



BY ERIK GOLDMAN
Editor-in-Chief

Dementia, depression, and insomnia are on a lot of people's minds these days. Cognitive dysfunction, mood disorders and other brain-related conditions are consistently among the top health concerns cited in consumer surveys.

Several such surveys have shown that Alzheimer's disease (AD) and related dementias are the most feared illness for upwards of one-third of US adults, and with good reason: cognitive disorders destroy lives, there are still no pharmaceutical quick-fixes, and the prevalence statistics are grim.

According to the [Population Reference Bureau \(PRB\)](#)—an independent non-profit research organization, roughly 3% of Americans between ages 70 and 74 had some form of dementia in 2019, and among those between 85-89 years old, the number was 22%. By age 90, the stat jumped to 33%.

The [Alzheimer's Association](#) estimates that 5.8 million Americans over 65—that's roughly one in ten—have AD. All the population indicators point to a rise in prevalence of dementia as the Baby Boom and Millennial generations enter their elder years. PRB notes that if present demographic and health trends continue, more than 9 million Americans will have some form of dementia by 2030, and that number could hit 12 million by 2040.

And this is happening at a time when there's already a major caregiver shortage, and many families are struggling with precarious finances.

Depression and anxiety are also rampant in this country. According to 2023 data from the [Centers for Disease Control \(NHANES survey\)](#), roughly 17% of adults between the ages of 20 and 39 had depression; among those between age 40 and 59, the prevalence was 11%. An estimated 21 million people in the US have had at least one major depressive episode—that's 8.3% of the country's total population.

Among all age brackets, the prevalence was higher than in 2013-2014. This upward trend shows no sign of stopping.

According to the [National Institute of Mental Health](#), overall lifetime prevalence of anxiety among US adults is approximately 24%. In any given year, roughly 19% of adults have significant episodes of anxiety, and 22% of those cases are serious.

The stats on sleep disorders are also troubling. The [current estimate](#) is that one in every three Americans—that's roughly 84 million people—is experiencing some form of sleep dysfunction and not getting enough sleep to support mental and physical health.

It's no wonder that people are seeking brain health remedies wherever and however they can find them. The volume of nutritional supplements, herbs, devices, and apps claiming to mitigate cognitive or mood disorders is staggering.

Americans will spend close to \$1.5 billion on cognition-related products by the end of this year, according to [Nutrition Business Journal](#), which tracks the nutrition, supplement, and natural products industries. Globally, the "brain health" category is set to grow from \$8.2 billion in 2024 to \$15.2 billion by 2034. And this isn't just a trend among older people worried about Alzheimer's. Much of the growth is coming from younger people concerned about mental performance, plagued by depression and anxiety, and struggling with sleep problems.

It may be tempting to dismiss all of this as faddism and shameless marketeering. But the truth is, despite billions of dollars spent over decades, the pharmaceutical

industry has yet to come up with a viable prescription drug therapy to thwart AD and other forms of age-related cognitive decline. This has prompted holistically-minded neurologists like [Dale Bredeesen](#) and [David Perlmutter](#) to question the obsessive focus on amyloid- β that has guided AD research and clinical practice for years.

Bredeesen, Perlmutter and a growing vanguard of practitioners contend that dementia is preventable, reversible, and by no means an inevitable consequence of aging. The disorder is largely driven by dietary, lifestyle, and environmental variables which, once understood, are mostly reversible. The buildup of amyloid- β is indeed a defining pathological feature of AD, but it is a consequence not a root cause (see *Rethinking Alzheimer's*, p. 2).

In addition to [Bredeesen's groundbreaking work](#), which led to the development of the ReCODE lifestyle protocol, there have been a number of recent controlled clinical studies showing that dietary interventions, exercise, and stress management can indeed have measurable impact on objective measures not only of cognitive function, but of brain anatomy and biochemistry as well.

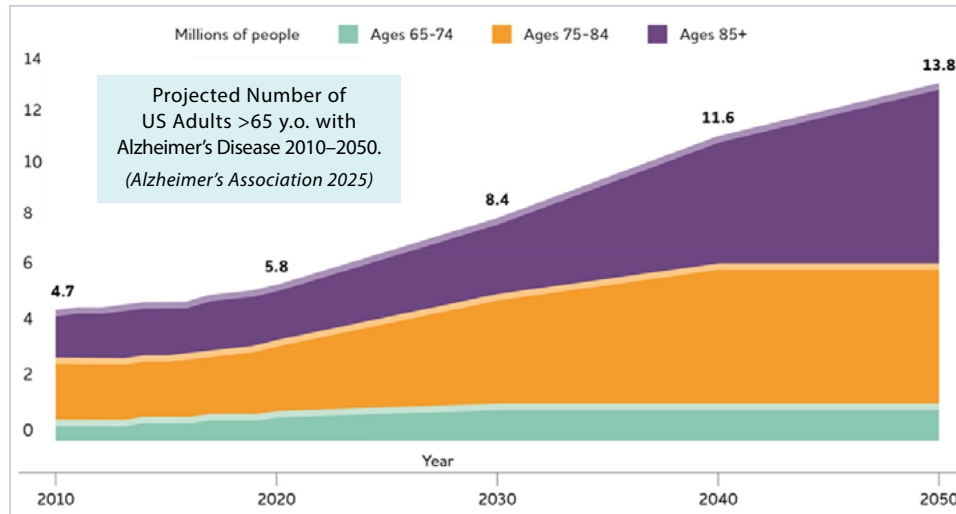
Notably, pioneering preventive medicine researcher Dean Ornish, MD, just published a study of patients with early Alzheimer's, showing that a whole-food, plant-based diet—without calorie restriction, combined with intensive targeted supplementation, regular exercise, and guided stress reduction, could improve cognitive performance across a range of scales. The intervention also increased clearance of amyloid- β from the brain, and improved other biomarkers of AD progression.

Another recent study from Harvard researchers showed that strict adherence Mediterranean style diet exerted the strongest neuroprotective effect in subjects who are homozygous for the APOE4 gene.

Diet and lifestyle changes can also have marked benefits on sleep and mood. But to obtain these benefits, patients and practitioners alike need to break the habit of viewing sleep disturbance, depression, and anxiety as flaws to be fixed with drugs. Rather, as Dr. Ron Grisanti explains in his contribution to this special report (see *To Help Patients Sleep, Ask the Right Questions*, p. 4), we need to consider the obvious symptoms as messages pointing toward deeper physiological imbalances.

Of course, none of this is easy. As integrative practitioner Corey Schuler points out (see *Beacons Through the Brain Fog*, p 6) it takes time, a willingness to do the detective work, and a commitment on the part of a patient to make the changes that will ultimately optimize cognitive health, improve mood states, and minimize the risk of dementia.

The goal of this *Holistic Primary Care* special report is to review some of the new lines of research, thinking, and clinical practice with regard to cognitive health, and to help you make sense of the bewildering array of products now being promoted for better brain function. It is by no means comprehensive, but it will provide guidance from some of the nation's top holistic and functional medicine practitioners, as well as a look at some of the new and emerging nutraceuticals and botanicals that show real promise. ☺



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Rethinking Alzheimer's: The Role of Microglial Cells Is Key

BY ERIK GOLDMAN
Editor-in-Chief

For decades, Alzheimer's disease research—and the clinical approaches that derive from it—have been hyper-focused on amyloid-β and its deleterious effects. But despite billions spent, this has yet to yield a single truly effective drug therapy.

That's because there's far more to the Alzheimer's equation than amyloid plaques. In fact, by the time plaques are detectable, the underlying disease processes have been going on for years, if not decades.

According to functional neurologist David Perlmutter, MD, it's time to expand the focus and recognize the role of the microglia—the resident macrophages of the brain and central nervous system—in the etiology of Alzheimer's.

Putting it very simply, microglial cells have two main phenotypes: one form nourishes and protects neurons, the other form destroys them. It is this latter phenotype that is central to the development of Alzheimer's.

Speaking at the 2025 Integrative Healthcare Symposium, Dr. Perlmutter said:

"The standard medical view of AD is as follows: The cause of AD is amyloid plaque buildup. And the standard course of management is to wait until there are obvious symptoms of cognitive decline, and then put someone on an amyloid-targeting drug that is not likely to be effective. But all that we're now learning about the risk of AD and other forms of dementia converge on one pathway: a shift in microglial cells from the M2 to the M1 phenotype."

Microglial phenotypic expression is complex and not entirely binary. There is a range of phenotypic permutations. But generally speaking, the M2 and M1 types predominate. The cells have the same genetics, yet the expression and behavior change, said Dr. Perlmutter, author of the popular book, *Grain Brain*, among others.

M2 microglia function like 'loving nurturers' for neurons. They phagocytize amyloid-β, remove dead and dying neurons, secrete neurotrophic factors like BDNF, NGF, IFG, regulate synaptic pruning, and maintain the blood-brain barrier. M2 cells also secrete anti-inflammatory cytokines, and support synaptic repair. Metabolically, M2 microglia operate by oxidative phosphorylation.

M1 microglia spread misfolded proteins, phagocytize healthy neurons, increase reactive oxygen species, and promote inflammation by secreting inflammatory cytokines. Though they are activated by amyloid-β, they can actually impair amyloid-β clearance if activation persists. The M1 phenotype is associated with chronic inflammation, synaptic loss, and neurodegenerative conditions. In contrast to M2, the M1 cellular metabolism is based on glycolysis.

