The Medical Xchange
MEETING REPORT
Toronto, Ontario | October 18-23, 2011

AACAP/CACAP Joint Annual Meeting

New Data Confirm Efficacy of Long-acting Stimulant Therapy for ADHD

Toronto - Management of children with attention-deficit hyperactivity disorder (ADHD) remains a challenge, in part due to the stigma associated with the disorder and parents' reluctance to initiate drug therapy. New agents with novel mechanisms to enhance drug delivery and extended durations of action have emerged in the last few years. A study presented here provides supplemental data on the efficacy, safety and tolerability of a new long-acting stimulant for children and adolescents with ADHD.

Given the spectrum of symptoms, signs and severity in attention deficit hyperactivity disorder (ADHD), as well as variations in patients' functional problems and goals, parental concerns and family challenges, there is no one-size-fits-all approach to the treatment of this disorder. Along with therapeutic efficacy and side effects, factors such as family schedules and timing of medication administration, among other elements in patient preference, may be considered. "I believe that having more medication options in the future will be of tremendous benefit for my patients with ADHD and their families," commented Dr. Shawn Kao, a pediatrician in Etobicoke, Ontario.

There is no one-size-fits-all approach to the treatment of this disorder.

Medical Therapy

Current guidelines from the Canadian ADHD Resource Alliance (www.caddra.ca) recommend long-acting stimulants as initial therapy for children with uncomplicated ADHD. Long-acting agents typically offer slower and/or more sustained drug delivery, which allow for better coverage during a child's school hours and after-school activities. Extended-release formulations also are less prone to abuse or diversion and some data indicate compliance with once-daily dosing may be better than that for short-acting agents requiring multiple daily doses.

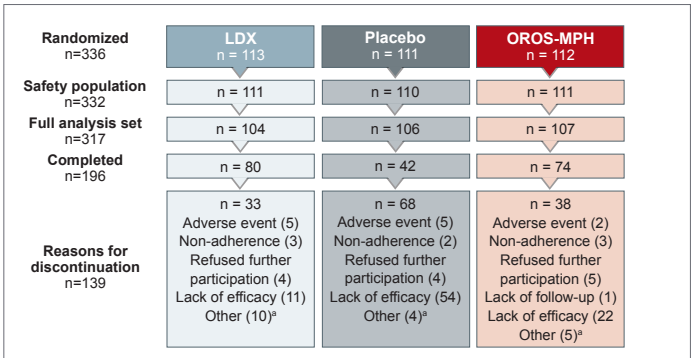
Among long-acting stimulants, lisdexamfetamine dimesylate (LDX) is unique in that it is a "prodrug": only after oral ingestion is the medication converted to its active metabolite d-amphetamine. In several clinical trials, its efficacy and safety have been shown to be at least similar to that of other long-acting stimulants. Its effects last up to 13 hours in children and slightly longer in adults. "The prodrug technology takes the delayed-release mechanism of out the gastrointestinal tract.... The medication is absorbed extremely reliably," commented Dr. Kenny Handelman, Adjunct Professor of Medicine, University of Western Ontario, and author of *Attention Difference Disorder*.

Current guidelines from CADDRA recommend long-acting stimulants as initial therapy for children with uncomplicated ADHD.

Multicentre Study: Efficacy

A multicentre study provided new data on the efficacy and safety of LDX in children and adolescents with ADHD. Conducted at 48 sites in Europe, it enrolled 336 patients aged six to 17 years of age (mean age, 11; about 80% male) with at least moderate symptoms, defined as baseline ADHD-RS-IV total score of ≥ 28 (mean, 49). Approximately equal numbers of patients were assigned to LDX, placebo or osmotic-release oral system methylphenidate (OROS-MPH) (Figure 1). Doses were optimized to LDX 30, 50 or 70 mg/day or OROS MPH 18, 36 or 54 mg/day, until an acceptable therapeutic response was attained (defined as a composite of a 30% reduction in ADHD-RS-IV total score, Clinical Global Impression of Improvement (CGI-I) score of 1 or 2, and absence of intolerable side effects).

FIGURE 1 | Patient Distribution



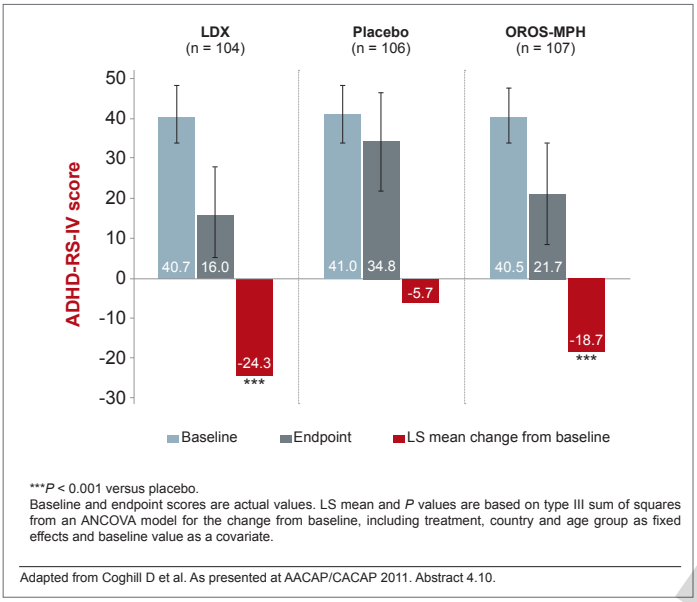
Four randomized patients did not receive investigational product and are not in the safety population; 19 were excluded from the full analysis set; information was not available for one patient at the point of database lock.
[a]Other reasons for discontinuation included: unable to swallow capsule, personal family reasons and medical monitor decision.

