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ABSTRACT & COMMENTARY

Kratom Alert: FDA Concerns

By David Kiefer, MD, Editor

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

SYNOPSIS: Kratom, a plant that is banned in some countries, is available in the United States and has some safety concerns, mostly related to its opioid-like effects.

SOURCE: FDA Statement. Statement from FDA Commissioner Scott Gottlieb, M.D. on FDA advisory about deadly risks associated with kratom. Nov. 17, 2017. Available at: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm584970.htm. Accessed Jan. 7, 2018.

This Abstract & Commentary is drawn from a U.S. Food and Drug Administration (FDA) press release, differing from the focus on randomized, controlled trials, as is more typical for *Integrative Medicine Alert* reviews. The primary reason for this is to highlight an important safety concern, and weave in some of the recent background research relevant to this natural product.

Kratom (*Mitragyna speciosa*, Family Rubiaceae) is a tree found in Southeast Asia and Africa, and its leaves are used medicinally, usually as a tea, for a variety of health conditions.[1] In the United States, it is marketed as a safe natural substance for the treatment of pain, anxiety, and depression. As per the FDA press release, there is the concern about the self-treatment of these serious conditions, but also the fact that kratom appears to have opioid-like effects and the expected issues of addiction, withdrawal, and death; 36 deaths have been reported. Outside of the supervision of a licensed health-care provider, kratom also is being used to treat opioid withdrawal, another FDA concern. There has been a marked increase in calls made to U.S. poison control centers about the use of kratom-containing products.

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Summary Points

- Kratom leaves have a long history of traditional use in Southeast Asia for a variety of health conditions.
- At low doses, it appears to have stimulant effects; at higher doses, opioid-like effects are seen.
- Adverse effects have been demonstrated, often associated with opioid effects or withdrawal.

At the end of the press release, the FDA director reminded the scientific community and the public at large about the process that exists for drug applications and the evaluation of dietary supplements, a path that he recommended for kratom or any other substance touted to be part of the solution to the opioid epidemic. The FDA considers kratom to be an unapproved drug and has "taken action against kratom-containing dietary supplements." Officials are seizing the shipments and destroying the product, as the FDA continues the process of investigating the safety and efficacy of this botanical medicine.

■ COMMENTARY

Not all plants or natural products are safe. Kratom is one plant that may fall into this category, but the story is more complicated. Kratom contains more than 40 phytochemicals in the class of indole alkaloids, the primary one being mitragynine, although 7-hydroxymitragynine also is mentioned commonly in the literature.[1,2,3] The content of the alkaloids varies depending on geographic location, plant age, and numerous other factors, affecting the physiological effect of the plant. Storage also may play a role; mitragynine may be converted to 7-hydroxymitragynine upon exposure to air.[3]

An additional layer of complexity stems from the effect of kratom on opioid receptors. At the mu-opioid receptor, kratom extracts show both agonist (mitragynine) and antagonist (other alkaloids) activity.[1,2] Kratom extracts appear to be weak competitive antagonists at kappa-opioid receptors and weak antagonists at delta-opioid receptors, although extrapolating from some of this animal research to human effects is difficult and still needed.[1,3] Mitragynine also may bind to other central nervous system receptors, including alpha-2-adrenergic, adenosine, serotonin, and dopamine.[1] Much of the differential receptor binding is thought to be dose dependent, with opioid effects occurring at higher dose ranges. It is thought that the opioid effects of mitragynine are 13 times more potent than morphine, and those of 7-hydroxymitragynine are even more potent.[4]

Most people use kratom in a dose less than 8 grams per dose, delivering 120 to 180 milligrams of mitragynine.[1] It is thought that a stimulant effect may occur in doses of 1 to 5 grams, with more opioid-like effects occurring at or above 8 grams.[1,2,3] These latter effects are where kratom has been used for opioid withdrawal symptoms.

Adverse effects have been documented. Fatalities have occurred with the use of a product called Krypton, a blend of mitragynine and O-desmethyltramadol, although it is unknown which of the compounds ultimately caused the deaths.[2] Other adverse effects include hypertension, cognitive changes, dependency, and several cardiovascular and gastrointestinal system effects.[4] Kratom overdose has been described and may be associated with seizures. A withdrawal phenomenon, not unlike opioid withdrawal, also is being seen.[4]

As some experts have mentioned, there is potential for kratom to play a role in the opioid epidemic, but there remains a lot of scientific work to be done to arrive at a consistent recommendation about safety and efficacy.[3] More human clinical trials are necessary as are basic pharmacokinetics. Does basic science research on animals extrapolate to humans? Quality control and product labeling seem to be important given the phytochemical variations that have been documented, and they could affect the physiological effects of kratom significantly. This

latter issue is not unlike challenges facing many other herbal products — one of the reasons for the development of such initiatives as the Botanical Adulterants Program through the American Botanical Council and the widespread use of third-party certification programs.

