BRAIN HEALTH | PSYCHIATRIC HEALTH

TOWNSENDLETTER.COM

# Townsend Letter

*The Examiner of Alternative Medicine*

October 2022
Issue #471

## Treating Anxiety Without Pharmaceuticals

## Preventing Clinician Burnout

## Steven Sandberg-Lewis, ND
### Reducing GERD with Lifestyle Factors

JUMP TO TABLE OF CONTENTS

# Thank you for purchasing this issue of *TOWNSEND LETTER*

On the cover (previous page) you will find a button that will take you directly to the table of contents. Once there, you can click page numbers that take you directly to articles. Click on "return to table of contents" at the bottom of each page to take you back to the TOC.

Most web and email addresses are clickable within the articles and in the calendar. We do not guarantee the accuracy of each address/URL, or that it is clickable.

Please don't overlook our advertisers, without their support *Townsend Letter* would not exist. Take the time to discover companies you might not be familiar with, many of whom offer special pricing for *Townsend Letter* subscribers. An advertiser list is printed on page 78 with clickable page numbers that will take you directly to their ad(s).



## Subscription Rates and Options

**Prices valid through 1/1/2023**

Name _____ Email/Phone _____

Address _____

City/State/Zip _____

**Payment accepted in US funds, payable by check / money order / credit card / or billed via PayPal**

Payment by: Visa/MC/AMEX/Discover # _____ Expiration date: _____

Signature _____

**Click here to subscribe online**

| | Description | Print Version | E-Edition | Combined |
|---|---|---|---|---|
| US Addresses (except WA state) | 1-year Domestic US | $76.99 | $66.99 | $91.99 |
| | 2-year Domestic US | 136.99 | 116.99 | 166.99 |
| | 6-month Domestic US | 45.99 | 41.99 | – |
| | 1-year Student Domestic US | 56.99 | 41.99 | 66.99 |
| Washington State Residents | 1-year Washington state (w/tax) | 86.99 | 74.99 | 99.99 |
| | 2-year Washington state (w/tax) | 146.99 | 127.99 | 183.99 |
| | 6-month Washington state (w/tax) | 33.99 | 46.99 | – |
| | 1-year Washington Student (w/tax) | 56.99 | 46.99 | 66.99 |
| 1st Class | 1-year First Class Domestic US | 96.99 | 66.99 | 111.99 |
| | 2-year First Class Domestic US | 176.99 | 116.99 | 206.99 |
| International Rates | 1-year International (US$) | 105.99 | 66.99 | 120.99 |
| | 2-year International (US$) | 202.99 | 116.99 | 232.99 |
| | 6-month International (US$) | 63.99 | 41.99 | – |
| | 1-year International student (US$) | 76.99 | 41.99 | 93.99 |

**SPECIAL RECEPTION ROOM OFFER:**
Purchase a 2nd subscription for your waiting room

$57.99 US addresses – $87.99 International
Offer valid with current existing subscription

**E-Edition Single Issue: $15.00**

**E-Edition Single Issue WA State (includes tax): $16.00**

**Single Print Issues: cover cost (for each issue), plus shipping charges, applicable taxes, and $3 per-order handling fee.**

**Townsend Letter**
**911 Tyler Street | Port Townsend WA 98368**
**info@townsendletter.com**
**360.385.6021 | 360.385.0699 (fax)**
**www.townsendletter.com**

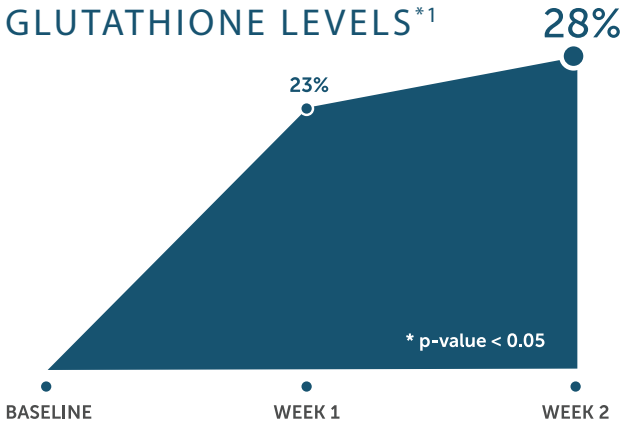
# Tri-Fortify®

## *Liposomal Glutathione*

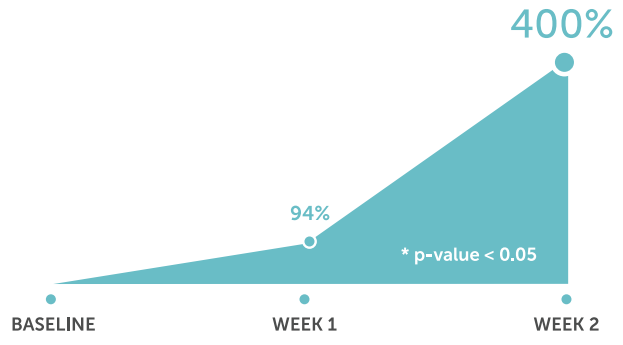
Researched Nutritionals®
solutions for life

# Backed by *peer-reviewed, published* clinical research.[1]

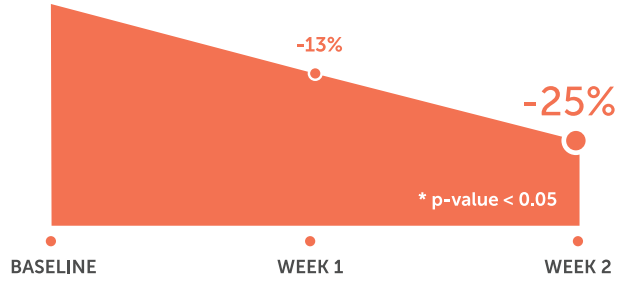

## GLUTATHIONE LEVELS*[1]




## NATURAL KILLER CELL FUNCTION*[1]




## OXIDATIVE STRESS MARKERS*[1]




**Learn more.**

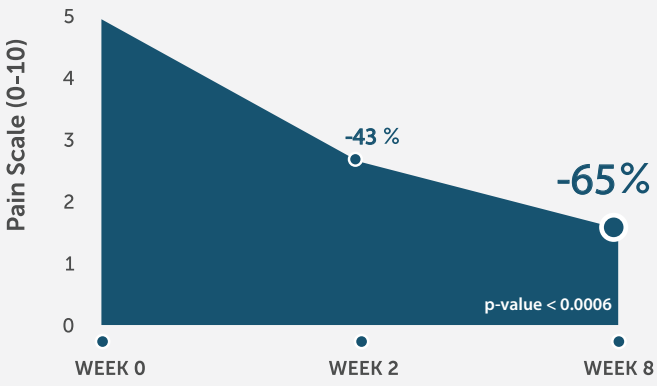
Tri-Fortify

[1]Sinha R, Sinha I, Calcagnotto A, et al. Oral supplementation with liposomal glutathione elevates body stores of glutathione and markers of immune function. Eur J Clin Nutr. 2018;72(1):105-111. doi:10.1038/ejcn.2017.132

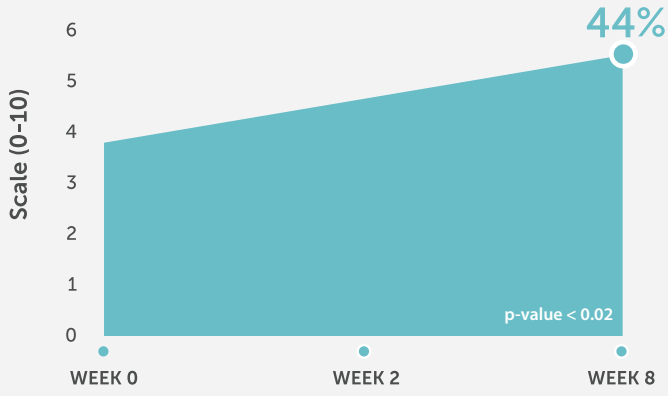
800.755.3402 • Info@ResearchedNutritionals.com • ResearchedNutritionals.com | Available only through healthcare professionals.

# Research is the difference.

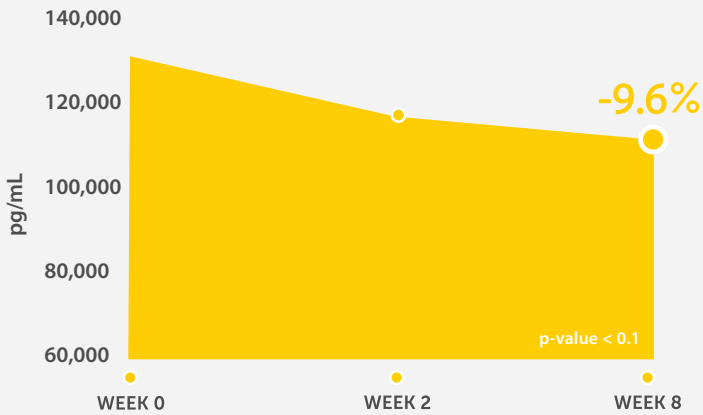

## PHYSICAL DISCOMFORT*




## SLEEP IMPROVEMENT*1




## MMP-9*1




Learn more

Learn more: researchednutritionals.com/cytoquel

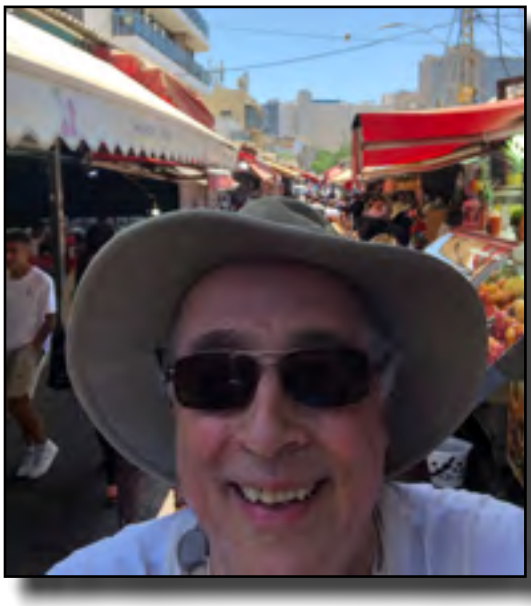
[1] Journal of Pain Research (D Hamilton, G Jensen). Pain reduction and improved vascular health associated with daily consumption of an anti-inflammatory dietary supplement blend. J Pain Res. 2019; 12: 1497–1508.

Researched Nutritionals solutions for life

800.755.3402 • Info@ResearchedNutritionals.com • ResearchedNutritionals.com | Available only through healthcare professionals.

*These statements have not been evaluated by the Food and Drug Administration. These products are not intended to diagnose, treat, cure, or prevent any disease.*

Carmel Market in Tel Aviv



# From the Publisher

**Hydrotherapy *à la Française***

The proverbial question kids are asked during their first week back at school is "what did you do this summer?" "Went to the beach," "stayed on the lake," "hiked in the mountains," "visited relatives," "traveled to the city," or "attended sleep-away camp" are the usual answers. My "camping" experience for two weeks was sojourning in Tel Aviv at a hotel with a lovely view of the Mediterranean, beach, and city avenue. (It was just what the Doctor ordered!). I was visiting my 94-year-old Aunt Lucy who has lived in Israel nearly since its founding. My brother, David, and his family joined me for the vacation. For someone who spends the year in the rains of the Pacific Northwest, Tel Aviv provided me with beach therapy and natural vitamin D.

The naturopathic profession has long touted hydrotherapy as an important component in the treatment process. During the late 1800s and early 1900s many of the naturopathic pioneers established clinics offering cold showers, foot baths, wraps, massages and more. US physicians like Benedict Lust learned from ole timers in Europe. While the spas in Europe gained wide-spread renown and popularity, practitioners in the US were more typically loners needing to advertise their services. Lust and other practitioners wrote articles and pamphlets discussing the scientific basis for water treatment. NUNM (formerly the National College of Naturopathic Medicine in Portland, Oregon) has collected an extensive library of the writings of these early

Clock Tower in Jaffa

naturopaths. Sussana Czeranko, ND, edited a 12-volume collection of these writings entitled *The Origins of Naturopathic Medicine,* published as the Helvert Collection (available for purchase).

Recently, I saw a posting on the social media site, LinkedIn, by Dr. Mark Hyman, renowned functional medicine MD. He was immersed in a bath filled with ice cubes and water. Hyman's typical pedantic discussion explaining how nutrition improves one's health was shockingly replaced with a photograph of himself sitting upright in the tub, all smiles. He didn't explain how long he was in the icy water, but I imagine it could not have been much more than 60 seconds – just long enough to pose for a photo with an expression of nervous bliss. I know there is value to a cold shower in getting the circulation going and there is an invigorating feeling once one has finished and dried off. However, I think the plunge into the ice water is a little too extreme for my comfort. As far as I know, Hyman hasn't touted the benefits accrued from this frigid immersion on LinkedIn since the original posting.

In France hydrotherapy is neither cold nor the sole domain of naturopathic physicians. Instead, it is usually warm, sometimes quite warm, and the thermal cure is prescribed by one's physician. There are 113 official thermal spas in France, and the cost for the water cure as long as you are a French citizen is covered by the state's social security system. Lauren Collins, a writer for *The New Yorker*, discusses her experiences with "social thermalism" in the May 30, 2022 issue in an article entitled "Soaking It In." Just like there is a provincialism with wine and cheese in France, thermal spas also have their own "terroir"; a spa in central France's Vichy is entirely different from one on the Atlantic, like Roscoff.

