Sustained-release MPH and Dexedrine Spansules, although slightly longer acting than immediate-release (IR) formulations, often require multiple daily dosing (therefore administration at school is necessary) and might be combined with IR tablets for faster onset. These regimens tend to be complicated to adhere to and result in the child having to carry medication to schools or care facilities, increasing risk of drug diversion and theft. Once-daily psychostimulant preparations, while more expensive, might improve adherence to therapy and decrease abuse and diversion risk. Once-daily preparations not only obviate the need for doses during the school day, but have

Table 1. Comparison of agents for attention deficit hyperactivity disorder: *For more detailed comparisons, precautions, side effects, monitoring, dosing titrations, etc, see the ADHD Treatment Chart[18] available on-line at CFPlus.*

AGENT OR INTERVENTION	ONSET AND DURATION	DOSING IN PEDIATRICS (AGE ≥ 6 Y; WEIGHT ≤ 40 KG)	PRICE, $*	COMMENTS
Short-acting psychostimulant				
Methylphenidate IR Ritalin, generic • Immediate release	O: 30-60 min D: 3-5 h	Initial: 5 mg morning and noon Typical: 10 mg 3 times daily Maximum: 60 mg/d	15 25	• Small doses available for initial treatment in small children (< 16 kg) • Offers flexibility in dose titration • Less expensive but must be taken 2-3 times during the day • Generic products might have lower street value
Dextroamphetamine IR Dexedrine • Immediate release	O: 30-60 min D: 4-6 h	Initial: 2.5 mg morning and noon Typical: 10 mg 2 times daily Maximum: 30 mg/d	26 82	
Intermediate-acting psychostimulant				
Methylphenidate SR Ritalin SR, generic	O: 60 min D: 4-8 h	Initial: 20 mg every morning Typical: 40 mg every morning Maximum: 60 mg/d	22 35	• Extended duration but often requires multiple daily dosing (eg, addition of midafternoon dose) • Less expensive than long-acting drugs • Erratic release pattern in some
Dextroamphetamine SR Dexedrine Spansules	O: 60 min D: 6-8 h	Initial: 10 mg every morning Typical: 15 mg every morning Maximum: 30 mg/d	34 40	
Long-acting psychostimulant				
Methylphenidate long-acting Concerta (tablet) • 22% immediate and 78% delayed release	O: 30-60 min D: 8-12 h	Initial: 18 mg every morning Typical: 36 mg every morning Maximum: 54 mg/d	80 103	• Equally as effective as short-acting drugs • Once-daily dosing might be an advantage (convenient, no need to give a dose at school providing enhanced confidentiality, less interdose dysphoria or "wear-off" effect) • Nondeformable shell of Concerta tablet might decrease abuse or diversion risk as it is difficult to break, cut, or crush
Methylphenidate long-acting capsule Biphentin (capsule) • 40% immediate and 60% delayed release	O: 30-60 min D: 10-12 h	Initial: 10 mg every morning Typical: 30 mg every morning Maximum: 60 mg/d	31 66	
Amphetamine mixed salts Adderall XR (capsule) • 50% immediate and 50% delayed release	O: 30-60 min D: 8-12 h	Initial: 10 mg every morning Typical: 30 mg every morning Maximum: 30 mg/d	86 123	
Nonstimulant (selective norepinephrine reuptake inhibitor)				
Atomoxetine Strattera	O: NA D: 24 h	Initial: 10 mg every morning or 0.5 mg/kg/d Typical: 25 mg every morning or 1.2 mg/kg/d Maximum: 60 mg/d or 1.4 mg/kg/d	150 150	• Option if no response to stimulants or there is abuse risk or stimulant side effect concerns (eg, mood changes, tics) • Relatively expensive, slow onset (6-12 wk); causes suicidal thoughts in rare cases
Other drug options (off label)				
Bupropion, clonidine, TCAs (desipramine, imipramine, nortriptyline), risperidone, modafinil	NA	NA	NA	NA
Nondrug intervention options				
Behavioural therapy, environmental interventions (eg, more regular or structured schedule)	NA	NA	NA	NA

D—duration, IR—immediate release, NA—not applicable, O—onset, SR—sustained release, TCA—tricyclic antidepressant, XR—extended release.

Data from Virani,[3] McDonagh et al,[9] Virani et al,[17] and Lee et al.[18]

*Reflects initial and typical approximate cost per 30 days in Saskatchewan; includes markup and dispensing fee; price for generic product used where available. Provincial formulary coverage might vary.

also been shown to be as effective as MPH administered 3 times daily[12] and are less likely to be abused owing to barriers within their formulations. Physicians might also want to consider using treatment agreements* as part of the patient education process to decrease abuse and diversion risk. The RxFiles ADHD newsletter, available on CFPlus,* offers other strategies to reduce stimulant abuse and diversion risk. Once-daily administration allows for a 10- to 12-hour duration of effect, which essentially provides therapeutic drug levels throughout the entire school day and into the early evening. This is important for after-school peer and parent interactions and also for completing homework tasks. Additionally, long-acting stimulants might result in less rebound hyperactivity.

For the purposes of promoting adherence to therapy and maintaining his therapeutic gain, it is reasonable to consider converting Fred's current regimen of thrice daily MPH IR to a once-daily preparation, although this might have cost implications. As he has responded adequately to MPH without side effects, it is reasonable to convert him to a once-daily MPH preparation or alternate psychostimulant (eg, extended-release Adderall). The dosage conversion from an IR product to a long-acting preparation or another dosage form of the same drug is not necessarily 1 to 1.[9,10] For example, Fred's 10-mg dose of MPH 3 times daily might be converted to a 27-mg or 36-mg dose of Concerta once daily.