A Metabolic Shift

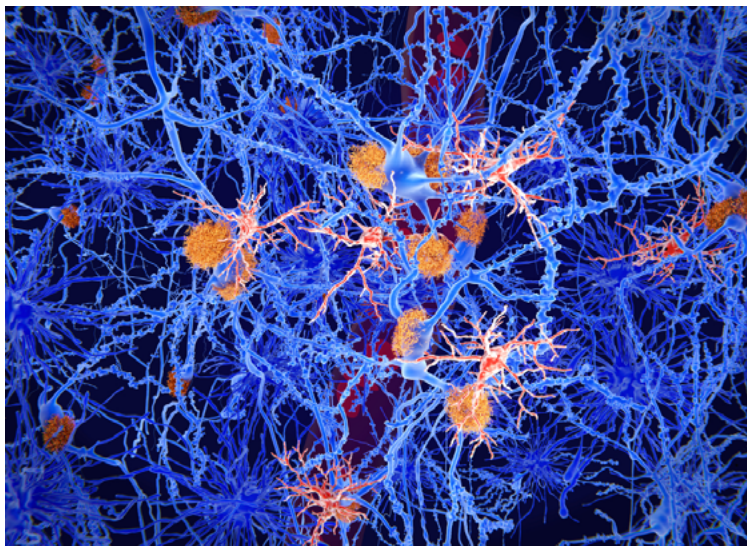
The key point is that under conditions of systemic metabolic dysregulation and inflammation, M2 microglia can shift their phenotype and morph into the M1 form. As this happens, there's a widespread shift toward glycolysis within the brain. And that's not a good thing. By the time symptoms of dementia begin to manifest, this microglial metabolic shift has been happening for years.

At its core, the M2-to-M1 shift reflects a change in microglial cellular metabolism. In a paper published last year, researchers at the University of California-Davis, described Alzheimer's as "an acquired mitochondropathy." The change in microglial phenotype is primarily a consequence of impaired ability to make ATP, and the metabolic change occurs prior to microglial activation and subsequent neuroinflammation.

What drives this M2 to M1 shift? Many factors, said Dr. Perlmutter, whose forthcoming book, *Brain Defenders*, explores this subject in great detail. The presence of amyloid-β is certainly a trigger, but there are others, including poor diet, dysregulated glucose metabolism, leaky gut, elevated LDL, pollution exposure, smoking, trauma, excessive alcohol intake, lack of restorative sleep.

Researchers and clinicians alike are slowly realizing that AD and other forms of dementia, like cardiovascular disease, are end-stage manifestations of chronic inflammation.

"Systemic inflammation is a big driver of the M2 to M1 shift," Perlmutter said, adding that advanced glycation end products (AGEs)—sugars covalently bound to proteins or fats—can bind to microglial cells causing them to shift from M2 to M1 expression. "This partly explains how high blood sugar drives AD and neurodegeneration."



Microglial cells (red), are key players in the dementia equation. Depending on their phenotypic expression these cells can either remove β-amyloid (orange) via phagocytosis, or impair amyloid clearance.
Image: Juan Gaertner/Shutterstock

"All that we're now learning about the risk of AD and other forms of dementia converge on one pathway: a shift in microglial cells from the M2 to the M1 phenotype."

Is It Reversible?

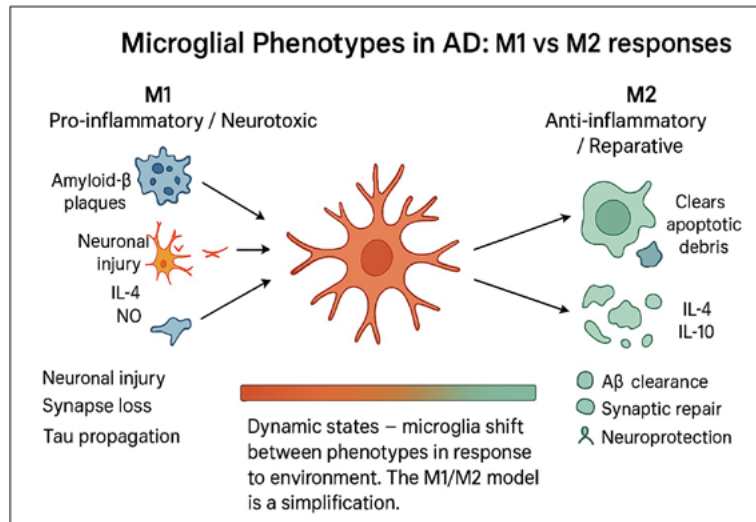
The big question, of course, is whether the detrimental shift is reversible. To that, Dr. Perlmutter answers with a resounding "Yes!"

He contends that 80%–90% of AD cases can be delayed substantially or actually prevented. "Target the metabolism! Don't wait until there are amyloid plaques and then try to treat them!"

The brain is only 2–3% of the body's total weight, but it uses 25% of the body's resting metabolic energy. It's the most metabolically active organ. "We've been hyper-focused on the neurons, but we need to refocus on metabolism and metabolic patterns."

Lifestyle factors are very relevant to microglial cell function. "Obesity is the top modifiable risk factor for AD," Perlmutter said. Citing a comprehensive 2024 research review on prevention of dementia published in *The Lancet*, he noted that many of the most significant risk factors are essentially metabolic and inflammation-related.

Diet and lifestyle changes to reestablish healthy glucose and lipid metabolism, and to reduce systemic inflammation are essential. There are some



signals from animal studies that ketogenic diets may be particularly effective in decreasing microglial activation, and reducing pro-inflammatory cytokines (Fairley LH, et al. *Front Immunol.* 2021). This needs confirmation from human studies, but mechanistically, it makes sense.

Beyond dietary changes and exercise, Dr. Perlmutter says hyperbaric oxygenation therapies are showing promise. "They enhance mitophagy and oxidative phosphorylation. And that's the key—to push oxidative phosphorylation."

A Role for GLP Agonists

He also noted that some of the GLP1 agonist drugs have beneficial effects on mitochondrial function. Since there are GLP receptors on neurons, astrocytes, and microglia, these metabolic changes would presumably affect the brain in a good way.

Pointing to a 2023 study by a multicenter team of Spanish researchers, he said that, "Some GLP drugs do a lot of things that are good for the brain. They enhance mitochondrial function, increase oxygen consumption, and reduce IL-6 and other inflammatory cytokines."

In a study of 204 mild AD patients, those randomized to treatment with liraglutide—one of the lesser-known GLP1 agonists—showed a 50% reduction in tissue loss in several areas of the brain, compared with those on placebo. Clinical and cognitive measures also improved in the liraglutide-treated group. The downside is that the drug is not exactly user-friendly. Treatment requires daily subcutaneous injections.

Dr. Perlmutter stressed that not all GLP drugs have potential for prevention of dementia. For example, the popular semaglutide (aka

Ozempic, Rybelsus, and Wegovy) is a relatively large molecule, and cannot possibly cross the blood-brain barrier.

GENUS Shows Potential

Perlmutter said he is also enthusiastic about **Gamma Entrainment Using Sensory stimulation (GENUS)**, an emerging non-invasive light-based therapy developed by researchers at Massachusetts Institute of Technology. The technique involves exposing someone to 40Hz light alone, or in combination with sound. Animal studies show that this can reduce amyloid and tau protein buildup in the brain, and stimulate beneficial changes in microglial cells and astrocytes.

A phase II human clinical trial of GENUS showed that it can slow brain atrophy, preserve white matter, and improve some measures of cognitive performance. A nationwide phase III study is now underway.

As is the case with the Th1 and Th2 branches of the immune system, or the sympathetic and parasympathetic branches of the nervous system, both the M1 and M2 microglial cells play a role in overall brain health. The problems arise when systemic factors shift the balance toward the M1 expression pattern.

The clinical goal, therefore, is not to "eliminate" or "suppress" the M1 phenotype, but to restore a healthy balance.



David Perlmutter, MD

"Systemic inflammation is a big driver of the M2 to M1 shift. Advanced glycation end products (AGEs) bind to microglial cells causing them to shift from M2 to M1 expression. This partly explains how high blood sugar drives AD and neurodegeneration."

Lifestyle Factors Influencing Microglial Phenotype

PHYSICAL EXERCISE

- Aerobic activity reduces microglial pro-inflammatory activation.
- Increases anti-inflammatory cytokine profiles (IL-10) and BDNF release.
- Improves synaptic health and cognitive resilience.

SLEEP QUALITY

- Poor sleep or sleep apnea increases M1 polarization and amyloid burden.
- Restorative sleep supports glymphatic clearance and reduces microglial activation.

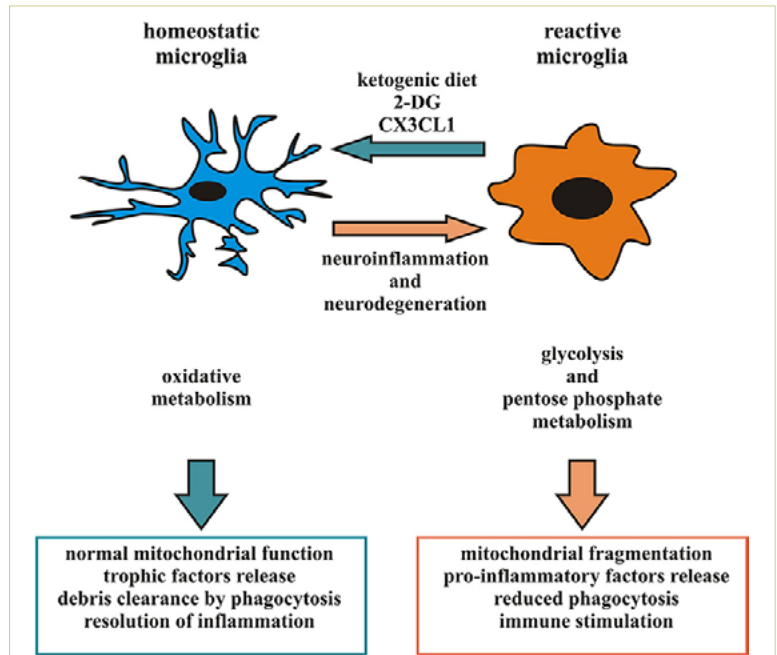
STRESS & GLUCOCORTICOID EXPOSURE

- Chronic stress promotes M1 activation via HPA-axis-driven inflammation.
- Stress reduction (e.g., mindfulness, meditation) is associated with reduced neuroinflammation markers.

