PATH-D Study: MBCT Improves Symptoms of Treatment-Resistant Depression

Written by Nicola Parry

Stuart Eisendrath, MD, University of California at San Francisco, San Francisco, California, USA, presented initial data from the PATH-D study [NCT00871299], which investigated whether mindfulness-based cognitive therapy (MBCT) was an efficacious augmentative treatment for reducing symptoms in adults with treatment-resistant depression (TRD). The initial results demonstrated that MBCT improved depressive symptoms in patients with TRD, in association with enhanced regulation of cognitive control areas, as demonstrated by functional magnetic resonance imaging (FMRI).

The study was a single-blind, randomized controlled trial of MBCT plus medication vs a health-enhancement program (HEP) plus medication. Dr Eisendrath explained that the HEP is a psychoeducation-based plan, with an emphasis on physical fitness, agility, nutrition, and music therapy, while MBCT comprises mindfulness meditation with cognitive-behavioral therapy.

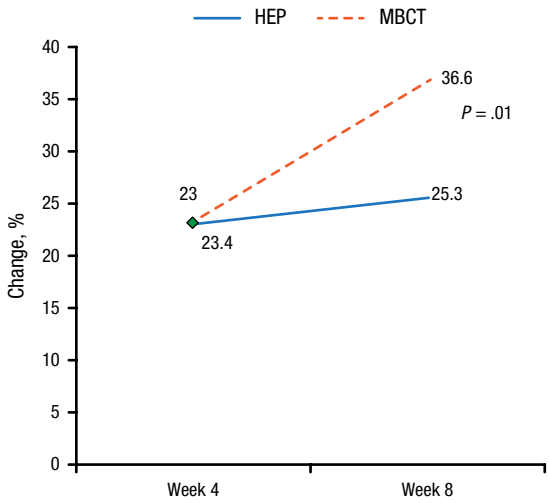
One hundred and seventy-three participants were randomized to either the MBCT (n = 87) or the HEP (n = 86) group, for 52 weeks. The primary outcome was percentage reduction in the Hamilton Depression Rating Scale 17-item (HAM-D) score. Inclusion criteria included patients with major depressive disorder with a minimum HAM-D score of ≥ 14 who were currently in medication management. Exclusion criteria included patients with a history of psychotic disorder or substance abuse, as well as those currently using meditation or yoga practice.

The percentage reduction in the HAM-D score was significantly greater in the MBCT group compared with the HEP group (Figure 1).

A greater percentage of the MBCT group also responded to treatment (29.58% vs 17.19%; $P = .0293$), as defined by ≥ 50% reduction in HAM-D total score from baseline. However, although treatment remission (defined by a HAM-D total score ≤ 7) was also greater in the MBCT group, it was not statistically significant (21.12% vs 15.63%; $P = .1797$), which Dr Eisendrath noted was not surprising in the treatment-resistant patient population.

FMRI subset analysis was also performed in the MBCT (n = 44), HEP (n = 44), and healthy control (n = 40) groups. According to Dr Eisendrath, the dorsal executive control center in the brain includes the dorsolateral prefrontal cortex (DLPFC), while the ventral affective processing system includes the ventrolateral prefrontal cortex (VLPFC) and amygdala.

Figure 1. Effect of Treatment on Hamilton Depression Rating Scale Score



HEP, health-enhancement program; MBCT, mindfulness-based cognitive therapy.
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FMRI analysis showed increased VLPFC activation and decreased DLPFC activation in patients with TRD at baseline, suggestive of deficient cognitive control mechanisms in these patients, explained Dr Eisendrath. However, 8 weeks of MBCT, but not HEP, was associated with a reversal of these baseline findings, he added. Improvement in the HAM-D score in the MBCT group was associated with a greater decline in amygdala activation during working memory retrieval compared with baseline ($P = .036$) and working memory maintenance ($P = .05$). Overall, these data show that MBCT is associated with activation of cognitive control areas and decreased activation of the affective processing areas, concluded Dr Eisendrath.

CEES: Nighttime Controlled-Release Methylphenidate Eased Next-Day ADHD Symptoms

Written by Brian Hoyle

In the 6-week, open-label phase of the CEES trial [NCT02255513], nighttime dosing of delayed- and controlled-release oral methylphenidate reduced attention-deficit/hyperactivity disorder (ADHD) symptoms in the early morning, with symptom control maintained through the day, according to a poster presented by Mary Ann A. McDonnell, PhD, Northeastern University, Boston, Massachusetts, USA. This phase of

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