the trial, which was carried out with 43 children diagnosed with ADHD as an effort to optimize the dose of the central nervous system stimulant, was a prelude to a 1-week, double-blind, placebo-controlled phase to assess the safety and efficacy of the approach.

This trial assessed a proprietary oral delivery system, HLD200, intended to be used in the evening, with the goal of lessening early morning ADHD symptoms in children. The 43 children (20 girls; 46.5%) ranged in age from 6 to 12 years (mean, 9.7 ± 1.7 years). Most of the children were aged 8 to 10 years (n = 22; 51.2%), followed by > 10 years (n = 14; 32.6%). Most were white (n = 34; 79.1%). All had confirmed ADHD, current or prior response to methylphenidate, and no other major medical condition.

In the dose-optimization process, HLD200 at the second visit was administered to deliver the same dose of methylphenidate that a patient had previously been taking or, at the discretion of the investigator, a dose of about 1.4 mg/kg. The dosage was altered in subsequent weekly sessions until a concentration deemed satisfactory was reached at visit 8. This dosage was then carried forward in the 1-week double-blind, randomized, placebo-controlled trial.

The current data are from the initial 6-week period of dose optimization. Analyses during this time included the ADHD Rating Scale–IV (ADHD-RS-IV), Before School Function Questionnaire (BSFQ), and Daily Parent Rating of Evening and Morning Behavior–Revised (DPREMB-R).

The mean starting dose at baseline (visit 2) was 32.02 ± 17.93 mg. The subsequent dose adjustment yielded an optimal and significantly greater dose of 65.58 ± 24.81 mg ($P < .0001$).

The time the doses were given remained constant (9:00 PM ± 0 minutes and 8:56 PM ± 19.8 minutes; $P = .18$). The mean ADHD-RS-IV score decreased significantly during the dose-adjustment period, from 38.23 ± 8.90 at visit 2 to 12.51 ± 6.62 at visit 8 ($P < .0001$).

The mean BSFQ scores likewise decreased significantly from visit 2 (36.21 ± 13.31) to visit 8 (10.12 ± 7.25; $P < .0001$). DPREMB-R scores in the morning and evening also differed significantly as treatment progressed. The mean morning score at visits 2 and 8 was 4.91 ± 2.42 and 1.21 ± 1.21, respectively ($P < .0001$). The corresponding evening score at visits 2 and 8 was 15.14 ± 5.91 and 7.65 ± 5.68, respectively ($P < .0001$).

The 6-week trial was successful in establishing a dose that produced significant lessening of morning ADHD symptoms. Furthermore, symptom control was maintained through the day. Full results are forthcoming.

## Post hoc FOCUS Analysis: Vortioxetine Improves Cognitive Functioning in MDD

Written by Kathy Boltz, PhD

Patients with major depressive disorder (MDD) who received vortioxetine 10 or 20 mg/d had statistically superior cognitive function in the domains of processing speed, executive functioning, and attention vs patients who received placebo. This post hoc analysis of the FOCUS trial [NCT01422213]—as presented in a poster from Søren Lophaven, PhD, H. Lundbeck A/S, Copenhagen, Denmark, and colleagues—used the Digit Symbol Substitution Test to assess cognitive function.

Patients aged 18 to 65 years who had recurrent MDD as classified by the DSM-IV-TR were enrolled in the multinational, randomized, double-blind, placebo-controlled FOCUS study. Patients who had a current major depressive episode (MDE) of ≥ 3 months and a Montgomery-Åsberg Depression Rating Scale total score ≥ 26 at both screening and baseline visits were eligible. The patients were randomized 1:1:1 to vortioxetine 10 mg/d (n = 195), vortioxetine 20 mg/d (n = 207), or placebo (n = 196) for 8 weeks of double-blind treatment.

Both doses of vortioxetine were statistically superior to placebo for patients aged ≤ 50 years and > 50 years (all $P < .01$) and regardless of educational level or working status (all $P < .05$). Both doses were also statistically superior in both sexes, though with stronger significance in women ($P < .001$) than in men ($P < .01$).

Both doses were statistically superior to placebo for patients whose body mass index (BMI) was < 25 (n = 233; $P < .01$ for 10 mg/d and $P < .001$ for 20 mg/d), whereas only vortioxetine 20 mg/d was statistically superior to placebo for patients whose BMI was ≥ 25 and < 30 (n = 202; $P < .05$). In obese patients (BMI ≥ 30; n = 156), vortioxetine did not reach statistical significance with this smaller group.

All patients had ≥ 1 MDE, and both doses of vortioxetine were statistically superior to placebo for all patients (n = 591, $P < .001$ for both doses), for patients who had ≥ 2 MDEs (n = 354, $P < .001$ for both doses), and for patients who had ≥ 3 MDEs (n = 186, $P < .01$ for 10 mg/d and $P < .001$ for 20 mg/d). For patients who had ≥ 4 MDEs (n = 103), only vortioxetine 20 mg/d was statistically superior to placebo ($P < .05$).

