

PSYCHOPHARMACOLOGY

A Review of Long-Acting Medications for ADHD in Canada

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Abstract:

Objective: To review and comment on the long-acting medications presently marketed in Canada for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in terms of design, composition, mode of action and efficacy including other long-acting products that are not yet available in Canada. **Method:** A literature review was conducted using MEDLINE, PsycInfo, CINAHL, and PubMed with additional information gathered from other sources. **Results:** The American Academy of Pediatrics (AAP), the American Academy of Child and Adolescent Psychiatry (AACAP) and the Canadian Attention Deficit Hyperactivity Disorder Resource Alliance (CADDRA) while endorsing the stimulants as first line medications to treat ADHD also recommended the use of long-acting once-a-day medication for better efficacy, convenience and adherence. Most studies rated the controlled release and the immediate release medications as similar in efficacy. However, long-acting medication was shown to be superior in terms of remission rates. **Conclusion:** When a child is receiving a long-acting medication for treatment of ADHD, he may feel less stigmatized, is more likely to be adherent and achieve remission. A child in remission can benefit from other treatment modalities thus improving long-term prognosis.

Key words: Attention Deficit Hyperactivity Disorder, long-acting, stimulants, methylphenidate, amphetamine

Introduction

In the treatment of ADHD, studies (The MTA Cooperative Group, 1999, Conner, 2002) have demonstrated superior efficacy for stimulants over other modalities including behavioral and psychosocial treatments. In its 2001 guidelines (American Academy of Pediatrics, 2001) the American Academy of Pediatrics recommended stimulant medications as first line treatment of ADHD again due to their demonstrated efficacy in treating this condition. In its 2002 clinical practice guidelines the American Academy of Child and Adolescent Psychiatry referred to methylphenidate (MPH) and amphetamines (AMP) for use as first-line stimulants (AACAP Official Action, 2002). There were increasing concerns with the immediate release stimulant preparations. Adherence was becoming an issue due to the need for administration of multiple doses per day. This created a lack of privacy and some children are unwilling to take medication at school, thus missing doses. There were also concerns about the peaks and troughs of stimulant blood levels occurring at the most unstructured times of the day when symptom control is most needed. Implications of these variations in blood levels over the long term as well as the occurrence of the rebound or relapse phenomenon in the evening have raised concerns. Clinicians had to constantly adjust doses to help children function optimally throughout the entire day including evenings, for homework or other activities. In its 2006 Canadian ADHD practice guidelines CADDRA refers to the long-acting, once-a-day preparations as First Line Agents while designating the immediate-release (IR) and intermediate-acting (IA) stimulants as Second Line or Adjunctive agents (Canadian Attention Deficit Hyperactivity Disorder Resource Alliance, 2006). This designation led the phar-

maceutical industry to focus on developing more long-acting, once-a-day preparations. Four of these are now in use in Canada and other formulations are currently available in other countries. It is important for clinicians treating children diagnosed with ADHD to become familiar with the different aspects of these long-acting, controlled release medications before newer agents arrive on the market. This review, based mainly on medications marketed in Canada was done with this goal in mind.

Methodology

A literature review of published papers on ADHD long acting and short acting medication was conducted using MEDLINE, PsycInfo, CINAHL, and PubMed. Additional information was gathered from other sources such as product monographs, scientific meeting proceedings, presentation material and provincial health care programs. All information was systematically reviewed and relevant clinical information was extracted to provide a clinical summary.

Long acting preparations:

The pharmaceutical industry has focused mostly on finding an adequate system to deliver the same two stimulants (MPH or AMP) in a more prolonged fashion. The reason for this lies in the fact that most studies have consistently shown a greater effect size for the stimulants compared with other drugs when treating ADHD (Faraone et al., 2003). The challenge has been to find a system that will deliver these drugs in adequate amounts to provide a fairly rapid onset of action followed by a prolonged duration of action covering the entire day. Several delivery systems exist, and are sometimes referred to as the Pulse, the Pump, the Prodrug and the Patch. The

Pulse and the Pump are presently available in Canada including a double-pulse Canadian designed multilayer-release bead formulation. The Prodrug is likely to be marketed in Canada fairly soon. There is no news on whether the Patch will be available in a near future.