Is the FDA approach of product seizure and action against kratom-containing dietary supplements justified? Clinicians are comfortable with a "do no harm" approach to patient care, so perhaps for now, as some of the basic pharmacokinetics and clinical effects are clarified, a "use no kratom" strategy seems warranted. ■

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CARDIOVASCULAR DISEASE

ABSTRACT & COMMENTARY

Are All Plant-based Diets Created Equally (in Terms of Health Benefits)?

By Ellen Feldman, MD

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

SYNOPSIS: This large-scale, observational, prospective study investigating types of plant-based diets found an increased risk of cardiovascular disease in adherents to plant-based diets containing foods such as fruit juices, refined grains, sweetened beverages, and desserts.

SOURCE: Satijam A, Bhupathiraju S, Spiegelman D, et al. Healthful and unhealthful plant-based diets and the risk of coronary heart disease in U.S. adults. *J Am Coll Cardiol* 2017;70:411-422.

It is widely accepted that vegetarian diets are associated with lower risk of coronary heart disease (CHD).[1] Or are they? Although many studies have demonstrated this association, Satijam et al noted two crucial limitations of these earlier studies. Specifically, they postulated that all plant-based foods are not equally protective of cardiovascular risk and noted that even incremental shifts in composition of diet may affect the degree of cardiovascular protection. Furthermore, they ascertained that previous studies were not designed to discern these subtleties of diet.

To investigate further, the researchers obtained dietary data from the Nurses' Health Study[2] beginning in 1976, Nurses' Health Study 2[2] beginning in 1989, and the Health Professionals Follow-up Study[3] beginning in 1986 to analyze any association between specific dietary factors and later development of CHD. After excluding participants with baseline CHD and other specified conditions, baseline data from 160,000 women and 40,000 men were available for analysis.

They created three types of indices for plant-based diets — each index allowed for continuous gradation within the general category. The expectation was that this approach allows analysis of gradual changes in diet. The plant-based diet index (PDI) weights plant-based foods over animal foods; a healthful plant-based diet index (hPDI) weights dietary consumption of whole grains, fruits, nuts and vegetables, and vegetable oils; and an unhealthful plant-based diet (uPDI) emphasizes processed foods, refined grains, sweetened beverages, and sweets. As all the diets allowed for gradation, each included some degree of animal-derived foods.

Satijam et al examined dietary data from the participants' food frequency questionnaire completed every two to four years and created 18 food groups. The food groups were assigned positive or negative scores depending on the index. (*See Table 1.*) For example, fruits were assigned positive scores for PDI and hPDI and negative scores for uPDI, while sweets were assigned positive scores for PDI and uPDI and negative scores for hPDI. All animal food products were assigned negative scores. The indices were obtained by summing the scores for the 18 food groups; these were adjustable to account for changes over time. Higher indices indicated lower consumption of animal foods; however, it is important to note participants in the highest PDI decile still consumed an average of three servings a day of animal food

Summary Points

- Dietary data from the Nurses' Health Study and the Health Professionals Follow-Up Study included information from more than 200,000 health professionals in the United States; foods consumed were categorized according to health benefits and derivation (plant or animal.)
- Three general dietary indices allowing for gradation within each were created: a generic plant-based diet index (PDI); a healthy plant-based diet index emphasizing whole grains, fruits, and vegetables (hPDI); and an unhealthy, plant-based diet containing more processed foods and sweetened foods (uPDI).
- Researchers used a statistical analysis to study the development of cardiac heart disease over time in each decile of each index and accounted for variables including development of disease over time, smoking, exercise, and aging.
- The strongest inverse association with coronary heart disease was found in the top decile with hPDI ($P < 0.001$) and less so with PDI ($P = 0.003$); on the contrary, there was a positive association with uPDI and coronary heart disease ($P < 0.001$).

(the lowest contained five to six servings of animal food daily). Additionally, the authors conducted a separate analysis by assigning positive values to healthy animal foods, such as fish and eggs, and reverse scores to unhealthy animal foods, including red meat and animal and dairy fat. This was a prospective study, first collecting the dietary information, adjusting for variables over time, and then looking at incidence of CHD over a period of 20 to 30 years.

SELECTED RESULTS

Each index was divided into deciles reflecting increasing compliance with the diet, and cumulatively averaged over time to evaluate the effect of a long-term diet. Each decile was evaluated separately from each data source (Nurses' Health Study, Nurses' Health Study 2, and Health Professionals Follow-up Study); data then were pooled for further analysis.

The pooled results adjusted for multiple variables revealed an inverse association between CHD and adherence to either PDI and hPDI. This inverse association was strongest when comparing the first decile (lowest compliance with diet) to the last decile (highest compliance with diet.) The association was more pronounced for hPDI than for PDI (*See Table 2.*) Interestingly, the inverse association was evident by the second decile for adherents to both diet types, but appeared to accelerate by the sixth decile. On the other hand, the association between uPDI and CHD was positive in all deciles. Table 2 includes results from decile 10 for each index (most compliant with diet), with pooled data from all three sources and applying multivariable adjustment for age, smoking status, and weight, among other factors.