ENVIRONMENTAL ENRICHMENT

(social engagement, cognitive stimulation)

- In animal models, social engagement reduces pro-inflammatory microglial activation and promotes synaptic repair.
- May delay onset or severity of neurodegenerative pathology.



SOURCE: Lauro C, et al. *Front Immunol.* 2020.

Music & the Mind: Frequent Listening Mitigates Dementia Risk

A new study based on 10 years' worth of data from nearly 11,000 older people indicates that those who regularly listen to music had a 39% lower risk of developing dementia, and a 17% lower risk of non-dementia cognitive impairment, compared with people who seldom listen. Playing an instrument was associated with a 35% drop in dementia risk.

Researchers at Monash University, Melbourne, Australia, quantified frequency of engagement in musical activity—defined as listening to recorded music, playing an instrument, or both—among 10,893 generally healthy, community-dwelling Australians over age 70. They then plotted the music engagement data against the prevalence of cognitive impairment and



dementia based on annual cognitive assessments. Daily listeners showed better scores on tests of global cognition and memory.

Though the findings reflect correlation not causation, they are compelling. Joanne Ryan, the senior investigator on this new study, believes listening to music is neuroprotective. It activates a wide range of motor, sensory, and memory processing centers in the brain.

Listening to old, familiar music can activate memories linked with past experiences, reinforcing those neural pathways. New and unfamiliar music can prompt creation of new pathways. Both are beneficial for stimulating various aspects of cognitive function which, ultimately, helps to stave off cognitive impairment.

To Help Patients Sleep, Ask the Right Questions

BY RON GRISANTI, DC
Contributing Writer

Conventional medicine tends to view insomnia as an isolated problem—a nuisance to be ameliorated. The solutions offered usually fall into three categories:

- **Basic sleep hygiene advice:** Recommendations like reducing screen time, keeping the bedroom dark, or sticking to a bedtime routine are helpful, but rarely enough on their own. For someone with underlying hormonal imbalances, chronic inflammation, or environmental stressors, these tips are like putting a bandage on a deeper wound.
- **Prescription drugs:** Sedative-hypnotics or benzodiazepines force the brain into a sleep-like state, but they often interfere with normal sleep architecture. Deep sleep and REM—the very stages responsible for healing, memory consolidation, and hormone regulation—are reduced when people take these drugs. Many also develop tolerance, dependency, or “hang-over” grogginess the next day.
- **Over-the-counter remedies:** Melatonin supplements or antihistamine-based sleep aids may provide short-term benefit. But melatonin only works if the insomnia is caused by circadian rhythm misalignment, not if the underlying drivers involve blood sugar imbalances, stress hormones, inflammation, or toxins. Likewise, antihistamines can leave people foggy, and do not address deeper biological imbalances.

The common thread between all these approaches is that they all aim to suppress the symptom—the lack of sleep—without asking why the body can’t naturally restore itself. Alone or in combination, they are coping tools, but not true healing.

To truly help our patients with sleep problems, we need to shift the question from: “How do we make you sleep?” to “What’s preventing your body from sleeping in the first place?”

Living with insomnia feels like being locked out of your own body’s most basic repair system. What should be the most natural act of renewal feels like an unpredictable luxury.

To add to the struggle, many people—practitioners, family members, friends—often dismiss insomnia. They’ll say the problem is simply “stress,” “getting older,” or “bad habits.” This leaves patients feeling blamed, misunderstood, or hopeless.

In truth, insomnia is a signal that something deeper is out of balance.

A Functional Medicine Lens on Sleep

When viewed through the functional medicine lens, this signal becomes an opportunity: an invitation to investigate the underlying systems that control rest, repair, and resilience. The functional medicine model looks at insomnia not as an isolated problem, but as the end result of losing the natural rhythm of repair.

Sleep doesn’t simply “switch off and on”—it depends on a finely tuned orchestra of hormones, neurotransmitters, nutrients, and circadian cues. When one instrument is out of tune, the entire symphony of sleep becomes discordant.

Instead of asking “How do we make you sleep?,” functional medicine asks, “Why is your body resisting sleep?” It might seem like semantics, but this shift in perspective opens the door to explore the underlying networks that influence rest.

Let’s take a closer look at the physiological dynamics of sleep. There are five broad categories of factors that influence sleep patterns:

Hormonal rhythms—Cortisol and melatonin must rise and fall at the right times to keep the body aligned with day and night.

Glucose Metabolism—Fluctuating blood sugar can jolt the brain awake as it scrambles to correct energy dips.

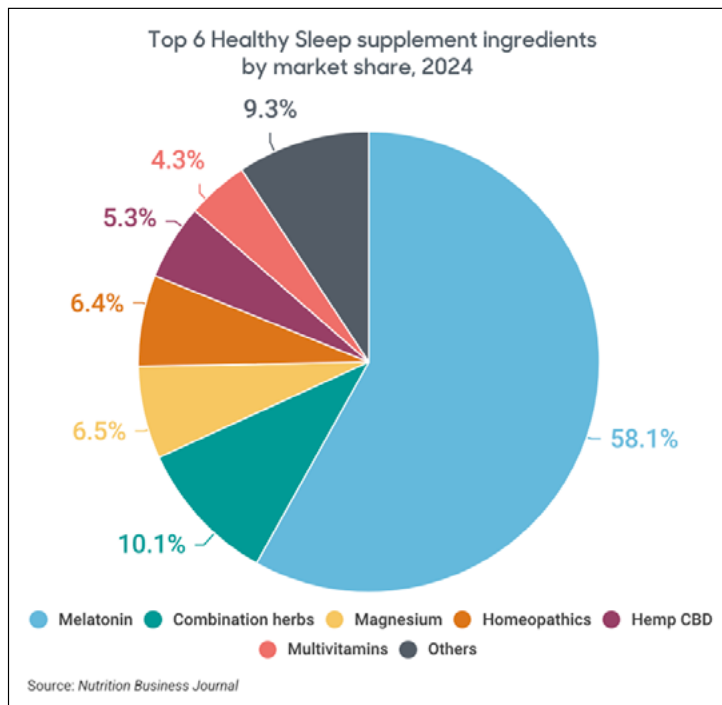


image: DimaBerlin/Shutterstock

Detoxification and repair—The liver, mitochondria, and immune system all perform deep repair work during sleep; if they’re overburdened, the body can’t settle into rest.

Neurotransmitter signaling—GABA and serotonin help the brain shift from alertness to calmness.

Gut & nervous system health—The gut produces important calming messenger molecules, while the nervous system sets the tone for whether the body feels safe enough to release into sleep.



And this is just the surface. In reality, there are dozens of influences—from genetics to inflammation to hidden toxins—that can silently disrupt sleep. A thorough evaluation doesn’t stop at the obvious five; it maps out the broader landscape to uncover what’s uniquely at play in each individual.

The Insomnia Iceberg: What Lies Beneath

Think of insomnia like an iceberg. The part above the surface is what someone experiences: difficulty falling asleep, night waking, restlessness, racing thoughts, grogginess, irritability. Beneath the surface are dozens of biological and environmental factors:

- Hormonal dysregulation (cortisol, melatonin, DHEA, thyroid)
- Metabolic instability, especially related to glucose
- Impaired liver detoxification and high toxin burdens
- Neurotransmitter imbalances (GABA, serotonin, glutamate)
- Diminished mitochondrial energy capacity
- Inflammation and immune system dysregulation
- Dysbiosis, alterations in microbiome composition, and other gut problems
- Environmental stressors (mold, EMFs, chemicals, noise, light exposure)
- Genetics that affect stress response or circadian timing

Key Functional Medicine Questions

With so many variables, how do we get at all this within the limits of an office visit? By asking the right questions!

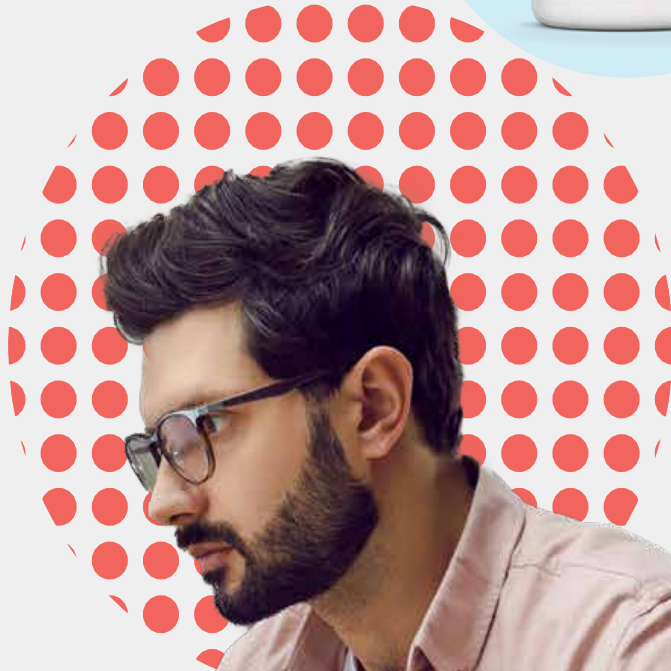
see *Helping Patients Sleep* p. 12



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Beacons Through the (Brain) Fog: Corey Schuler on Holistic Approaches to Cognitive Dysfunction

BY ERIK GOLDMAN
Editor-in-Chief

Assessing and treating cognitive dysfunction is a challenge. The problems can show up in myriad ways, with multiple potential causes. Cognitive impairment is often connected with, and reflective of, disease and dysfunction in other organ systems. Though surveys consistently show that many people worry about developing dementia, individual patients may not always be forthright about their concerns.

