treated with cariprazine vs placebo (50.5% vs 29.1%; OR, 2.43; $P = .0002$). Also, at the end of treatment, the percentage of patients with mild or no symptoms on all 11 YMRS domains was significantly higher with cariprazine vs placebo (22.5% vs 13.5%; OR, 1.85; $P = .0004$).

Another pooled analysis of the same 3 cariprazine studies, from Lakshmi N. Yatham, MBBS, University of British Columbia, Vancouver, British Columbia, Canada, found that the standard definition of treatment response (≥ 50% improvement in YMRS total score) from baseline was met by a significantly higher percentage of patients treated with cariprazine (57%) vs patients who received placebo (36%; $P < .0001$), and the number needed to treat for response was 5 (95% CI, 4 to 7).

The standard definition of disease remission (YMRS total score ≤ 12) was met by a significantly higher percentage of patients who received cariprazine vs patients who received placebo (46% vs 30%; $P < .0001$), with a number needed to treat for remission of 7 (95% CI, 5 to 10). Using the stringent remission criteria of complete symptom resolution (YMRS total score ≤ 4), remission rates were 15% with cariprazine vs 9% with placebo ($P = .0012$), with a number needed to treat of 17 (95% CI, 11 to 49).

Cariprazine was effective and associated with clinically meaningful benefits, as suggested by the low number needed to treat (< 10) using the standard definitions for YMRS response and remission. Cumulative remission rates, based on YMRS score ≤ 12, indicated that a significantly greater percentage of patients treated with cariprazine achieved early remission that was maintained until the end of treatment vs patients who received placebo.

Overall, cariprazine was associated with clinically meaningful improvements on all 11 YMRS symptom domains, suggesting clinically meaningful improvements across a broad spectrum of mania symptoms.

Fixed-Dose Lisdexamfetamine More Effective Than Methylphenidate in Adolescents With ADHD

Written by Dennis Bittner, PhD

Amphetamine-based treatments such as lisdexamfetamine dimesylate (LDX) and methylphenidate (MPH)-based agents are first-line treatments for adolescents with attention-deficit/hyperactivity disorder (ADHD), and each has been proven superior to placebo in numerous trials [Woolraich M et al. *Pediatrics.* 2011; Atkinson M, Hollis C. *Arch Dis Child Educ Pract Ed.* 2010]. A meta-analysis of clinical trials reported that amphetamine-based agents have greater effects than MPH-based agents [Faraone SV, Buitelaar J. *Eur Child Adolesc Psychiatry.* 2010]. Another meta-analysis indicated that amphetamine-based treatments were associated with higher probability of response when compared with various MPH-based agents [Roskell NS et al. *Curr Med Res Opin.* 2014]. Although such systematic assessments of existing data provide useful information about differential efficacy, they are indirect by nature.

Jeffrey Newcorn, MD, Icahn School of Medicine at Mount Sinai, New York, New York, USA, and colleagues conducted 2 studies directly comparing LDX with osmotic controlled-release MPH (OROS-MPH) in adolescents with ADHD. The primary end point was efficacy, as measured with the ADHD Rating Scale IV. Study 1 [NCT015529115] was an 8-week flexible-dose study, and study 2 [NCT01552902] was a 6-week forced-dose titration study. In study 1, patients were randomized 2:2:1 to once-daily LDX 30 to 70 mg, OROS-MPH 18 to 72 mg, or placebo. In study 2, the randomization was 2:2:1 to once-daily LDX 70 mg, OROS-MPH 72 mg, or placebo.

The least squares mean ± standard error of the mean was greater with LDX than with OROS-MPH in the flexible-dose study, but the difference was not significant (Table 1). The benefit of LDX over OROS-MPH was significant in the forced-dose study.

The key secondary end point was Clinical Global Impressions–Improvement scale score. Similar to what was seen with the ADHD scores from the 2 agents in each study, the scale score was greater with LDX than with OROS-MPH in the flexible-dose study (Table 1), but the difference was not significant. In the forced-dose study, the score was significantly greater with LDX than with OROS-MPH.

Table 1. Efficacy End Point Data From ADHD Studies

Scale: Dose Study	Placebo	LDX	OROS-MPH
ADHD Rating Scale IV[a]			
Flexible	−13.4 ± 1.19	−25.6 ± 0.82	−23.5 ± 0.80[b]
Forced	−17.0 ± 1.03	−25.4 ± 0.74	−22.1 ± 0.73[c]
CGI-I, %			
Flexible	34.8	83.1	81.0[d]
Forced	50	81.4	71.3[e]

ADHD, attention-deficit/hyperactivity disorder; CGI-I, Clinical Global Impressions–Improvement; LDX, lisdexamfetamine dimesylate; OROS-MPH, osmotic controlled-release methylphenidate.

[a]Least squares mean ± standard error.

[b]LDX vs OROS-MPH, Δ: −2.1 ± 1.15; $P = .0717$.

[c]LDX vs OROS-MPH, Δ: −3.4 ± 1.04; $P = .0013$.

[d]LDX vs OROS-MPH: $P = .6165$.

