

Advances in ADHD Treatment

By Jacques R. Leroux, MD, CSPQ, Atilla Turgay, MD, FRCPC and Declan Quinn, MB, ChB, FRCPC

Many physicians see pediatric patients whose ADHD warrants pharmacotherapy for an optimal outcome. In selecting an appropriate treatment plan, there are many factors to consider for each individual patient. This review will highlight three considerations: treatment objectives, pharmacotherapy with prodrugs for ADHD, and how to interpret clinical trial data.

Jacques R. Leroux, MD, CSPQ

Pediatrician

Clinique des Troubles de l'Attention

Hôpital Rivière-des-Prairies

Montreal, Quebec

Atilla Turgay, MD, FRCPC

Professor, Faculty of Medicine

University of Toronto

Director, Toronto ADHD Clinic

Toronto, Ontario

Declan Quinn, MB, ChB, FRCPC

Child and Adolescent Psychiatrist

College of Medicine

University of Saskatchewan

Saskatoon, Saskatchewan

Redefining ADHD Treatment Objectives

By Jacques R. Leroux, MD, CSPQ

Although the recognition and management of attention deficit hyperactivity disorder (ADHD) have progressed significantly over the past decade, there is still considerable work to be done in helping children with this disorder.

Clinicians, parents, teachers and the children themselves have a wealth of resources available to them to help deal with ADHD. The Canadian Attention Deficit Hyperactivity Disorder Resource Alliance (CADDRA), for example, provides information tailored to each of these concerned groups.¹ These resources discuss the diagnosis of ADHD in considerable detail and also present the many options for treatment.

What are the objectives of treatment? Because the presentation of the disorder can be markedly different from child to child, CADDRA and other expert sources do not list specific therapeutic goals.

For many children, the disorder is identified as a result of scholastic struggles. Since school performance is perhaps most easily tracked, it often becomes the surrogate marker for success or failure of therapy. Indeed, for many children who take medication for their ADHD, clinicians may tailor the dosing regimens such that the optimal medication coverage only occurs during the times when the child is at school.

In addition to the important parameter of school performance, however, one should also take into account the child's quality of life and overall wellness. Although school is a significant component of a child's life, it is far from being the only component. Enjoying life outside of school is an extremely important aspect of childhood and adolescence. Children who have difficulties in maintaining focus and sustaining concentration on academic tasks will likely also have difficulty in social situations (*i.e.*, interaction with family and friends) and with extracurricular activities (*e.g.*, music lessons, swimming lessons, hockey, etc.),² with a resultant decrease in quality of life.

One of the key objectives of treating ADHD should, therefore, be improvement in all aspects of the child's life—to perform adequately in school, to enjoy a healthy relationship in the home, and to interact successfully with friends and with members of extracurricular groups (e.g., sports teams, social groups). Failure in any of these domains should be considered a failure overall.

The CADDRA recommendations recognize the importance of non-school performance, stating that “parents also need to help the child to develop appropriate social behaviours with peers and adults outside of school in both one-to-one and small group settings.”¹ Parents are an integral part of the care team, and can promote improvements outside of school if properly educated on contingency management and problem-solving communication techniques.³

Considerations for pharmacotherapy. Due to side effects, some families will request drug holidays—CADDRA recommendations state that continuous medication administration allows side effects to settle more rapidly.¹ Others will ask for drug holidays because they feel that they can cope with their child's disorder. Continuous medication enables the child to behave more consistently in all aspects of his/her life. In this way, the child becomes able to cope with his/her disorder.

CADDRA also recommends that long-acting agents be administered as the first-line pharmacologic therapy for ADHD. These agents are designed to minimize fluctuations (*i.e.*, reducing inpatient variability) and provide consistent and continual drug levels. Clinicians prescribing long-acting agents can also expect less variability in response between patients (*i.e.*, reducing interpatient variability), as the drug levels are maintained in a more consistent manner over the course of the dosing interval. It should be noted, however, that even with the currently available longer-acting formulations, many physicians still experience intra- and/or interpatient variability in efficacy and duration of effect. Dosing strategies often need to be individualized to overcome these issues. For example, if there is evidence of inadequate control towards the end of a dosing interval, one might choose to add a short-acting agent near the end of the interval. Alternatively, one might consider adding a second dose of the long-acting agent four to five hours after the initial daily dose, or delaying the morning dose so that the coverage lasts later into the day.