It may be tempting to refer patients to a neurologist at the first indication of significant cognitive problems. But this is not always the best course of action. There's much that primary care practitioners can do to mitigate cognitive dysfunction—especially in the early stages. In fact, neurology consultations may not even be practical in many cases. In some regions, neurologists are few and far between. Wait times can be months-long.

So, how to find the beacons in the fog that will help you and your patients deal effectively with cognitive problems? How to discern when a case truly requires specialist expertise? What are the most effective nutrition and lifestyle-based approaches for early or mild cognitive impairment?

To explore these, and other issues, *Holistic Primary Care* spoke with Corey Schuler, PhD, FNP, CNS, one of the nation's top holistic practitioners. Schuler is a family nurse practitioner at [Synergy Family Physicians](#) in White Bear Lake, MN, and has extensive experience using non-pharma approaches to cognitive problems. In addition to his clinical work, he also serves as medical affairs director for [Allergy Research Group](#).

EG: First off, tell us how do cognitive problems show up in your clinic? Do people come in saying, "Hey, I'm really concerned about my cognitive health?" Do they describe specific symptoms they're having? Or is it something you have to draw out of them?"

CS: It's a good question. My patients tend to divide really distinctly. Typically, the people suffering from longer term memory loss that fit more into the dementia-neurodegenerative category, usually aren't the ones complaining about it. More likely, it's the partners, the spouses, who come in with them and say, "Things aren't the way they should be."

At the opposite end are young executives, the high performers. They tell me right away, "Something's not right. I'm feeling older than I should be. My mental clarity is not where I want it to be. 'Help me, help me.' So, it's a significant divide.

EG: Holistic, functional, and naturopathic medicine all posit that cognitive problems reflect other systemic imbalances. They don't necessarily start in the brain. There's a lot under the tip of the cognitive impairment iceberg. How do you unpack that clinically?

CS: This is a "peeling of the onion" situation if there ever was one. Alzheimer's and blood sugar dysregulation go hand in hand. We know that now. So that's the first thing we try to rule out. I'll go as far as doing CGMs (continuous glucose monitors) on these individuals. If I can rule out dysregulated glucose metabolism, then I proceed to other questions like, Is this a neuro-inflammation thing? Is it more of a long-term thyroid issue? An autoimmune problem? Is it related to gut problems?

But first we have to determine if it is actually cognitive decline, or if it is more on the occasional working memory side of things.

We sometimes send patients out for the [Montreal Cognitive Assessment \(MoCA\)](#), even though they get really irritated with me, and the wait for a neurologist is longer than it should be. I'm not trained to do the 30-question MoCA, so I send that out. And we screen for depression and anxiety, and do our best to screen for ADHD, which all show up in similar ways.

EG: Once you've ruled out glucose dysregulation and serious neurodegeneration, how do you make sense of all the other potential variables?

CS: I try to get an understanding of what the core symptoms are: Is it actually memory loss? Is it face-name allocation? Is it focus and attention? Word-finding? Mental fatigue? Is this a dopamine issue? That's an important one, because a lot of common medications like Ritalin, Adderall, those sorts of things—they



Image: Eva Kristin Almqvist / Shutterstock

stimulate big dopamine surge, and then a big crash down. It's an important thing to assess.

Alcohol also boosts dopamine, which makes that poison so pleasurable. But the day after, it can cause a big dopamine crash. So, when I look at mental fatigue and focus problems, I wonder if it's a dopamine issue. It becomes top of mind because of the wide use of those drugs, including alcohol. It becomes complicated when somebody has ADHD, and on ADHD meds, and then they have an additional layer of brain fog. That can be very confusing to sort out. Often, we do a drug holiday to identify if it's still present without the meds.

Sleep apnea and hearing loss are also important to consider. They're sort of boring, but very, very real. There's a nice body evidence that shows hearing deficits and cognitive function are intimately related. Those cases are usually refer-outs, maybe a sleep study, if they're having trouble sleeping. If there's any hearing deficit, I want to get to that as early as possible. A hearing aid is better than neurodegeneration.

Occasionally, we have to do a deep dive, to assess if there's inflammation related to a latent infection. I do screen for inflammatory markers, as well as Epstein-Barr virus, Lyme disease, and mold mycotoxins, if there's any suspicion for any of those. These can be expensive panels to run, but anything I can find that I can work with, I will do.

EG: Once you have a sense of the main drivers, how do you go about treating them?

CS: First, we do the foundational stuff that everybody should be doing. Good, healthy living. Right away, I tell patients, I want them to do 20 minutes of regular walking a day. There was a study that showed like 15 minutes of fast walking—and this was in a lower income group—improved overall health and reduced morbidity and mortality. Just getting outside, especially before 10 AM, a few times a week is so beneficial.

Being outside and taking time to wonder about the world is so beneficial. It is a form of meditation that's easier, I think, for some people to grasp, than formal techniques like transcendental meditation or other versions.

Sleep hygiene and sleep consistency are super important. I pay close attention to that. And I do encourage patients to meditate, and to exercise if they haven't been exercising. It can take a while to implement if they're not already doing it.

I drop right into supplementation very quickly. The process takes a while, and it takes time for the interventions to make any real difference. I say to patients that our trials of therapy are going to be about 90 days, and I'm going to stack the supplements as best I can. But it will take time, and it's a lot of supplements.

I base that 90-day projection on one of my favorite nootropic supplements, which is **spearmint**. The **Neumentix** ingredient, from Kemin Labs. In a clinical study it showed no real effect after 60 days. But after 90 days, it was very impactful.

I think it's an unsung hero. Five clinical studies have been done on it. There's also a version of spearmint and **EGCG** together, for sleep. Dr. Andrew Tubbs, a neuroscientist at the University of Arizona, did a study of that and saw results in next-day mental clarity within 30 days.



Corey B. Schuler, PhD, FNP, CNS

So, I have a strong opinion about that one. I've tried a lot of nootropics and most are overly stimulating. Neumentix is not. So that, and **L-theanine** are at the top of my list. **Citicoline** and **omega-3 fatty acids** are also on the list, but most people have already tried them when they come into our clinic.

For a very few supplements—**Bacopa** maybe one of them, and perhaps **Lion's Mane**—sometimes you get an early response. But most other supplements will need a long time to have an effect.

Two things that people often overlook are **DHEA** and **pregnenolone**. I'm relatively cavalier with these two. I dose DHEA based on the patient's IGF-1 status. If IGF-1 is too high, there's cancer risk. If it's too low, frailty risk. I usually find that people that have cognitive dysfunction are on the lower side of IGF-1, and low DHEA. I can get a big benefit on sleep and brain function with DHEA.

Some people respond well to pregnenolone, but it is a goofy one. There's a study that looked at 30 mg of pregnenolone versus 100 mg, and some people did better on the lower dose. So, I have to be a bit careful with that. I start at 100 mg. And if they feel more depressed, or they have mood lability, I will back down to 30 mg or even lower.

EG: You mentioned Spearmint, and Bacopa. What are some of your other go-to brain and cognitive supplements?

CS: I am cavalier with L-theanine. My starting dose is 400 mg, which I know is on the high side. It goes as low as 50 mg. I just scoot right past that and go right to the 400 mg. Sometimes that's 200 mg twice a day, and sometimes 400 all at once.

Acetyl L Carnitine was popular years back. **Robert Crayhon** (the influential nutritionist/educator who co-founded **Designs for Health**) introduced me to the power of this ingredient. And he taught me a trick, which is not really a trick. He explained that when you see triglyceride elevated, remember that carnitine shuttles triglycerides into mitochondria. So, if you see high triglycerides and especially if they're not eating an ugly high-sugar diet, think "mitochondria," and give them L-carnitine. That has stuck with me for over 20 years.

EG: Is that something someone would stay on indefinitely?

CS: I think it can be. We top out at about 1,500 mg, because there is some risk of thyroid function suppression with very high-dose acetyl L-carnitine. But I'll go as high as that 1,500 mg, if that's what it takes to give them the benefit. And then I try to cycle them down to lower doses, and support them in other ways. But, if they've been on acetyl L-carnitine, high dose, for a year or so, and that's all that seems to be helping them, then I think I've missed something. And I need to go back to the drawing board.

EG: Say more about sleep. Roughly, what percentage of the cognitive health game is won simply by normalizing and re-regulating people sleep cycles?

CS: In my practice, it's probably 60 to 75%, in that range. Even those who say, "I'm sleeping fine," usually are not. Once we start using wearables, and figuring out what someone's duration of sleep actually needs to be—like, how much do they need to sleep without an alarm before they can wake up, and after an hour of being awake, feel well rested—we start getting at the truth. I've rarely found people needing less than eight and a half hours, every single night. And very regularly, like regular bedtime, regular wake time.

I know we hear that a lot. And we brush it off like, "Oh, yeah, yeah, but I have a life and I can't really do that." But it's so important. It's actually the biggest lift I can find. As soon as somebody figures that out and they dial that in for a while, when they go off of it for whatever reason, they absolutely know it. It's sort of like the people that find out that they're sensitive to gluten, so they stay away from it, and then when they're reintroduced to it, they're like, "Oh, that was terrible." It's the same with sleep.

EG: What are your thoughts on coffee and cognitive function? You said before that alcohol is problematic for people with cognitive issues, and there seems to be consensus on that. But there's a lot of controversy about coffee. What's your what's your take?