As Collins discusses in her article there are two types of hydrotherapy – a sulfurous one and a salty one. The first

definitely has the odor of rotten eggs and cabbage soup; the latter is known as thallasotherapy (from thallaso-, Greek, for the sea) using sea water. Thermal spas were originally discovered and used by Gauls and Romans thousands of years earlier. However, it was not until Henry IV in the 17th century officially decreed thermal baths for medical use that thermalism become an institution in France. Napoleon III designed palatial buildings in Vichy making for a very aesthetic version of hydrotherapy. By the late 1800s spas were cropping up throughout France in mountain hamlets and coastal locales affording hydrotherapy treatment for all. Recently the thallasotherapy spas are no longer reimbursed by the French social security meaning all clients must privately pay. Nevertheless, millions come to spas for a three-week session of treatments each year. Moreover, the thermal sulfurous spas remain a mostly government-paid medical hydrotherapy for all who get a physician's prescription.

Those who have read Georges Simenon's "Maigret in Vichy" (also a TV series entitled "Maigret") may recall the boring and tedious aspects of a Vichy water cure:

> They would have sworn that they had been at Vichy for an eternity, while it was only their fifth day. Already, they'd created for themselves a schedule that they followed meticulously, as though it was of importance, and the days were marked by a certain number of rituals, to which they lent themselves with the utmost seriousness.

In fact, the curistes, as they are called, who come for water treatment know that they must diligently participate in their hydrotherapy treatments if they are to succeed in turning around their ills. Carrots and other root vegetables are considered part of the treatment to be consumed daily. At Vichy there are five different waters all at different temperatures ranging from 22 to 43 degrees Centigrade. One is generally prescribed to drink a half liter of a certain water six times daily (more or less). One patron described the water as tasting awful, "super nasty." When the author, Collins, took a sip it not only tasted like "rotten eggs" and "cabbage soup" but also it had a chalky sensation, "like she had licked a blackboard." A hydrotherapy series at Vichy might include "18 mud baths, 18 high pressure underwater showers, 18 pool sessions, 9 water massages, and 9 steam-chair treatments over 3 weeks." For some curistes, the program also may require sessions of *enteroclyse* meaning colonic enemas using the Vichy water. For each spa there is a doctor and the curiste is examined by the physician before treatment, then half-way through the three weeks, and at the completion of the program. Most physicians undergo special training and accreditation as a spa doctor.

For the thallasotherapy, Collins visited Roscoff, a region known for its pink, sweet onions that are enjoyed not

➤

➤

just in France but in England as well. The favorite treatment at Roscoff is known as the *douche a jet*, which the director described as a "vigorous jet of water that left one's legs feeling like they were made of cotton." Collins' description of it gives a personal perspective:

> Soon I was standing stark naked at the far end of a narrow, gray-tiled room, clutching the side bars of a waist-high metal support. About 10 feet away, the therapist was unfurling a thick hose from a wall mount.
>
> "'Turn to the right,'" she said. "'Ready?'"
>
> I braced myself. The water pressure was intense – almost strong enough to clean a sidewalk. I could taste the salt. The therapist was yelling instructions, but I could hardly hear them over the roar of the spray. She started with my ankles, working methodically up the line: calves, thighs, butt, triceps, shoulders.
>
> "'Lift up your feet,'" she said.
>
> She hosed down my soles. Then my palms. My whole body was being spray painted, and she was determined not to miss a spot.
>
> At the end of the treatment, the therapist had me turn toward her. Here it was: the full-on *douche a jet*, straight to the gut. I closed my eyes.
>
> When she asked if I'd like a final blast of cold water, I surprised myself by saying 'yes.'

In the US hydrotherapy is not recognized as a medical treatment. Of course, patients are encouraged to go swimming for exercise, enjoy sauna and steam baths, bathe in a jacuzzi. Unfortunately, going to a spa for hydrotherapy is considered tourism not medical therapy and is not covered by insurance. Still we need to consider hydrotherapy for our patients. It may help the illness, relax the patient, and does no harm.



**Jonathan Prousky, ND, MSc, on Physician Burnout**

Dr. Jonathan Prousky is the chief medical officer as well as professor at the Canadian College of Naturopathic Medicine. Prousky's specialty lies in treatment of mental illness combining his knowledge of conventional psychiatry and psychology, naturopathic medicine, as well as orthomolecular medicine. He has been a contributing writer to the *Townsend Letter* submitting many articles over the past two decades. One of his earliest submissions was awarded the Best in Naturopathic Medicine *Townsend Letter* award. We are pleased to include his writing substantiating naturopathic and orthomolecular mental health treatment contrary to the psychiatric profession's disdain for such therapy. Indeed, while skeptics such as the contributors and moderators of Wikipedia have belittled nutritional and natural treatments for mental health, Prousky's examination of the literature establishes evidence-based medicine for such approaches.

The Greek proverb, "Physician, Heal Thyself," which also appears in the biblical Old and New *Testaments* as well as Aeschylus's *Prometheus Bound* and in *Aesop's fables* behooves the physician to heal oneself before healing others. Of course, contemporary medical ethics according to the AMA stipulate that a physician should not treat oneself or one's family members, which presents an awful dilemma for the doctor who is burned out. After all, we all should take care that we know how to balance work and life and not overwork to the point of burnout.

Unfortunately, burnout is all too common. According to statistics cited by Prousky between 25-50% of physicians in the US and Canada experience burnout. These numbers are dramatically higher than non-medical workers in both countries. We all talk about how stress contributes to illness, but doctors are no better at managing stress than those in other professions or work activities. Burnout is not just stress but a state of dysfunction impairing a physician's ability to practice effectively while potentially harming the patient. It is manifested by depression, anxiety, cognitive impairment, and overall work life imbalance. But how does one diagnose and treat burnout?

Prousky reviews allostasis, the ability to adapt to stresses that we experience. We generally describe this as impairment to the HPA axis with diurnal dysfunctioning of cortisol levels. However, Prousky points out that allostasis involves much more than cortisol dysfunctioning. Changes in our neurochemistry especially involving mono-amino acids such as norepinephrine, epinephrine, dopamine, and serotonin transpire during burnout. Brain derived neurotrophic factor (BDNF) is noted in research studies to be substantially lower in the burned-out individual compared to the normal one.

What is the physician to do if he/she is burned out? Lifestyle changes are key. Work responsibilities at office and home need to be reduced and more time must be allotted for relaxation, exercise, nutrition, and sleep. Elimination of toxic exposures both chemical and interpersonal is necessary. Prousky presents the evidence of micronutrient and herbal support. And not just for a few of us, counselling and meditation will be part of the prescription.

Perhaps the most difficult part for the physician is admitting that one is suffering from burnout.

**Cover Article:**
**Steven Sandberg-Lewis, ND, on Reflux**

In the late 1970s while practicing in Bellevue, Washington a patient consulting with me recommended that I go visit his hometown, Port Townsend, 60 miles and a ferry ride away. After enjoying its local county fair, I became interested in moving to the Victorian town on the Olympic Peninsula. In 1981, Dr. Steven Sandberg-Lewis was looking to spread his wings and put his practice and cottage on the market. I thought

*continued on page 6* ➤


# Find Your Zen,
## anytime, anywhere*

### 200 mg of Zen
Supports a Sense of Calmness*

Our original best-selling Zen formula. A combination of GABA and L-theanine for relaxation without sedation.*

Also available as Liposomal Zen®, a soy-free liposomal formulation for rapid absorption.*

### Zen Adapt
Calmness and Stress Resilience*

Promotes a balanced, healthy response to everyday stress.*

The foundational ingredients of 200 mg of Zen, enhanced with a standardized ashwagandha extract.

### Zen Sleep
Calmness and Quality Sleep*

Promotes serotonin and melatonin production for a good night's sleep.*

Enhances the foundational ingredients of 200 mg of Zen with vitamin B6 as P5P and 5-HTP.

We use only Suntheanine®, pure L-theanine from Taiyo International, Inc.

SENSORIL® is protected under U.S. Patent No. 7,318,938 and CA Patent No. 2,508,478, and is a registered trademark of Natreon, Inc..

AllergyResearchGroup®
Innovative Nutrition

NSF GMP Registered

Fullscript

**Call or order online**
800.545.9960
allergyresearchgroup.com

*This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.

# From the Publisher

➤ *continued from page 4*

that this was a splendid opportunity to do the same and we worked out an agreement for me to give it a trial for one year. After that year the deal was finalized, and I have continued to practice medicine as well as publish the *Townsend Letter* in Port Townsend.

Meanwhile, Dr. Sandberg-Lewis moved back to Portland where he established a private practice and served as adjunct faculty at NCNM. From 1996-2019 he served as a full-time professor at the National College of Naturopathic Medicine (now NUNM). His specialty at the college was in gastroenterology, establishing in 2010 a center for the study of SIBO. Sandberg-Lewis is the author of *Functional Gastroenterology: Assessing and Addressing the Causes of Functional Digestive Disorders.*

In this issue we publish an excerpt of Dr. Sandberg-Lewis's new book: *Let's Be Real About Reflux: Getting to the Heart of Heartburn.* He wants us to differentiate between reflux and heartburn – they are not the same thing. For one thing one can have reflux without heartburn (rare) and heartburn without reflux (not so rare). It is reflux that we need to be concerned about. Long standing untreated reflux can lead to Barrett's as well as cancer of the esophagus.

In a word, one of the most effective ways to reverse GERD is by lessening dietary intake of carbohydrates. Dr. Sandberg-Lewis has a mnemonic, CARBS to keep in mind those carbohydrates most responsible for reflux symptoms. Cola, coffee, and chocolate; alcohol and acidic foods; and refined carbohydrates are among those foods to restrict. He also cautions against eating big meals and snacking.

Sandberg-Lewis's prescription is a welcome alternative to the prescribing of antacids and proton-pump inhibitors.

Jonathan Collin, MD


# Townsend Letter

ISSN 1940-5434

**Subscriptions • Editorial • Advertising**

**360/385-6021**

**24 Hr. Fax – 360/385-0699**

**911 Tyler Street | Pt. Townsend, Washington 98368 USA**
**http://www.townsendletter.com | info@townsendletter.com**

| | |
|---|---|
| **Editor-in-Chief** | Jonathan Collin, MD |
| **Publisher** | Jonathan Collin, MD |
| **Editor** | Jule Klotter |
| **Contributing Medical Editor** | Alan Gaby, MD |
| **Managing Editor** | Barbara Smith |
| **Circulation Manager** | Joy Reuther-Costa |
| **Managing Assistant** | Julie Reuther |
| **Advertising Projects & Accounts** | Barbara Smith<br>Joy Reuther-Costa<br>Jonathan Collin |





Published by
Townsend Letter for Doctors & Patients, Inc.
Jonathan Collin, President
Deborah Nissen-Collin, Vice-President




Disclosure: The *Townsend Letter* publishes information about alternative medicine written by researchers, health practitioners, and patients. As a forum for the entire alternative medicine community, we present information discussing a wide variety of alternative and integrative medicine practices. In addition to publishing original research and literature abstracts and reviews, we encourage case studies and anecdotal reports. Detailed anecdotal reports are not viewed as proof but as possibilities that need further investigation. All authors are requested to submit their reports to other professionals for review.

The editors of the *Townsend Letter* recommend that all patients (and physicians) review further reports provided in the article's references and investigate the practitioner's techniques before undertaking an alternative diagnosis, examination, or treatment. Please discuss such treatments and examinations with a reputable health practitioner in your community. If you do use an alternative treatment discussed in the *Townsend Letter*, we would appreciate your report of the outcome, any side effects, and costs.

# When water isn't enough.


## A lozenge for temporary relief from DRY MOUTH.

- Naturally increases saliva production
- Fresh citrus taste
- Helps prevent tooth decay
- No interaction with medications
- Safe for diabetics
- Available in convenient flip-top container

Improved Formula with **XYLITOL**

**Ingredients:** • Xylitol • Citric Acid • Apple Acid • Sodium Citrate Dihydrate • Sodium Carboxy Methyl Cellulose • Dibasic Calcium Phosphate • Silica Colloidal • Magnesium Stearate • Stearate Acid.

***Safe. Effective. Convenient.***

**Available from major distributors such as** Threshold Enterprises, Emerson Ecologics, SuperNatural Dist., McKesson, Cardinal/Kinray

Scandinavian Formulas

Sellersville, PA 18960 • P: 215-453-2507 800-688-2276
F: 215-257-9781 • scandinavianformulas.com

# Shorts

**briefed by Jule Klotter**
**jule@townsendletter.com**

**Acetaminophen (Paracetamol) and Neurodevelopment**

For over four decades, acetaminophen (paracetamol), a fever reducer and pain reliever used in Tylenol and many other over-the-counter products, has been promoted as safe for infants and children. Two recent reviews from senior author William Parker (Duke University; Durham, North Carolina) and colleagues tracked down early safety studies and reviewed more recent evidence that show this drug affects adults and children differently: "Paracetamol is known to cause liver damage in adults under conditions of oxidative stress or when used in excess, but increasing evidence from studies in humans and in laboratory animals indicates that the target organ for paracetamol toxicity during early development is the brain, not the liver."

In the 2022 review, led by Jasmine Cendejas-Hernandez, the Duke researchers say a 2008 case-controlled study, led by Stephen T. Schultz, was the first to indicate acetaminophen's adverse effect on neurodevelopment. Using an online parental survey, Schultz et al found that children with autistic disorder (n=83) were far more likely to have received acetaminophen after measles-mumps-rubella (MMR) vaccination than healthy control children (n=80). Ibuprofen use was not associated with autism. As Cendejas-Hernandez and colleagues found, this 2008 study is one of the rare few that looked at the drug's effect on children's neurodevelopment.

Cendejas-Hernandez et al conducted a systematic review with citation tracking. They searched PubMed for articles in English, published between 1974 and 2017, that made claims about acetaminophen being safe for children and found 218 studies, 103 of which were considered "sources of authority for the safety claim." Fifty-two of the 103 gave experimental evidence to support the claim: "Although several of those 52 studies provided measures of liver function…none of the studies provided any assessment of neuropsychiatric function." Moreover, the median follow-up time in these studies was 48 hours – far too short to observe neurological effects even if they were looking for them. The longest follow-up was one year and simply looked at re-admission for pediatric surgery.

