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PARKINSON'S DISEASE

ABSTRACT & COMMENTARY

Bright Light Therapy in Depression and Insomnia Associated With Parkinson's

By Ellen Feldman, MD

Altru Health System, Grand Forks, ND

Dr. Feldman reports no financial relationships relevant to this field of study.

SYNOPSIS: Bright light therapy (10,000 lux intensity for 30 minutes twice daily) and a low intensity control light showed similar efficacy in treatment of depression associated with Parkinson's disease; the bright light therapy showed some advantages in improving subjective quality of sleep.

SOURCE: Rutten S, Vriend C, Smit JH, et al. Bright light therapy for depression in Parkinson disease: A randomized controlled trial. *Neurology* 2019;92:e1145-e1156.

"Sleep that knits up the ravell'd sleave of care
The death of each day's life, sore labour's bath
Balm of hurt minds, great nature's second course,
Chief nourisher in life's feast."
—William Shakespeare, Macbeth

Shakespeare did not need medical training to recognize a connection between sleep quality and mood! However, it took several centuries for medical science to catch up with the observations of this 17th century bard. The pivotal work of Kleitman in the 1950s and his discovery of rapid eye movement (REM) sleep sparked renewed interest in the essential role of sleep in health.[1] Sleep medicine, a new branch of medicine devoted to the study and treatment of

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Summary Points

- This Netherlands-based, randomized controlled study involving 72 patients with Parkinson's disease (PD) and major depressive disorder (MDD) aimed to see if bright light therapy (BLT) showed efficacy in treatment of depressive symptoms in this population.
- Participants were treated with BLT (10,000 lux twice daily) in their homes for three weeks. Follow-up continued for six weeks.
- Control group used the same light device as the BLT group but with a filter, thereby reducing light intensity to 200 lux.
- The Hamilton Depression Rating Scale (HDRS) decreased in both the control and intervention arms without significant difference, except for a significantly lower score in the control arm at the conclusion of the six-month follow-up period.
- Secondary outcome measurements showed a significant improvement in subjective sleep quality in the intervention group at the end of the three-week intervention period ($P < 0.001$).

sleep disorders, emerged from Kleitman's work and other related work of the time. With advances in technology, a new understanding of the electrical activity of the brain during wake and sleep cycles propelled investigation of the science behind the link between sleep and mental health disorders.[1,2]

Over the last 20 years, a growing recognition of a bidirectional relationship (think chicken and egg) between sleep and disorders of mood led to a focus on improving sleep in treatment and prevention of mood disorders.[3] Rutten et al designed a randomized controlled trial investigating bright light therapy (BLT) to treat depression in Parkinson's disease (PD). The researchers noted the high prevalence of both depression (17%) and insomnia (30%) in this population, as well as the significant functional impairment associated with each of these states. The group also noted the likelihood that disruptions in circadian rhythm (known to be associated with PD) may be a key factor in the development of both of these states. The researchers postulated that BLT would be more effective than a control light in treating patients with depression associated with PD. Secondary outcomes in the study included measuring markers of circadian rhythm (including cortisol) and sleep quality.

Previous studies have shown a positive impact of BLT on sleep, mood, and motor improvement in PD, but this is the first known randomized controlled trial to review the effects on depression in PD with the use of BLT.

To be included in this Norwegian study, patients needed to have a diagnosis of idiopathic PD and major depressive disorder (MDD) and be stable on medications used for these conditions. Exclusion criteria revolved around comorbid medical factors that could contraindicate use of BLT (such as photosensitivity from medication and bipolar disorder) or instability of PD or MDD. The study was controlled to account for the impact of seasonal changes on ambient light.

There were significant difficulties recruiting and retaining participants for the study. Out of 389 volunteers over a five-year period (between 2012 and 2017), only 83 met the inclusion criteria. Of those 83 volunteers, 11 withdrew before the end of the first week of the study, resulting in only 72 participants.

After randomizing into two groups, all participants received a light box and were instructed to use it for 30 minutes twice daily at specified times.

Light boxes for the intervention arm emitted daylight spectrum light at 10,000 lux; a filter placed in the boxes for those in the control arm lowered the light intensity to 200 lux. In addition, members of both groups were asked to keep a sleep diary and collect and submit saliva samples periodically during the study.