The Pump (Concerta[®], OROS-MPH):

Concerta[®] (manufactured by Janssen-Ortho) uses an osmotic pump system known as the "Osmotic-Release Oral System" (OROS). The tablet consists of a hard oblong shell which does not dissolve in the stomach and is excreted intact in the feces. It has both a immediate release as well as a controlled release component with a duration of action around 12 hours. In order to achieve this release pattern, 22% of the MPH dose is coated on the outside of the shell for immediate release. The remaining 78% is divided into two compartments inside the shell with second compartment containing a higher dose of MPH. A third compartment contains a polymer which expands in the presence of water. The ingredients in each compartment are gradually released in a controlled and timed fashion throughout the day. Water absorbed from the gastrointestinal tract by osmosis through a tiny laser-drilled hole in the tablet expands the polymer which slowly pushes the active ingredient out. By having each release of MPH greater than the previous one an ascending gradient is created to avoid the possibility of acute tolerance (tachyphylaxis) (Swanson et al., 1999). In terms of starting and adjusting doses the weight-adjusted titration method (such as 0.3 – 0.8mg/kg/day for MPH-IR or half of this for DEX-IR) commonly used with the older tablets which could be easily cut is no longer practical given the design of the long-acting medications. More convenient in office practice is the fixed-dose (whole pill) method with a recommended starting dose and a maximum (or optimal) daily dose for the various age groups. The recommended starting dose of OROS-MPH is 18mg once daily in the morning with a dose titration schedule increasing by 9mg every 7 days until a daily maximum of 54mg daily for both children and adolescents (Janssen-Ortho Inc., 2004).

In terms of efficacy, studies comparing OROS-MPH versus IR-MPH t.i.d. versus placebo found significant but similar improvements with both stimulant formulations and both were superior to placebo. In one study of 68 children, aged 6-12 years, a double blind comparison of placebo, IR-MPH t.i.d. and OROS-MPH performed both in laboratory and natural settings reported that on virtually all measures (parent and teacher SNAP and IOWA Conners ratings) and in all settings the two drugs were not different from each other (Pelham et al., 2001). Another large multi-centre randomized clinical trial (RCT) of 282 children, aged 6-12 years, randomized to placebo, IR-MPH and OROS-MPH in a double blind 28 day trial, reported that the children in the OROS-MPH and IR-MPH t.i.d groups showed greater reductions in core ADHD

symptoms than did the children on placebo. OROS-MPH and IR-MPH did not differ significantly on any direct comparison on the basis of the mean teacher and parent IOWA Conners ratings (Wolraich et al., 2001). However, when the emphasis was placed on achieving remission an 8 week randomized controlled Canadian study, with a strict definition of complete remission, indicated that subjects receiving OROS-MPH displayed twice the rate of complete remission compared to subjects receiving IR-MPH i.e. at four weeks (36% versus 14%) and at end point (44% versus 16%) (Steele et al., 2006). The duration of action well into the evening was demonstrated in a study of the driving performance of adolescents which showed that a decrease in impairment from baseline was maintained until 11pm with OROS-MPH. (Cox et al., 2004). The 12 hour duration of action has also been demonstrated in laboratory classroom settings (Pelham et al., 2001).

Discussion:

OROS-MPH does work as a long-acting agent but the relatively slow onset of action can be a drawback in some cases. In order to create an ascending profile, OROS-MPH uses a smaller dose (22%) of the MPH as an IR bolus. Thus a child receiving 36mg per day only gets approximately 8 mg in the early morning which may not be adequate for children whose mornings are disorganized and chaotic. When faced with this issue clinicians have often augmented with an IR-MPH in the morning (CADDRA, 2006, Banaschewski et al., 2006). This could defeat the whole purpose of the product design which is based on achieving an ascending release profile to avoid acute tolerance (Swanson et al., 1999). Instead the strategy recommended is an increase in the dose of the OROS-MPH (Swanson & Hechtman, 2005, Canadian Attention Deficit Hyperactivity Disorder Resource Alliance, 2006). Underdosing may be an issue when children are not responding to OROS-MPH. Success rates and achievements of remission are higher when adequate doses are used. In one study remission rates were reported to be between 40% to 60% on 36mg-54mg per day of OROS-MPH and only 25-32% on 18mg per day (Stein et al., 2003). Another study of adolescents aged 13-18 years reported that 37% were taking 72mg per day compared to 28% taking either 36mg or 54mg per day (Spencer & Greenhill, 2003). The maximum amount per day is important for optimal response but can also be a source of confusion. For example, the CADDRA Board (Canadian Attention Deficit Hyperactivity Disorder Resource Alliance, 2008) quotes higher maximum daily values than the product monograph. For a child weighing up to 40 kg the product monograph mentions 54mg per day maximum while CADDRA Board recommends 72mg per day. Similarly for adolescents (up to 40kg-70kg) the product monograph sets the maximum per day at 54mg versus CADDRA's recommendation of 81mg. Therefore titration for different age groups and weights may be confusing. It may be useful to

refer to the first edition of the Canadian ADHD practice guidelines where the optimal doses for children are quoted by assuming an equivalency as close to 0.5mg/kg/dose MPH t.i.d. and 0.3 mg/kg/dose MPH t.i.d. for adolescents due to a lower metabolism and kidney excretion as compared to children (Canadian Attention Deficit Hyperactivity Disorder Resource Alliance, 2006). Regular follow-ups are necessary to ensure optimal response as dosages often have to be adjusted over time. It has been argued that there has been little evidence of the development of tolerance to the behavioral effects of MPH or a need to increase the dose to maintain the same response (Safer & Allen, 1989). However, an open label study of 407 children, aged 6 to 13 years, showed that although effectiveness of OROS-MPH was maintained over 12 months the number of children whose dose increased to 54 mg per day from 36mg jumped from 24.1 % to 45% over the same period (Wilens et al., 2003). This is consistent with a previous suggestion that an upward dose adjustment is required over time (Satterfield et al., 1979). The fact that OROS-MPH only comes in four different sizes can be problematic in office practice when adjusting doses as combining different sizes can be costly. A dose of 45 mg requires a 36 mg plus an 18 mg tablet. Similarly a 72 mg dose requires a combination of either 36mg + 36mg or 54mg + 18 mg which may be too expensive for some patients. While the hard oblong outer shell may be a problem for younger children with swallowing difficulties, the formulation presents less risk of abuse especially in adolescents as it is very difficult to get the active ingredient out of the tablet for sniffing or snorting.

The Multi-Layer Release (Biphentin[®], MLR-MPH):

Biphentin[®] (marketed by Purdue Pharma) is a product of Canadian Research and Development. It consists of a multilayer-release (MLR) bead formulation. The active ingredients are arranged in concentric layers in equal amounts in each bead for a biphasic release. 40% of the total MPH dose is situated in the outermost bead layer for immediate release while the other 60% sits in the innermost bead layer for delayed release. The two active layers are separated by a delayed release and a controlled release coating. MLR-MPH is available in 8 strengths: 10, 15, 20, 30, 40, 50, 60, and 80 mg capsules. It is administered as a single morning dose starting at 10 mg per day (or up to 0.3 mg/kg/ according to weight) with weekly increments of 10 mg/day up to a maximum of 60mg/day (or up to 1 mg/kg/day) (Purdue Pharma, 2007). The maximum is 60 mg/day for a 40 kg child and 80 mg/day for an up to 40-70kg adolescent (Canadian Attention Deficit Hyperactivity Disorder Resource Alliance, 2008).