Table 1: Examples of Food Groups and Scores

Foods assigned positive scores for hPDI/negative scores for uPDI	Foods assigned positive scores for uPDI/negative scores for hPDI
Whole grains, cooked oatmeal, brown rice	Refined grains, white bread, white rice, sweets
Fruits and vegetables	Fruit juices
Nuts, legumes	Potatoes
Tea, coffee	Sugar-sweetened beverages

■ COMMENTARY

"Eat food. Not too much. Mostly plants." This plain-spoken advice comes from Michael Pollan, well-known writer about food and health topics and author of several books, including *The Omnivore's Dilemma*.[4] Many in the general public and in medicine alike view his message (along with confirming medical studies regarding the health benefits of plant-based diets) quite seriously, and strive to adjust diets accordingly. However, the application of a plant-based dietary approach varies widely. For example, in a recent *U.S. News & World Report* article regarding the "best" plant-based diets, the experts whittled the choices to no less than 12, including Mediterranean, vegan, vegetarian, and flexitarian to name just a few.[5] A basic internet search reveals a range of even more vegetarian diets, including pesco-vegetarian and lactovegetarian.[6] When faced with a seemingly endless array of choices, finding the type of plant-based diet most beneficial to health seems a formidable task.

Satijam et al helped to clarify and put a scientific spin on this endeavor by investigating what types of "mostly plant" foods are beneficial for cardiovascular health and by trying to understand if partial compliance or gradation of dietary adherence confers cardiovascular benefits. Additional information from this study is the analysis of data pertaining to diets containing animal foods, such as fish, eggs, and some dairy, thought to be beneficial to health.

The numbers behind this study are impressive, with more than 200,000 subjects studied for more than 20 years. However, one limitation is the lack of geographical, racial, occupational, and socioeconomic diversity in

Table 2: Selected Results of the Top Decile, With HR and *P* Values Reflecting Comparison of Extreme Deciles Within Each Group

Diet	Hazard Ratio (95% CI)	*P* value
PDI decile 10	0.92 (0.83-1.01)	= 0.003
hPDI decile 10	0.75 (0.68-0.83)	< 0.001
uPDI decile 10	1.32 (1.20-1.46)	< 0.001
When hPDI was modified to score fish, egg, and most dairy positively (rather than lumping these with all other animal products), results changed very little. The row below illustrates these results.		
hPDI including egg, fish, most sources of dairy	0.78 (0.71-0.86)	< 0.001

subjects — by definition all are U.S. healthcare professionals. Extending the pool to encompass a more diverse group would help confirm or further define the health effects of dietary changes. Likewise, looking at the health effects of dietary change at specific ages can assist in giving patients relevant and applicable information. Other limitations might be the lack of inclusion of fat source(s) or dairy consumption, known contributors to health outcomes.

Other recent studies support the benefits of plant protein intake in particular. In 2016, Song et al examined U.S. health professionals' diet and all-cause mortality and concluded that higher ingestion of animal protein was associated with higher mortality rates (and the converse for higher intake of plant protein).[7]

The Satijam et al study as it stands has immediate clinical applications. The results clearly support the premise that all plant-based diets are not "created equal;" that is, every plant-based food does not convey equal health benefits. The inverse association of the hPDI with CHD risk implies that a diet rich in whole grains, fruits, vegetables, nuts, and legumes conveys cardiovascular protection and can be recommended "whole-heartedly." The positive association with uPDI and CHD implies the opposite — that "vegetarian" foods, such as processed grains and sweetened beverages, do not convey health benefits. Furthermore, it is useful to be able to tell patients that strict adherence to a diet with healthy foods is not necessary to achieve a degree of protection and that this study looked at gradation of adherence, that is with an emphasis on these healthy foods in a diet rather than absolutes.

When working with patients preventively, providing information that stepwise dietary changes can help with cardiovascular protection may make the prospect of dietary modification seem attainable. Reminding patients that protein can be obtained from plant sources, that not all non-animal foods are equally beneficial, and that some animal foods, such as fish, eggs, and nonfat dairy, may convey health benefits are important elements to consider when helping shape a heart-healthy diet.

If a patient has clear cardiovascular risk or has suffered a cardiovascular event, this information grows in importance. Providing patients with clear data and information helps move vague dietary recommendations to clear and concrete implementation — a useful and natural step for the integrative provider in clinical practice. ■

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DEMENTIA

ABSTRACT & COMMENTARY

Aerobic Exercise and Cognitive Impairment

By Jessica Orner, MD

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

SYNOPSIS: Progressive aerobic exercise training appears to be a low-risk and effective intervention for improving cognitive function in community-dwelling adults with mild subcortical ischemic vascular cognitive impairment.

SOURCE: Liu-Ambrose T, Best JR, Davis JC, et al. Aerobic exercise and vascular cognitive impairment: A randomized controlled trial. *Neurology* 2016;87:2082-2090.