When choosing an agent to recommend to parents, clinicians should use the principles of evidence-based medicine and select agents proven to be effective in clinical trials.

Importance of monitoring. Defining success in ADHD is an elusive concept for some. This is why regular monitoring plays such a key role. CADDRA recommends that clinicians establish a routine follow-up schedule with patients and parents. Furthermore, baseline assessments need to be done with standardized tools, which will then be repeated throughout the course of follow-up.¹ The tools that are made available through CADDRA include rating scales that are to be completed by the child's parents and educators: the Turgay Child and Adolescent Psychopathology Screener (T-CAPS), Weiss Symptom Record, and SNAP-IV (developed by Swanson *et al.*). CADDRA recommends that these follow-up assessments be done as often as once per week.¹

Conclusion

The ultimate goal of ADHD management is to establish overall wellness, which encompasses all aspects of the child's life. Both clinicians and parents need to remain focused on achieving complete wellness, which can only be accomplished if the child experiences success both inside and away from the classroom.

Pharmacotherapy for ADHD: The Utility of Prodrugs

By Atilla Turgay, MD, FRCPC

For most conditions that can be treated pharmacologically, there are a number of different therapeutic options to choose from. ADHD is no exception. Some of the variables to consider in recommending a particular agent in ADHD include: long-acting versus short-acting (N.B.: the CADDRA guidelines recommend using a long-acting agent first-line) and stimulant versus nonstimulant.

Another possible difference between agents is whether they are intrinsically active upon entering the body or whether they are prodrugs. Among long-acting stimulants used to treat ADHD, most agents are initially active compounds. A new long-acting prodrug stimulant, lisdexamfetamine (LDX), is the lone exception. LDX is not yet available in Canada.

Initially active compounds do not require any

metabolism in the body to exert their therapeutic effects. They enter the body as active compounds and are subsequently converted to inactive metabolites.⁴ Prodrugs, on the other hand, are transiently inactive derivatives of an active compound, which require conversion in the body to become active.⁴

Rationale for Prodrug Development

Prodrugs may be developed for any number of reasons. Compared to the parent compound, prodrugs may have advantages in terms of solubility, absorption, chemical stability (*e.g.*, protection from gastric pH or gastrointestinal transit time), or duration of action. As such, prodrugs may be designed to overcome any such shortcomings of a parent compound.⁴

In addition to LDX, there are numerous examples of prodrugs in other therapeutic areas. These include the proton pump inhibitor omeprazole, the antibiotic cefuroxime axetil, the antiviral agent valacyclovir, the angiotensin-converting enzyme (ACE) inhibitor enalapril, and the lipid-lowering agent simvastatin. Each of these prodrugs has an established record of efficacy and safety. Some of the potential differences between prodrugs and their parent compounds are illustrated below.

Omeprazole. The drug omeprazole was not specifically designed as a prodrug for use as an acid-reducing agent. However, subsequent to its efficacy being discovered for this application, it was determined that it is not omeprazole itself, but one of its metabolites that actively inhibits the proton pumps of parietal cells. Its prodrug composition is, however, an essential component of its mechanism of action. The inactive compound omeprazole is able to readily penetrate to the site of action, where it is converted to the active compound. The metabolite itself would not be able to reach its intended destination if ingested directly.

Cefuroxime axetil. This prodrug formulation was developed to overcome the poor oral absorption of the parent drug cefuroxime, which is a potent cephalosporin antibiotic available only for intramuscular or intravenous injection.

The parent compound's chemical structure was such that transport across intestinal mucosa was unlikely. Chemical reformulation into the cefuroxime axetil prodrug allowed for intestinal absorption. The oral compound is used to treat infections of the respiratory tract,

urinary tract and skin.