MLR-MPH provides an initial rapid release of MPH (40%) followed by a delayed more prolonged release creating a biphasic concentration-time profile. It is rapidly and extensively absorbed with peak blood levels reached

in 1 to 3 hours. In children the initial peak concentration occurred at 2.6 hours compared to 2.1 hours for IR-MPH at equivalent doses (Purdue Pharma, 2007). It has a relatively rapid onset of action with symptom improvement occurring within 1 hour (Schachar et al., 2008) and duration of action of about 12 hours. The effectiveness goes beyond the end of the school day into the early evening (Weiss et al., 2007). One study comparing MLR-MPH with IR-MPH showed that MLR-MPH was similarly bioavailable compared to an equivalent dose of the IR-MPH given twice daily. A rapid initial increase in plasma concentration occurred in the first 2 hours after ingestion similar to that with IR-MPH but high plasma concentrations of MPH were still evident at approximately 10-12 hours (Quinn et al., 2007). Another two-way crossover study in healthy young adults, ages 18- 25 years, comparing concentration / time profiles reported that a higher proportion of administered MPH was delivered in the first 4 hours by the MLR-MPH. There was a significant difference in the mean plasma profiles during the first 4 hours after administration with higher levels for MLR-MPH compared to the closest marketed dose of OROS-MPH but comparable blood levels were reported at the end of the day (Reiz et al., 2008). In terms of efficacy, one study of 79 children, ages 6.4 to 17.5 years, reported significant but equivalent improvements on both twice-daily IR-MPH and MLR-MPH on the primary outcome measures as rated on all four subscales of Conners' Parent and Teacher Rating Scales (CPRS and CTRS). The teachers reported the same level of improvement on the clinical global impression-improvement (CGI-I) scale on both MLR-MPH and IR-MPH at equivalent doses (Weiss et al., 2007). Equivalent improvements in behavioral and cognitive measures have also been reported on MLR-MPH given once daily and IR-MPH given twice-a-day (Schachar et al., 2008). These studies showed that MLR-MPH has comparable efficacy as IR-MPH with the exception that it has a longer duration of action and can cover the entire school day well into the early evening without the peaks and troughs.

Discussion:

MLR-MPH offers an alternative to OROS-MPH when initiating treatment with a long-acting formulation of MPH. At present, there are no markers to indicate which formulation is preferable. However if cost is an issue, MLR-MPH is less expensive than comparable doses of OROS-MPH. Both medications have shown good efficacy in different studies when compared to equivalent doses of IR-MPH. There has not been a head to head study comparing effect sizes with other long-acting formulations and MLR-MPH is only available in Canada. Extrapolating and comparing effect sizes from studies with different methodologies may not be accurate. MLR-MPH has 40% of the methylphenidate for immediate release compared to 22% with OROS-MPH. Since greater control of ADHD behaviors have been documented with formulations that

have significantly higher plasma MPH concentrations (Reiz et al., 2008). MLR-MPH may be favored when morning coverage is needed. OROS-MPH is often preferred when symptom control for evening activities is important although both MLR-MPH and OROS-MPH have demonstrated similar plasma concentrations in the evenings. MLR-MPH may be easier to titrate with eight strengths presently available for dose optimization compared to the four strengths of the OROS-MPH formulation. The capsule can be opened and sprinkled on soft foods such as apple sauce, yogurt or ice cream.

The Pulse: (Adderall-XR®, MAS-XR):

Adderall XR (marketed by Shire) is a beaded double-pulse type formulation designed to produce a bimodal release of a mixture of amphetamine salts similar to the release of two equal doses of short-acting d-amphetamine given 4 hours apart. MAS-XR comes as a capsule containing 50% uncoated immediate release beads and 50% enteric-coated controlled release beads. Each bead contains 76% of the d-isomer and 24% of the l-isomer in a ratio of 3:1 as a mixture of 4 salts: d-amphetamine saccharate, d, l-amphetamine aspartate, d-amphetamine sulphate and d, l-amphetamine sulfate in equal amounts (McKeage & Scott, 2003). The combination of different amphetamine enantiomers and salts results in increased and prolonged dopamine release in the striatum with the d-isomer activity 3-4 times more potent than the l-isomer (Joyce & Glaser, 2007). MAS-XR is designed to last throughout the entire day with a single morning dose. It comes in 6 dosage strengths: 5, 10, 15, 20, 25 and 30mg. The starting dose is 10 mg once daily with 30mg once daily being the maximum dose recommended for children up to 40 kg and 50mg once daily for adolescents between 40-70 kg (Canadian Attention Deficit Hyperactivity Disorder Resource Alliance, 2008). The capsule can be swallowed whole or it can be opened and the beads sprinkled on apple sauce or other soft foods.