At least 14 cohort analyses of acetaminophen use in pregnant women indicate that it adversely affects neurodevelopment in the fetus. As authors of the second Duke review article, led by Esha Patel, state: "Based on these studies, it can be concluded that prenatal exposure to paracetamol causes statistically significant risks of developmental delays, attention deficit hyperactivity disorder, and a subtype of autism spectrum disorder (ASD) associated with hyperkinetic behavior." The effects on children after birth appear to be even greater.

In their 2022 narrative review of direct and indirect evidence, Patel et al point out that the body can convert a portion of the drug to a toxic metabolite called N-acetyl-p-benzoquinone imine (NAPQI), which can be neutralized if enough glutathione is present. "NAPQI reacts with a wide range of proteins, permanently damaging those proteins and resulting in toxicity to the associated cell." Animal studies show that acetaminophen is "more deadly in young pups than it is in older animals." What produces acetaminophen death in young animals has not been investigated, but "*even at doses that are lethal, young pups suffer no statistically significant liver damage* [author emphasis]."

Animal experiments have also shown that even a couple doses of acetaminophen given to young pups has "eliminated" their ability to learn how to run a maze and produces asocial behavior later in life. Interestingly, adult human studies have shown that acetaminophen "temporarily blunts social trust and awareness, emotional response to external stimuli and the ability to identify errors, indicating that the drug targets regions of the brain affected in patients with ASD." Animal studies have also shown that male brains are more sensitive to the drug than female brains – which corresponds to the higher incidence of ASD in human males.

In addition to prenatal human and animal studies, Patel et al present "overwhelming circumstantial evidence for harm." The researchers point out that ASD began to rise in the early 1980s when physicians began to recommend that parents use acetaminophen for their children instead of aspirin, which was associated with Reye syndrome. Direct-to-consumer advertising in the US, which began in the 1990s, further contributed to the drug's increased use – and a parallel rise in ASD. "Although it is well known that association does not indicate causation, it is also correct that causation cannot occur without association," the authors write.

According to Cendejas-Hernandez et al, the American College of Obstetricians and Gynecologists (ACOG) has refused to caution

against acetaminophen use during pregnancy: "'ACOG's clinical guidance remains the same and physicians should not change clinical practice until definitive prospective research is done.'" The Duke researchers respond:

> ..it is difficult to rationalize the need for such a high level of certainty regarding a drug never demonstrated to be safe or life-saving, where judgment should presumably err on the side of caution and avoidance of harm....the drug would not meet current safety standards during preclinical testing due to adverse, long-term neurological effects in laboratory animals, and thus would never reach phase 1 testing under the current regulatory system.

Patel et al conclude: "The scientific community may disagree on how strong the evidence is. But there should be no disagreement that (a) the evidence is very concerning, (b) physicians and the public should be notified of the current evidence, and (c) the gravity of the issue demands rapid resolution."


Cendejas-Hernandez J, et al. Paracetamol (acetaminophen) use in infants and children was never shown to be safe for neurodevelopment: a systematic review with citation tracking. *European Journal of Pediatrics.* 2022;181:1835-1857.

Patel E, et al. The safety of pediatric use of paracetamol (acetaminophen): a narrative review of direct and indirect evidence. *Minerva Pediatrics.* July 13, 2022.

Schultz ST, et al. Acetaminophen (paracetamol) use, measles-mumps-rubella vaccination, and autistic disorder: the results of a parent survey. *Autism.* 2008;12(3):293-307.


**California Medical Board Sued**

On July 29, 2022, Richard Jaffe, Esq., filed an amended complaint in federal court against the Medical Board of California on behalf of plastic surgeon Douglas MacKenzie, MD, and the not-for-profit organization Physicians for Informed Consent. The medical board opened a "misinformation" investigation against Dr. MacKenzie in December 2021, because of covid-related comments he made in a Zoom meeting of the Santa Barbara Unified School District four months earlier. During that meeting, he spoke out against over-testing, masking, and vaccine mandates for children and criticized the drive to reach "zero covid": "...It's time to realize, like some countries are, that SARS-CoV2 is endemic. We are not going to get to Zero Covid ever," he said. At least two other California doctors have also been under investigation for "misinformation."

The medical board closed its investigation against Dr. MacKenzie six days after Jaffe filed the original lawsuit – a move that would allow the Board to claim the lawsuit was moot. In the amended complaint, Jaffe argues that a statement by the Board's president in the February 2022 minutes indicates that the Board intends to target physicians who "spread Covid misinformation." As a result, Dr. MacKenzie, other unnamed doctors, and members of Physicians for Informed Consent (PIC) are under continuous threat of investigation, which has a "chilling" effect on free speech. As Jaffe writes: "PIC's educational mission depends entirely upon protected speech by physicians and is directly thwarted by the Board's unlawful conduct targeting that protected speech by physicians."

California's Assembly is considering a bill that would require the state medical boards to take action against any MD or DO who "disseminates misinformation or disinformation related to covid-19" (See "Shorts," *Townsend Letter.* July 2022). The definitions of "misinformation" and "disinformation" are vague. Bill 2098 focuses on communication between doctors and patients, not public speech and has not passed into law (as of August 8, 2022).

The plaintiffs are asking the Court to order the Board to stop all "misinformation" investigations against physicians who engage

➤

➤

in constitutionally protected public speech as well as damages and attorney's fees. Jaffe writes:

> There is nothing wrong with government agencies or established medical science changing their positions as new information is assimilated. In fact, it is a good thing. The problem, especially acute, in a fast-changing public health situation like Covid, is the governmental arrogance that physicians who challenge the accepted science are dishonest and need to be censored, sanctioned and reeducated for expressing their opinions in public. That is something the courts should not tolerate.

In his July 11, 2022, blog post, Rick Jaffe says this is a 100% community-funded lawsuit. If you want to support this effort to protect physicians' free speech, please click on the "donate" link at https://rickjaffeesq.com/. Updates on the lawsuit are also posted at that site.

**The Serotonin Theory of Depression**

In a July 20, 2022, review article, European researchers report finding "no support for the hypothesis that depression is caused by lowered serotonin activity or concentrations." The researchers conducted an 'umbrella' review of the most recent systematic reviews, meta-analyses, and database studies found in PubMed, EMBASE, and PsychINFO until December 2020. The quality of each study was rated independently by at least two of the researchers. Seventeen articles met their inclusion criteria. Only half of these studies "adequately accounted for risk of bias when interpreting the results of the review."

The researchers sought reviews and studies that addressed the following areas related to the serotonin hypothesis.

*Evidence of lower levels of serotonin and 5-HIAA in body fluids in depression.* Two meta-analyses (totaling 12 different studies) found no association between 5-HIAA concentration in cerebrospinal fluid and depression. A third meta-analysis of three large observational cohort studies found lower 5-HT in plasma in postmenopausal women with depression, but it was not statistically significant. However, antidepressant use, independent of depression, was strongly associated with lower serotonin levels.

*Serotonin receptor levels in people with depression.* The authors explain, "…if depression is the result of reduced serotonin activity caused by abnormalities in the 5-HT1A receptor [inhibits the releases of serotonin pre-synaptically], people with depression would be expected to show increased activity of 5-HT1A receptors compared to those without." The meta-analyses "suggested either no difference…between people with depression and controls, or a lower level of these inhibitory receptors…" Both meta-analyses included studies in which patients were taking or had recently taken antidepressants or other psychiatric medications.

*Higher levels of the serotonin transporter protein (SERT)* in people with depression would support the serotonin hypothesis. SERT transports serotonin out of the synapse, lowering its availability. Data from three "overlapping" meta-analyses "indicated possible reductions in SERT binding in some brain areas, although areas in which effects were detected were not consistent across the reviews." Again, the 40 studies in these meta-analyses included people who were taking antidepressants. The European researchers comment that animal studies have shown that antidepressants reduce SERT.

*Tryptophan depletion (which can lower serotonin) is believed to promote depression.* Studies in which healthy volunteers or people with a history of depression were given amino acid drinks without tryptophan (as a way to reduce tryptophan levels) showed no effect on mood when compared to controls.

*Higher levels of the SERT gene (5-HTTLPR), resulting in less synaptic serotonin, would be expected in people with depression.* Two recent studies and a high-quality meta-analysis found no association between the SERT gene polymorphism and depression.

*Moreover, two recent high-quality studies found no association between the SERT gene and stress and/or maltreatment* in people with depression.

The researchers note that the less-than-ideal quality of the studies in the reviewed studies are a limitation: "Most of the included studies were rated as low quality on the AMSTAR-2, but the GRADEW approach suggested some findings were reasonably robust." They conclude:

> This review suggests that the huge research effort based on the serotonin hypothesis has not produced convincing evidence of a biochemical basis to depression. This is consistent with research on many other biological markers. We suggest it is time to acknowledge that the serotonin theory of depression is not empirically substantiated.

Moncrieff J, et al. The serotonin theory of depression: a systematic umbrella review of the evidence. *Molecular Psychiatry.* July 20, 2022.

**One More Lawsuit**

Association of American Physicians and Surgeons Education Foundation has filed a complaint against three certification boards: American Board of Internal Medicine (ABIM), American Board of Obstetrics & Gynecology (ABOG), and American Board of Family Medicine (ABFM). ABIM and ABFM have sent letters to doctors who have publicly spoken about alternatives to government-sanctioned covid measures. The letters threaten to suspend or revoke their board certification. Peter McCullough, MD, Pierre Kory, MD, and Paul Marik, MD – all of whom have advocated early covid treatment with repurposed drugs – are among the doctors who received letters from ABIM. According to the lawsuit, a AAPS member-doctor received a similar threatening letter from ABOG due to the doctor's views on abortion.

The lawsuit, filed in the United States District Court for the Southern District of Texas, says that these certifying boards, which conduct written multiple-choice examinations in specific fields of medicine, have no authority to discipline doctors because of their public statements. The lawsuit states:

> Although only official state medical boards have the proper authority to regulate the practice of medicine, certifications by the Board Defendants constitute a *de facto* essential credential for practicing in most hospitals and participating in most networks. By threatening to revoke board certification of physicians, the Board Defendants improperly chill speech by physicians without the political accountability of official state medical boards.

Lawsuit to Stop Retaliation by Medical Specialty Boards Filed by AAPS Educational Foundation. July 12, 2022. https://aapsonline.org/lawsuit-to-stop-retaliation-by-medical-specialty-boards-filed-by-aaps/.

◆

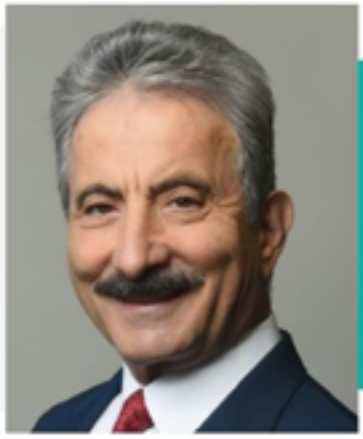
IMMUNOSCIENCES LAB, INC.

# THE AUTOIMMUNE VIRAL TRIO


## MAJOR CONTRIBUTORS TO AUTOIMMUNITY

Testing that shows a significant elevation in IgM or IgG antibodies against any of these viruses should be followed by our Autoimmune Panel, which comprises ANA, ENA, Actin, Mitochondrial Antibodies, Rheumatoid Factor, and C1Q Immune Complexes. IgG and IgM antibodies against this trio may help identify the major triggers of autoimmunity.

"Based on **35 years of R&D** on the role of environmental triggers in autoimmunity, I came to the conclusion that **EBV, HHV-6 and SARS-CoV-2 contribute the most towards autoimmunity."**

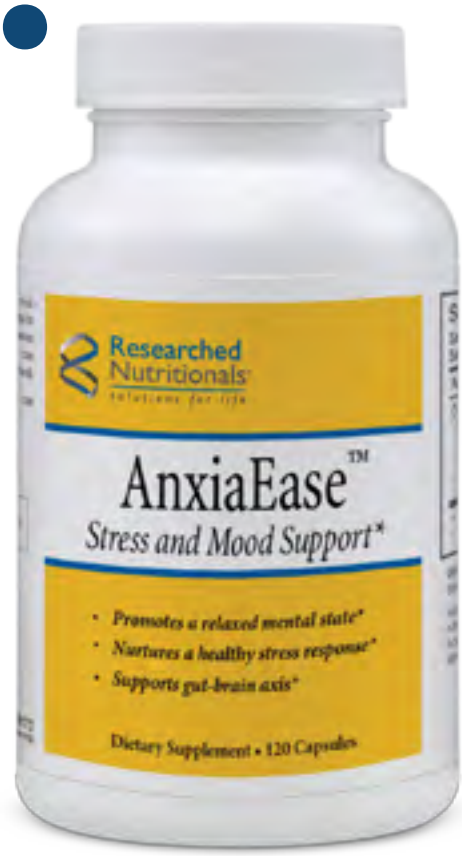


**Aristo Vojdani, PhD, MSc, CLS**
CEO, Immunosciences Lab., Inc.

Website: immunoscienceslab.com
Email: immunsci@gmail.com
**Call Us at (310) 657-1077**

# Stressed?

## Support the brain and the gut for a healthy, systemic stress response.




## Mechanisms of Action:

- Optimizes the gut-brain axis via targeted probiotics*
- Supports healthy cytokine, serotonin, and cortisol function*
- Adaptogenic herbs promote a healthy biological response to stress*

### Supplement Facts

**Serving Size: 2 capsules**
**Servings per Container: 60**

| Amount Per Serving | | %Daily Value** |
|---|---|---|
| **Vitamin B-6** (as pyridoxal 5-phosphate) | 25 mg | 1471% |
| **Magnesium** (as magnesium taurate) | 25 mg | 6% |
| **Healthy Stress Response** | 460 mg | † |
| Holy Basil Extract (*Ocimum sanctum*) (leaf), Ashwagandha Extract (*Withania somnifera*) (whole plant), Sharp-PS® Green Phosphatidylserine (from sunflower) | | |
| **Calming Complex** | 610 mg | † |
| Lemon Balm Extract (*Melissa officinalis*) (aerial), English lavender Extract (*Lavandula officinalis*) (aerial), Passionflower Extract (*Passiflora incarnata*) (aerial) | | |
| **Gut-Brain Soother** | 1.5 Billion CFU I 60 mg | † |
| *Lactobacillus helveticus* Rosell®-52, *Bifidobacterium longum* Rosell®-175 | | |

** Percent Daily Values are based on a 2,000 calorie diet.
† Daily Value not established.

**Other Ingredients:** Hypromellose (veggie capsule), leucine.
**Contains:** Trace amounts of soy and milk used in the fermentation of the probiotic strains

Manufactured without eggs, fish, crustacean shellfish, tree nuts, peanuts, wheat, corn and gluten. Produced in a facility that may process other ingredients containing these allergens.