Severity of depression as measured by the Hamilton Depression Rating Scale (HDRS) and several other measurements of secondary outcomes were assessed at baseline, midway, and at the conclusion of the three-month study. After the study period, patients were encouraged to assume care as usual, and researchers continued to follow up for six months, with assessments at months one, three, and six.

PRIMARY OUTCOME MEASURES

Scores on the HDRS are one way to measure and follow the severity or intensity of symptoms of MDD. Individuals with scores under 10 are generally not reporting depressive symptoms; scores between 10 and 13 represent mild distress; scores between 14 and 17 represent mild to moderate distress; and scores above 17 represent moderate to severe distress. In this study, mean HDRS at baseline was 14.5 for the control group and 14.7 for the BLT group.

At the three-month endpoint of the active intervention, both groups showed a decrease in HDRS, to 8.3 for the control group and 7.6 for the BLT group. These values were not significantly different, but both were under the threshold measurement for the diagnosis of MDD.

At the conclusion of the six-month follow-up period, the mean HDRS in the control group had dropped to 5.9, while the mean HDRS in the BLT group remained close to the last measured value at 8.5. This difference was significant with a $P = 0.03$. (*See Table 1.*)

SECONDARY OUTCOME MEASURES

Geriatric Depression Rating Scale: There were decreases in both groups without significant difference between the two groups.

Subjective quality of sleep (measured with the Scales for Outcomes in Parkinson's Disease — Sleep): After correcting for confounders at the end of the three-month study period, scores improved in both groups but improved more significantly in the BLT arm ($P < 0.05$). This difference was no longer significant at the conclusion of the six-month follow-up period.

Circadian rhythm markers: Measurements reflected estimates of total cortisol secretion and of cortisol level on awakening. Cortisol has a complex relationship to sleep and depression; in general, sleep disruption is associated with elevated levels of cortisol, as are some forms of depression.[5]

Estimated total cortisol levels decreased in the intervention arm and increased in the control arm during the study period, with the BLT group having a significant decrease at the end of the intervention period ($P = 0.04$). This difference was no longer significant at the end of the six-month follow-up period, with both arms showing an increase in cortisol levels from baseline.

Adverse effects were mild and occurred less in the control group than the intervention group. These included mild nausea, dizziness, and transient photophobia.

■ COMMENTARY

This Rutten et al randomized controlled trial not only provides Class I evidence that BLT is not more effective than control light in treatment of depression associated with PD, but also gives rise to other thought-provoking results.

It is interesting to consider the results in a different "light." Although there was no significant difference, results from both the control and BLT arms showed a reduction in mean HDRS values to non-depressed levels at the end of the three-month intervention period. While the low light intensity of the control group (200 lux) is thought to be too low to impact circadian rhythm, it certainly is possible that the use of the light box itself was helpful in addressing symptoms of depression. Rutten et al note that proper use of the box required a participant to structure their day, and that the schedule imposed at least an outline of a daily routine. A regular sleep and wake time can be helpful in re-establishing circadian rhythms and is an established adjunct tool for treating depression. The group recommends that future work incorporates a control arm without a scheduled time for the light box as well as another arm with scheduled sleep and wake times without use of the box. Such a study will help distinguish the actual active intervention.

It is useful to note that the improvement in HDRS scales occurred in both arms, but the sleep quality measures were significantly improved in the BLT arm only. It makes sense that this improvement in sleep is linked with the decrease in cortisol levels seen in the BLT arm as well. However, it does

Table 1: Results for Depression, Sleep Scales, and Serum Cortisol for Control and Intervention Groups at Baseline, Three Months, and Six Months

	Baseline	Three-month mark (end of active intervention)	End of six-month naturalistic follow-up (treatment as usual)
Mean HDRS	Control: 14.5 BLT: 14.7	Control: 8.3 BLT: 7.6 *P* = 0.59	Control: 5.9 BLT: 8.3 ***P* = 0.03**
Geriatric Depression Rating Scale	Control: 17.1 BLT: 17.9	Control: 14.9 BLT: 13.7 *P* = 0.80	Control: 12.3 BLT: 13.2 *P* = 0.90
Scales for Outcomes in PD — Sleep	Control: 2.0 BLT: 1.7	Control: 2.1 BLT: 2.2 *P* < 0.05	Control: 2.2 BLT: 2.0 *P* = 0.46
Total Cortisol (estimate)	Control: 25 BLT: 23.1	Control: 26.9 BLT: 19.6 ***P* = 0.04**	Control: 28.4 BLT: 27.2 *P* = 0.81

HDRS = Hamilton Depression Rating Scale; PD = Parkinson's disease; BLT = Bright light therapy
Significant findings are in bold.

give rise to question how the control arm patients noted a decrease in depressive symptoms without an improvement in sleep and if depressive disorder linked to PD is unique in this regard. Again, this clearly is an area for future investigation.

