Dasotraline Is Clinically Effective for Adults With ADHD

Written by Brian Hoyle

A 4-week, randomized, double-blind, placebo-controlled trial [Koblan KS et al. *Neuropsychopharmacology*. 2015] demonstrated clinically meaningful effects with dasotraline, an inhibitor of the reuptake of dopamine and norepinephrine, in the treatment of adults with attention-deficit/hyperactivity disorder (ADHD).

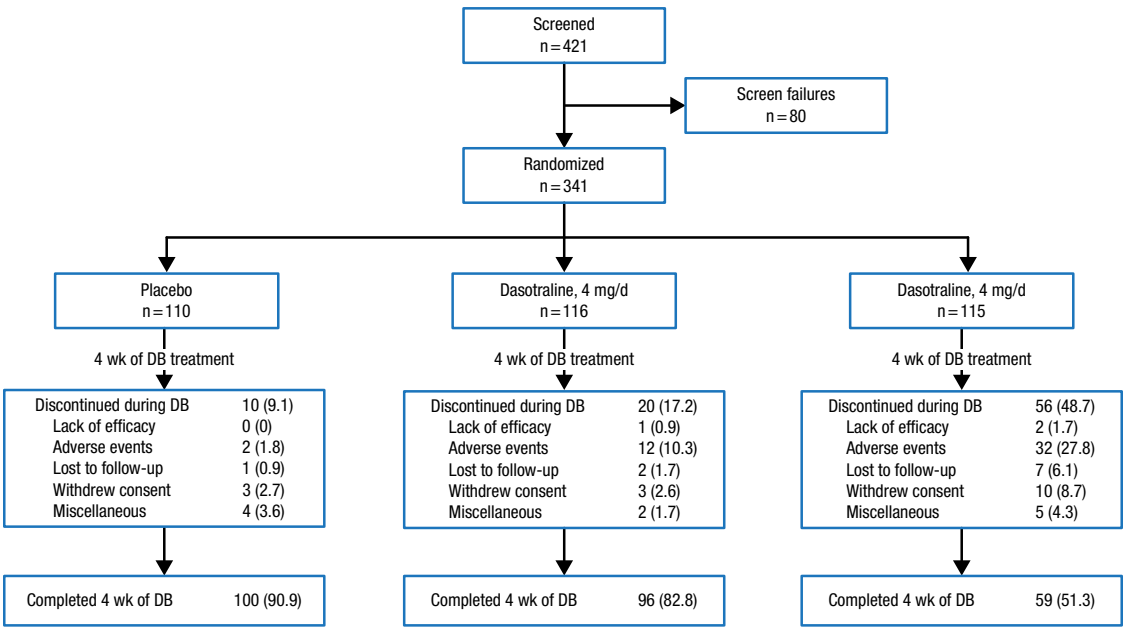
Symptoms of ADHD, including restlessness, impulsive behavior, forgetfulness, and distractibility, can hamper social interactions and work/school performance, and ADHD that is first evident in childhood can continue into adulthood. Drugs that increase dopamine and norepinephrine transmission have proven clinical value in the management of ADHD symptoms. Dasotraline blocks the presynaptic reuptake of dopamine and norepinephrine, increasing their levels in the brain.

This trial, conducted by Kenneth S. Koblan, PhD, Sunovion Pharmaceuticals, Marlborough, Massachusetts, USA, and colleagues, explored the potential value of dasotraline in adults with ADHD. Secondary objectives included evaluations of dasotraline safety and tolerability.

Adult outpatients aged 18 to 55 years (n = 341) with a primary diagnosis of ADHD based on DSM-IV-TR criteria were randomized 1:1:1 in a double-blind fashion to a 4-week oral regimen of dasotraline 4 or 8 mg/d, or to placebo. The treatment period was followed by a 2-week washout (Figure 1).

Inclusion criteria other than diagnosis of ADHD included prior treatment with at least one ADHD medication (stimulant or nonstimulant), and a Clinical Global Impression, Severity (CGI-S) score ≥ 4 at baseline. Exclusion criteria were history of bipolar disorder, schizophrenia, or

Figure 1. Study Design



Data presented in No. (%).

DB, double-blind.

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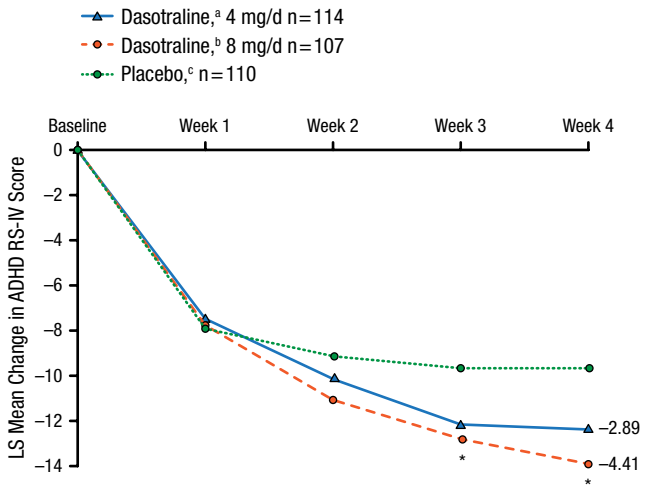
Figure 2. Primary Outcome



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