Learn more

**Learn more: ResearchedNutritionals.com/AnxiaEase**

Researched Nutritionals solutions for life

800.755.3402 • Info@ResearchedNutritionals.com • ResearchedNutritionals.com | Available only through healthcare professionals.

*These statements have not been evaluated by the Food and Drug Administration. These products are not intended to diagnose, treat, cure, or prevent any disease.*

# In this Issue

October 2022 | #471



## ONLINE ONLY



**ON THE COVER:** Steven Sandberg-Lewis, ND – Reducing GERD with Lifestyle Factors (pg. 26); Treating Anxiety Without Pharmaceuticals (pgs. 32, 38, 42); Preventing Clinician Burnout (pg. 46)

## – Coming Up –
## Our November Issue
## Focusing on Fibromyalgia

**Jacob Teitelbaum, MD, tackles sensitivity to everything: Addressing the "immune system gone wild."**

**Prof. Garth Nicolson, PhD, MD, examines research on lipid nutrient replacement therapy in chemically exposed veterans.**

# Literature Review & Commentary

**by Alan R. Gaby, MD**
**drgaby@earthlink.net**

**Can Flavonoids Prevent Cognitive Decline?**

The association between long-term dietary flavonoid intake and risk of subjective cognitive decline (SCD) was examined in prospective cohort studies of 49,493 women from the Nurses' Health Study (NHS) (1984-2006) and 27,842 men from the Health Professionals Follow-Up Study (HPFS) (1986-2002). SCD was defined as an increase of 3 points or more on a 6- or 7-point assessment scale. For the NHS, long-term average flavonoid intake was calculated from seven repeated food frequency questionnaires, and SCD was assessed in 2012 and 2014. For the HPFS, average flavonoid intake was calculated from five repeated food frequency questionnaires, and SCD was assessed in 2008 and 2012. Higher intake of total flavonoids was associated with lower odds of SCD after adjustment for age, total energy intake, intakes of various micronutrients (carotenoids, vitamin C, vitamin D, vitamin E, and long-chain omega-3 fatty acids), smoking history, body mass index, physical activity level, depression, and alcohol intake. In the pooled analysis, after adjustment

for potential confounding variables, individuals in the highest quintile of total flavonoid intake (as compared with the lowest quintile) had a 19% lower risk of SCD. Many flavonoid-rich foods such as strawberries, oranges, grapefruits, citrus juices, apples/pears, celery, peppers, and bananas were significantly associated with lower risk of SCD.

Comment: Oxidative stress appears to play a role in age-related cognitive decline. Flavonoids have antioxidant activity, and therefore have the potential to prevent age-related cognitive decline. Flavonoids are present in a wide variety of plant foods, including fruit, vegetables, nuts, seeds, and legumes. There is evidence that certain flavonoids may also be useful for preventing or treating atherosclerosis, hypertension, venous insufficiency, hemorrhoids, lymphedema, and other conditions.

Yeh TS, et al. Long-term dietary flavonoid intake and subjective cognitive decline in US men and women. *Neurology*. 2021;97:e1041-e1056.

**Exercise Is Beneficial for People with Cognitive Decline**

A meta-analysis was conducted on 19 randomized controlled trials that examined the effect of physical exercise in patients with Alzheimer's disease or mild cognitive impairment. The results demonstrated that exercise improved scores on the Mini-Mental State Exam (MMSE) in both groups of patients. In the group with mild cognitive impairment, exercise appeared to have a stronger effect for those with lower MMSE scores at baseline (lower scores indicate more cognitive impairment). The effect sizes for physical exercise were similar to those achieved with donepezil (a cholinesterase inhibitor used to treat dementia).

Comment: This meta-analysis found that physical exercise is an effective intervention for people with Alzheimer's disease or mild cognitive impairment. Future studies should examine what types of exercise and what level of exercise intensity and frequency are the most effective for preventing and treating these conditions.

Pisani S, et al. A meta-analysis of randomised controlled trials of physical activity in people with Alzheimer's disease and mild cognitive impairment with a comparison to donepezil. *Int J Geriatr Psychiatry*. 2021;36:1471-1487.

**Meat Consumption and Dementia**

The association between meat consumption and risk of developing dementia was examined in the UK Biobank cohort, which is a population-based cohort study of participants aged 40-69 years recruited in the United Kingdom between 2006 and 2010. During a median follow-up period of eight years (excluding cases that occurred in the first year of follow-up), among 493,888 participants, 2,896 new cases of all-cause dementia were identified (1,006 cases of Alzheimer's disease, and 490 cases of vascular dementia). Each additional 25 g per day intake of processed meat was associated with increased risks of all-cause dementia (hazard ratio [HR] = 1.44; p for trend < 0.001) and Alzheimer's disease (HR = 1.52; p for trend = 0.001). In contrast, a 50 g per day increase in unprocessed red meat intake was associated with reduced risks of all-cause dementia (HR = 0.81; p for trend = 0.01) and Alzheimer's disease (HR = 0.70; p for trend < 0.01). There were no significant associations between consumption of unprocessed poultry or total meat and risk of Alzheimer's disease or all-cause dementia. In addition, there were no significant associations between meat consumption and risk of vascular dementia.

Comment: In this observational study, there was an increased risk of developing Alzheimer's disease or any type of dementia with increasing consumption of processed meats. In contrast, consumption of unprocessed meat was associated with decreased risk of developing these conditions. While observational studies cannot prove causation, it is noteworthy that consumption of processed meat has also been associated in other studies with an increased risk of developing colon cancer and type 2 diabetes and an increased risk of readmission to the hospital in people with chronic obstructive pulmonary disease. Based on the available evidence, it would be prudent to keep consumption of processed meats such as ham, sausage, pepperoni, hot dogs, beef jerky, corned beef, and canned meat to a minimum.

Zhang H, et al. Meat consumption and risk of incident dementia: cohort study of 493,888 UK Biobank participants. *Am J Clin Nutr*. 2021;114:175-184.

**Can Low-Dose Lithium Prevent Psychiatric Disorders?**

A meta-analysis was conducted on 27 observational studies (including a total of 113 million subjects) that examined the association between lithium concentrations in drinking water and neuropsychiatric outcomes. Meta-analysis of 14 studies including 94 million people found that higher lithium concentrations were associated with lower suicide rates ($p < 0.001$). Meta-analysis of two studies including 5 million people found that higher lithium concentrations were associated with fewer hospital admissions for psychiatric disorders ($p = 0.035$).

Comment: Lithium appears to modulate genes involved in neuroprotection, neuronal plasticity, and other neuronal functions. High-dose lithium (such as 900 mg per day of lithium carbonate, providing 169 mg per day of elemental lithium) is a mainstay of treatment for patients with bipolar disorder. However, high-dose lithium can damage the kidneys and frequently causes a wide range of other side effects. In contrast, low-dose lithium is generally well tolerated. In a previous randomized trial, supplementation with low-dose lithium (300 µg per day) slowed the rate of cognitive decline in patients with Alzheimer's disease.[1] The results of the present study raise the possibility that a modest increase in lithium intake could help prevent other types of psychiatric disorders as well. Additional randomized trials using low-dose lithium should be conducted.

Eyre-Watt B, et al. The association between lithium in drinking water and neuropsychiatric outcomes: A systematic review and meta-analysis from across 2678 regions containing 113 million people. *Aust N Z J Psychiatry*. 2021;55:139-152.

**Coenzyme Q10 for Male Infertility**

Two hundred twelve infertile men with idiopathic oligoasthenoteratospermia who were seeking medical attention for infertility were randomly assigned to receive, in double-blind fashion, 300 mg per day of coenzyme Q10 (CoQ10) or placebo for 26 weeks, followed by a 30-week treatment-free phase. In the CoQ10 group, significant improvements were seen in sperm density and motility (each $p = 0.01$).

Comment: This paper, published in 2009 in the *Journal of Urology*, is one of many large randomized double-blind studies published by Iranian urologist, MR Safarinejad. A number of years ago, I had concerns about the integrity of some of his work, but my attempt in 2013 to interest the *Journal of Urology* in conducting an investigation of one of his other papers was

➤

➤

unsuccessful. Now that 11 of Safarinejad's papers have been retracted by medical journals, I thought it might be worthwhile to contact the *Journal of Urology* again. Below is an email I sent to the editor in May 2022. A representative of the *Journal* replied within hours and assured me that the matter would be investigated. We'll see how it goes.

Dear editor:

In 2013 the *Journal of Urology* published my letter,[2] which raised questions about the integrity of research published by MR Safarinejad et al. Although it was my belief that Safarinejad's reply[3] did not adequately address the issues I raised, I was not permitted to send a follow-up letter.

As of 2013, only one paper by Safarinejad had been retracted by a medical journal. Now that 11 of his papers have been retracted,[4] it would seem that an investigation of his entire body of work would be appropriate (particularly the 6 randomized clinical trials Safarinejad published in the *Journal of Urology*).

I respectfully submit comments below about one of the papers Safarinejad published in your journal, comments which I believe raise concerns about the integrity of the work. This paper is not the same one I wrote about in the 2013 letter to the editor.

Comments about Safarinejad MR. Efficacy of coenzyme Q10 on semen parameters, sperm function and reproductive hormones in infertile men. *J Urol*. 2009;182:237-248.

1. Implausibly large sample size: Randomized clinical trials that enroll as many as 212 participants are typically conducted by multiple investigators. A single investigator does not typically have the time or the resources to conduct such a large trial by himself. A number of other published papers in which Safarinejad was the sole author also had implausibly large sample sizes. Many of these papers have been retracted by other journals.

2. Implausible study protocol: The paper stated that all participants visited the clinic at weeks 0, 4, 8, 12, 16, 20, 26, 32, 40, 46, 52, and 56. Participants collected 2 semen samples at baseline, as well as 2 samples (within a 1- to 2-week period) around the time of each follow-up visit. All semen samples were obtained after 3 days of recommended sexual abstinence. Thus, each participant had to collect 24 semen samples, with a total of at least 72 days of abstinence over a 13-month period. Collecting so many samples (instead of engaging in sexual intercourse) and having 72 days of required abstinence would presumably decrease the probability of achieving a pregnancy. It is difficult to imagine that many infertile men who "were seeking medical attention for their disease" (i.e. they were trying to impregnate their wives) would agree to participate in such a study.

3. Implausible logistics regarding semen collections and semen analyses: While half of the 24 semen samples could be collected at scheduled visits, the other half (12 samples per person; 2,544 total samples) would have to be collected between visits. The paper stated that the samples were delivered to the fertility lab within 1 hour after they were produced. In order to deliver the samples during normal business hours, participants would, on 12 different occasions, have to become sexually aroused during their workday, collect the sample, and drive it to the clinic within 1 hour of production. It is difficult to imagine that many men would tolerate this type of disruption to their lives on 12 different occasions, and it is even more implausible that essentially all 194 men who completed the trial delivered all 12 of their between-visit semen samples. (The conclusion that essentially all 194 men who completed the trial delivered all 12 of their between-visit samples is derived from the number of men who completed the trial [Figure 2] and the number of samples analyzed at each time point [Figure 3]).

The paper also stated that all semen analyses were performed by the author and the same laboratory technicians. Because sperm cells start to die after about an hour, semen analyses are typically done within 1 hour after the sample is produced. Thus, on 2,544 different occasions, the author would have had to stop whatever he was doing at his urology clinic in order to complete a semen analysis in a timely fashion. It would seem difficult to conduct a normal urology practice under those circumstances.

4. Issue with generating frequent data points: Data for semen analyses and blood tests were generated at 12 different time points. Around 2,500 tests were conducted for each of serum LH, FHS, testosterone, and inhibin B; around 5,000 semen samples were analyzed; and participants had a total of about 2,500 office visits during the study. The amount of useful information that could be generated from having data at 12 different time points is at best only slightly greater than what could be learned from having half as many or even one-third as many data points. Thus, the protocol as described in this paper seems to have created a lot of unnecessary additional work and expense for the investigator and made participation in the trial unnecessarily more tedious and time-consuming.

5. Issue regarding the evaluation of the female partners: Men were eligible to participate in the trial only if they had a "normal fertile female partner according to investigations." These investigations included a history, physical examination, extensive laboratory testing, and a hysterosalpingogram. Conducting these investigations on 212 women would be expensive, time-consuming, and apparently outside the scope of a urology practice. There was no mention of who conducted these investigations and who paid for them. Safarinejad was the sole author of this paper, and there was no mention of a funding source.

6. Issues with baseline data: Table 1 lists comparisons between the coenzyme Q10 group and the placebo group for 17 different variables. The means for nearly every comparison are surprisingly similar: for example, 28 vs. 28; 26.6 vs. 26.4; 15.8 vs. 15.6; 86 vs. 87; 3.27 vs. 3.29. For each comparison, I calculated the p value for the difference between the means (based on the means and standard deviations). Among the 17 comparisons, the lowest p value was 0.36. The probability that none of 17 legitimately generated comparisons would have a p value below 0.36 is approximately 0.05% (1 in 2,000).