Finally, it is notable that at the six-month follow-up point, the HDRS scores in the control group were significantly lower than the comparable scores for the intervention group. As there was no control in place regarding treatment during the six-month period, it is difficult to know how to interpret this finding.

Again, future studies with long-term follow-up and active intervention during a longer period could be very useful.

It is important to keep in mind that the mean HDRS of patients in both groups at baseline indicated a mild to moderate severity of depression. Therefore, findings from this study cannot be generalized to those with more severe depressive disorder.

Given that this is a Norwegian study, it is worth considering that geographic factors (long winters with short daylight hours) affected results. Replication of this work in diverse locations and latitudes will help clarify this possibility.

Obtaining a light box may be a challenge for some patients. Guidelines can be found online and many online vendors have a range of devices with prices well under the $100 mark.[7] There may be some insurances that will reimburse for the boxes with a prescription indicating that 10,000 lux is to be used up to 40 minutes daily.

What is the take-home message from this study? It appears that in patients with PD who have mild to moderate MDD, use of any intensity light in the morning and evening may be associated with lowering depressive symptom intensity. Additionally, use of BLT at 10,000 lux for 30 minutes, twice daily may have the added advantage of improving subjective quality of sleep. With a relatively low cost and few adverse effects, the risk of recommending such a treatment is quite low and seems well worth the potential benefit.

The results remind providers to be attentive to the role that depression and insomnia play in functional impairment in PD, and to consider the potential for functional improvement by addressing the symptoms of these states. ■

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CANNABIS

ABSTRACT & COMMENTARY

Stopping Cannabis Improves Cognitive Function in Patients With Multiple Sclerosis

By Ulrike W. Kaunzner, MD

Assistant Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Kaunzner reports no financial relationships relevant to this field of study.

SYNOPSIS: The authors of a recent study evaluated the effect of discontinuing cannabis use in patients with multiple sclerosis. Stopping cannabis led to significant improvements in memory, processing speed, and executive function.

SOURCE: Feinstein A, Meza C, Stefan C, Staines RW. Coming off cannabis: A cognitive and magnetic resonance imaging study in patients with multiple sclerosis. *Brain* 2019;142:2800-2812.

Cannabis, a botanical that is categorized as a Schedule I category drug, is the most commonly used psychoactive substance worldwide. The botanical's best described compounds are terpenoids, flavonoids, and cannabinoids. Cannabinoids alter the release of neurotransmitters, and can be separated into phytocannabinoids, endocannabinoids, and synthetic cannabinoids. The two best-studied cannabinoids are tetrahydrocannabinol (THC) and cannabidiol (CBD), which interact differently with the known cannabinoid receptors CB1 and CB2. The legal use of cannabis, for recreational purposes as well as in its medically prescribed form, varies internationally as well as throughout the United States.

Patients with multiple sclerosis often suffer from symptoms such as spasticity, pain, paresthesia, insomnia, or depression. Recent studies show that approximately 16-20% of patients with multiple sclerosis (MS) currently are using cannabis, 47% have considered using cannabis, 26% have used cannabis in the past, and 20% have spoken with their physician about using cannabis. However, consistent benefit from cannabis use needs further investigation, and potential harmful effects on the central nervous system require careful evaluation. Because 40-80% of patients with MS have cognitive dysfunction, researchers need to assess cautiously if and how cannabis use might contribute to cognitive changes seen in patients with MS. Feinstein et al investigated the cognitive response of patients with MS who stopped using cannabis. They enrolled 40 patients who all started cannabis — smoked, vaped, or ingested — after their initial MS diagnosis. Fifteen participants took medically prescribed cannabis, and all participants reported cannabis use of at least four times per week. Only subjects who showed some baseline cognitive impairment were enrolled. Exclusion criteria were other neurological disorders, mental illness, and recent steroid use. Patients were divided into two groups, one continuing to use cannabis and the other discontinuing cannabis use. The latter group was offered counseling and alternative therapies in case of withdrawal symptoms or increased MS symptoms. The two groups matched neurologically and demographically. The tester was blinded at the beginning of the study, and all participants underwent a battery of cognitive testing at baseline and after 28 days. In addition, baseline and 28-day magnetic resonance imaging results were obtained. Participants who stopped using cannabis had better cognitive function on several cognitive tests and faster reactive times after being off cannabis for 28 days. The patients who stopped cannabis also showed increased brain activation in regions associated with the test performance.