Duration of a current MDE did not affect the effectiveness of vortioxetine; both doses of vortioxetine were statistically superior to placebo for all patients whose current MDE was ≥ 3 months (n = 591), ≥ 4 months (n = 429), or ≥ 5 months (n = 276; $P < .001$ for these

MDE lengths). Both doses of vortioxetine were also statistically superior to placebo for patients whose current MDE was ≥6 months (n=202; $P<.01$ for 10 mg/d and $P<.001$ for 20 mg/d).

Overall, Digit Symbol Substitution Test scores were statistically superior with vortioxetine 10 and 20 mg/d vs placebo, indicating improved executive function, processing speed, and attention in treated patients.

## ADAPT: High-Dose Venlafaxine Benefits Older Adults With Pain and Depression

Written by Nicola Parry

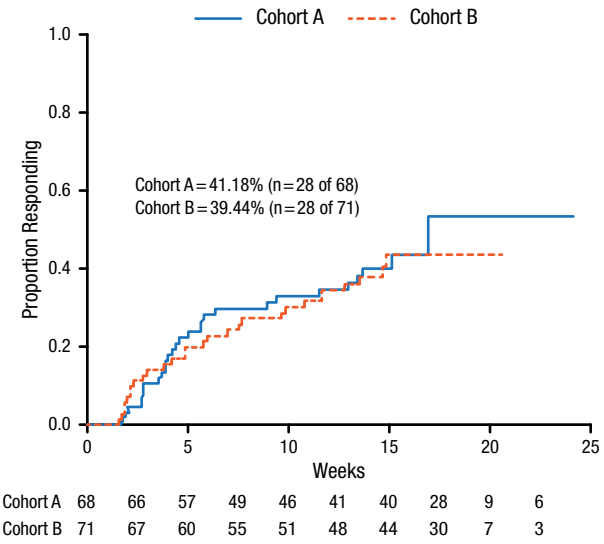
Jordan F. Karp, MD, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA, presented data from the ADAPT trial [NCT01124188], which demonstrated that venlafaxine with supportive management (SM) led to significant response rates, especially for pain, in older adults with depression and chronic low back pain (CLBP). However, there was no additional benefit of problem-solving therapy for depression and pain (PST-DP) in terms of improved response.

According to Dr Karp, late-life depression is a significant public health problem that decreases quality of life and survival in affected patients, contributes to a poorer prognosis for comorbid conditions, and is a risk factor for suicide. In addition, it is associated with increased health care utilization and costs. He noted that, when treating older adults, late-life treatment-resistant depression is the rule, not the exception. In the United States and Canada, 25% to 50% of older adults in community settings and 49% to 83% in nursing homes suffer chronic pain, reported Dr Karp. Anxiety and depression are also more common in these patients than in those without pain, and the pain can lead to memory and cognition problems. CLBP in particular has a prevalence of 12% in the community, and it is the most common referral to pain clinics.

The ADAPT study was therefore conducted to compare high-dose venlafaxine with PST-DP with high-dose venlafaxine with SM in older adults living with CLBP and depression. Inclusion criteria were men and women aged >60 years experiencing CLBP and low mood. Primary outcomes were measures of depression, pain, and disability.

Two hundred and twenty-seven patients with comorbid depression and CLBP started the trial. In the first phase, all participants received 150 mg/d of venlafaxine for 6 weeks and SM. Phase 1 nonresponders had a higher medical burden than responders, said Dr Karp. They had more severe depression (Patient Health Questionnaire-9 [PHQ-9] score 16.5 vs 14.3; $P=.004$), more treatment-resistant depression (as measured by the Antidepressant Treatment History Form; 55.3% vs 18.4%; $P=.0002$), greater pain extensity (as demonstrated by the number of painful areas on a pain map; 13.5 vs 9.2; $P=.01$), and more pain-related functional disability (Roland Morris Disability Questionnaire score 15.61 vs 12.87; $P=.0007$). In phase 1, a 2-week change in the numeric rating scale was the only significant predictor of improvement in depression and pain.

Figure 1. Response Rate in Phase 2 of the ADAPT Study




Cohorts A and B represent the 2 cohorts in the second phase of the study (cohorts remain blinded at this time).

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Patients who responded poorly during phase 1 went on to the second intervention phase, while those who responded well were excluded. Patients received up to 300 mg/d (median dose 244 mg) of venlafaxine for 14 weeks and were randomized to also receive either SM or PST-DP (an average of 8 to 9 sessions). Response during phase 2 was characterized by 2 sequential visits of PHQ-9 ≤ 5 and ≥ 30% reduction in the numeric rating scale.

The results in phase 2 demonstrated a 40% response rate in depression and pain at any point during the study (Figure 1).

Although there was no additional benefit of PST-DP in terms of improved response, patient follow-up will continue for 12 months to investigate whether PST-DP decreases the rate of relapse and health care utilization, Dr Karp concluded.