CS: Well, I've a biased opinion, because I like coffee! We do know that there's some metabolic benefit to it, whether it's from the chlorogenic acids or some other phytochemical complex in the coffee. It seems to benefit both blood sugar metabolism and probably cognitive function. But when you get into the atrial fibrillation range of like four or five cups of coffee, that's probably too much.

One big problem is that people don't know how to portion their coffee anymore, thanks to commercial entities, saying, "This is a cup of coffee," and it's 32 ounces! So, we need mediate based on caffeine intake.

For some people, coffee is a huge uh no-no. This is just purely my own speculative clinical thought, but it seems that women in perimenopause tend to do really great when they cut out coffee, even if they've been coffee drinkers their whole lives. Hot flashes, night sweats, vasomotor symptoms seem to improve rapidly. So, I've learned to be okay with saying that coffee is not okay for some people.

And there are nice coffee alternatives now. **Dandelion root tea** is awesome because it has a dark roasted flavor, and some other aspects of coffee. And now there's all these mushroom teas and coffees, and things like that. Finding a palatable replacement is just a lot easier now.

EG: You've said that your treatment protocols are 90 days, minimum, and that it often takes even longer to optimize cognitive function. How often do you see the patients during the course of treatment? How do you guide patients through the process?

CS: I'm really clear with them. I let them know, we're going to see each other every four to six weeks, and we're going to keep each other on track. We're going to do labs every 12 weeks. And you're going to monitor the heck out of yourself. I tell them not to go nuts, because we don't want to increase anxiety. But I suggest they get an old-fashioned notebook and pen, and write down all of their stuff. The point is to stay off the phones!

I try to create systems that work for each patient. I've had people do calendars with smiley faces. Other people like numbers, so we decide these are the five symptoms we're going to track on a 1-5 scale, on either a daily basis or even multiple times a day basis. I want to know the mid-morning, mid-afternoon, and early evening mood and energy profiles. So, they end up filling their notebook full of stuff. And when we get together in six weeks, we squint and see if we can detect some patterns.

EG: Do patients stay on your supplement protocols indefinitely? Or is there a point at which they can discontinue without any negative consequences?

CS: Well, we are evaluating and adjusting all along the way. Often, there comes a point where it's like, I can keep pushing and trying to optimize, optimize, optimize. But it may not be worth the time, the energy, and the cost. I always tell patients that I'm like a dog with a bone with this sort of stuff, so they're gonna have to call me off! Periodically, we need to evaluate and assess what's worth continuing.

Sometimes, a patient is not really experiencing improvement despite our best efforts. There may be something going on that's out of my league. Luckily, I have some trusted functional neurologists that can take the next steps with them. Oftentimes these functional neurology people see things that I just wouldn't have ever thought about.

EG: Are there any emerging cognitive health herbs or nootropic ingredients that you think will be impactful in the next few years?

CS: Well, there's a renewed interest in **polyphenols**. A lot of cognitive dysfunction is ultimately due to oxidative stress. Vitamin C and other vitamins, and even CoQ10 fall short. So, I think from an innovation standpoint, we're going to see the next generation of cognitive tools be polyphenol- or flavonoid-based. Berries are going to be our best options. There are the exotic "superfood" berries—Maqui and Wolfberry (aka Goji), and so on. But it might not need to be that. It might be just good ol' blueberries. Can't say enough good about blueberries!

EG: Okay, last question: What does Allergy Research Group offer in the cognitive health space?

CS: Our **Advanced NeuroPlus** is one that is of interest. It contains that Neumentix spearmint I mentioned, as well as citicoline, and lion's mane...it's the whole ball of wax. It's pretty broad. It also has a coffee fruit extract, but it's really minimal caffeine. So that one is a really good, useful product.

And because of the recent introduction of the Metabolic Maintenance product line into our portfolio, we now have one called **MetaCalm**, for the people that lean towards anxiety. And then **MetaMIND**...that one has **Nutricog** (a fixed combination of *Boswellia* and a south Asian herb called *Haritaki*). So that's likely working on the neuro-inflammatory aspect. And it also has lutein and zeaxanthin in it, which I really like because of the blue light blocking effect. We're developing our own body of evidence on these two carotenoids, looking beyond blue-blocking, an actually looking at cognitive function. So, MetaMind is a really nice addition to the portfolio. 🍌

"Alzheimer's and blood sugar dysregulation go hand in hand. We know that now. So that's the first thing we try to rule out."

Better Nutrition—Better Brain

BY JANET GULLAND
Contributing Writer

If we have any chance of mitigating the rising tide of Alzheimer's and other forms of dementia, it's going to be via diet and lifestyle interventions, not expensive but minimally effective prescription drugs.

Fortunately, there is a swell of new data to support the notion that nutrition-based interventions can slow the progression of dementia, and may even be able to prevent it. The idea that holistic approaches can avert cognitive decline is no longer speculative. Increasingly, it is evidence-based.

Case in point, the [June 2024 randomized, controlled study](#) published by a multicenter team led by Dean Ornish, MD, founder of the [Preventive Medicine Research Institute](#). The study involved 51 patients with mild cognitive impairment or early-stage Alzheimer's (AD), randomized to usual care with no lifestyle changes (N=25), or a 20-week intensive diet and lifestyle intervention centered on a whole food vegan diet, with daily exercise, stress reduction, social activity, and a sizeable stack of nutraceuticals.

Study participants ranged in age from 45-90 years, with a mean of 73. At baseline, there were no differences between the groups in terms of cognitive function, as measured by standardized, well-validated assessment tools.

Significant Impact

This is the first randomized trial to look at the impact of a multimodal lifestyle intervention for prevention of AD progression, and the results are impressive.

After 20 weeks, the intervention group showed statistically significant improvements on the Clinical Global Impression of Change (CGIC), Clinical Dementia Rating Global (CDR-G), Clinical Dementia Rating Global (CDR-G) scales, compared with their baseline scores. They also showed borderline significant improvement on the Alzheimer's Disease Assessment Scale (ADAS-Cog).

These beneficial changes were corroborated by an increase in the A β 42/40 ratio, a biomarker indicating the degree of amyloid- β transport out of the brain and into the bloodstream.

The "usual care" control group had worse scores on all four cognitive function rating scales, and the A β 42/40 ratio dropped, suggesting amyloid clearance was declining.

Comprehensive Lifestyle Change

The diet & lifestyle protocol in this trial was quite comprehensive. It consisted of:

- **A whole foods minimally-processed vegan diet**, high in fruits, vegetables, whole grains, legumes, soy, seeds and nuts, and low in harmful fats, sweeteners and refined carbs. Generally, the diet consisted of 14-18% of calories as fat, 16-18% protein, and 63-68% mostly complex carbohydrates. Subjects received 21 meals per week along with snacks. Calories were unrestricted, and people with higher caloric needs got extra portions.
- **Exercise & activity**: Participants committed to walking at least 30 minutes per day, along with three physiologist-guided strength training sessions per week. Exercise was custom-tailored to each patient's age and fitness level.
- **Stress reduction**: Patients participated in daily, hour-long sessions of meditation, yoga-based postures, stretching, breathing exercises and guided imagery, facilitated by a certified stress management specialist. They also had the option to use pulsed light glasses (at a theta frequency of 7.83 Hz) with relaxing music, as a sleep aid.
- **Group social support**: Patients and their spouses or study partners participated in thrice-weekly group support sessions, supervised by licensed mental health professionals. In-person sessions were augmented with Zoom sessions.
- **Supplements**: The study provided supplement packs consisting of:
 - Omega-3 fatty acids with Curcumin (1,680 mg omega-3 & 800 mg Curcumin, Nordic Naturals ProOmega CRP, 4 capsules/day).
 - Multivitamin and Minerals (Solgar VM-75 without iron, 1 tablet/day).
 - Coenzyme Q10 (200 mg, Nordic Naturals, 2 softgels/day).
 - Vitamin C (1 gram, Solgar, 1 tablet/day)
 - Vitamin B12 (500 mcg, Solgar, 1 tablet/day)
 - Magnesium L-Threonate (Mg) (144 mg, Magtein, 2 tablets/day)
 - Hericium erinaceus (Lion's Mane mushroom) (Host Defense, 2 g/day):
 - Super Bifido Plus Probiotic (Flora, 1 tablet/day).



Cognitive Improvements

"Despite the inherent limitations of self-reported data, we found statistically significant correlations between the degree of lifestyle change from baseline to 20 weeks, and the degree of change in three of four measures of cognition and function," the authors report.

On the CGIC scale, 10 of the 26 patients (38%) in the lifestyle group showed improvement at 20 weeks, versus none in the control group. Seven people in the intervention group showed a slight worsening of cognition on CGIC, versus 14 people among the control subjects. None of the lifestyle group showed moderate worsening versus 3 in the control group.

Mean CDR-Global scores improved in the intervention group, as indicated by a score reduction from 0.69 at baseline to 0.65. In contrast, the mean CDR-G score worsened in the usual care group, going from 0.66 to 0.74.

ADAS-Cog scores also improved in the lifestyle group, dropping from 21.6 at baseline to 20.5 at the 20-week mark. Among the control subjects, ADAS-Cog rose from 21.3 to 22.2, indicating progression of cognitive decline. CDR-SB scores worsened among the usual care subjects, going from 3.3 to 3.8. Among the lifestyle change subjects, there was minimal change on this measure.

Given the complexity of the lifestyle intervention, it is not surprising that compliance varied. Those who were most compliant definitely got the best results. The authors describe a "dose-response correlation." The more they changed their diets and lifestyle routines, the greater was the impact on their cognitive function.