■ COMMENTARY

This is an important study. Feinstein and colleagues demonstrated that cognition and processing speed improved in those patients with MS who were taken off cannabis, indicating that

cannabis may have a negative effect on mentation in these patients. A small number of studies so far have evaluated the effect of cannabis on cognition, especially in patients with MS, and this is an excellent and much-needed contribution to the field.

As acknowledged by the authors, a challenge was that the subjects were on different forms of recreational and medically prescribed cannabis, and the respective amounts of THC and CBD were not known. They concluded that the majority of products contained potent levels of THC. According to other studies, there is some evidence that THC, the psychoactive cannabinoid, has a positive effect on nausea, sleep, and pain. However, it might have a negative effect on memory, cognitive processing, attention, and executive function. On the other hand, CBD reportedly has anxiolytic, anticonvulsant, and anti-inflammatory effects. There is some preliminary evidence of the effect of CBD on cognition, suggesting that it might have a neutral, beneficial, or, if taken in conjunction with THC, protective effect.

The overall reported cannabis use among patients with MS is around 20%, and the percentage could increase with legalization of cannabis and increased use of prescribed medical marijuana. Because patients with MS subjectively report positive effects after cannabis use, further studies with larger cohorts, longer observation times, and comparisons of patients with relapsing-remitting vs. progressive MS are needed to evaluate the positive and negative effects of cannabis. Recreational cannabis and medically prescribed cannabis contain both THC and CBD, and it might be important to decipher the effects of each compound and investigate their effects on the nervous system independently.

In conclusion, this is an important study, since cannabis is a frequent topic of discussion in daily neurological practice and is more and more part of symptom management of patients with MS. This study prompts a careful review of risks and benefits of medical and recreational cannabis use in this patient population, and the effect on cognitive function needs to be discussed carefully. ■

ANEMIA

SHORT REPORT

Iron Absorption in Iron Deficiency Anemia With Alternate-Day Dosing

By Jessica Orner, MD

Family Medicine Physician, Lebanon, PA

Dr. Orner reports no financial relationships relevant to this field of study.

SYNOPSIS: In a cohort of 19 women with iron deficiency anemia, alternate-day doses of iron led to 40-50% more iron absorption compared to consecutive-day doses.

SOURCE: Stoffel NU, Zeder C, Brittenham GM, et al. Iron absorption from supplements is greater with alternate day than with consecutive day dosing in iron-deficient anemic women. *Haematologica* 2019. pii:haematol.2019.220830. doi:10.3324/haematol.2019.220830.

Researchers in this study evaluated iron absorption in women with iron deficiency anemia using an alternate-day administration. Study participants were recruited from otherwise healthy women participating in a blood donation drive in Switzerland. A cohort of 19 women participated in two study cycles of six days in length with 16 days between the cycles. The participants were randomly assigned to receive three doses of either 100 mg or 200 mg of ferrous sulfate on days 2, 3, and 5 of the study cycles. If the participant received 100 mg during the first cycle, she received 200 mg during the second and vice versa. The median hemoglobin level was 11.5 mg/dL.

Summary Point

- Oral iron intake was associated with increased hepcidin levels and decreased subsequent iron absorption for at least 24 hours after the first iron dose.

Iron absorption was measured by labeling the ferrous sulfate with iron isotopes. The doses given on days 2, 3, and 5 each had a different isotope label. Iron absorption was assessed by measuring isotopic enrichment in red blood cells 16 days after the third dose of ferrous sulfate was administered. Fractional iron absorption was found to be 40-50% higher on days 2 and 5 compared to day 3 ($P < 0.001$). Absorption on days 2 and 5 did not differ significantly from each other, meaning that 40-50% more iron was absorbed when there were at least 24 hours between iron doses compared to consecutive days of dosing.