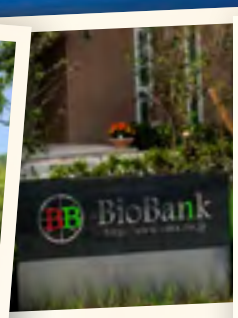
Safarinejad MR. Efficacy of coenzyme Q10 on semen parameters, sperm function and reproductive hormones in infertile men. *J Urol*. 2009;182:237-248.

***continued on pge 18*** ➤

# **Dr. Iichiroh Ohhira:** A Pioneering Genius in Probiotic Science

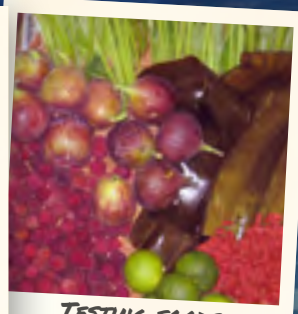
MALAYSIAN MYSTERY – 'DRINKING FERMENTED ELIXIR'

ADVANCED RESEARCH – OKAYAMA UNIVERSITY




FOUNDED BIOBANK

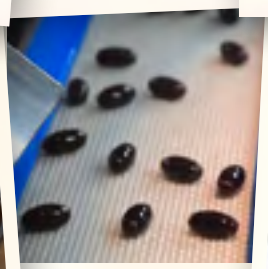
DISCOVERY LAB TH-10



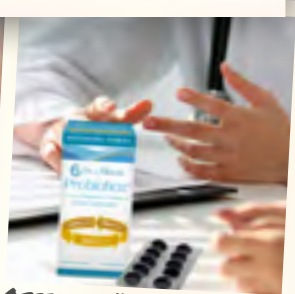
TESTING FOODS FOR PEAK NUTRITION

EXCLUSIVE 5-YEAR FERMENTATION

NATURE'S PERFECT PROBIOTIC W/POSTBIOTICS



PATENTED ENCAPSULATION



OFFERING "LONG LIFE AND GOOD HEALTH TO ALL!"


DR. OHHIRA AWARDED GUSI PEACE PRIZE


## Developed Natures 'Perfect Probiotic' over 40 Years ago!

Dr. Ohhira has proven to be one of the world's most influential researchers in the history of probiotic science as his discoveries continue to be confirmed. He intrinsically understood restorative timeline when developing a 5-year natural temperature fermentation method that produces herculean strains of probiotics as well as therapeutic **Postbiotics Metabolites**, recently proven to be the most beneficial aspect of probiotic supplementation. Recent research on Dr. Ohhira's Probiotics revealed that his formula contains over 400 kinds of these health-promoting postbiotic metabolites!

**Discover the Dr. Ohhira's Difference!™**

ESSENTIAL FORMULAS®

www.EssentialFormulas.com • (972) 255-3918

* These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.

# Gaby's Literature Review

➤ *continued from page 16*

**Zinc Supplementation Resolves Cervical HPV Infection, or More Iranian Research Fraud?**

Eighty Iranian women (aged 21-55 years) with human papilloma virus (HPV) infection of the cervix (documented by DNA testing) and abnormal cervical cytology on a Pap test (atypical squamous cells of undetermined significance or low-grade squamous intraepithelial lesions) were randomly assigned to receive 50 mg of zinc (as zinc sulfate) twice a day or no zinc (control group) for 3 months. All women had normal serum zinc at baseline. After three months, the proportion of women whose HPV infection had resolved (57.5% vs. 15%; $p < 0.001$) and the proportion of women who had a normal Pap test (52.5% vs. 25%; $p < 0.04$) was higher in the zinc group than in the control group. The authors concluded that zinc supplementation increased the rate of HPV clearance and promoted the normalization of cervical cytology in women with an abnormal Pap test associated with HPV infection.

Comment: If oral zinc supplementation could accomplish what it was reported in this paper to accomplish, that would be a major advance in healthcare. However, I have a number of concerns about this study.

1. The paper stated that treatment allocation was random, whereas the Iranian Registry of Clinical Trials (IRCT) document that is associated with the paper stated that the treatment allocation was not randomized.
2. The paper stated that the participants were enrolled from October to December 2018. The IRCT document was registered on April 15, 2021 and it stated that the expected recruitment start date was April 9, 2021.
3. The study was approved by the ethics committee on December 12, 2018. If the study did indeed start in October 2018, that would mean it started before it was approved by the ethics committee.
4. Serum zinc was measured at the start of the study. Serum zinc was measured again in the control group at the time the zinc-treated group stopped taking zinc. However, the serum zinc measurement was not repeated in the zinc-treated group until 30 days after zinc supplementation was stopped. There was no apparent logical reason to delay the test by 30 days in the zinc-treated group. Measuring serum zinc at the end of the supplementation period would have been of some value to assess treatment compliance. Measuring serum zinc 30 days later would not be useful for assessing compliance, and it is difficult to imagine any other useful data that this measurement would generate. Requiring 40 women to make another trip to the clinic to have their blood drawn for a lab test that is essentially useless seems like an unnecessary burden on study participants.
5. The paper stated that all 80 women completed the trial. Having no drop-outs in a study of 80 participants is uncommon, and it would be even less common in a study that required 40 women to return for a third visit to have their blood drawn for a lab test of questionable value.
6. The authors stated that the results of their study were similar to those of a study from South Korea, in which a solution of 0.5 mM zinc citrate was administered as an intravaginal douche twice a week for 12 weeks. Zinc is a potent antiviral compound that can kill a number of different viruses. However, it is unlikely that orally administered zinc could achieve zinc concentrations in cervical tissue as high as those achieved by intravaginal administration. Therefore, the observation that oral zinc produced benefits similar to those seen with intravaginal administration is of questionable biological plausibility.

Ayatollahi H, et al. Efficacy of oral zinc sulfate supplementation on clearance of cervical human papillomavirus (HPV); a randomized controlled clinical trial. *Asian Pac J Cancer Prev*. 2022;23:1285-1290.

**Can Vitamin D Prevent Autoimmune Disease?**

In the Vitamin D and Omega 3 Trial (VITAL), 25,871 U.S. adults (men aged 50 or older, women aged 55 or older; mean age in the whole group, 67.1 years) were randomly assigned to receive, in double-blind fashion, 2,000 IU per day of vitamin D, 1,000 mg per day of omega-3 fatty acids, both treatments, or placebo for a median duration of 5.3 years. The primary endpoint was

all new cases of autoimmune diseases confirmed by medical record review, including rheumatoid arthritis, polymyalgia rheumatica, autoimmune thyroid disease, psoriasis, and all others. Autoimmune disease developed in 123 participants who received vitamin D and in 155 who did not receive vitamin D (hazard ratio = 0.78; p = 0.05). Autoimmune disease developed in 130 participants who received omega-3 fatty acids and in 148 who did not received omega-3 fatty acids (hazard ratio = 0.85; p = 0.19).

Comment: This study found that vitamin D supplementation for a median duration of 5.3 years significantly decreased the incidence of autoimmune disease by 22%. Omega-3 fatty acid supplementation reduced the incidence of autoimmune disease nonsignificantly by 15%. The mechanism by which vitamin D might prevent autoimmune disease is not known. A few studies have found that vitamin D decreases inflammation, but the majority of studies found that vitamin D had no effect on various measures of inflammation. Vitamin D also has a number of other complex interactions with the immune system, but the clinical significance of those interactions is not clear.

Hahn J, et al. Vitamin D and marine omega 3 fatty acid supplementation and incident autoimmune disease: VITAL randomized controlled trial. *BMJ*. 2022;376:e066452.

**L-Theanine for Tourette Syndrome or Chronic Tic Disorder**

Thirty-four 34 children (mean age, 10.4 years; range, 4-17 years) with anxiety symptoms associated with Tourette syndrome or chronic tic disorder were randomly assigned to receive, in open-label fashion, a daily supplement containing 200 mg of L-theanine and 2.8 mg of vitamin B6 for two months or eight sessions of psychoeducation and supportive psychotherapy (designed to teach the children and their parents about the disease and to reduce anxiety). The mean score on the Yale Global Tic Severity Rating Scale improved by 43% in the supplement group and by 18% in the psychoeducation group. The mean score on the Multidimensional Anxiety Scale for Children improved by 20% in the supplement group and by 13% in the psychoeducation group. The mean improvement on each of these scales was significantly greater in the supplement group than in the psychoeducation group.

Comment: L-Theanine is an amino acid found mainly in green tea and to a lesser extent in black tea and some other foods. It is generally well tolerated and has been reported to improve stress and anxiety-like symptoms. In the present study, administration of L-theanine along with a small amount of vitamin B6 was significantly more effective than psychoeducation in reducing tics and anxiety in children with Tourette syndrome or chronic tic disorder.

Rizzo R, et al. Use of nutritional supplements based on L-theanine and vitamin B6 in children with Tourette syndrome, with anxiety disorders: a pilot study. *Nutrients*. 2022;14:852.

**References**


1. Nunes MA, et al. Microdose lithium treatment stabilized cognitive impairment in patients with Alzheimer's disease. *Curr Alzheimer Res*. 2013;10:104-107.
2. Gaby AR. Re: Effects of the reduced form of coenzyme Q10 (ubiquinol) on semen parameters in men with idiopathic infertility: a double-blind, placebo controlled, randomized study: M. R. Safarinejad, S. Safarinejad, N. Shafiei and S. Safarinejad. *J Urol*. 2012; 188: 526-531. *J Urol*. 2013;190:364-365.
3. Safarinejad MR. Reply to letter to the editor. *J Urol*. 2013 Jan 30;S0022-5347(13)00225-5.
4. retractiondatabase.org/RetractionSearch.aspx#?auth%3dSafarinejad


◆

# Irritability, Anger, and Rage: Lithium Deficiency Syndrome


## by James Greenblatt, MD

### Medical Director, TZ Health


Irritability and anger are often not well addressed in standard psychiatry. Usually, they are seen as a component of a diagnosis, such as bipolar disorder or depression. As such, irritability and anger are often relegated to the status of symptoms and not directly treated. Yet considering the problems and damage to an individual's personal and professional life that can stem from irritability, anger, and rage, effective treatment is often critical for better long-term outcomes.

With an almost myopic focus on the patient's clinical intake interview and symptoms, mainstream psychiatry typically doesn't investigate physiological causes underlying mental illness. Unfortunately, this often leads to symptomatic polypharmacy – the prescription of numerous medications based on symptoms – and poor treatment outcomes. Unrecognized is the fact that anger issues are often caused by problems with neurotoxicity or nutrient deficiencies. A simple, well-researched example is the psychiatric symptoms associated with lead toxicity. While lead toxicity is an accepted cause of increased aggressive and antisocial behaviors in the research literature,[1] it is still infrequently evaluated in clinical settings.[2,3]

Beyond lead, two other commonly overlooked metals stand out from my own clinical experience due to their relationship with irritability, anger, and rage: lithium and copper. While not officially considered a micronutrient, research suggests lithium is essential, with some researchers giving a provisional recommendation of one milligram per day.[4] Data also suggests that individuals deficient in lithium may have an increased propensity towards issues with anger and irritability.[5] High-dose lithium has even been explored as a treatment for aggressive behaviors.[6-10]

And while copper is a necessary micronutrient, too much of the mineral is neurotoxic, contributing to a number of different mental health conditions. Data suggests increased rates of depression in individuals with high copper exposure.[11] Wilson's disease, a cause of elevated copper levels, commonly presents with symptoms of irritability, anxiety, depression, personality changes, and disinhibition.[12]

**Lithium Deficiency and Anger**

Lithium, unfortunately, has a bad reputation. Before there was a full understanding of the risks from high-dose use, lithium chloride was introduced as a salt substitute in the middle of the last century. Tragically, liberal use of lithium salt substitutes caused lithium intoxication in some individuals, even leading to death in several cases.[13] Additionally, pharmacologic lithium has a risk profile that includes hypothyroidism and kidney damage, which has further tarnished the reputation of the mineral. Due to these concerns, doctors often view lithium with suspicion and avoid prescribing the mineral for any indication.

This negative view of lithium has impeded the utility of lithium in modern medicine. Lithium is a natural mineral, found in low quantities in the environment. Humans have been exposed to lithium throughout our evolution. Consumption of lithium from lithium-containing groundwater to low levels found in fruits, vegetables and other food sources is part of a normal, healthy diet.

For years, data has been building that lithium is a required mineral for maintaining health.[14] Research has also found that, for many conditions, low nutritional doses can lead to clinical benefits without the risks from high-dose or standard pharmacological use.

Some of the initial studies documenting reductions in anger and violence with lithium were clinical trials in prison populations. Based on previous animal studies showing reductions in aggression, studies on pharmacological lithium administered to violent prisoners were undertaken. One of the initial studies, a three-month case series with 12 inmates, found reductions in infractions for violent or aggressive behaviors with prescription lithium.[7]

Based on these short-term results, a separate non-blinded trial on lithium and prisoners with a history of violence both in and outside prison was initiated. In the study, disciplinary action for violent infractions decreased by 77% for individuals treated with lithium.[9]

This study was followed by a double-blind, placebo-controlled trial on incarcerated males with a history of violence. Lithium treatment significantly reduced threatening and assaultive behaviors over the course of treatment.[8] With the positive findings, the researchers suggested that "lithium can have a clinically useful effect upon impulsive aggressive behavior…."[8]

While well recognized as a treatment in higher doses for bipolar disorder, the prison studies suggest potential for lithium and the reduction of aggressive and violent behaviors. However,

nutritional, low-dose lithium is also of relevance for mental health, including in cases of irritability, anger, and aggression. For decades, data has been accumulating that individuals with higher lithium exposure from groundwater have better mental health outcomes. The data also suggests that low-level exposure to lithium reduces aggressive behaviors, both self-directed as suicide and violent behavior towards others.

