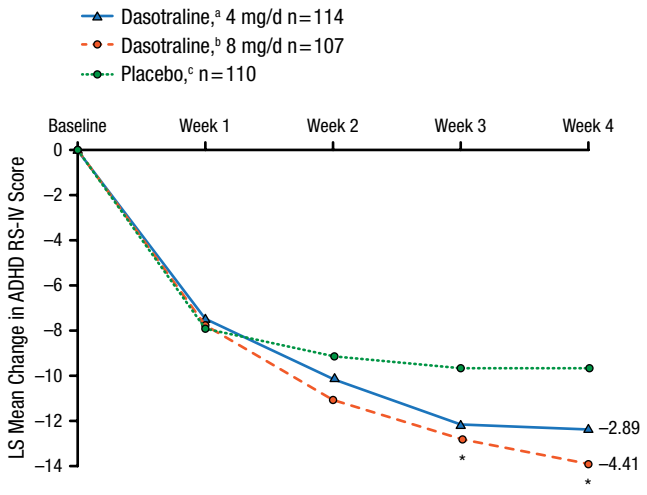
Figure 2. Primary Outcome



The primary efficacy measure of ADHD RS-IV (with adult prompts) total score was reduced by dasotraline 4 mg (adjusted $P=.076$) and 8 mg (adjusted $P=.019$) at 4 wk compared with placebo.

ADHD RS-IV, Attention Deficit Hyperactivity Disorder Rating Scale version IV; LS, least squares.

[a]Baseline mean, 36.8.

[b]Baseline mean, 36.6.

[c]Baseline mean, 36.7.

*$P<.05$.

Adapted by permission from Macmillan Publishers Ltd: *Nerophsychopharmacology*. Koblan KS et al. Dasotraline for the Treatment of Attention-Deficit/Hyperactivity Disorder: A Randomized, Double-Blind, Placebo-Controlled, Proof-of-Concept Trial in Adults. Advance online publication 3 June 2015; doi: 10.1038/npp.2015.124. Copyright (2015).

other psychotic disorder; substance abuse/dependence in the prior 12 months, or a positive alcohol or drug screen test result during trial screening; and treatment in the preceding 6 months with specified medications. Use of zolpidem, zaleplon, and eszopiclone for insomnia management was allowed.

The intention-to-treat arms for dasotraline 4 mg, 8 mg, and placebo were demographically/clinically comparable at baseline. The primary outcome of mean change from baseline in the ADHD Rating Scale, version IV score at 4 weeks was reduced by dasotraline 4 and 8 mg vs placebo (Figure 2).

Both doses of dasotraline significantly improved the CGI-S score compared with placebo at 4 weeks (4 mg, $P=.021$; 8 mg, $P=.013$). Significant improvements in the hyperactivity/impulsivity ($P=.027$) and inattentiveness ($P=.016$) subscales were also evident with the 8 mg dose arm.

Adverse events that occurred more often in those receiving dasotraline included insomnia, decreased appetite, anxiety, nausea, and dizziness. Events leading to patient withdrawal for the 4 and 8 mg doses of dasotraline were insomnia (2.6% and 10.8%), anxiety (2.6% and 1.8%), and panic attacks (0% and 2.7%); these events did not occur in the placebo arm. The mean changes in the Insomnia Severity Index scores for both doses of dasotraline were significantly higher at weeks 1 through 4 compared with placebo.

The proof-of-concept trial demonstrated clinically meaningful benefits in adults with ADHD using dasotraline, with benefits being significantly better than placebo for the 8 mg dose. The observation of increased plasma levels of the norepinephrine metabolite dihydroxyphenylglycol with increasing dasotraline dose supports the view that the drug's beneficial effects reflect inhibition of dopamine and norepinephrine reuptake. Further clinical trials, including dose optimization, are anticipated.

Cariprazine Leads to Clinically Meaningful Improvements in Bipolar Symptoms

Written by Kathy Boltz, PhD

Cariprazine was associated with clinically meaningful improvements across a broad spectrum of mania symptoms in a majority of adult patients with manic or mixed episodes associated with bipolar disorder, according to pooled analyses of phase 2/3 trials of cariprazine presented in 2 posters. The pooled analyses included 3 cariprazine studies [NCT00488618, NCT01058096, NCT01058668] in patients with bipolar mania that all used a design with 3 weeks of double-blind treatment. These studies included 608 patients who received cariprazine and 429 patients who received placebo.

In a poster by Stephen Zukin, MD, Forest Research Institute, Jersey City, New Jersey, USA, at baseline, the majority of patients had at least moderate symptom severity on 8 of 11 individual items on the Young Mania Rating Scale (YMRS). After 3 weeks of cariprazine treatment, the majority of the patients treated with cariprazine had mild or no symptoms on all 4 core YMRS items (irritability, speech, thought content, and disruptive/aggressive behavior; $P<.0001$). The odds ratios for changes in each of the YMRS single items ranged from 1.6 for increased motor activity to 2.7 for irritability (all $P<.001$).

Category shift analysis found that patients with moderate or worse symptom severity at baseline had significantly greater shifts to no or mild symptoms with cariprazine treatment vs placebo for each of the 11 items of YMRS. On all 4 YMRS core items, a shift from moderate or worse symptom severity to no or mild symptoms occurred for a significantly greater percentage of patients

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: $P = .0188$.