Stoffel et al also evaluated serum hepcidin levels in relation to iron absorption as a secondary outcome in women with iron deficiency. Hepcidin is the main regulator of iron in the body. High serum hepcidin levels are associated with decreased dietary iron absorption and storage.[1] There is a theory that enterocytes exposed to large doses of iron do not absorb subsequent iron doses over the next five to six days, also known as the "mucosal block" theory. The researchers aimed to evaluate if there was a continued decrease in iron absorption after the serum hepcidin levels tapered that may be linked to decreased enterocyte absorption. In this study, hepcidin levels did increase after iron intake and those increases persisted for 24 hours. There was not a decrease in iron absorption after 48 hours, which argues against the "mucosal block" theory. From this study, it would be difficult to know if there was any mucosal block in the first 24 hours due to the confounding presence of hepcidin.

While small, this study provides evidence that alternate-day dosing of iron would be beneficial in women with iron deficiency. It showed that they have increased serum hepcidin levels and decreased absorption of iron for at least the first 24 hours after a dose of 100 mg to 200 mg of ferrous sulfate. Based on this information and the information already known about hepcidin's role in iron absorption, clinicians should consider counseling iron-deficient patients to take their iron supplements every other day for better absorption. While alternate-day dosing of iron may lead to better absorption, there is the concern for adherence to an alternate dosing schedule. It would be interesting to see a future study on adherence to this type of schedule to determine efficacy. ■

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VITAMIN D

SHORT REPORT

Mortality and Vitamin D Supplementation: A Meta-Analysis

By Jessica Orner, MD

Family Medicine Physician, Lebanon, PA

Dr. Orner reports no financial relationships relevant to this field of study.

SYNOPSIS: In this systematic review and meta-analysis of randomized controlled trials, researchers determined that when compared with placebo or no treatment, vitamin D supplementation alone was not associated with an increase in overall all-cause mortality, though there were some nuances based on vitamin D form and type of mortality.

SOURCE: Zhang Y, Fang F, Tang J, et al. Association between vitamin D supplementation and mortality: Systematic review and meta-analysis. *BMJ* 2019;366:l4673. doi:10.1136/bmj.l4673.

Researchers from observation studies have shown an association between low serum vitamin D levels and higher mortality. In this systematic review and meta-analysis of randomized controlled trials, researchers investigated whether vitamin D supplementation was associated with lower mortality in adults. The researchers conducted an analysis of 52 randomized controlled trials involving a total of 75,454 participants

Summary Point

- When evaluating specific forms of vitamin D, sub-analyses found that all-cause mortality was lower in trials with vitamin D_3 than with vitamin D_2.

gleaned from Medline, Embase, and Cochrane Central Register databases from inception through Dec. 26, 2018.

Trials excluded from analysis were those including pregnant or lactating women, the critically ill, vitamin D analogs, or in which all participants received vitamin D. For example, if both arms of a study included vitamin D supplementation, that trial was excluded. The analysis focused on vitamin D supplementation vs. placebo or no treatment. If other agents, such as calcium, were given in a trial, it had to be the same dosage in all groups. All-cause mortality was the primary outcome, with cerebrovascular disease mortality, ischemic heart disease mortality, cancer mortality, cardiovascular mortality, and non-cancer or non-cardiovascular mortality, being secondary.

Researchers determined that when compared with placebo or no treatment, vitamin D supplementation alone was not associated with either a positive or negative effect on overall all-cause mortality (risk ratio [RR], 0.98; 95% confidence interval [CI]; 0.95-1.02; I2 = 0%). However, when evaluating specific types of vitamin D, sub-analyses found that all-cause mortality was lower in trials with vitamin D_3 (cholecalciferol) than with vitamin D_2 (ergocalciferol) (*P* for interaction = 0.04). Vitamin D supplementation was associated with a reduction in cancer mortality (RR, 0.84; 95% CI; 0.74-0.95; I2 = 0%), but only in those receiving vitamin D3 supplementation. There was no significant reduced risk of cardiovascular mortality, death from cerebrovascular disease, or ischemic heart disease.