While initial studies suggested correlations between lower risks of heart disease and lithium in drinking water,[15,16] studies soon turned to mental health outcomes. One of the first studies out of Texas found that lithium content in local drinking water ranged from undetectable to 160 micrograms per liter. Mental health hospital admissions and hospital diagnoses of psychosis, neurosis, and personality disorders all inversely correlated with lithium levels. The authors concluded "that naturally occurring lithium exerts a measurable and statistically significant influence on the incidence of patients admitted to our state's mental hospitals and on… certain diagnostic categories of mental illness."[17] The findings raised significant controversy, with other researchers initially attempting to explain away the results.[18]

And while some studies contradicted the findings,[19] confirmatory data have slowly continued to accumulate. A study in Texas found that counties with higher lithium levels in the water supply, between 70 and 170 micrograms per liter, had significantly reduced rates of suicide, homicide and rape.[20] Rates of robbery, burglary, theft, and arrests for opiate or cocaine possession were also inversely correlated with lithium levels.

A study out of Japan found reduced rates of suicide in municipalities with higher lithium drinking water levels. The effect was significant even with low concentrations of lithium, ranging from 0.7 to 59 micrograms per liter and was stronger in males than females.[21] The study inspired a watershed of additional studies on the correlation of suicide and lithium levels in drinking water.

A more recent study out of Greece found reduced rates of homicide correlated with drinking water lithium.[22] In a similar vein, a study out of Japan found an inverse association with crime and levels of lithium in drinking water.[23] A meta-analysis of lithium in drinking water and psychiatric outcomes concluded that suicide and psychiatric hospital admissions are inversely associated with lithium drinking water exposure and recommended more research for other outcomes.[24] The population studies included over 100 million individuals.

**Two minerals, lithium and copper, can be related to anger and irritability.**

The data available is incredibly compelling. Lithium, even in microdoses, has clinically relevant effects on psychiatric outcomes. And the data on lithium in drinking water and crime, homicide, suicidality, and drug use strongly suggests that lithium has effects on helping to reduce aggression and violent behaviors. In my own clinical experience, lithium is often key in helping resolve anger issues. While hair testing can sometimes identify individuals that are deficient, I am also suspicious of deficiency in individuals with long-standing symptoms of depression, anxiety, irritability, bipolar disorder, compulsive behaviors and a current or past history of drug abuse or a family history of similar mental health problems. Supplementing low doses of the mineral, between one and 20 milligrams of elemental lithium daily (typically as lithium orotate), often provides noticeable relief.

**Copper Toxicity and Anger**

Copper, in low quantities, is a necessary micronutrient. It is important for energy production, connective tissue formation, synthesis of the neurotransmitter norepinephrine and other biological functions. It also is inversely related to zinc, with high copper typically corresponding to low zinc and supplemental zinc helping to reduce excess copper.

As stated previously, research suggests that elevated copper plays a role in mental health. A meta-analysis of the studies on copper levels in depressed patients concluded that elevated copper may be a biomarker of depression.[11] And while the evidence isn't as clear, some studies have found associations between high copper-to-zinc ratios correlated to attention-deficit hyperactivity disorder.[25] In a similar fashion, studies have also been somewhat mixed on the relationship between copper and aggression. However, a study of young males with a history of assaultive behaviors found a clear elevation in copper-to-zinc ratio as compared to controls. In boys with a history of aggression, the ratio averaged 1.4, whereas in normal controls, the ratio was 1.02.[26]

The other main body of research that links excess copper to mental illness comes from research into Wilson's disease. Wilson's disease is a genetic disorder of copper metabolism. The condition causes a slow accumulation of copper throughout the organs of the body, including the liver and brain. Some of the earliest work to quantify the incidence of mental illness in Wilson's disease found correlations with a number of symptoms. Some of the strongest correlations were for irritability, aggression, and incongruous behavior, a catch-all term for disinhibition or for engaging in bizarre and reckless activities.[27]

More recent research seeking to categorize the psychiatric implications of Wilson's disease and copper excess found similar conclusions. One-third of patients with Wilson's initially present with behavioral symptoms, which often delays diagnosis. Personality changes in individuals with Wilson's disease can affect between 46% and 71% of patients. And typical personality changes seen in patients with Wilson's disease almost always include irritability and aggressiveness.[28]

Evidence suggests that excess copper, and not the genetic defects, in Wilson's disease is the cause of mental-emotional symptoms. Studies of patients have found that chelation strategies to reduce copper generally result in improved psychiatric and neurological symptoms.[29,30] Based on

➤

## Lithium Deficiency

➤

the published research, and my own clinical experience, copper can and does play a role in initiating and maintaining symptoms of irritability, anger, and rage.

Identifying copper excess can include hair analysis and blood tests, including serum copper, zinc, and ceruloplasmin – a protein carrier molecule for copper in the bloodstream. However, blood levels of both copper and zinc are influenced by recent food intake and other factors. As such, they are not always reliable indicators of nutritional status.[31,32]

In cases where excess copper is identified, supplemental zinc can often reduce levels and reverse symptoms. Zinc supplementation increases metallothionein, a chelating enzyme that binds certain metals, blocking their gastrointestinal absorption. Metallothionein is more effective at binding copper than zinc. As such, high-dose zinc supplementation can reduce or even deplete copper levels. While higher doses of zinc may be necessary, it's worth recognizing that doses over 40 mg per day can eventually cause copper deficiency. If severe, copper deficiency can result in anemia and nerve damage.[33] It can be important to track copper levels carefully over treatment to ensure patient safety.

**Other Causes**

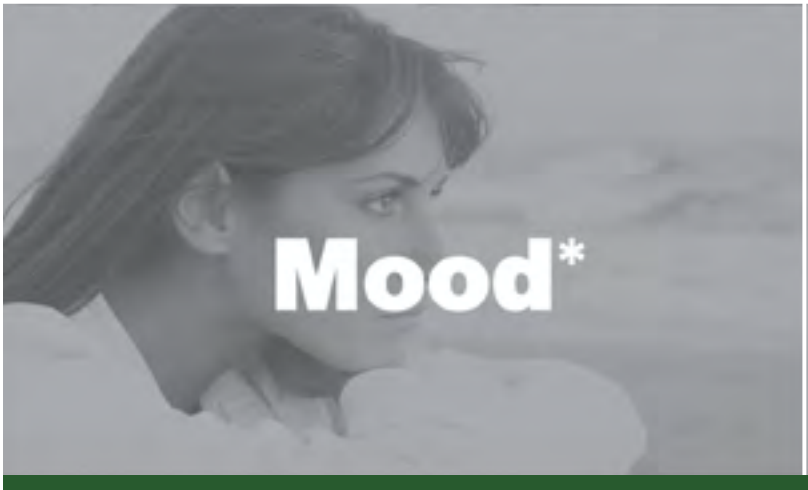
While copper and lithium are commonly overlooked causes of anger, irritability, and rage, they aren't the only causes. In every case, a complete functional evaluation should be initiated. Other contributing factors can include additional nutritional deficiencies, hormonal dysregulation, gut dysbiosis, fetal alcohol syndrome, medication side effects and psychological concerns, including a history of trauma or bullying. For best results, all of the underlying factors need to be addressed.

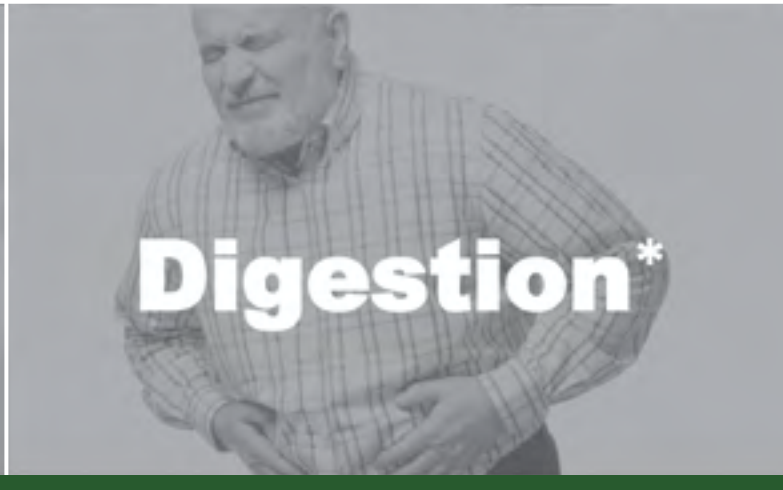
Medications that are more commonly implicated in increased anger and irritability include selective serotonin reuptake inhibitors (SSRIs) and stimulants. A number of population studies have recently confirmed increased violent crimes for younger individuals prescribed SSRIs.[34,35] Stimulant medications can also contribute to aggression. A recent meta-analysis suggests that the risk is mostly associated with amphetamine-based stimulants.[36] Regardless, it's worth keeping medication side effects in mind, especially in cases with worsening irritability or aggressive behaviors after a new prescription or increased dose.

The gut flora is often implicated in mental health concerns, including in cases of anger and aggression. Testing levels of 3-(3-hydroxyphenyl)-3-hydroxypropionic acid (HPHPA) can help identify a subset of individuals with an overgrowth of clostridium that can also contribute to symptoms of aggression and irritability. For a more full discussion on HPHPA, you can refer to chapter 5 in my book *Finally Focused*. While HPHPA can contribute to more severe symptoms, other causes of dysbiosis may also be present that benefit from treatment.

***continued on page 25*** ➤






# Holistic Brain Support*


**Lion's Mane Amyloban**® - a unique formulation containing the active constituents of Lion's Mane mushroom, standardized for consistency and grounded in science.

- All-around brain and nerve support*
- Supports healthy cognitive function*
- Memory, mood, clarity, and focus support*
- Unique concentrated extract unlike any other Lion's Mane product.

*Available at* Fullscript™

MUSHROOM WISDOM®

**Mushrooms As Nature Intended**

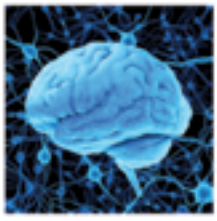
*Also Available at* emerson ECOLOGICS®

**1-800-747-7418 • www.MushroomWisdom.com**

*These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.

# Relax Far Infrared Saunas & Lamps

## FAR INFRARED SAUNAS ARE GREAT FOR BRAIN HEALTH



In one shocking study on saunas, people that used a sauna 4-7 times per week had a 66% REDUCED RISK of dementia and Alzheimer's versus those who used the sauna only once a week. If only there were a pill that could do this! Additionally, heat stress, the good kind of stress, like working out, activates one of the genes associated with longevity called FOXO3, which makes cells resilient to age-related stresses. Evidence suggests that heat therapy, intensified by far infrared energy, can increase longevity & endurance, extend life and quality of life, create healthier genes and positive, lasting changes in the body. Surprisingly, those with depression who used a sauna ONLY ONCE reported great and lasting effects in their mental health!

Far infrared rays harmonize our nervous system into a more calm and relaxed state. This beneficial healing light also lowers cortisol, the stress hormone and puts us into peaceful and euphoric moods. So, the more often you activate your nervous system with far infrared light, this practice of enjoyable persistence trains the body to deal with stress in a more relaxed, easy going and less reactive way.

Far infrared and sweating helps our nervous system switch into a parasympathetic state that is more calming and relaxing which creates more tranquility. The parasympathetic (rest and digest) nervous system will send the blood flow back to the brain and you'll be able to think more clearly. It can also help reactivate your digestive system. A less chaotic digestion process sends signals to the brain that all is ok to rest peacefully. This gut-brain connection is a crucial fundamental of overall immune health as all systems are connected and each must be content and in sync for symbiotic optimal conditions of the whole.

## The Relax Sauna can increase body temperature 3° in 25 minutes. Significantly more then any other sauna

### Increasing core temperature will:

- Mobilize Lymphatic & Immune System
- Increase Circulation & Microcirculation
- Oxygenate Cells & Increase Absorption
- Activate Parasympathetic Nervous System
- Help Mitochondria create ATP + nitric oxide

*Only Sauna Company with Medical Lamps using a PATENTED ENERGY*

## Preferred by hundreds of medical professionals

**Dr. Bill Akpinar - M.D., D.S., O.M.D., Chi Gong Master - Voted Best Cancer Dr - NY City - 2007**

*"We recommend the Relax Sauna to many of our patients. ... We could not find this technology in any other sauna. The amount of Heat Shock Proteins produced with the Relax Sauna is phenomenal !"*

***Dr. Paul Anderson - N.D. - Former Chief of IV Services for Bastyr Oncology Research Center***

*"When we put on our last integrative clinic in the U.S. we used the Relax Sauna because becuse it can get the body hotter than other kinds of saunas. It has worked quite well to get into a level of therapeutic hypothermia even though it was a sauna treatment."*

***See over 800 testimonials on YouTube relaxsaunas.com/youtube***

**phil@relaxsaunas.com CALL 626.200.8454 relaxsaunas.com**

Go to: relaxsaunas.com and use code **relax10** to get **$125 OFF** the cost of a Relax Sauna until Oct 31, 2022

➤ *continued from page 22*

When addressing anger issues, treating each individual as an individual and identifying the unique factors that need to be addressed can profoundly improve clinical outcomes. In my experience, applying a more comprehensive treatment approach that includes physiological as well as psychological factors consistently yields better outcomes.

**Conclusion**

Mental illness often has roots in overlooked biological causes. And since irritability and anger are often seen as symptoms, rather than as diagnoses, they are frequently undertreated by standard psychiatry. Two minerals, lithium and copper, can be related to anger and irritability. Proper assessment and treatment of copper and lithium, along with the other underlying factors that affect mental health, can help improve symptoms, leading to better outcomes. Considering the costs of untreated anger issues – including social, professional and interpersonal – patients need additional, effective, and comprehensive treatment. Fortunately, assessing and treating lithium deficiency and copper excess, when appropriate, is typically straightforward and inexpensive. In my experience, it also can help bring relief, especially when combined with a comprehensive functional assessment and treatment. ◆

**References are available online at www.townsendletter.com.**

A pioneer in the field of functional and integrative medicine, board-certified child and adult psychiatrist, James M. Greenblatt, MD, has treated patients since 1988. After receiving his medical degree and completing his psychiatry residency at George Washington University, Dr. Greenblatt completed a fellowship in child and adolescent psychiatry at Johns Hopkins Medical School. He currently serves as Chief Medical Officer at Walden Behavioral Care in Dedham, Massachusetts.