Cognitive impairment affects an estimated 16 million people in the United States. Dementia affects between 2.4-5.5 million, with approximately 1 million new cases projected per year.[1] Cognitive decline and dementia are common concerns among older adults and can bring significant financial and emotional burden to many families. In 2012, the total healthcare cost for dementia was approximately $200 billion annually, not including the estimated $210 billion from informal care givers.[1] With all these concerns, there is increasing research on preventive treatment options for cognitive impairment. Cognitive impairment generally is a limitation in mental functioning. Cognitive impairment can be further divided into areas such as mild cognitive impairment and dementia. Whereas mild cognitive impairment does not affect independent activities of daily living (IADL), dementia is defined as a decline in at least two of five cognitive domains (memory, attention, language, praxis, and executive functioning) not due to another medical or psychiatric condition and that affects IADLs.[1]

This article focused on subcortical ischemic vascular cognitive impairment (SIVCI), a subset of vascular cognitive impairment. Although vascular dementia is the second most common cause of dementia, SIVCI is the most common form of vascular dementia.[2] With the criteria used in this study, the participants were classified as having mild cognitive impairment with a high risk of developing dementia.

In this proof-of-concept, blind, randomized, controlled trial, the researchers examined the role of a progressive exercise training program on cognition and function symptoms in adults with mild SIVCI. The researchers considered a proof-of-concept study because of its small size and preliminary evidence of efficacy. They also believed that application of biomarkers would be useful to evaluate the role of exercise in cognitive functioning more rigorously.[2]

Participants included adults with a clinical diagnosis of mild SIVCI based on the presence of small vessel ischemic disease and cognitive syndrome. Small vessel ischemic disease was defined as evidence of neurologic signs consistent with subcortical brain lesions and evidence of cerebrovascular disease on brain MRI or CT. Cognitive syndrome was defined as a Montreal Cognitive Assessment (MoCA) score < 26/30 and a Mini-Mental Status Examination (MMSE) ≥ 20 at the initial screening.[2]

Study participants were randomized to progressive aerobic training for six months or usual care with education on vascular cognitive impairment. Participants were assessed at baseline, after six months of intervention, and six months after formal cessation of aerobic training.[2]

Summary Points

- There is preliminary evidence that progressive aerobic training improves cognitive function in people with mild subcortical ischemic vascular cognitive impairment.
- Improvements in cognitive function were not sustained six months after cessation of aerobic therapy.
- There was a small but not statistically significant improvement in executive function and activities of daily living.

The aerobic training involved thrice weekly classes lasting 60 minutes: 10-minute warm-up, 40-minute walk, and 10-minute cool down. The intensity of the program was monitored using heart rate, the Borg Rating of Perceived Exertion, and the "talk test." The talk test was defined as a starting at a pace that allowed comfortable conversation and progressing to a pace at which conversation was difficult.[2] The initial intensity of 40% of age-specific target heart rate was increased to 60-70% over the first 12 weeks of therapy, with a goal of 65%. Once at that goal, it was sustained for the remainder of the intervention period. If patients were on a beta-blocker, the subjective measures were given priority.

Study participants in the usual care with education group received monthly phone calls from research staff and education materials about vascular cognitive impairment and healthy nutrition. Based on the article, it is unclear if the aerobic training group also received educational materials.

For assessment, the researchers chose to assess cognitive performance primarily, global executive functions, and performance on ADL. The Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog), Executive Interview (EXIT), and Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL), respectively, were chosen as the assessment tools. Secondary outcomes included: six-minute walk test, body mass index, resting heart rate, and blood pressure.

Seventy-one individuals were recruited, of which 70 were included in the analyses. One participant was deemed ineligible because of a diagnosis of mixed dementia.

At six months, there were statistically significant differences in the ADAS-Cog performance (-1.71 point difference, 95% confidence interval [CI], -3.15 to -0.26;

P = 0.02), six-minute walk test (30.35 meter difference; 95% CI, 5.82-54.86; *P* = 0.02), and diastolic blood pressure (-6.89 mmHg difference; 95% CI, -12.52 to -1.26; *P* = 0.02), which decreased and were no longer significant by the six-month post-intervention assessment. No statistically significant differences were observed for EXIT and ADCS-ADL at the end of the intervention and six months post-intervention.

There were three adverse events, all of which were falls. Two occurred in the aerobic training group and one in the usual care group.

Compliance and feasibility were assessed during the study. The researchers determined that the intervention would be feasible if the following conditions were met:
1. Recruitment rate > 15%;
2. Withdrawal rate < 15%;
3. Average aerobic training class compliance of 60%.

The observed recruitment rate via telephone was 16%, while in person, the rate was 85%. The withdrawal rate was 10% in the overall sample, with 17% in the usual care group and 3% in the intervention group. Compliance with the aerobic training group was measured though attendance and was 68%.