Regarding mortality benefits, there is not strong enough evidence to recommend vitamin D supplementation for the general adult population. Vitamins D_2 and D_3 come from different sources, with D_2 mainly coming from plant and some culinary mushrooms, whereas animal sources contain D_3. It appears that if vitamin D has a mortality benefit, it is more likely to be the D_3 form; however, more studies researching that form are needed before changing clinical practice. In this study, researchers did not provide commentary on the role of serum vitamin D levels or whether study participants had known deficiencies, which arguably may be even more important than the form of vitamin D ingested. ■

PROBIOTICS

ABSTRACT & COMMENTARY

Effects of Probiotics on Cognition and Falls Risk in Patients With Cirrhosis

By Neal S. Parikh, MD, MS

Assistant Professor of Neurology, Weill Cornell Medical College

Dr. Parikh reports no financial relationships relevant to this field of study.

SYNOPSIS: Patients with cirrhosis and mild cognitive impairment and falls were randomized to a probiotic formulation vs. placebo. Probiotic treatment improved cognitive outcomes and reduced the risk of falls.

SOURCE: Román, E, Nieto JC, Gely C, et al. Effect of a multistrain probiotic on cognitive function and risk of falls in patients with cirrhosis: A randomized trial. *Hepatol Commun* 2019;3:632-645.

Editor's Note: Integrative Medicine Alert *has run numerous articles over the years detailing the effects of probiotics on human health, albeit with a focus on gastrointestinal conditions. Recently, the net on important probiotic research is being cast wider, and this article is a perfect example of that expanded hypothesized role for supplemental "good" bacteria. Cognitive impairment in people with cirrhosis is a limited demographic that may or may not have direct applicability to our patient panels. However, these patients have a particularly compelling need (poor outcomes with cognitive impairment), and this research also begs the question of which other central nervous system disorders may respond to probiotic supplementation. Hopefully, in future issues, we can offer updates as researchers share their results relevant to the brain-gut connection that possibly can be mediated by probiotics.*

— David Kiefer, MD

Hepatic encephalopathy is a hallmark feature of decompensated liver cirrhosis. Cognitive impairment in the form of minimal or covert hepatic encephalopathy is also common in cirrhosis without decompensation. Individuals with cirrhosis and cognitive impairment have poor outcomes, including traffic accidents and falls.

Cognitive impairment in cirrhosis is thought to be caused by hyperammonemia and neuro-inflammation. Gut dysbiosis, or the disruption of a healthy gut microbiome, is an area of increasing research interest as pertains to vascular and cognitive disorders. In cirrhosis, dysbiosis may contribute to systemic inflammation when there is a high burden of pathological bacterial translocation through a disrupted intestinal barrier. For these reasons, Román and colleagues and other research groups have identified the gut microbiome as a potential target for the treatment of cognitive impairment in patients with cirrhosis. Several prior studies demonstrated a favorable effect of probiotics on cognitive measures in this population.

Prior studies focused on the prevention and amelioration of hepatic encephalopathy, whereas Román and colleagues shifted their focus to include falls prevention. They hypothesized that multistrain probiotic supplementation would decrease falls risk in part through improved cognition. Secondarily, they hypothesized that probiotic supplementation would decrease systemic inflammation and intestinal barrier disruption. They did not perform explicit tests of mediation to test these hypotheses.

The authors included consecutive patients from a single center with cirrhosis and mild cognitive dysfunction and/or prior falls. Cognitive dysfunction was defined using the Psychometric Hepatic Encephalopathy Score (PHES), which is a gold standard, comprehensive, validated battery for the assessment of hepatic encephalopathy. Importantly, they excluded patients with overt hepatic encephalopathy, active alcohol users, and those on treatment for hepatic encephalopathy.

Patients were randomized to a probiotic vs. placebo for 12 weeks. They were evaluated at baseline, after 12 weeks of treatment, and eight weeks after the end of treatment. Their key clinical outcomes were cognitive function using the PHES, risk of falls using validated gait metrics, and incidence of falls. Additionally, they measured C-reactive protein (CRP), tumor necrosis factor alpha (TNA-α), interleukins 6 and 10, neutrophil oxidative reserve, and markers of intestinal barrier integrity.