The efficacy, safety and extended duration of action of MAS-XR have been established in several studies. A multi-centre (47 sites) randomized, double-blind, parallel-group, placebo-controlled study of 563 children, ages 6–12 years, reported significant dose-related improvements in morning, afternoon and late afternoon behaviors on all measures of efficacy as rated on the Conners Global Index Scale for Teachers (CGIS-T), Conners Global Index Scale for Parents (CGIS-P) and The Clinical Global Impressions Scale for Improvement (CGI-I) (Biederman et al., 2002). Rapid improvements in behavior and cognition were seen by 1.5 hours post dose and sustained for up to 12 hours. Although a strong response was seen within the first week, increasing the dose by 10mg/day at weekly intervals to a maximum of 30mg per day resulted in further improvements on the CGIS-T scores (55% improvement on 10 mg, 60% improvement on 20 mg and 68% improvement on 30mg). In another randomized,

double-blind analog classroom assessment of 51 children on 7 consecutive Saturdays, blind ratings of attention, behavior and performance on a math test were obtained every 1.5 hours over a 12 hour period. Dose-dependent improvement were seen on all measures after 1.5 hours but only the 20mg and 30mg daily doses showed continued activity at 10.5 and 12 hours for classroom behavior and math test performance (Newcorn et al., 2009).

Discussion:

MAS-XR is a long-acting once-a-day stimulant with a strong early response by 1.5 hours and duration of action well into the evening (12 hours). Improvements are dose-dependent with both greater efficacy and duration of effects seen at higher doses (Greevich, 2001). Adequate doses are required for optimal responses; up to 30mg per day in children and up to 60mg per day in adults. It is reported to have an acceptable side-effect profile which does not appear to be dose-dependent, except for anorexia and in one study ECG and vital signs changes were not deemed clinically significant during treatment (Goodman et al., 2005). However, cardiovascular side effects have been and continue to be a concern with the use of stimulants including MAS-XR, especially after the latter's sudden removal from the market by Health Canada on February 9th, 2005. This decision was taken due to concerns over 20 cases of sudden death (14 children, 6 adults) in patients taking both Adderall-IR and MAS-XR, although none of those deaths occurred in Canada. With the implementation of labeling changes, previously proposed by Shire, MAS-XR was reinstated on August 26th, 2005. Health Canada concluded that there was insufficient evidence to support the belief of an increased risk of sudden cardiac death or stroke with MAS-XR compared to other ADHD treatments.

Atomoxetine (Strattera®, ATMX):

Strattera® (marketed by Eli Lilly) is a non-stimulant medication for the treatment of ADHD. It is a highly selective and potent inhibitor of the presynaptic norepinephrine transporter with minimal affinity for dopamine and serotonin transporters or other noradrenergic receptors (Eli Lilly Canada Inc., 2009). ATMX causes dose dependent increases in the extra-cellular concentrations of both norepinephrine and dopamine in the prefrontal cortex by local inhibition of the norepinephrine transporter (Bymaster et al., 2003). Administered once daily in the morning it provides continuous symptom relief that lasts not only into the evening but also into the morning hours. ATMX is metabolized by the cytochrome P450 2D6 (CYP 2D6) enzymatic pathway and care should be taken when combining it with another medication that inhibits CYP 2D6 such as fluoxetine or paroxetine. Such drug interaction could result in a 6-8 fold increase in the plasma level of ATMX and may increase side effects requiring dosage adjustment. A gradual titration every 10 days to reach the

effective dose is recommended in 3 steps starting at 0.5mg/kg/day increasing to 0.8mg/kg/day and finally to 1.2mg/kg/day (rounding up to the nearest capsule size). The manufacturer recommends that total daily dose of ATMX should not exceed 1.4mg/kg/day or 100 mg whichever is less. In Canada ATMX is available as 10mg, 18mg, 25mg, 40mg and 60mg capsules. The capsules are not intended to be opened and should be taken whole with or without food.