The authors noted several concerns and possible pitfalls. As mentioned above, the positive cognitive effects of progressive aerobic training dissolved by the six-month post-intervention re-evaluation.[2] The reason for this was unclear. Further studies are needed to determine ways to improve compliance and if sustaining the regimen would leave positive effects intact. The authors mentioned that there may be a more sensitive tool for detecting modest changes in cognition, such as Vascular dementia Assessment Scale-cognitive (VADAS-Cog) instead of ADAS-Cog, but there were not enough data on these tools at the time of their intervention.[2]

■ COMMENTARY

This study suggests that progressive aerobic exercise therapy can improve cognitive function in mild sub-cortical ischemic vascular cognitive impairment. It is a low-risk intervention provided the participant is safe to exercise. It is also feasible to provide in the community setting.

Accessing instructors for progressive exercise therapy may be difficult in some areas. However, clinicians could calculate the goal heart rate and instruct patients on how to take their pulse and perform the talk test when exercising, provided their cognitive impairment does not affect understanding of the tasks. It may be useful to elicit the help of the patient's support system.

Vascular cognitive impairment is second to Alzheimer's disease as the most common cause of dementia. The improvements in ADAS-Cog correlated with decreased diastolic blood pressure, and this may be a way in which aerobic exercise improved cognition in those with mild SIVCI.[2] It would be interesting to see if the results could be generalizable to people with other types of dementia, including Alzheimer's disease, and non-community dwelling elders, such as those in nursing facilities.

It is also notable that many of the assessment tools were not created specifically to study vascular cognitive impairment. The ADAS-Cog is designed to measure cognitive areas that are seen to decline in Alzheimer's disease.[3] It is the most commonly used cognitive testing instrument for measuring cognitive change in dementia studies.[3] It consists of 11 parts and assesses cognitive functions, such as praxis, learning, and memory. However, studies show that ADAS-Cog is more precise for measuring the severity of cognitive dysfunction than the MMSE most used in the clinical setting.[4]

Designed to be administered by trained personnel, the EXIT is a 25-item questionnaire that assesses executive cognitive dysfunction in patients with mild dementia. ADCS-ADL comes in two versions: a 19-item version for patients with more severe dementia and a 23-item version for the assessment of ADLs in mild to moderate dementia.[5] The 23-item version was used for this study.

Although this study is promising for the possibility of using exercise training for treatment of cognitive impairment, more evidence is needed on the role of exercise in the prevention of dementia or cognitive decline.[6] ■

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A Novel Approach to Using Mind-Body Therapies for Chronic Pain

By Rebecca L. Fahey, PhD, MD, MBA

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

SYNOPSIS: Chronic pain is a multifactorial public health issue and the treatment plan needs to address all biopsychosocial aspects of this disease.

Chronic pain usually is defined as pain lasting more than three months. It can be devastating to patients and their families, with more than half of these patients ending up disabled.[1] Chronic pain is a worldwide public health crisis affecting more than 1.5 billion people, with the total costs in the United States reaching $635 billion, including lost work and medical expenses.[2,3] As a result of the growing public health concern and the prescription opioid crisis, the overall treatment plan for pain management is evolving into an integrative model that includes acupuncture, massage, and mind-body techniques to encourage patients to engage in multiple forms of self-care to promote long-lasting health.[4] The biopsychosocial approach to chronic pain includes all aspects of an individual's response to chronic pain.[5] A new approach incorporates the physical, social, psychological, and cultural aspects of a human being's perception of pain.[6]

Summary Points

- Patients should explore different mind-body therapies until they find some that reverberate with their lives. It may take several tries to find therapies that match each patient's pain profile because of bio-individuality.
- Non-pharmacologic therapies include exercise, multidisciplinary rehabilitation, acupuncture, mindfulness-based stress reduction, yoga, progressive relaxation, electromyography biofeedback, operant therapy, cognitive behavioral therapy, or spinal manipulation.
- Mind-body therapies can empower patients to begin a journey of healing. The physicians' role is one of support and encouragement.

In his book, *Quantum Healing*, Deepak Chopra, MD, described the conceptual analysis for understanding this phenomenon and provided the pathway from materialism, or focusing only on the body, into a real-life model focusing on the holistic perception of pain.[7] The issue with the materialistic viewpoint is that it considers the vast influence that a person's daily life has on his or her understanding and perception of chronic pain. Chopra illustrated that DNA encodes all of the biological processes in the body, defining it as the connection between the body and the mind, including the perception of pain, and that it governs the mechanisms of healing.[7] Mind-body techniques, such as meditation and mindfulness, directly affect the genes because the mind-body connection is completely spawned in the genes.[7] This idea reinforces the research examined in *Quantum Healing* that mind-body therapies are able to influence gene expression, that genes are alive, and that they may upregulate or downregulate in response to every patient experience.[7]

According to the theory of *Quantum Healing*, the starting point in the management of an integrative approach to healing begins with an examination of the patient's self-awareness regarding his or her perception of pain. Next, the approach to chronic pain management should be multifactorial to focus on addressing the messages from multiple sources, including genes. In effect, every signal of pain and the perception of pain originate within the DNA, as per this hypothesis. Then, with respect to treatment, mind-body therapies fortify the signals from the mind to the body, creating a situation in which wellness and happiness are possible. In this way, mind-body therapies give the patient many different ways to address and manage the stress in his or her life, and the pain signals alluded to above.[8] (*See Table 1.*)