Dr. Greenblatt has lectured internationally on the scientific evidence for nutritional interventions in psychiatry and mental illness. He is the author of seven books, including *Answers to Anorexia*, *Finally Focused: The Breakthrough Natural Treatment Plan for ADHD*, and *Functional & Integrative Medicine for Antidepressant Withdrawal*.

Dr. Greenblatt was inducted into the Orthomolecular Hall of Fame in 2017 by the International Society of Orthomolecular Medicine. He is also the founder of Psychiatry Redefined, an educational platform dedicated to the transformation of psychiatry, which offers online courses, webinars, and fellowships for professionals. Dr. Greenblatt is the medical director of TZ Health, a virtual clinic dedicated to personalized, patient-centered care utilizing a functional medicine model for the treatment of mental illness. Please visit www.PsychiatryRedefined.org and www.tzhealth.com/ for more information.

## Lithium Deficiency


## On the Cover

# Let's Be Real About Reflux: Getting to The Heart of Heartburn

### by Steven Sandberg-Lewis, ND, DHANP

The following is one of the key chapters from my soon-to-be published book *Let's Be Real About Reflux: Getting to the Heart of Heartburn*. My new book is not another "it's all about too much acid" rehash of misconceptions about heartburn. It provides a fresh approach to understanding the multiple causes and presents a thorough explanation of evidence-based lifestyle hacks and natural medicine treatments.

"Reduce CARBs: Relieve Reflux" presents a mnemonic for lifestyle-based approaches any one of which may significantly reduce heartburn depending on an individual's underlying reflux etiology and personal habits.

Each chapter has a glossary of terms and is written so both those with medical training and those without can benefit from reading.

**TABLE OF CONTENTS for *Let's Be Real About Reflux***



**GLOSSARY:**

**Body composition analysis** – a measurement of body percentages of fat, water and muscle

**Body mass index (BMI)** – a ratio calculated by dividing one's weight in kilograms by the square of one's height in meters. This is used as an indicator of obesity, overweight, normal weight and underweight status.

**Central adiposity/apple fat** – the fat that surrounds the abdominal internal organs

**Crossover trial** – A type of clinical trial in which all participants receive the same two or more treatments, but the order in which they receive them depends on the group to which they are randomly assigned.

**DeMeester score** – a composite score of the acid exposure during a 24-hour ambulatory pH monitoring test. It has been used to definitively diagnose GERD since the 1970s.

**Gluteofemoral adiposity/pear fat** – the type of fat measured by thigh circumference, hip circumference, and fat deposits on the legs.

**Glycemic load** – how specific foods affect blood sugar levels

**Meta-analysis** – the examination of data from several independent studies of the same topic, in order to summarize overall trends.

**Nonsteroidal anti-inflammatory drugs** – a class of drugs which reduce pain, decrease inflammation, decrease fever, and reduce the formation of blood clots (eg. Ibuprofen, aspirin, naproxen)

**Prospective trial** – a study that observes a group of people over a period of time to gather information and record outcome.

**Supine** – lying face upward, on the back

**Systematic review** – A compilation of research on a specific question. It is done by collecting and summarizing all research evidence that fits pre-specified eligibility criteria.

**Chapter 8 – Common Lifestyle Factors Promoting GERD**

Below is a mnemonic device to list the more important lifestyle factors that can trigger or increase heartburn and other reflux symptoms. It is unlikely that they are all significant triggers for any one person, but one or more may be important. People with reflux may choose to avoid these various foods, drinks, drugs (check with your doctor before making any changes to your prescription medications) or activities. Removing one factor at a time while monitoring symptoms has resulted in heartburn relief for many people.

The mnemonic is "Reduce CARBS, Relieve Reflux"

- **C** – cola (soda in general), coffee, chocolate, cigarettes (tobacco in general)
- **A** – alcohol, acidic foods, aspirin (and other over-the-counter pain and inflammation medicines)
- **R** – refined carbohydrates; excess carbohydrate intake, even unrefined such as whole grains or starchy vegetables (see Chapter 9 for more dietary details); rapid eating; Rx (certain prescription medicines discussed in Chapter 1)
- **B** – big meals (eating too much at a meal); bigger waist circumference; bedtime eating/eating within 3 hours of going to bed
- **S** – snacking; sleeping position; shallow chest breathing; saturated fat, (high intake of any type of fat); spicy food; sensitivity to specific foods

The above is your mnemonic. Here is more detail.

**Cola and other soda** – The Melbourne Collaborative Cohort Study is a large **prospective trial** that found carbonated beverages increased the risk of GERD in both men and women (Wang SE, 2021). Agrawal, (2005) found carbonated soft drinks were highly acidic and caused almost immediate acid pH in the lower esophagus. Another study found that although extreme acidity lasted only 90 seconds, an acid pH of less than 4.0 could persist as long as 13 minutes after exposure (Shoenut JP, 1998). Others speculate that carbonated drinks cause more distention of the stomach, increasing intragastric pressure which may cause laxity of the lower esophageal sphincter (LES), the anatomical safeguard against reflux. Perhaps the best evidence of a mechanism of carbonated beverages causing reflux comes from Pouderoux et al. Their research found that carbonated rather than distilled water increased the retention of food and liquid in the gastric fundus, where stomach contents would have the most reflux potential.

**Coffee** – Drinking espresso, filtered coffee or instant coffee all significantly raise serum gastrin levels within 15 minutes of consumption. This effect on gastrin, a potent stimulator of acid production by the parietal cells in the body of the stomach, wears off after about an hour (Papakonstantino E, 2016). A **meta-analysis** of 15 studies found that the symptom of heartburn did not correlate with coffee consumption, whereas the presence of erosive esophagitis on upper endoscopy did (Kim J, 2014). There are commercial acid-free coffees that taste like regular coffee, which may be less likely to trigger GERD.

**Chocolate** – According to Surdea-Blaga et al, chocolate induces reflux and increases the lower esophageal exposure to acid. Research published at Stanford University adds that chocolate reduces lower esophageal sphincter pressure (Kaltenbach, 2006).

**Cigarettes** – A meta-analysis of smoking as a risk of Barrett's esophagus found a consistent association. The greater number of packs per day over years of smoking increased the risk (Andrici J, 2013). In smokers, laryngopharyngeal reflux symptoms and upper endoscopy findings significantly improved after two months of tobacco cessation (Dinc ASC, 2020). Kahrilas reports that smokers have chronically diminished LES pressure and smoking increases the rate of reflux events. The most important mechanisms are thought to be decreased effectiveness of saliva in clearing refluxed material from the esophagus as well as increased intra-abdominal pressure.

## Lifestyle-based approaches can significantly reduce heartburn.

**Alcohol** – Alcohol consumption can reduce the LES pressure, which facilitates reflux. Alcohol also has a direct toxic effect on the esophageal mucosa, predisposing to acid/pepsin injury (Ness-Jensen E, 2017). German researchers report that alcohol use reduces the strength of contraction of the lower esophagus leading to decreased clearance of refluxed material (Franke A, 2005). These effects also increase the risk of esophageal cancer. A meta-analysis of twenty-nine research studies found that any regular use of alcohol increases the rate of reflux by just under 50% compared to non-drinkers or occasional drinkers. Alcohol use is more of a risk for erosive esophagitis rather than for non-erosive reflux disease (Pan J, 2019).

**Acidic foods** – The consumption of citrus fruit, vinegar, and tomato can either aggravate or ameliorate GERD. I often ask my reflux patients how they respond if they take a teaspoon of apple cider vinegar in two ounces of water just before a meal. Some get relief and others feel more burning and reflux symptoms. My theory is that patients with erosive esophagitis or gastritis are more sensitive to the acidity of vinegar and feel it as burning or pain. In addition, I theorize that those with hypochlorhydria and NERD often respond positively to the addition of vinegar, lemon juice, bitter herbs or betaine hydrochloride capsules taken with meals. A 2018 Italian study found that daily intake of citrus fruit and tomato along with a sugar-free diet was effective in treating GERD. They suggest that the acids in lemon, orange, and tomato lowered the pH

➤

➤

of the stomach which reduced the production of gastrin and therefore hydrochloric acid, relieving heartburn symptoms (Langella C, 2018).

**Aspirin** and **non-steroidal anti-inflammatory drugs** (NSAIDs) – A 2018 meta-analysis of ten research studies from around the world found a significant increase in reflux symptoms in people taking NSAIDs or aspirin (25.5%) compared to non-users (19.6%). These medications can also cause upper GI erosions and ulcerations. Aspirin is sold in both low dose (81 mg tablets) and regular dosage (325 or 500 mg tablets). A Japanese study of over 5500 people undergoing upper endoscopy compared subjects who took low dose aspirin compared to non-users, The incidence of erosive esophagitis was only 3% higher in the aspirin group, but there was a 10% higher risk for developing a peptic ulcer. According to Zographos et al, "aspirin disrupts the normal cytoprotective (cell protective) barrier in the mucosa of the stomach and a similar process has been found to occur in the esophagus… Esophageal emptying is slow in the elderly, resulting in a prolonged exposure of the mucosa to their irritant action. Nonsteroid anti-inflammatory drugs should be prescribed with caution in the presence of symptomatic gastroesophageal reflux."

**Refined and excessive dietary carbohydrates** – A very low carbohydrate diet may be effective for reflux (Surdea-Blaga T, 2019). It was found to be significantly effective in eight obese subjects with GERD. 24-hour esophageal pH impedance testing was performed before and after a six-day diet containing less than 20 grams of carbohydrate per day. The DeMeester score for reflux dropped from an average of 34.7 to 14.0 (normal is less than 14.7). The percentage of time the esophageal pH was more acidic than 4.0 dropped by half (Austin GL, 2006). In another study, 33 obese white women and 9 obese black women followed a 16-week diet which was lower in simple and complex carbohydrate and higher in fat (saturated, polyunsaturated, and monounsaturated). The control group was 70 white women and 32 black women with comparable body types but no GERD symptoms (Pointer SD, 2017). Prior to the dietary intervention, the women with GERD ate a diet with a higher **glycemic load,** which included more total carbohydrate, sucrose, total sugar, and starch. They had higher insulin resistance and inflammation markers. Body composition analysis, blood inflammatory markers, glucose, and insulin as well as GERD symptoms and use of GERD medications were monitored during the study. The overwhelming result was that *all* the women with reflux had resolution of GERD symptoms within ten weeks and discontinued their reflux medications. The white women had the highest carbohydrate intakes prior to starting the study and had the greatest reduction in insulin resistance by following the 16-week low carbohydrate diet. All the women lost similar amounts of weight.

Certain indigestible forms of carbohydrate, such as psyllium seed powder or fenugreek fiber powder, may reduce reflux (DiSilvestro RA, 2011). A Russian study using a sucrose sweetened psyllium seed powder (five grams three times/day) found a significant increase in LES pressure and significant reduction in acidic and weakly acidic reflux episodes. Reflux time dropped in half (Morozov S, 2018). Some have suggested that the gel that forms when psyllium fiber is mixed with water may create a barrier which prevents reflux. It is interesting that fenugreek is also used in traditional medicine for insulin resistance since this is also a risk factor for GERD (Zhou C, 2020).

**Rapid eating –** Increased numbers and duration of transient lower esophageal sphincter relaxations (TLESRs) are thought to be an important cause of GERD. TLESRs are triggered when the stomach is distended by solids, liquids and/or gas and the LES opens for longer periods of time than needed to allow food to pass. Remaining open permits the venting of pressure and gas. A study of 20 normal adults (13 women and 7 men without reflux) measured the difference in 24-hour pH impedance results between identical meals eaten either in five minutes or eaten in thirty minutes (Wilde SM, 2004). The two test meals were spaced a day apart. A significant increase in the number of reflux events followed the five-minute meal compared to the thirty-minute meal. The increased reflux was predominantly non-acid in the first hour after eating and more acidic in the second hour. Of note: An earlier study showed that subjects with hiatal hernia had twice the number of TLESRs, so a combination of rapid eating, larger meals and a hiatal hernia may be the most significant trigger for reflux (Kahrilas PJ, 2000).

**Rx – Prescription Medications Causing or Increasing GERD**

*Asthma medications:* albuterol (Ventolin, Proventil); metaproterenol (Alupent); pirbuterol (Maxair); terbutaline (Brethaire); isoetharine (Bronkosol); levalbuterol (Xopenex); salmeterol (Serevent).

*Cardiac and hypertension medications:* isosorbide mononitrate (Imdur, Monoket); isosorbide dinitrate (Isordil); propranolol (Inderal); amlodipine (Norvasc); diltiazem (Cardizem); felodipine (Plendil); nicardipine (Cardene); nifedipine (Adalat, Procardia).

*Osteoporosis medications:* bisphosphonates (Fosomax, Boniva and Actonel).

*Additional drugs* include the following:

- Tricyclic antidepressants: amitriptyline (Elavil); imipramine (Tofranil); desipramine (Norpramin); nortriptyline (Pamelor, Aventyl).
- Anticholinergics, such as atropine in Lomotil.
- Narcotics, such as morphine, oxycodone, Vicodin, etc. (sources differ on this effect)
- Sedatives, such as diazepam (Valium) and barbiturates.

**Big meals (overeating) –** Similar to rapid eating, large meals can distend the stomach enough to trigger more TLESRs and increase reflux symptoms.

**Big waist circumference –** Compared to lower weight adults, the odds of having GERD are three times greater in obese men and four times greater in obese women (Pointer SD, 2016). A study of 743 subjects in Taiwan found increasing

waist circumference and **body mass index** (BMI) is associated with insulin resistance, rising blood sugar levels and GERD. These were most strongly associated in men (Hsu CS, 2011). Two meta-analyses found a positive association among increasing BMI, GERD symptoms and complications such as erosive esophagitis (Corley D, 2006 and Hampel H, 2005).