They screened 279 patients to randomize 36. The two groups were well-balanced. Overall, two patients (6%) died during the short study period. Cognitive function improved over 12 weeks with probiotic treatment ($P = 0.006$) but not with placebo. Similarly, patients randomized to probiotic treatment had significantly improved gait by two parameters, without changes in the placebo-treated patients. While they lacked power to detect statistically significant differences in incident falls, probiotic treatment resulted in nominally fewer falls (0 vs. 4; $P = 0.10$). They also lacked power for safety outcomes, but did not detect a difference in serious events.

These findings correlated with reductions in systemic inflammation as measured by CRP and TNF-α, in addition to improved neutrophil oxidative reserve, among only probiotic-treated patients. In parallel, probiotic treatment decreased markers of intestinal barrier disruption. The authors concluded that probiotic treatment may improve cognition and decrease falls in patients with cirrhosis, perhaps through amelioration of pathological bacterial translocation, intestinal barrier breakdown, and systemic inflammation.

■ COMMENTARY

As the authors acknowledge, the small sample size is a key limitation. However, their study is elegant and rigorous. The found a consistent direction of effect across multiple complementary outcomes, which increases the validity of their results. The authors allege that their exacting exclusion criteria — excluding those with overt hepatic encephalopathy — is a limitation. While this certainly limits generalizability, their selection criteria had a fortuitous outcome: they demonstrate the effectiveness of probiotic treatment among patients with minimal or covert hepatic encephalopathy. This is important because minimal and covert encephalopathy are far more common and present earlier in cirrhosis. These patients have a longer period during which to derive cognitive and falls-related safety benefits. In this light, the findings of this study may in fact have more clinical translational potential. With increasing interest in understanding the role of chronic liver diseases in cognitive impairment, their findings may have therapeutic potential in a larger population than they anticipated. Further validation of their findings in patients with milder chronic liver diseases may yield novel opportunities for the treatment of cognitive impairment and the prevention of falls. ■

SHORT REPORT

Predictors of Response to a Specific Psychological Treatment in Chronic Low-Back Pain

By Ellen Feldman, MD

Altru Health System, Grand Forks, ND

Dr. Feldman reports no financial relationships relevant to this field of study.

SYNOPSIS: A theoretical model employed to predict response to either mindfulness meditation, cognitive therapy, or mindfulness-based therapy in patients with chronic low-back pain showed evidence that this type of model may be useful in determining which patients are most likely to benefit from a specified intervention.

SOURCE: Day MA ,Thorn B, Ehde DM, et al. Moderators of mindfulness meditation, cognitive therapy, and mindfulness-based cognitive therapy for chronic low back pain: A test of the limit, activate, and enhance model. *J Pain* 2019. pii:S1526-5900(18)30909-X. [Epub ahead of print].

Psychological treatment such as cognitive therapy or a mindfulness-based intervention have a good track record in treatment of chronic low-back pain (CLBP), especially when combined with exercise.[1,2] However, data to support recommendation of one type of psychological treatment over the next is lacking.

Day et al noted that while pooled results of trials with these interventions show evidence of efficacy, individual responses to psychological interventions in CLBP vary. The goal of this study is to apply a theoretical model to understand individual variation and help predict which patient characteristics are most significant in determining response to a specified behavioral therapy. In a pilot trial involving 69 adults with CLBP, Day et al compared mindfulness meditation (MM), mindfulness-based cognitive therapy (MBCT), and cognitive therapy (CT) in treatment of CLBP. This article reports a secondary analysis of the results from the pilot trial and looks at the differential response to these interventions.

Hypothesized moderators of response were degree of pain catastrophizing (measured with a scale), data regarding alpha and theta waves (measured via electroencephalography [EEG]), and baseline strength in mindfulness (measured with two scales).

Alpha and theta waves are termed "slow-wave" oscillations and represent a nonaroused, relaxed state of mind.[3] The initial hypothesis was that participants with low levels of these waves would have a strong response to mindfulness interventions.

Scales and EEG data were collected pretreatment on the 69 eligible adult patients with CLBP; the entire group was then randomized to receive one of the three therapies over an eight-week period.

Summary Points

- Researchers performed a secondary analysis of results from a trial of 69 patients comparing mindfulness meditation, cognitive therapy, or mindfulness-based therapy to treat chronic low-back pain.
- A theoretical model of moderation — Limit, Activate, and Enhance (LA+E) — is employed to see if specified patient characteristics measured pretreatment are associated with greater or lesser response to each of the evidence-based psychosocial treatments utilized in the study.
- While the findings do not support hypothesized results in full, the findings do support the likelihood that patient response to a specified intervention is based on individual characteristics; further study may help in selecting the optimal intervention for individuals.