Researchers have established that a patient's ability to handle stress affects how he or she deals with chronic pain. The research reflects many benefits of mindfulness-based stress reduction (MBSR) on improving a broad range of natural processes. Yet, current understanding of the effects of MBSR on the immune system and the neural networks within the brain is limited. Some researchers have begun to examine these effects at the cellular level. In a study by Kaliman et al, after a day of intense meditation, a group of expert meditators vs. controls showed swift changes in their expression of histone deacetylase

Table 1: Mind-Body Therapy Definitions	
Therapy	**Definition**
Mind-body therapies or medicine	Mind-body medicine uses the patient's emotions and thoughts to guide the body into healing.
Yoga	Yoga is a group of physical (asanas), mental (pranayama), and spiritual (dhyana) practices created more than 4,000 years ago in India. Yoga combines this group of practices into a flowing series of postures and stretches controlled by the breath.
Meditation	Meditation is when patients observe their thoughts and develop or begin to accept them by practicing disassociation from the thoughts without judgment.
Mindfulness	Mindfulness is a form of meditation that is employed in daily life; it is a way to observe life without judgment, with an accepting attitude toward the present.
Mind-body stress reduction	A form of mindfulness mediation that helps patients deal with pain and illness-related traumas by concentrating on the moment.
Acceptance and commitment therapy	Acceptance and commitment therapy uses mindfulness to work on values, behavior change, and commitment, and is offered for chronic pain patients.
Progressive relaxation	Patients imagine a beautiful place and relax each body section a little at a time.
Electromyography biofeedback	Patients are trained to control heart rate and blood pressure.
Operant therapy	Patients modify their behavior by learning about the consequences of their choices.
Cognitive behavioral therapy	Cognitive behavioral therapy is designed to help patients discontinue harmful thoughts.

genes (HDAC 2, 3, and 9; regulate transcription), global histone modifications, and proinflammatory genes (RIPK2 and COX-2). Individuals with lower levels of some of these genes (HDAC 2, -0.137; 95% confidence interval [CI], -0.250 to -0.025; $P < 0.05$; and RIPK2, -0.25; 95% CI, - 0.39 to -0.11; $P < 0.01$) showed better recovery from stressful social situations.[9]

More research is needed to examine whether these changes in gene expression produce a physical reduction in the proteins. Every process in the body, including the mind, comes from the genes and is governed by genetic activity. In essence, the brain is thought to be plastic, meaning that every interaction in the world (what we eat, our thoughts, choices, feelings, and self-awareness) also affects the way the genes are expressed.

It is within this dynamic model that meditation and other mind-body therapies begin to allow the patient to quiet the mind. In this state, the patient can listen to his or her inner voice or pain to heal. Chopra and his colleagues call this phenomenon Self-Directed Biological Transformation. A quasi-randomized trial was performed on 69 healthy women and men who participated in a six-day Ayurvedic intervention program (meditation, yoga, healthy diet and herbs, massage, presentations, and journaling) or a six-day vacation (control group) at the same setting. The Ayurvedic group showed improvements across the surveys (spirituality, $P < 0.01$; gratitude, $P < 0.05$; self-compassion, $P < 0.01$) and had a decrease in anxiety after the one-month follow-up ($P < 0.05$), while the vacation group showed no improvements.[10]

The Self-Directed Biological Transformation Initiative, conducted at the Chopra Center, Harvard, Duke, and other top U.S. universities, was a controlled trial that examined the effects (changes in plasma metabolites) of Ayurveda (Panchakarma) and meditation vs. relaxation on the genes, the microbiome, telomeres, and cardiovascular physiology in 65 healthy participants and controls. The results indicated that 12 metabolites classified as phosphatidylcholines significantly decreased (Bonferroni adjusted $P < 0.01$) in 75-90% of Panchakarma program participants. These studies have begun to map the effects of integrated mind-body programs, their effects on the human genome, and the subsequent link to body processes.[11]

Blankfield's physiological explanation of the mind-body connection centers on the underlying effects that inflammation and diet have on serotonergic pathways.[12] Tryptophan is a precursor of serotonin. Serotonin (body) has been proven as a marker for an individual's psychological responses (mind) to life stimuli.[12] Now that a possible pathway has been found for the connection between the mind and the body, mind-body therapies may be explored from a new perspective. This new treatment strategy focuses on the patient's perception of the psychological, social, cultural, and physical aspects of chronic pain to direct the mind to heal the body. With this approach, clinicians may implement these therapies by focusing on the patients' strengths.

Mind-body treatments comprise an extensive assortment of tactics, including a focus on reducing or eliminating

the need for opiates in the treatment plan. These treatments collectively concentrate on the influence of the mind on the body and the body's response to thoughts, feelings, and emotions.[13] Mind-body therapies include various techniques, such as yoga, meditation/mindfulness, electromyography biofeedback, progressive relaxation practices, cognitive behavioral therapy, and operant therapy. These therapies and others are defined in Table 1. In addition to the *P* value, these references use the effect size, which is the difference in magnitude between two groups and gives a value to the difference between groups. See Table 2 for the description of small, medium, and large effect sizes.