The efficacy of ATMX was demonstrated in a randomized, placebo controlled, dose response study of 297 children, ages 8-18 years, on 3 doses 0.5, 1.2 and 1.8mg/kg/day (Michelson et al., 2001). Significant improvements versus placebo were reported for both the inattentive and hyperactive/impulsive subtypes on the primary outcome measure, the Attention Deficit/Hyperactivity Disorder Rating Scale (ADHD RS). The findings also indicated improvement in the quality-of-life measures of social and family functioning. ATMX exhibited a graded dose response where 0.5 mg/kg/day was associated with only an intermediate efficacy and both 1.2mg/day and 1.8mg/kg/day demonstrated superior outcomes although there was no difference between the latter two. 1.2 mg/kg/day was as effective as 1.8mg/kg/day and it seemed to be an appropriate initial target for most children. Another study of 297 children, ages 8-18 years, reported that youths with ADHD and comorbid Oppositional Defiant Disorder (ODD) showed statistically significant improvement in both ADHD and ODD symptoms at 1.8mg/kg but not at 1.2mg/kg in contrast to youths without ODD who showed improvement at 1.2mg/kg per day and no incremental benefit at 1.8mg/kg/day (Newcorn et al., 2005). In another study of 171 children treated with ATMX the outcomes were reported to be superior to placebo as assessed by investigator, parent and teacher ratings with a treatment effect size of 0.71 (Michelson et al., 2002). This study also indicated that the therapeutic benefit of a single morning dose was sustained well into the evening. A prospective multi-centre study of 228 children randomized to open label ATMX or MPH for 10 weeks at 23 sites in the US and Canada showed that ATMX was associated with therapeutic effects comparable to methylphenidate on the primary measure of symptom response, the investigator rated ADHD RS (Kratovich et al., 2002).

Discussion:

Several studies have demonstrated that ATMX is an effective and safe medication to treat ADHD. As a non-stimulant it provides an alternate long acting medication for those children who cannot tolerate the side effects of a stimulant or for those whose parents want to avoid the use of a stimulant. However, with reported effect sizes between 0.6 and slightly over 0.7 it ranks behind the stimulants with effect sizes around 0.9 to 1 (Faraone et al., 2004). One meta-analysis rated ATMX effect size as 0.62

versus 0.91 for IR stimulants and 0.95 for controlled release stimulants (Faraone et al., 2003). A comparison of MAS-XR and ATMX indicated that MAS-XR had a larger effect on the hyperactivity rating scale (Wigal et al., 2005). A recent meta-analysis of 6 US Randomized Controlled Trials of 618 children, aged 6-18 years, showed a bimodal response for ATMX with 47 % of patients rated as very much improved, 40% did not respond and 13% responded only minimally (Newcorn et al., 2009). There is also a lag period of 6-10 weeks before full effectiveness is observed and this can make it a long and costly waiting period if it turned out to be ineffective. There is no consistent way of predicting whether a patient will respond to ATMX. Some clinicians prefer to use ATMX when anxiety is prominent or a mood disorder is also present. It has been augmented with low cost IR stimulants for a better response or added to stimulants to extend the duration of symptom relief, to decrease intolerable side effects, and to alleviate certain impairing symptoms which may not be possible with either medication alone (Brown, 2004). The lack of dopamine effect on the striatum gives it an advantage for use in the presence of tics or a co-morbid Tourette's disorder. Similarly, due to the lack of dopamine effect on the nucleus accumbens, it has little potential for abuse or diversion and can be a good choice for adolescents at risk to abuse substances. ATMX can be discontinued without tapering the dose since there is no acute discontinuation syndrome. Because of post-marketing reports of rare but severe liver injury, monitoring is advised for any signs or symptoms of liver dysfunction (e.g. pruritus, dark urine, jaundice or unexplained flu-like symptoms, etc.). Routine laboratory tests are not required but testing for liver enzyme levels is strongly advised upon the first symptom or sign of liver dysfunction. Rigorous clinical monitoring for suicidal ideation or other indicators of potential for suicidal behavior is also advised for patients of all ages since an increased risk over placebo was identified for suicide-related events in a pooled analysis of 1357 children, ages 7-12 years. Five children (0.37%) reported suicidal ideation in addition to 1 suicide attempt compared to 851 children on placebo. No such events were reported in older adolescents (Eli Lilly Canada Inc., 2009).