Biomarkers Bolster Credibility

The difference in A β 42/40 ratios between the two groups is one of the most important findings from this study. This ratio is clinically relevant, and indicative of AD progression. It increased by a mean of 6.4% in the lifestyle group, but decreased by 8.3% in the usual care group. Since it reflects clearance of amyloid from the brain, a decreasing A β 42/40 ratio correlates with progression while an increase indicates improvement.

In a [2022 trial of the drug Lecanemab](#), there was a significant ratio increase among the treated patients after 18 months, while the control group showed a decrease. Ornish notes that his team's lifestyle program gave similar results, but in a mere five months.

The lifestyle intervention also resulted in statistically-significant beneficial changes in several other biomarkers, including hemoglobin A1c, insulin, glycoprotein acetyls (GlycA), LDL, β -Hydroxybutyrate (ketone bodies), and pTau181.

"Improvement in these biomarkers provides more biological plausibility for the observed improvements in cognition and function, as well as more insight into the possible mechanisms of improvement."

Microbiome Benefits

The intervention also led to beneficial microbiome changes. Organisms in the *Blautia* and *Eubacterium* genera both increased in the intervention group, but not in the controls. These genera are linked to lower risk of AD in prior studies. Moreover, there was a concomitant reduction in *Prevotella* and *Turicibacter*, both of which are associated with AD progression.

"These results support the hypothesis that the lifestyle intervention may beneficially modify specific microbial groups in the microbiome: increasing those that lower the risk of AD and decreasing those that increase the risk," Ornish and colleagues report. It's not possible to determine if the observed changes were due solely to the probiotic supplement, or if the plant-intensive diet also played a role.

The Ornish study is indeed good news at a time when new technologies have improved early AD detection, but conventional drug-based medicine still has little to offer.

“Many people do not want to know if they are likely to get AD if they do not believe they can do anything about it,” Ornish and colleagues say. If diet and lifestyle changes can improve cognition and AD-related biomarkers in people with early AD, it is reasonable to think the same approach would be effective in preventing the disease.

Since publication of the Ornish study, several other large trials have also confirmed the impact of dietary factors on the progression of dementia.

Med Diet Mitigates Genetic Risk

A recent Harvard study of genomic, metabolomic, and nutrition data from more than 5,700 subjects (4,215 women and 1,490 men), showed that a Mediterranean style diet is particularly effective in modulating dementia-related metabolic pathways. The strongest effect was in people homozygous for the APOE4 gene.

APOE4 confers a very high risk of developing AD, to the point where many people believe that the gene is practically a guarantee for dementia. This study, headed by epidemiologist Yuxi Liu, challenges that notion.

“A key distinction between metabolomics and genetics is that metabolites can be modified by exogenous factors and may serve as targets for intervention; in particular, diet significantly impacts the metabolome. We thus examined whether diet, specifically the MedDiet, which has been implicated in cognitive health, could modulate metabolite levels in individuals with different genetic predispositions to AD and AD-related dementias”

People who were most adherent to the Med diet had lower risk of dementia, and better cognitive function. “Greater adherence... was associated with higher levels of unsaturated glycerides and lower levels of saturated glycerides, lipid patterns potentially beneficial for cognitive health, as well as increased levels of established neuroprotective compounds, including piperine, betaine, and pantothenic acid.”

The impact of the diet was greatest among those at highest genetic risk—the people who were homozygous for APOE4. In this subgroup, close adherence to the MedDiet mitigated AD risk by an estimated 35%. The finding pokes a big hole in the notion that AD is an inevitable consequence of certain genes.

Liu and colleagues note that specific components of the MedDiet—nuts, fruit and monounsaturated fats—were strongly associated with metabolomic improvements.

Keep This in MIND

The Harvard study augments and amplifies key findings from the US POINTER trial, presented at the 2025 Alzheimer’s Association International Conference, and published in late July in the *Journal of the American Medical Association*.

This study, officially called the US Study to Protect Brain Health Through Lifestyle Intervention to Reduce Risk, randomized 2,111 elders at risk for AD to either a structured and guided comprehensive lifestyle intervention based around the MIND diet and supervised exercise, or a less intensive self-guided program which included similar recommendations but fewer points of in-person engagement.

The MIND diet is a hybrid of the Mediterranean and DASH diets. It is plant-centric, emphasizing green vegetables, whole grains, berries, beans and legumes, but it also encourages consumption of fish and poultry.

After two years, both groups showed improved cognitive function, as indicated by a composite measure of executive function, episodic memory, and processing speed. But the change was greater among those in the structured intervention group. The composite score increased by a mean of 0.243 standard deviations per year in the structured group, and by 0.213 standard deviations in the self-guided group.

“Among older adults at risk of cognitive decline and dementia, a structured, higher-intensity intervention had a statistically significant greater

benefit on global cognition compared with an unstructured, self-guided intervention,” wrote lead author Laura D. Baker, PhD, of Wake Forest University.

Protecting the Hippocampus

In another big win for the MIND diet, Rush University researchers showed that it can reduce the odds of developing hippocampal sclerosis (HS)—intensive neuronal loss and astrocyte overgrowth within the hippocampus. HS is a common feature in AD and other forms of age-related, limbic-predominant dementia.

The Rush team studied brain tissue from 809 deceased participants in the ongoing Rush Memory and Aging Project. They obtained validated food frequency data from questionnaires taken annually for up to 18 years prior to the participants’ deaths. They assessed the presence of HS using hematoxylin and eosin staining, and other histologic techniques, in 8 brain regions.

Higher adherence to a MIND diet pattern (based on the food questionnaire data) was associated with a 22% reduction in the odds of having HS, after controlling for age, gender, APOE-4 status, vascular disease, and other variables. A higher MIND diet score was associated with less hippocampal neuronal loss, and an estimated 21% reduction in severity of dementia at time of death.

This is the first study to document the impact of diet on hippocampal neuronal loss. “These findings support the role of the MIND diet for a common degenerative pathology of aging,” the authors state.

Speaking of the hippocampus, University of Michigan researchers showed that high consumption of fat and sugar had detrimental effects on hippocampus-dependent recognition memory and executive function, particularly in people between the ages of 50 and 65.

That conclusion was based on data from 472 subjects who filled out dietary fat and sugar questionnaires, and also completed a set of standardized pattern-separation recognition and face-name memory tasks.

Those at the highest self-reported fat and sugar consumption levels had more subjective memory complaints, after adjusting for other relevant variables. The impact of dietary fat and sugar on hippocampal function was affected somewhat by patient age, and by presence or absence of other comorbidities. High sugar and fat intake was associated with compromised memory performance only in those with no comorbidities. “Diet effects on cognition are more complex in older than younger adults,” the researchers concluded.

Animal studies suggest several different mechanisms by which high fat intake impairs hippocampal function. These are well-summarized in a thorough review article by Dr. Charles Platkin, and posted by the Center for Food & Medicine & Longevity. Fortunately, these studies also indicate that the damage associated with high fat consumption is reversible.

Lay Off the Sweet n’ Low

To preserve cognitive function, avoid artificial sweeteners. That’s the upshot of an 8-year study of 12,772 participants in the Brazilian Longitudinal Study of Adult Health. Researchers at the Universidade de Sao Paulo studied the impact of self-reported sweetener consumption on cognitive function, as measured by 6 different standardized tests. The food intake questionnaire included questions on seven different low- and no-calorie artificial sweeteners (aspartame, saccharin, acesulfame K, erythritol, xylitol, sorbitol, and tagatose).

Among people under age 60, those in the highest tertile for sweetener use showed declines in verbal fluency and overall global cognition compared with those in the lower tertiles. This pattern held for people with and without type 2 diabetes. Interestingly, the investigators saw no such effect in people over age 60.

“Our findings suggest the possibility of long-term harm from LNCS consumption.”

Dietary & Nutritional Impacts on Microglial Expression

- **High-fat / high-sugar (“Western”) diet**
 - Promotes microglial activation toward an M1-like, pro-inflammatory state.
 - Linked to increased production of IL-1 β , TNF- α , ROS.
 - Associated with impaired A β clearance and worsened AD pathology in animal models.
- **Omega-3 fatty acids (DHA, EPA)**
 - Drive microglial polarization toward M2-like, anti-inflammatory states.
 - Increase phagocytic activity and release of neurotrophic factors.
 - DHA-rich diets have shown reduced microgliosis and improved cognition in AD models.
- **Polyphenols** (e.g., resveratrol, curcumin, EGCG from green tea)
 - Suppress NF- κ B signaling and shift microglia toward anti-inflammatory phenotypes.
 - Promote A β clearance and synaptic protection in preclinical studies.
- **Caloric restriction / intermittent fasting**
 - Reduces systemic inflammation, dampens M1-like microglial activation.
 - Enhances autophagy and resilience to neurodegenerative stress.
 - Some animal studies show improved learning/memory outcomes.
- **Ketogenic diets**
 - May promote an M2-like phenotype through ketone-mediated signaling (β -hydroxybutyrate inhibits NLRP3 inflammasome activation).
 - Preclinical work suggests benefits for synaptic protection.

Helpful Herbs & Nutrients for Brain Health

BY AUGUST WEST
Contributing Writer

“Brain Health” is one of the largest and fastest-growing segments of the natural healthcare industry. Americans will spend close to \$1.5 billion on cognition-related products by the end of this year, according to [Nutrition Business Journal \(NBJ\)](#). Globally, the market for brain health products is projected to grow from its current \$8.2 billion, to \$15.2 billion by 2034.

To meet the public’s insatiable demand, supplement makers have launched an astonishing array of botanicals, fatty acids, probiotics, mushrooms, and neurotransmitter precursors for brain-related benefits. They now line retail shelves and online markets alongside older cognitive support products like omega-3s and *Ginkgo biloba*.