Table 2: Description of Effect Size

Effect Size	*d*	Description
Small	0.2	Negative/ineffective
Medium	0.5	Meaningful
Large	≥ 0.8	Positive/effective

YOGA

Yoga is a group of physical (asanas), mental (pranayama), and spiritual (dhyana) practices created more than 4,000 years ago in India.[14,15,16] Yoga combines this group of practices into a flowing series of postures and stretches controlled by the breath. There are many different types of yoga practiced around the world, but all the variations hold true to these three practices. Holtzman et al performed a meta-analysis on yoga for the treatment of chronic low back pain and disability using eight randomized, controlled trials involving 743 patients.[14] After treating participants with various types and durations of yoga, the effect size (medium to large) for functional disability was d = 0.645 (95% CI, 0.496 to 0.795), and it decreased (degree of heterogeneity was significant, x^2 = 15.86; df = 4; *P* = 0.003) after follow-up to d = 0.486 (95% CI, 0.226 to 0.746). The effect size (medium to large) for pain after yoga treatment was d = 0.632 (95% CI, 0.377 to 0.868), and it also decreased but remained significant (degree of heterogeneity was significant, x^2 = 15.86; df = 4; *P* = 0.003) after follow-up at d = 0.397 (95% CI, 0.053 to 0.848).

Cramer et al performed a systematic review and meta-analysis of 10 randomized, controlled trials involving 967 patients; their review corroborates the efficacy of yoga as an adjunct treatment for chronic low back pain.[17] There was strong support for yoga's short-term (standardized mean difference [SMD], -0.48; 95% CI, -0.65 to -0.31; *P* < 0.01) and long-term effects (SMD, -0.33; 95% CI, -0.59 to -0.07; *P* = 0.01) on pain. Strong support was shown for short-term effects (SMD, -0.59; 95% CI, -0.87 to -0.30; *P* < 0.01) and moderate support was shown for long-term effects (SMD = -0.35; 95% CI, -0.55 to -0.15; *P* < 0.01) on disability.[17] Crow et al performed another systematic review of six studies and 670 patients, and confirmed yoga's effectiveness in the treatment of back and neck pain.[18]

MEDITATION/MINDFULNESS

Meditation is the practice of observing one's thoughts and developing or beginning to accept the thoughts by practicing disassociation from the thoughts without judgment. Patients may be able to separate themselves enough from their thoughts to reduce stress and even change their vital signs.[19] On the other hand, mindfulness is the practice of being present in the moment. Mindfulness is a form of meditation that is employed in everyday life; it is a way to observe life without judgment, with an accepting attitude toward the present.[19] An example of mindfulness is to pay attention to the sensation created while brushing one's teeth, how the brush feels on the teeth and gums, the responses/feelings that this may invoke (such as pleasure or even pain), and any thoughts that may arise while practicing mindfulness.

The evidence supporting meditation and mindfulness for the treatment of chronic pain management is mixed. In two of the high-quality studies, meditation practice did not last beyond six months. In a review of 11 studies involving 1,209 participants, three of the five high-quality studies reported favorable effects on pain outcomes.[8] One study reporting unfavorable results was a single-blind, randomized, controlled trial that compared a mind-body program to a health education program for chronic low back pain. The authors concluded that the mind-body program increased function on the Roland Morris Disability Questionnaire (RMDQ, a higher number means less disability) at eight weeks (RMDQ = 1.1 points; mean, 12.1 vs. 13.1 points in the control) and six months (RMDQ = -0.04 points, with a decrease in function compared to control; mean, 12.2 vs. 12.6 points; d = -0.23 and -0.08), and provided relief for acute pain (RMDQ = -1.8 points; 95% CI, -3.1 to -0.05 points; d = -0.33) and chronic pain (-1.0 points; 95% CI, -2.1 to 0.2 points; d = -0.19), but did not provide lasting relief.[1]

In a 2017 meta-analysis of mindfulness-based interventions for chronic pain, 11 studies included the following chronic pain disorders: fibromyalgia, rheumatoid arthritis, chronic musculoskeletal pain, failed back surgery syndrome, and mixed complaints.[20] The studies were of varied methodological value and the outcomes reported were depression, sleep quality, mindfulness, and pain acceptance. Meta-analysis effect sizes (d) for clinical outcomes ranged from d = 0.12 (95% CI, -0.05 to 0.30) for depression, d = 1.32 (95% CI, -1.19 to 3.82) for sleep quality and for humanistic outcomes, d = 0.03 (95% CI, -0.66 to 0.72) for mindfulness, and d = 1.58

(95% CI, -0.57 to 3.74) for pain acceptance.[20] As a reminder, effect sizes of the Hartung-Knapp-Sidik-Jonkman effect model are used in meta-analyses when the number of studies is small. Cohen's d also is used to measure effect sizes in meta-analyses. Effect sizes can range in sizes from small (0.2), medium (0.5), and large (0.8), which are considered positive/effective, while smaller effect sizes are deemed less beneficial.