Follow-up outcome measures included pain interference, physical function, and depression.

The Limit, Activate, and Enhance (LA+E) model is a theoretical construct used in this study to anticipate which patients would respond better to MM, MBCT, or CT in treatment of CLBP. For example, the theory postulates that pain catastrophizing is a key limiting factor for interventions utilizing cognitive restructuring. Thus, the model predicts that patients with higher baseline catastrophizing would benefit selectively from such interventions. In fact, this was not the case, and patients who responded best to MBCT were those with low baseline levels of catastrophizing.

The LA+E model also predicted that patients with low levels of specific brain waves (alpha and theta) would selectively respond to mindfulness-based interventions. Again, this was not the case; higher levels of theta activity were associated with more robust treatment outcomes with MBCT.

Interestingly, the results indicate in many cases that there was an association between patient characteristics and differential response to a specific intervention. However, the responses were often at odds with the initial hypothesis, leading Day et al to speculate that there is a deeper complexity to predicting response than initially perceived.

In all, Day et al noted that the application of this theoretically derived model needs significant modification, but deeper analysis reveals the model has promise in understanding which patient characteristics are best suited for treatment with a specific psychological intervention. Revision of the model, replication with larger sample sizes, and control for factors, such as patient preference and cognitive deficits, are required to advance our understanding of the potential benefits of using such an approach.

Day et al bring to the table a unique, but preliminary method of determining patient suitability for a specified psychological intervention in the treatment of CLBP. The hope is that further investigation in this arena will lead to a clear indication of patient characteristics that point to a response from a specific intervention. For now, the resounding message from this study is that psychological treatment in CLBP is not "one size fits all." This study reminds providers that patients will often have a differential response to different psychological interventions to treat CLBP, and that there is a possibility of responding to a new method if the initial intervention is unsuccessful. ■

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CME QUESTIONS

1. **According to Rutten et al, bright light therapy may be helpful in Parkinson's disease in the treatment of:**
   a. Depression: Although it does not appear more useful than lower intensity light therapy, in this study both the intervention and control groups were associated with lower scores on the Hamilton Depression Rating Scale.
   b. Sleep quality: Although it does not appear more useful than lower intensity light therapy, in this study both the intervention and control groups were associated with better subjective sleep quality.
   c. Movement: Although it does not appear more useful than lower light therapy, in this study both the intervention and control groups were associated with increased mobility and flexibility.
   d. Speech: Although it does not appear more useful than lower light therapy, in this study both the intervention and control groups were associated with better articulation and expressive speech.

2. **The study findings by Stoffel et al support which of the following statements?**
   a. Increased hepcidin levels are associated with better iron absorption.
   b. Daily dosing of iron is more beneficial than alternate-day dosing.
   c. Fractional iron absorption was found to be 40-50% higher during alternate-day dosing.
   d. Increased serum hepcidin levels persist for 72 hours in women with iron deficiency.

3. **In the sub-analysis by Zhang et al, which form of vitamin D was associated with low all-cause mortality?**
   a. Vitamin D_2
   b. Vitamin D analogs
   c. Hydroxylated vitamin D
   d. Vitamin D_3

4. **Psychological interventions with evidence-based efficacy in chronic low back pain (CLBP) include mindfulness mediation, mindfulness-based cognitive therapy, and cognitive therapy. Which of the following is true about these interventions?**
   a. All three interventions can be used interchangeably for CLBP — there is no evidence that individual variation of response is significant.
   b. While these all have evidence-based efficacy, individuals vary in responsiveness and attempts are being made to categorize these individual variations.
   c. While these all have evidence-based efficacy, individuals vary in responsiveness but attempts to categorize these individual variations have little promise thus far.
   d. All three interventions can be used with caution for CLBP — there is emerging evidence that individual variation of response is significant, but only in a select population.

[IN FUTURE ISSUES]

- Heart Disease and Stroke Risk in Vegans and Vegetarians
- The Health Effects of Magnesium: Part 2
- Nuts vs. Carbohydrates in Patients With Diabetes
- Optimism and Longevity