NBJ reports that while omega-3s, typically as fish oil, still represent the largest category of brain-focused products, accounting for 22% of total cognitive health sales in 2024, growth has slowed to roughly 5% per year. In contrast, herbs for cognitive support grew by nearly 17% in 2024.

“Surveys show a clear trend: more people want to invest in their cognitive well-being earlier in life,” the NBJ report states. “This preventive mindset is driving steady growth in products positioned for long-term brain support.”

Here’s a review—by no means comprehensive—of some of the emerging and promising botanicals and nutraceuticals for cognitive support:



Turmeric/Curcumin (*Curcuma longa*)

Well known for its wide-ranging antioxidant effects, curcumin supports brain health by reducing inflammation. Preclinical studies show routine supplementation can improve memory function, increase synaptic plasticity, and reduce β -amyloid buildup. In short, it can mitigate the composite negative effects of “inflammaging.”

A [study of rats](#) subjected to induced traumatic brain injury (TBI) showed that curcumin supplementation dramatically reduced oxidative damage and normalized levels of brain-derived neurotrophic growth factor (BDNF) and other key mediators of neuronal activity. Functionally, this translated into a mitigation of the cognitive impairment caused by TBI.

A placebo [controlled study](#) of 60 generally healthy humans, aged 60–85 years, showed that daily supplementation with 400 mg of a standardized curcumin extract ([Verdure Science’s Longvida](#)®), for four weeks, improved working memory, attention, executive function, and mood. Subjectively, curcumin-treated subjects reported greater calmness, contentedness, and reduced fatigue. They also showed reductions in total and LDL cholesterol. This study is the first to look at the impact of curcumin on cognition and mood in older adults.



Ashwagandha (*Withania somnifera*)

This increasingly popular Ayurvedic herb is beneficial for multiple organ systems, including the brain and nervous system, as indicated in several recent clinical trials.

One such [study](#) involved 90 adults with mild to moderate stress, randomized to a placebo or a supplement containing a root-only ashwagandha extract standardized to 1.5% withanolide content ([OmniActive’s Zenroot](#)). At a dose of 125 mg per day, the ashwagandha extract reduced self-assessed stress, as indicated by changes on the Perceived Stress Rating Scale, and also on objective indicators ([the Mindfield® eSense Skin Response](#)). The improvements were apparent within 30 days. The herb-treated cohort also experienced improved sleep quality by day 28.

Another study, also published this year, looked at the impact of a different ashwagandha root extract ([KSM-66](#)) on cognition in a cohort of 120 generally healthy people experiencing problems with cognition and mood. The subjects, from India and Australia, ranged in age from 30–75 years. They were randomized to take 600 mg ashwagandha capsules, or an identical placebo, once daily, for 8 weeks.

On measures of cognitive performance, as assessed by the COMPASS (Computerized Mental Performance Assessment System) tool, the Ashwagandha-treated group showed improvements in episodic memory, working memory, and accuracy of attention, compared with the placebo group. Ashwagandha subjects also showed faster task learning speeds, and better scores on location learning tasks.

Ashwagandha also conferred improvements in mood, based on the Profile of Mood States scale, and better energy based on Multidimensional Fatigue Symptom Inventory.

“Given the current interest in the use of non-pharmacological/herbal supplementation for stress-management and improving the cognitive-behavioral function, this study holds great value,” say the researchers, headed by Sanjiv Kale, at Patil University School of Medicine, Mumbai. The current trial builds on earlier pilot and pre-clinical studies of KSM-66’s ashwagandha, all of which suggested this herb had beneficial brain effects.

Ashwagandha is one of the world’s most researched herbs. Back in 2017, authors Sunil C. Kaul and Renu Wadhwa published a compendium of then-available studies, entitled [Science of Ashwagandha: Preventive & Therapeutic Potentials](#).

Mango Leaf (*Mangifera indica*):

The leaves of this widely cultivated fruit tree contain a polyphenol called mangiferin which can induce a caffeine-like rise in mental energy and alertness, without altering blood pressure or heart rate. A [yet-to-be published industry-funded study](#) of 120 healthy college students showed that compared with placebo, a single dose of a standardized mangiferin extract (PLT Health Solutions’ [Zynamite](#)®) gave a 9% improvement in cognitive



Image: Kattecat/Shutterstock

processing speed, an 11% improvement on digit substitution tasks, and a 5% improvement in performance of trail-making tests, an indicator of capacity to manage complex problems. The changes were measurable within 30 minutes.

A subsequent [study of 70 adults](#) in a double-blind crossover protocol showed that a single 300 mg dose of mango leaf extract improved performance across an array of cognitive tasks in the COMPASS battery. Mangiferin also improved mood as measured by the Profile of Mood States (POMS) scale.

It remains to be seen whether mangiferin has lasting cognitive benefits, and whether it can benefit people at risk of dementia. But it is certainly an ingredient worth watching.

Resveratrol

This antioxidant polyphenol derived from grapes and berries is commonly promoted for its cardioprotective, anti-tumor, and phytoestrogenic effects, all of which have been [well-documented](#). It may soon find a role in prevention of dementia.

As far back as 2015, [researchers reported](#) that at very high doses, resveratrol could cross the blood brain barrier (BBB) in amounts great enough to affect cerebrospinal fluid levels of β -amyloid, tau protein, and other biomarkers of Alzheimer’s.

The problem is that resveratrol in its natural state—like curcumin—is poorly absorbed. It took daily doses of 2 grams per day to obtain the observed CNS effects. Many treated patients experienced side-effects—especially nausea and diarrhea. The resveratrol levels needed to produce meaningful CNS effects were also economically impractical.

Enter a pharmaceutical/nutraceutical company called [Jupiter Neurosciences](#). Making use of methods developed at University of Miami, Jupiter has micellized resveratrol, vastly increasing its overall bioavailability and ability to cross the BBB. This process, called JOTROL™, gives a 9-fold increase in bioavailability compared with ordinary non-micellized resveratrol, as demonstrated in a phase I clinical trial with AD patients, funded by National Institute on Aging (NIA).

A Phase II clinical trial in Parkinson’s disease patients is underway, and Jupiter has also applied for another NIA grant to fund a three-year phase II study of patients with mild cognitive impairment or early AD.

Over the summer, Jupiter launched a nutraceutical company called [Nugevia](#). Among its three flagship products is a fixed combination of [micellized resveratrol and curcumin](#) aimed at reducing neuroinflammation and oxidative stress, increasing mitochondrial metabolism, and improving mental clarity and memory function.



Aframomum melegueta (aka “Grains of Paradise”)

This plant, a member of the ginger family (Zingiberaceae), and native to West Africa, has seeds with a pungent flavor somewhere between black pepper and cardamom. It is widely used in West African cuisine, and has been an important crop for centuries.

Recent biochemical research shows that the seeds contain compounds that enhance the release of anandamide—the so-called bliss molecule—in human brains. On a practical level, this means reduced stress and improved sleep.

In a placebo-controlled crossover study of 30 healthy adults between the ages of 40 and 50, daily supplementation with a standardized extract of *Aframomum* (PLT Health Solutions' [Vanizem](#)) improved sleep quality and reduced time to falling asleep within three days. Participants reported less fatigue, less depression, and increased vigor.

The protocol tested two doses—100 mg and 150 mg per day. Both gave improvements compared with placebo, but the effect sizes were generally greater with the 150 mg dose. The study was funded by PLT Health Solutions.

Selenium

Often considered a “prostate health” nutrient, this mineral can reduce oxidative stress and neuroinflammation, while enhancing proliferation of neuronal progenitor cells. It also prevents ferroptosis and reduces microglial activation, two of the many physiological mechanisms underlying cognitive decline.

Selenium has a particular affinity for the hippocampus, where it can stimulate neurogenesis. Given the essential roles of the hippocampus in memory, spatial orientation, and mood regulation, this is a welcome discovery.

There are roughly 600 published studies on selenium and various aspects of brain physiology and cognitive function. The vast majority were published just in the last 5 years. In September, an international research team published a [thorough review of the research](#) on selenium and hippocampal neurogenesis.

Pentadecanoic Acid C15:0 (aka Fatty15)

This naturally-occurring, odd-chain, saturated fatty acid boasts a range of potential health benefits such as reduced risk of type 2 diabetes, heart disease, fatty liver disease, and overall reductions in all-cause mortality. Structurally, C15:0 contains no double bonds, making it highly resistant to oxidation.

The human body cannot produce C15:0. It must be obtained from diet. One of the main food sources of C15:0 and other even chained fatty acids is whole milk. But consumption of whole milk has declined significantly over the past decades due to “low-fat” and “fat-free” recommendations and policies. On a population level, intake of C15:0 has declined significantly over the last 40 years.

The importance of C15:0 emerged largely from research on cohorts of bottlenose dolphins maintained by the [US Navy's Marine Mammal Program](#). Dolphins are intelligent higher mammals that share many physiological traits with humans, including a propensity toward age-related chronic disease—despite the absence of junk food, alcohol, and other manmade risk factors.

Years back, Stephanie Venn-Watson, a veterinary epidemiologist for the Navy, noticed that roughly one-third of the dolphins in the Navy's San Diego cohort had developed metabolic conditions like [insulin resistance](#), chronic inflammation, [dyslipidemia](#), and fatty liver disease. Given that all the dolphins were free-swimming, and all ate more or less the same all-fish diets, Venn-Watson grew curious as to why some of the dolphins developed chronic disease patterns while others did not.

She and her team applied metabolomic screening methods to assess vast numbers of potential risk factors and longevity predictors. They found that pentadecanoic acid was far and away the strongest predictor of healthy dolphin aging.

At the same time, the Navy researchers began comparing the San Diego cohort with another dolphin pod living off the coast of Florida. These Florida dolphins had far lower incidence of metabolic conditions. It turns out they were eating different types of fish than the California cohort, and overall, their diets were much higher in C15:0.