In 2013, Reiner et al concluded that MBSR was effective in addressing stress and disability in the population.[21] In a medium-quality randomized, controlled trial, patients with chronic back pain were treated with MBSR and traditional therapy (d = 1.02 effect size; $P < 0.05$) and still showed pain reductions at 10 months (d = 0.10).[22]

Acceptance and commitment therapy (ACT) uses mindfulness to work on values, behavior change, and commitment, and is offered for chronic pain patients. ACT is not a formal meditation method; it illustrates that there are multiple ways to be mindful. In a 2007 study, Vowles et al found that ACT is effective for chronic pain patients ($P < 0.01$), and the pain reduction continued for three months (d = 0.48).[2]

OTHER MIND-BODY APPROACHES

Many mind-body studies are of low methodological quality, because of incorrect study designs, short duration, inadequate sample size, no control group, mistaken outcomes, and inappropriate interventions.[23] Chou et al assessed 32 trials on psychological therapies for chronic low back pain.[23] A systematic review included 28 studies (n = 3,090; range of participant number, 18 to 409), and the authors included four RCTs not included in the systematic review (n = 976; range of participant number, 54 to 701).[24] The researchers found that progressive relaxation (three trials: mean difference, -19.77 on a 0 to 100-point VAS; 95% CI, -34 to -5.20), electromyography biofeedback (three trials: SMD, -0.80; 95% CI, -1.32 to -0.28), operant therapy (three trials: SMD, -0.43; 95% CI, -0.75 to -0.1), and cognitive behavioral therapy (five trials: SMD, -0.60; 95% CI, -0.97 to -0.22) resulted in lower post-treatment pain intensity compared to controls. Progressive relaxation was the only therapy to improve function (three trials: SMD, -0.88; 95% CI, -1.36 to -0.39).[24]

SUMMARY

As the pathophysiology of the typical chronic pain patient has evolved into one involving a various biopsychosocial factors, the management of chronic pain has morphed to match these aspects. Experts such as Chopra recommend that people make time each day to meditate, eat a healthy diet, engage in some form of exercise, get a good night's rest, release emotional toxins, fortify loving relationships, and enjoy a good laugh.[7] Today's physician should move away from the materialistic approach, focusing only on the physical, to an understanding that the body registers every thought. The evidence supports the integration of mind-body therapies into an allopathic model to encourage patient self-care and personal responsibility for healing.

Barriers remain for the implementation of these mind-body practices. Many insurance plans do not cover these mind-body treatments, although some will cover a portion of the cost if the practitioner can provide the ICD-10 code. However, mediation and yoga classes routinely are offered at a low cost, $10 to 20 a class. Some MBSR courses can be reimbursed by insurance if recommended by a physician. There are even some games that have been created to help patients practice biofeedback and meditation that begin around $30. ■

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CME QUESTIONS

1. **Which of the following is true regarding kratom?**
   a. The root is used medicinally.
   b. At low dosesn it appears to be an opioid-like analgesic.
   c. Adverse effects have been seen, often with opioid-like effects or withdrawal.
   d. The active compound mitragynine is often dosed at 1 to 2 milligrams.
2. **What should clinicians say when speaking with patients about "heart-healthy" diets?**
   a. Advise patients to avoid meat and animal-derived products in general.
   b. Advise patients that "anything in moderation" is fine, but try to slant a diet toward whole grains and plant-based products.
   c. Advise patients that solid research shows a diet that moves toward healthy, plant-based foods, such as whole grains, fruits, and vegetables, can provide protection from coronary heart disease, but that less healthy, plant-based foods, such as refined grains and sweets, can be harmful for the heart.
   d. Advise patients that the benefits of a healthy plant-based diet are "all or nothing" — it is not protective for the heart to only partially shift a diet toward healthy plant-based foods.
3. **Mild cognitive impairment differs from dementia in that it:**
   a. affects all cognitive domains, including language, praxis, and executive functioning.
   b. is not severe enough to affect independent activities of daily living.
   c. is limited to two of the five cognitive domains.
   d. is severe enough to affect ADLs and IADLs.
4. **Subcortical ischemic vascular cognitive impairment:**
   a. is the most common cause of dementia.
   b. is the most common cause of vascular dementia.
   c. is a large vessel disease detected on brain MRI imaging.
   d. is the second most common cause of vascular dementia.

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- present evidence-based clinical analyses of commonly used alternative therapies;
- make informed, evidence-based recommendations to clinicians about whether to consider using such therapies in practice; and
- describe and critique the objectives, methods, results, and conclusions of useful, current, peer-reviewed, clinical studies in alternative medicine as published in the scientific literature.

[IN FUTURE ISSUES]

Vitamin B and lung cancer

Nutrition controversies

Echinacea for influenza

Noncow milk beverages and child height