The Prodrug: Lisdexamfetamine dimesylate (Vyvanse® , LDX):

Vyvanse® (marketed by Shire) is due to be launched in Canada soon. Health Canada issued a Notice of Compliance on February 19th, 2009 for use of LDX for children aged 6-12 years. LDX is a Prodrug which means that the active drug (d-amphetamine) is bound to an amino acid (lysine) to render it therapeutically inactive until it is released in the gastrointestinal tract upon cleavage of the lysine portion of the molecule. As it is activated only after oral ingestion it has a much lower potential for abuse. LDX is available in many dosage strengths in the US, but Health Canada has only approved the 30 mg and

50 mg capsules. The initial starting dose is 30 mg daily in the morning and at present the maximum recommended dose is 50 mg daily. It can be taken with or without food and can be taken whole, dissolved in water or sprinkled on ice cream, applesauce or yogurt prior to administration in children with swallowing difficulties.

The efficacy of LDX has been reported in a phase 3 randomized, placebo-controlled two way crossover study in a laboratory school where the children were monitored and scored throughout the entire day. The Swanson, Kotkin, Agler, M-Flynn and Pelham Department (SKAMP-D), a teacher(or observer) rating scale designed mostly to measure children's classroom behaviors, showed a clinically relevant effect size at 1.5 hours with a large effect size up to 10 hours and continuing benefits at 13 hours. The effect size for SKAMP-A, which measures attention was greater than that of the SKAMP-D by 0.42. The scores on the Permanent product Measure of Performance attention (PERMP), a math test of 400 questions, were still high (staying above 1) for attention at 13 hours (Medical Frontiers International, 2009).

Discussion:

LDX was created with the intention of a longer lasting and more difficult to abuse version of d-amphetamine. The fact that it requires conversion in the stomach to the active component increases its duration of action and renders it ineffective by any other administration route than oral. Unlike Adderall XR which contains about 75% d-amphetamine and 25% l-amphetamine, it contains 100% d-amphetamine which could have a better effect on hyperactivity and impulsivity and less effect on anxiety which tends to be more associated with l-amphetamine. As with all amphetamines the main side effects to watch for remain anorexia and insomnia but irritability and mood lability may also be a problem.

The Patch: (Methylphenidate Transdermal System, Daytrana®):

The patch (marketed by Shire) is a transdermal delivery system which contains methylphenidate as a thin film on an adhesive backing. The patch sticks to the skin where the methylphenidate is slowly and steadily absorbed. It delivers the medication directly into the bloodstream through the skin and it is usually placed on the hip area. It should be worn for at least 9 hours. It has an onset of action of about 2 hours and duration of action of about 12 hours which continues for at least 2-3 hours after it is removed. It comes as a 10mg, 15 mg, 20mg, 30mg patch, with a starting dose of 10 mg and a maximum daily dose of 30 mg.

Discussion:

The duration of action of the patch is proportional to the amount of time it is worn and the size of the patch varies according to dosages. Unlike a pill which once

ingested becomes invisible, restless and fidgety children can play with or remove the patch any time thus varying the exposure. Many ADHD children have sensory integration dysfunctions and may not be able to tolerate something sticking to their skin. Others could have skin reactions if it is worn daily for too long and thus has to be worn on alternate hips. Although it is meant to be waterproof it can come off during showers, baths or swimming and a new patch has to be applied. Nonetheless it provides an alternate delivery system for those who cannot use the oral route. The patch is not presently available in Canada although Shire has filed an application with Health Canada since November 2007.