So, the researchers began augmenting the California pod's diets with high C15:0 fish, and over time the prevalence of chronic conditions declined.

Several years later, Dr. Watson and her husband, Eric Venn-Watson, MD, formed [Seraphina Therapeutics](#), a nutraceutical company focused on translating the dolphin discoveries into C15:0 supplement products to benefit humans. They launched their first product, cleverly named Fatty15, last year.

With regard to neurological health, C15:0 has a number of important and potentially beneficial effects. It can activate AMPK while inhibiting mTOR, and it exerts a dose-dependent inhibition of Fatty Acid Amide Hydrolase (FAAH)—an enzyme that breaks down anandamide and other endocannabinoids—and of Monoamine Oxidase B (MAO-B), an enzyme that degrades dopamine.

Since FAAH and MAO-B overactivity is common in both Alzheimer's and Parkinson's, inhibition of these enzymes by C15:0 supplementation could potentially benefit at-risk people, or even those who are already diagnosed. These effects have not yet been confirmed in human clinical trials, but they do suggest plausible biochemical mechanisms for cognitive health benefits.

That said, there is one [human cross-sectional study](#) involving 372 individuals with type 2 diabetes, which showed that higher plasma concentrations of C15:0 were associated with higher scores on the Mini Mental State Exam, and the Montreal Cognitive Assessment. The subjects with the highest plasma C15:0 levels showed better visuospatial processing and stronger performance of delayed-recall tasks than those with the lowest levels. continued on next page

Who We Are

Since 1979, Allergy Research Group has developed premium, condition-specific supplements. Today, we are a global leader in nutritional supplements, trusted by integrative health professionals worldwide to improve their patients' health. Our clinically proven regimens and evidence-based efficacy support patients at the highest level. Quality, purity and efficacy are the pillars of our targeted nutritional supplements, making Allergy Research Group the go-to brand for even the most sensitive patients. As an established player with a leading position and loyal customer base, we continue to grow thanks to our innovative solutions backed by science, strong engagement with customers and educational initiatives





Greek Mountain Tea (*Sideritis scardica*):

A plant in the Lamiaceae family (which includes various types of mint, oregano, rosemary, and sage), *Sideritis scardica* proliferates throughout Greece, the Balkan region, and much of the Mediterranean. In ancient times, it was used to heal war wounds caused

by iron weapons—hence the name *Sideritis*, which means “made of iron.”

For centuries, Greeks and other Mediterranean peoples have drunk teas made from this herb, which is praised for its ability to increase vigor and mental acuity, but without causing caffeine-like jitters. More recently, herbal supplements made from the leaves of this plant have hit the market.

There is some clinical evidence to suggest that this venerable herb does indeed improve cognitive performance, and may even mitigate some of the drivers of Alzheimer’s.

Researchers at Northumbria University, UK, randomized 115 older adults (aged 50-70 years) to daily supplementation with Mountain Tea (475 mg/d or 950 mg/d), or Ginkgo biloba (240 mg/d), or a placebo for 28 days.

Compared with the placebo and Ginkgo groups, those in the Mountain Tea group showed better average scores on visual processing tasks, and lower levels of anxiety. The researchers measured oxygenated hemoglobin and oxygen saturation in the prefrontal cortex, and found that both measures increased in the subjects taking Mountain Tea. This effect was observable after just one dose of the supplement (Wightman E L, et al. *Nutrients*, 2018), and it is important given the role of the prefrontal cortex in learning and working memory.

An earlier [six-week pilot study](#) by Leibniz University Hannover researchers, assessed the cognitive impact of *S. scardica* supplementation (330 mg/d), in combination with B vitamins, in a cohort of 64 adults between the ages of 25 and 60. Compared with baseline measures, the supplement regimen conferred improvements on a host of working memory, cognitive flexibility, and stress measures. “The tested product alleviates stress-induced impairment of executive functioning,” the authors concluded.

There is also a preclinical study suggesting that *S. scardica* can inhibit the aggregation and toxicity of β -amyloid. Another animal study found that reductions in β -amyloid deposition following daily *S. scardica* supplementation correlated with [better cognitive performance](#). Again, these promising observations remain to be tested in human trials.

Greek Mountain Tea plays well with the very popular Ayurvedic herb, *Bacopa monnieri*, which is widely promoted for cognitive benefits.

A [2016 clinical study](#) of 32 people diagnosed with mild cognitive impairment showed that compared with placebo, a combination of 120 mg Bacopa extract plus 380 mg of *Sideritis* (along with vitamin B6, B12, folic acid, B5, and zinc), resulted in improved scores on tests of memory, mathematical calculation, and attention, after 4 weeks.

The researchers gathered EEG data from each patient, and found that those taking the herbal combination had increased beta wave activity—which is typically reduced in AD and MCI—compared with those on placebo. Beta wave activity is associated with attention and memory formation.

This *Sideritis*-*Bacopa* combination product is sold in Germany and other European countries as [memoLoges](#). 🍵

Help Patients Sleep

cont’d from page 4

When I evaluate insomnia, I ask about things many patients have never been asked before:

- Do cortisol and melatonin follow a healthy daily rhythm, or are they flipped?
- Could blood sugar swings at night be waking your brain with a nocturnal rush of cortisol and adrenaline?
- Might your liver over-burdened between 1–3 a.m., disrupting detox pathways, and spiking nighttime alertness?
- How healthy is your gut?—is it producing enough serotonin and GABA to calm your nervous system?
- Are inflammation or hidden infections elevating cytokines that interfere with sleep architecture?
- Might you be deficient in important nutrients such as magnesium, B6, vitamin D, omega-3s, which influence the body’s ability to relax into sleep?
- Is there a possibility you’re exposed to mold toxins or EMF radiation, both of which overstimulate the brain and lower endogenous melatonin levels?
- Might genetic factors, such as polymorphisms in the *COMT*, *GAD1*, *MTHFR*, or *CLOCK* genes, alter how you process stress or regulate circadian timing?

These aren’t “extra” questions. They’re central to decoding why someone’s natural sleep processes have broken down. There are more questions, to be sure. But these will give you and your patients good places to start.

The Big Three

Let’s take a closer look at three of the most common contributors to sleep disturbance:

Cortisol/Melatonin Rhythm Misalignment: These two hormones are the major determinants of someone’s circadian rhythms. Normally, cortisol should rise in the morning to signal arousal and return to activity, while melatonin rises at night to help induce sleep. But stress, late-night screen exposure, shift work, or irregular schedules can flip this rhythm. The flipped pattern—cortisol surges at night, absent or mis-timed melatonin release—are all-too-common these days. The result: someone’s wired at night, sluggish in the morning.

For assessment, I recommend the following tests: DUTCH or Rhein Hormone testing for cortisol curve and melatonin output.

Blood Sugar Instability: Night waking between 1–3 am is often tied to precipitous drops in blood glucose. In response, the body releases cortisol and adrenaline to bring it back up—but that same surge jolts the person awake with a racing heart. This, too, is very common. I recommend using a continuous glucose monitor (CGM), and checking the fasting insulin and HbA1c levels, to help people figure out what’s going on.

Environmental Triggers (Mold & EMFs): Mold toxins inflame the nervous system and disrupt hormone signaling. EMF exposure (from WiFi routers, phones, or smart devices) can suppress melatonin and overstimulate brain waves. I lump these two very different factors together because they are hidden, invisible triggers, and rarely screened for—or even considered—in the conventional approach. Mycotoxin testing, and home EMF assessments can help you get a handle on these overlooked sleep disruptors.

Insomnia is a Message

Insomnia isn’t random—it’s a communication. Every restless night, every 2 am wake-up, every foggy morning is the body’s way of saying: “Something deeper needs attention.”

When we ignore or suppress these signals, we may quiet the symptom, but we miss the opportunity to heal the underlying imbalance.

The functional medicine perspective is essential here because it reframes insomnia from a frustrating symptom to a valuable clue. By decoding that clue—identifying whether it points to glucose swings, stress hormones, inflammation, nutrient deficiencies, or environmental stressors—we help patients shift from coping to true healing.

At [Functional Medicine University](#), we teach you exactly how to do this. Our curriculum is built for practitioners who want to go beyond symptomatic care and master the art of root-cause investigation.

You’ll learn how to map seemingly unrelated factors—cortisol/melatonin rhythms, blood sugar stability, gut integrity, detox pathways, genetic vulnerabilities, and environmental triggers—into a coherent system that explains why a patient can’t sleep, and more importantly, how to help them heal.

This isn’t about memorizing protocols or replacing one pill with another supplement.

It’s about mastering a way of thinking that restores function at the deepest levels.

When you practice this way, not only do your patients finally find answers, but your practice and your professional life are reinvigorated. You transform from being another stop on a patient’s frustrating journey to being the clinician they recommend, trust, and credit with changing their lives. 🍵

Ron Grisanti, DC, DABCO, DACBN, MS, DIANM is a highly respected board-certified chiropractic orthopedist, Diplomate of the American Clinical Board of Nutrition, and a pioneer in the field of functional and integrative medicine. With nearly 40 years of clinical experience, he is recognized nationally and internationally for his expertise in solving complex, chronic health challenges that conventional medicine often leaves unresolved.

He earned his Doctor of Chiropractic degree, followed by an intensive 3–4 year post-doctoral orthopedic residency, achieving Board Certification in Chiropractic Orthopedics. Dr. Grisanti also completed 100 hours of postgrad education in the Chiropractic Sports Physicians program. Expanding his clinical reach beyond musculoskeletal care, Dr. Grisanti pursued a Master of Science in Human Nutrition at the University of Bridgeport.