[e]LDX vs OROS-MPH: $P = .0188$.

LDX was approved by the US FDA in 2007 for use in patients ≥6 years old with ADHD. The safety and tolerability profile of LDX has been consistent across clinical trials, with small increases in heart rate and/or blood pressure observed. The most frequently observed treatment-emergent adverse events (TEAEs) associated with LDX treatment include decreased appetite, decreased weight, and insomnia [Coghill D et al. *Eur Neuropsychopharmacol.* 2013; Findling RL et al. *J Am Acad Child Adolesc Psychiatry.* 2011].

Dr Newcorn and colleagues evaluated the safety and tolerability of LDX and OROS-MPH as secondary end points. Safety assessments included recording adverse events and vital signs. In the flexible-dose study, TEAEs were reported in 83.2% of patients receiving LDX, compared with 82.1% receiving OROS-MPH. In the forced-dose study, 66.5% of patients receiving LDX reported TEAEs, compared with 58.9% of patients receiving OROS-MPH. In the placebo groups, 63.7% and 44.5% of patients reported TEAEs in the flexible- and forced-dose studies, respectively. Consistent with known effects of LDX and OROS-MPH, TEAEs that occurred in ≥10% of patients included decreased appetite and headache with LDX and OROS-MPH in both studies, decreased weight with LDX in both studies and with OROS-MPH in the forced-dose study, and irritability with LDX in the flexible-dose study.

Dr Newcorn and colleagues concluded that LDX was not statistically superior to OROS-MPH in a flexible-dose design but was statistically superior in a forced-dose design, while the safety and tolerability profiles of both agents were consistent with those observed in previous studies.

Optimal Dosing of Lurasidone Studied in Acute Schizophrenia

Written by Lynne Lederman, PhD

Lurasidone, an atypical antipsychotic, showed efficacy in doses of 40 to 160 mg once daily in patients with acute schizophrenia in 5 short-term, fixed-dose, placebo-controlled trials [Loebel A et al. *Schizophr Res*. 2013; Nasrallah HA et al. *J Psychiatr Res*. 2013; Ogasa M et al. *Psychopharmacology*. 2013; Meltzer HY et al. *Am J Psychiatry*. 2011; Nakamura M et al. *J Clin Psychiatry*. 2009]. In short-term studies, early nonresponse to atypical antipsychotics predicted nonresponse [Kinon BJ et al. *Neuropsychopharmacology*. 2010; Kinon BJ et al. *Schizophr Res*. 2008], although evidence to support continuation of initial therapy, dose escalation change in medication, and other clinical decisions is lacking.

Antony Loebel, MD, Sunovion Pharmaceuticals, Marlborough, Massachusetts, USA, presented a poster with results from the 6-week, randomized, double-blind, placebo-controlled lurasidone low-dose–high-dose study [NCT01821378]. Lower doses of lurasidone were not evaluated in a placebo-controlled trial in which assay sensitivity was established. Therefore, the objective of this study was to evaluate the efficacy and safety of lurasidone 20 mg per day in adults with an acute exacerbation of schizophrenia (defined by a Positive and Negative Syndrome Scale [PANSS] total score ≥ 80, a PANSS item score ≥ 4 on ≥ 2 PANSS items, and a Clinical Global Impression-Severity [CGI-S] scale score ≥ 4), and to determine an effective treatment strategy for patients who did not have a meaningful reduction in the PANSS total score by week 2 of standard-dose lurasidone (early nonresponders).

After a washout and screening period, patients were randomly assigned 1:2:1 to fixed-dose lurasidone 20 mg per day (n = 1010), 80 mg per day (n = 198), or placebo (n = 112). Patients were well matched for baseline characteristics. Their mean age was 41 years, about a third were women, and 75% were white; the mean PANSS and CGI-S scores were 97 and 4.9.

Patients in the 20-mg group received the same dose throughout the study. After 2 weeks, patients in the 80-mg group classified as early responders (n = 100; ≥ 20% improvement in PANSS total score) continued that dose for the rest of the study; those classified as early nonresponders were randomly assigned 1:1 to continue 80 mg (n = 52) or 160 mg (n = 43) until study end. The mean changes in PANSS total score in the placebo, lurasidone 20-mg, and lurasidone 80- or 160-mg groups, respectively, were −14.5, −17.6, and −24.9 ($P < .001$ vs placebo).

Adverse events (AEs) associated with lurasidone included akathisia, headache, and nausea; AEs associated with placebo included insomnia and agitation. Serious treatment-emergent AEs were lower with lurasidone at each dose (3.0%) than with placebo (7.1%). No deaths occurred during the study. The incidence of AEs varied across the groups of early responders and nonresponders, but whether the differences were statistically significant was not reported.

Although 20 mg dosing was safe and tolerable, it did not lead to significant improvement; therefore, the minimum effective dose of lurasidone appeared to be 40 mg per day in the present study. Patients with acute schizophrenia whose symptoms do not respond to 80 mg per day of lurasidone after 2 weeks of treatment may benefit from a dose increase to 160 mg per day rather than continuing the initial dose, according to the investigators.