Discussion

The short-acting stimulants used for the treatment of ADHD have a proven track record in terms of efficacy. As such they are still being advocated as first line treatments by most provincial health systems in Canada which are hesitant to pay for the newer long-acting medications. As long as governments insist on trials of both short-acting MPH and d-amphetamine and provision of justifications before even considering a long-acting agent, current CADDRA guidelines cannot be widely implemented. At present only families that can afford the cost or who have private health insurance can take advantage of the long-acting medications. With awareness of their patient's financial situation and the cost of long-acting medications, clinicians are complying with provincial guidelines and immediate-release stimulants are still widely prescribed. There has been no outcry as many studies have demonstrated that IR-MPH when given 2-3 times per day has similar efficacy ratings as long-acting MPH at comparable doses (Weiss et al., 2007). However, when these medications are used in real life situations and not under the ideal conditions of a controlled study, concerns are being raised over the consequences of non-adherence, quality of life and poor long term outcomes. The MTA study raised some concerns as only 56% of patients responded to IR-MPH and 32% of patients did not reach remission even with combined medication and behavioral treatment (The MTA Cooperative Group, 1999). The initial positive medication effects was further lost upon long-term follow-ups. The 8 year follow-up mentioned that 62% of the MTA children taking medication at 14 months (post-treatment) had stopped despite the advances in long-acting medications (Molina et al., 2009). The MTA group study used a multiple dosage regimen of IR-MPH and adherence issues with a multiple dosage regimen remain a concern especially for long term usage. Even if a child's key symptoms are under adequate control on such regimen, he may not actually reach remission in a natural real-life setting in order to benefit further from other treatment modalities. The new goal of treatment focuses more on remission versus response (effectiveness versus efficacy). Studies looking at this issue are being designed to

address how medications behave in real life settings. A systematic review of remission rates in clinical trials found that OROS-MPH had a higher remission rate than IR-MPH (44% versus 16%; $P < 0.001$) while response rates were comparable at about 70-75% (Steele et al., 2006). Quality of life seems to be the new philosophy of treatment and the overall functioning of the child over the entire day (including after school activities) is the target, not just symptom control. There may be more hope with long-acting medications if they were used more consistently and with more rigorous follow-ups.

Summary

This paper has commented on some of the main aspects of the long-acting medications for ADHD currently being used in Canada. The designs of how these newer formulations deliver stimulants more smoothly over the entire day were reviewed. Comparisons were made with the short-acting stimulants. Children tend to show a preferential response to stimulants in that some will do better on methylphenidate and others on amphetamines (Arnold, 2000, Faraone et al., 2001). Thus both immediate-release methylphenidate and dextroamphetamine will likely continue to lead the market until provincial drug plan coverage of long-acting stimulants is more widespread. Many children continue to suffer from the complications of this disorder and long-term follow-up of medications with whatever regime that was used has been disappointing. If the goal of treatment is sustained remission in such a way that the child can be consistently free from impairing ADHD symptoms, be more available to benefit from other treatment modalities and enjoy a better quality of life he stands a better chance with long-acting medications. The cost of these medications may even be offset over the long-term by a decrease in the burden of illness and the high health-care utilization rates of children with ADHD.

Recommendations

The possible link between the therapeutic use of stimulants and sudden unexplained deaths in children without demonstrated heart abnormalities (Yan, 2009) makes it essential to follow certain guidelines before initiating treatment with a stimulant. The American Heart Association recommends taking a thorough patient history, paying special attention to cardiac history and cardiovascular status. A proper evaluation of any relevant symptoms and inquiring about any other medication use including over the counter preparations need to be done before initiating stimulant therapy (Gutgesell, 1999). Regular follow ups (with relevant ADHD rating scales) are essential to adjust medication doses for optimal response while monitoring side effects and vital signs including asking questions about symptoms such as palpitations or syncope. During each visit, it is also important to inquire about the addition of any other drugs to the present regimen from any other

source. Finally, clinicians should continue to follow the rule that medications should not be prescribed in isolation without concurrent psychotherapeutic and psychosocial interventions, including advocating for adaptations in the child's environment.

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