Lisdexamfetamine. The chemical composition of this agent consists of the stimulant d-amphetamine, bonded to the L-lysine, an essential amino acid.⁵ The inactive compound LDX was designed as a prodrug so that d-amphetamine is released in a controlled fashion, as the amino acid component of the molecule is removed in the GI tract and/or bloodstream.⁵ Practically speaking, the result is an extended-release agent. The difference between LDX and other long-acting stimulants is that with LDX, the compound itself is intrinsically long-acting, whereas other preparations are intrinsically short-acting but have been mechanically redesigned to deliver the drug in a sustained manner.⁵ The primary benefit of a long-acting stimulant compound is minimal inter- and inpatient variability in terms of efficacy and duration of action. A secondary benefit of longer action is lower abuse potential (immediate-release stimulants are favoured due to the immediate high induced by these compounds if snorted).⁶ The pharmacokinetics of LDX are also such that abuse potential is decreased.⁵ Parents may be concerned about abuse potential; educating them on the differences between short- and long-acting drugs should be part of the counselling that takes place when stimulants are prescribed.

Conclusion

Prodrugs are useful pharmacologic tools that can overcome deficiencies and/or shortcomings of a parent compound (*e.g.*, enhancing absorption, increasing potency, extending duration of action). As shown above, examples of clinically useful prodrugs are found in various therapeutic areas (*e.g.*, omeprazole, cefuroxime axetil). The prodrug LDX may also prove to be a useful addition to the therapeutic armamentarium of ADHD management.

Interpreting Clinical Trial Data: The Concept of Effect Size

By Declan Quinn, MB, ChB, FRCPC

Effect size is a very useful tool in the analysis of clinical trial data to help make management decisions. An understanding of the implications of effect size helps the reader quickly assess whether the observed difference between groups is a difference that matters.

Effect size is calculated by measuring the difference

Table 1 Calculation of the Effect Size	
Effect size =	$\frac{\text{Mean of group 1} - \text{Mean of group 2}}{\text{Standard Deviation}}$

between mean results for each group, divided by the standard deviation (Table 1).

The primary advantage to using effect size is that by including the standard deviation in the equation, effect size goes beyond the mean value to take into consideration how spread out the set of values may be. What this means in terms of data interpretation is that the higher the effect size value, the smaller the overlap between group results and the more relevant the between-group difference.

An effect size may be labelled as small, medium or large. Although these labels are somewhat arbitrary, “small” might apply to an effect size of 0.2 to 0.3; 0.5 might be considered a “medium” effect; and 0.8 and higher might be considered a “large” effect.

The effect size is helpful when trying to compare the results of one clinical trial to another. Its utility in this regard is illustrated by the fact that effect size is commonly used for this purpose by the authors of systematic meta-analyses.⁷⁻⁹ Effect size is also a useful tool in comparing different interventions for the same disorder. As such, it can serve as a helpful decision-making tool when faced with a choice between two or more interventions available to treat a patient’s condition, even if those two interventions have not been compared in a head-to-head, randomized, controlled trial.

Effect Sizes of Agents Used to Treat ADHD

For clinicians who treat patients with ADHD, an understanding of effect size is of critical importance

Table 2 Effect Sizes for Classes of ADHD Medications ¹⁰		
Medication	Condition	Effect size
Prodrug stimulant	ADHD	1.21
Long-acting stimulants	ADHD	0.95
Non-stimulants	ADHD	0.62
Selective serotonin reuptake inhibitors	OCD/ Depression	0.50
Atypical antipsychotics	Schizophrenia	0.25

given that it is commonly used in the literature for both psychiatric medicine and education—two fields that are intimately connected with ADHD.

An analysis of effect sizes for drugs used to treat ADHD is shown in Table 2,¹⁰ with the prodrug stimulant medications showing the largest (most favourable) effect size.

For comparison, the table also shows the effect sizes of other psychotropic drugs commonly used to treat other disorders (*e.g.*, selective serotonin reuptake inhibitors for depression, atypical antipsychotics for schizophrenia). Note that the effect sizes for each of the ADHD treatments are higher than the effect size for the agents used for these other conditions.

Conclusion

As this field continues to evolve and new interventions become available, researchers and commentators will use the effect size calculation to compare the utility of various interventions on all the meaningful parameters in the management of ADHD (*e.g.*, performance at school, at home and in extracurricular activities—see the section above about redefining ADHD treatment objectives).

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