Box 1. Individualizing therapy

What if ...

1) early-morning symptoms are not well controlled?
   - Add 1 dose of immediate-release methylphenidate at breakfast or switch to a long-acting agent with a higher ratio of immediate release (such as Biphentin or Adderall XR)

2) the patient develops reduced appetite or weight loss?
   - Give drug with meals; give high-calorie meals when stimulant effects are low (eg, breakfast, bedtime)
   - Engage child in meal selection and preparation
   - Consider nonstimulant treatment (eg, atomoxetine)

3) the patient has swallowing problems?
   - Adderall XR, Biphentin, and Dexedrine Spansules can be opened up and sprinkled onto food

4) the patient also develops comorbid aggression?
   - Reduce or discontinue stimulant; consider behavioural therapy; possibly consider atypical antipsychotics or clonidine

5) there is concern about growth retardation?
   - There is some evidence that growth might be attenuated in a subgroup of patients (eg, height and weight: 2 cm and 2.7 kg less than nonmedicated group after 3 y)[20]
   - Monitor height and weight 1-2 times/y; use the lowest effective dose; consider drug holidays during summers and school breaks; consider nonstimulant medications

XR—extended release.

Data from the Canadian Attention Deficit Hyperactivity Disorder Resource Alliance,[10] Lee et al,[21] and Swanson et al[22]

Alternatively, he could be switched to Biphentin, 20 or 30 mg daily.

Some individuals respond to or tolerate one formulation of stimulant differently than another. Furthermore, dosage conversions are only approximations and need to be individualized. It is essential to closely monitor patients for both effectiveness of the drug and any adverse effects. Therefore, during the dose-titration process it is useful to have information about Fred's progress from multiple sources, including his teachers. Regular documentation (every few months) of ADHD symptoms and impairment should be made through the appropriate use of rating scales, such as SNAP-IV (Swanson, Nolan and Pelham Teacher and Parent Rating Scale)[19] and CGI (Clinical Global Impression scale),[20] and also based on academic performance. The Canadian Attention Deficit Hyperactivity Disorder Resource Alliance website (**www.caddra.ca**) contains links to scales and other useful monitoring tools. Management of side effects will depend on their severity. Mild appetite suppression and insomnia are usually expected and tolerable. Moderate to severe side effects warrant reduction of the dose, discontinuation of the medication, introduction of a different formulation, or use of adjunctive treatments. **Box 1**[10,21,22] offers ideas on individualizing therapy. The RxFiles newsletter* provides a more comprehensive list of comorbidities and side effects and further information on their management.

Some patients might require a small dose of additional MPH IR in the late afternoon or early evening to control evening symptoms for activities such as school events, homework, and family functions.[9] Alternatively, the 22% of drug released immediately from Concerta might not be sufficient to manage morning symptoms in some patients. In such instances, morning supplementation with MPH IR or a change to another long-acting formulation with a higher percentage of drug released immediately (eg, 40% with Biphentin or 50% with extended-release Adderall) might be beneficial.

Concerns have been raised regarding use of psychostimulants and the possible, rare association with cardiac events and sudden death.[23,24] There is inadequate evidence to establish a causal relationship; however, patients with known cardiac structural or rhythm abnormalities or signs and symptoms suggestive of cardiac disease should not be prescribed these drugs.[25] Whether a routine electrocardiogram (ECG) is necessary has been open to debate.[25,26] An ECG increases the likelihood of identifying serious cardiac conditions, especially if there

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*A sample patient agreement for psychostimulant therapy, the "Attention-Deficit Hyperactivity Disorder (ADHD) Drug Therapy. Evidence, Clinical Issues & Comparisons" newsletter, and the ADHD treatment chart are available at **www.cfp.ca**. Go to the full text of the article on-line, then click on **CFPlus** in the menu at the top right of the page.

are suspicions of high-risk conditions; ECGs should be read by physicians with expertise in reading pediatric ECGs. Pediatric cardiology should be consulted if there are serious cardiac findings, abnormal ECG results, or family history of sudden cardiac death in relatives younger than 35 years of age.[25]

In some patients, a "drug holiday" might be considered during school breaks or summer holidays to assess the level of ADHD symptoms while not taking therapy and reassess the clinical need for medication. Decisions regarding drug holidays must be made on a case-by-case basis. In addition, the patient, parents, and physician should review the goals of therapy every 2 years.

Conclusion

This case illustrates that psychostimulants administered once daily in a long-acting formulation can offer some advantages, particularly in school-aged children. However, as with all medication, adherence to ADHD medication regimens can decrease over time. It is essential, therefore, that strategies are employed to improve adherence. Other strategies that have been effective for improving adherence included the following[14]:

- Educate patients and parents about anticipated results, benefits, and possible adverse effects.
- Provide frequent follow-up early in treatment, especially during dose titration.
- Strive for dose optimization.
- Identify and treat comorbid conditions.

Ms McLeod is a pharmacist currently enrolled in the Doctor of Pharmacy Program at the University of Toronto in Ontario. **Dr Laubscher** is an Assistant Professor of Academic Family Medicine at the University of Saskatchewan in Saskatoon. **Mr Regier** is Program Coordinator of the RxFiles Academic Detailing Program for Saskatoon Health Region. **Mr Jensen** is a pharmacist for the RxFiles Academic Detailing Program.

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Correspondence

Mr Regier, Saskatoon Health Region, RxFiles Academic Detailing, c/o Saskatoon City Hospital, 701 Queen St, Saskatoon, SK S7K 0M7; telephone 306 655-8505; fax 306 655-7980; e-mail **regierl@rxfiles.ca**; website **www.RxFiles.ca**

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