Adapted from Coghill D et al. As presented at AACAP/CACAP 2011. Abstract 4.10.

The primary efficacy measure was change from baseline in ADHD-RS-IV total score after a treatment duration of up to seven weeks (Figure 2). Optimized dosing of LDX

was significantly more effective than placebo, achieving a mean change from baseline of -24.3 compared with -5.7; the reduction achieved with OROS-MPH was -18.7. The difference between active agents and placebo was -18.6 for LDX (*P*<0.001) and -13 for OROS-MPH (*P*<0.001).

FIGURE 2 | Effects on ADHD-RS-IV Total Score in the Three Study Arms

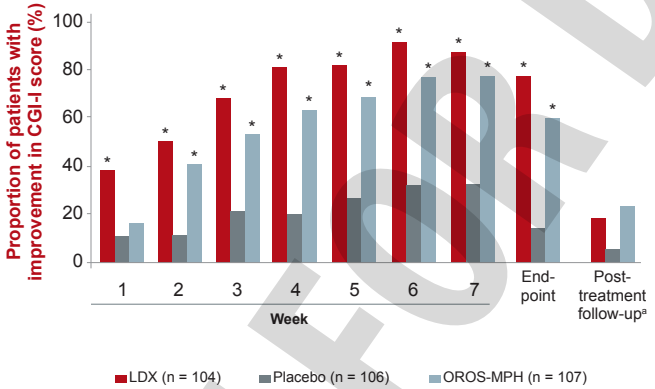


***P < 0.001 versus placebo.
Baseline and endpoint scores are actual values. LS mean and *P* values are based on type III sum of squares from an ANCOVA model for the change from baseline, including treatment, country and age group as fixed effects and baseline value as a covariate.

Adapted from Coghill D et al. As presented at AACAP/CACAP 2011. Abstract 4.10.

At the end of treatment, 78% of patients receiving LDX, 61% assigned to OROS-MPH and 14% receiving placebo had an improvement in CGI-I score (Figure 3).

FIGURE 3 | Proportion of Subjects with CGI-I Scores Improved at Each On-treatment Visit



*P < 0.001 versus placebo.
[a]Follow-up after 1 week of washout.
P value is based on Cochran-Mantel-Haenszel test controlling for country and age group.

Adapted from Coghill D et al. As presented at AACAP/CACAP 2011. Abstract 4.10.

"This study clearly shows LDX works well, far better than placebo, in the acute treatment of ADHD." said Dr. Handelman.

Safety Parameters

Parents may express anxiety about the side effects of stimulant medications, which can include decreased appetite and sleep, as well as rare but possibly important cardiovascular effects. In this study's safety population (n=332), the treatments were well tolerated. Adverse effects of treatment were reported by 57%, 65% and 72% of patients in the placebo, OROS-MPH and LDX groups, respectively. There were modest changes in vital signs and ECG among patients receiving the stimulant medications. The ECG changes were deemed not clinically significant.

Additional Evidence

The data from European centres presented here is consistent with those from prior studies of LDX and provides essential evidence on safety, tolerability and efficacy for clinicians on both sides of the Atlantic seeking to optimize ADHD treatment for their patients. "Lisdexamfetamine is an excellent choice for a long acting stimulant. However, it is not for every patient; not every patient needs a 12- to 14-hour duration. Side effects can also be overwhelming for some patients and families. But I also believe that not all clinicians are equal in addressing side effects," remarked Dr. Kao.

Conclusion

"Despite better education efforts, there still is a bias against medications among parents, teachers and sometimes, surprisingly, health professionals," Dr. Kao noted. Dr. Handelman added that ensuring proper diagnosis and pervasive misinformation about ADHD remain challenges to management. Their observations were echoed in a presentation by Coletti et al. (AACAP/CACAP 2011, Abstract 1.26), which noted that parental ambivalence about the benefits and risks of drug therapy for ADHD and having a child labelled as having a psychiatric issue may influence treatment adherence. A new score developed by these US investigators, entitled Parent Attitudes to Medication, correlates with the intention to try medication and successful treatment initiation. While their questionnaire requires further validation, the authors indicated that such systematic screening of parental beliefs may possibly promote better communication to address their fears, thereby ensuring effective therapy for the child with ADHD.●