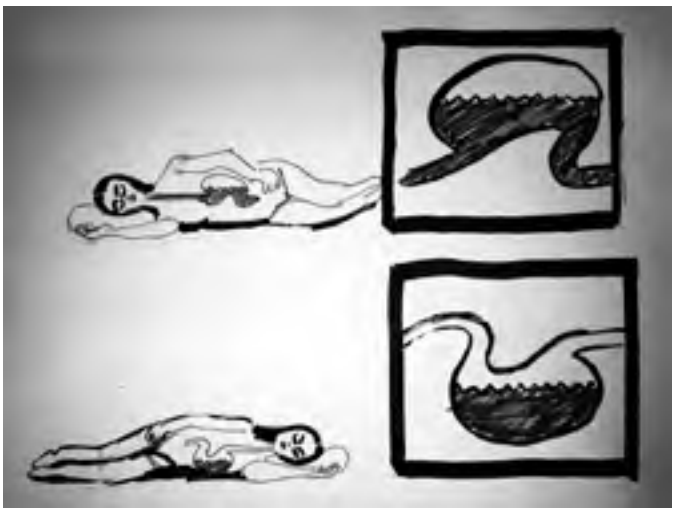
Of note, people with increased girth at the waist have a higher risk of GERD. Singh et al found that **central adiposity** ("apple fat") leads to nearly twice the risk of developing GERD with erosive esophagitis than other body types (Singh S, 2013). In contrast, men with increased hip circumference or **gluteofemoral** ("pear-fat") girth were protected against developing GERD symptoms, erosive esophagitis, type 2 diabetes, cardiovascular disease as well as Barrett's esophagus (Rubenstein JH, 2013 and Kendall BJ, 2016). The protective effect was not significant for women.

**Bedtime meals** - Eating within three hours of bedtime increases the risk of reflux by as much as seven and a half times (Zhang M 2021).

**Snacks –** A pilot study found that meal spacing for two weeks with no snacking resolved heartburn in 75% of subjects with erosive esophagitis. By eating two meals per day with only liquids between, the subjects were able to discontinue heartburn medication (Randhawa MA, 2015).

**Sleep position** – During the daytime, the average person produces over a liter of saliva. About every minute, the saliva is swallowed, bathing the esophagus in mildly alkaline fluid. This can help neutralize refluxed material from the stomach. During sleep, we swallow less frequently, and secrete less saliva. Research shows that esophageal acid clearance is significantly slower during sleep, even in studies of people sleeping upright!

In a recent study of 57 subjects, pH impedance testing was used to evaluate clearance of acid from the esophagus in various spontaneous sleep positions. Clearance was twice



as fast sleeping on the left side compared to sleeping **supine**. Sleeping on the right side slowed the clearance even more than supine (Schuitenmaker JM, 2021). There is a reflux smartwatch app that can be used to train people to sleep on the left side. From homeopathic research we know that some people find it nearly impossible to sleep on the left side. For some, sleeping on the left side may cause rapid heartrate or palpitations. In such cases, if sleeping supine is possible, it would be better than sleeping on the right with respect to reflux.

Elevating the head of the bed by six inches significantly reduces esophageal acid levels in subjects with laryngopharyngeal reflux (Scott DR, 2015). A 2021 **systematic review** evaluated five research studies that used either

sleeping on a wedge pillow or elevating the head end of the bed with blocks. "The four studies that reported on GERD symptoms found an improvement among participants in the head-of-bed elevation; a high-quality **crossover trial** showed a clinically important reduction in symptom scores at six weeks and less acidic esophageal pH readings. Although the researchers suspected some of the findings less reliable, they determined elevating the head of the bed to be a cheaper and safer alternative to drug interventions (Albarqouni L, 2021)

**Shallow chest breathing** - Eherer A., 2014 showed that training GERD patients to use diaphragmatic breathing can strengthen the LES. They conducted a randomized trial and used breathing exercises as the intervention. GERD patients using diaphragmatic breathing techniques were found to have fewer GERD symptoms as well as improved quality of life, better pH-impedance findings, and PPI use.

**Saturated fat –** There is a strong belief that consuming saturated fat increases GERD. While some studies have shown that fat increases perception of reflux and causes more symptoms in patients with gastroparesis (Homko CJ, 2015), a recent study of over 3000 Iranians using questionnaires to assess reflux and dietary fat found no correlation (Ebrahimpour-Koujan S, 2021). Overall, research on dietary fat is less conclusive that research on carbohydrate intake and GERD.

**Spicy food –** There are many variables in researching the effect of spicy food on reflux symptoms because individuals respond uniquely to the wide variety of spices. An Iranian questionnaire and symptom study of over 4600 men and

➤

➤

women found high consumption of spicy foods was associated with a greater risk of heartburn in men, but not in women. The men eating spicy food more than ten times per week had three times more heartburn than men who did not eat spicy food. Occasional ingestion of chili may aggravate abdominal pain and burning symptoms whereas frequent, long-term use of chili in food has been found to improve functional dyspepsia and GERD symptoms (Gonlachanvit S, 2010).

**Sensitivity** to specific foods – Published case studies have shown that individuals have resolved LPR by removing specific foods to which they are sensitive (Vora A, 2021).

### References


Wang SE et al, Diet and risk of gastro-oesophageal reflux disease in the Melbourne Collaborative Cohort Study, Public Health Nutr. 2021 Oct;24(15):5034-5046.

Agrawal A, Tutuian R, Hila A, Freeman J, Castell DO. Ingestion of acidic foods mimics gastroesophageal reflux during pH monitoring. Dig Dis Sci 2005; 50: 1916–20.

Shoenut JP, Duerksen D, Yaffe CS. Impact of ingested liquids on 24-hour ambulatory pH tests. Dig Dis Sci 1998; 43: 834–9.

Pouderoux P, Friedman N, Shirazi P, Ringelstein JG, Keshavarzian A. Effect of carbonated water on gastric emptying and intragastric meal distribution. Dig Dis Sci 1997; 42: 34–9.

Kim J et al, Association between coffee intake and gastroesophageal reflux disease: a meta-analysis. Diseases of the Esophagus (2014) 27, 311–317

Papakonstantinou E et al, Acute effects of coffee consumption on self-reported gastrointestinal symptoms, blood pressure and stress indices in healthy individuals. Nutr J. 2016; 15: 26.

Surdea-Blaga et al, Food and Gastroesophageal Reflux Disease. Curr Med Chem. 2019;26(19):3497-3511.

Kaltenbach T, Crockett S, Gerson LB, Are lifestyle measures effective in patients with gastroesophageal reflux disease? An evidence-based approach. Arch Intern Med. 2006 May 8;166(9):965-71.

Andrici J, Cox, MR, Eslick GD, Cigarette smoking and the risk of Barrett's esophagus: a systematic review and meta-analysis. J Gastroenterol Hepatol 2013 Aug;28(8):1258-73.

Dinc ASK, Cayonu M, Sengezer T, Sahim, MM, Smoking Cessation Improves the Symptoms and the Findings of Laryngeal Irritation. Ear Nose Throat J. 2020 Feb;99(2):124-127.

Kahrilas PJ, Cigarette smoking and gastroesophageal reflux disease. Dig Dis .1992;10(2):61-71.

Ness-Jensen E, Lagergren J, Tobacco smoking, alcohol consumption and gastro-oesophageal reflux disease. Best Pract Res Clin Gastroenterol. 2017 Oct;31(5):501-508.

Franke A, Teyssen S, Singer MV, Alcohol-related diseases of the esophagus and stomach. Dig Dis. 2005;23(3-4):204-13.

Pan J, Cen L, Chen W, Yu C et al, Alcohol Consumption and the Risk of Gastroesophageal Reflux Disease: A Systematic Review and Meta-analysis. Alcohol Alcohol. 2019 Jan 1;54(1):62-69.

Langella C et al, New food approaches to reduce and/or eliminate increased gastric acidity related to gastroesophageal pathologies. Nutrition. 2018 Oct;54:26-32.

Zografos GN et al, Drug-induced esophagitis. Dis Esophagus. 2009;22(8):633-7.

Surdea-Blaga T, Negrutiu DE, Palage M, Dumitrascu DL, Food and Gastroesophageal Reflux Disease. Curr Med Chem. 2019;26(19):3497-3511.

DiSilvestro RA, Verbruggen MA, Offutt EJ, Anti-heartburn effects of a fenugreek fiber product. Phytother Res. 2011 Jan;25(1):88-91.

Morozov S, Isakov V, Konovalova M, Fiber-enriched diet helps to control symptoms and improves esophageal motility in patients with non-erosive gastroesophageal reflux disease. World J Gastroenterol. 2018 Jun 7; 24(21): 2291–2299.

Zhou C et al, Fenugreek attenuates obesity-induced inflammation and improves insulin resistance through downregulation of iRhom2/TACE. Life Sci. 2020 Oct 1;258:118222.

Pointer SD et al, Dietary Carbohydrate Intake, Insulin Resistance, and Gastroesophageal Reflux Disease (GERD): A Pilot Study in European- and African-American Obese Women. Aliment Pharmacol Ther. 2016 Nov;44(9):976-988.

Wildi AM, Tutuian R, O Castell D, The influence of rapid food intake on postprandial reflux: studies in healthy volunteers. Am J Gastroenterol. 2004 Sep;99(9):1645-51.

Kahrilas PJ, Shi G, Manka M, Joehl RJ, Increased frequency of transient lower esophageal sphincter relaxation induced by gastric distention in reflux patients with hiatal hernia. Gastroenterology. 2000 Apr;118(4):688-95.

Hsu C-S et al, Increasing insulin resistance is associated with increased severity and prevalence of gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2011 Oct;34(8):994-1004.

Corley DA, Kubo A, Body mass index and gastroesophageal reflux disease: a systematic review and meta-analysis. Am J Gastroenterol. 2006 Nov;101(11):2619-28.

Hampel H, Abraham NS, El-Serag HB, Meta-analysis: obesity and the risk for gastroesophageal reflux disease and its complications. Ann Intern Med. 2005 Aug 2;143(3):199-211.

Singh S et al, Central adiposity is associated with increased risk of esophageal inflammation, metaplasia, and adenocarcinoma: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2013 Nov;11(11):1399-1412.e7.

Rubenstein JH et al, Protective role of gluteofemoral obesity in erosive oesophagitis and Barrett's oesophagus. Gut. 2014 Feb;63(2):230-5.

Kendall BJ et al, Inverse Association Between Gluteofemoral Obesity and Risk of Barrett's Esophagus in a Pooled Analysis, Clin Gastroenterol Hepatol. 2016 Oct;14(10):1412-1419.e3.

Zhang M, Hou Z-K, Huang Z-B, Chen X-L et al. Dietary and Lifestyle Factors Related to Gastroesophageal Reflux Disease: A Systematic Review. Ther Clin Risk Mana. 2021 Apr 15;17:305-323.

Randhawa MA et al, An old dietary regimen as a new lifestyle change for Gastro esophageal reflux disease: A pilot study. Pak J Pharm Sci. 2015 Sep;28(5):1583-6.

Schuitenmaker JM et al, Associations Between Sleep Position and Nocturnal Gastroesophageal Reflux: A Study Using Concurrent Monitoring of Sleep Position and Esophageal pH and Impedance. Am J Gastroenterol. 2021 Dec 20.

Scott DR, Simon RA, Supraesophageal Reflux: Correlation of Position and Occurrence of Acid Reflux-Effect of Head-of-Bed Elevation on Supine Reflux, J Allergy Clin Immunol Pract. May-Jun 2015;3(3):356-61.

Albarqouni L et al, Head of bed elevation to relieve gastroesophageal reflux symptoms: a systematic review. BMC Fam Pract. 2021; 22: 24.

Eherer A et al. Management of Gastroesophageal Reflux Disease: Lifestyle Modification and Alternative Approaches. Dig Dis 2014;32:1490151.

Homko CJ et al, Effect of dietary fat and food consistency on gastroparesis symptoms in patients with gastroparesis, Neurogastroenterol Motil. 2015 Apr;27(4):501-8.

Ebrahimpour-Koujan S, Keshteli AH, Esmaillzadeh A, Adibi P, Association between Dietary Fat Intake and Odds of Gastro-esophageal Reflux Disorder (GERD) in Iranian Adults. Int J Prev Med. 2021 Jul 5;12:77.

Rajaie S et al, Spicy Food Consumption and Risk of Uninvestigated Heartburn in Isfahani Adults. Dig Dis. 2020;38(3):178-187.

Gonlachanvit S, Are rice and spicy diet good for functional gastrointestinal disorders? J Neurogastroenterol Motil. 2010 Apr;16(2):131-8.

Vora A, Vance D, Alnouri G, Sataloff RT, Food Sensitivity and Laryngopharyngeal Reflux: Preliminary Observations. J Voice. 2021 May;35(3):497.e5-497.


◆


Steven Sandberg-Lewis, ND, DHANP, has been a practicing naturopathic physician since his graduation from the National University of Natural Medicine (NUNM) in 1978. He has been a clinical and didactic professor since 1996, teaching a variety of courses but primarily focusing on gastroenterology and GI physical medicine. His private practice is at Hive Mind Medicine in Portland, Oregon (www.hivemindmedicine.org).

Sandberg-Lewis is a popular international lecturer at functional medicine seminars, presents webinars and is frequently interviewed on issues of digestive health and disease.

In 2010 he co-founded the SIBO Center at NUNM which is one of only four centers in the USA for Small Intestine Bacterial Overgrowth diagnosis, treatment, education, and research.

He is the author of numerous articles and the column entitled "Functional Gastroenterology Bolus" in the *Townsend Letter*. His medical textbook is *Functional Gastroenterology: Assessing and Addressing the Causes of Functional Digestive Disorders*, Second edition, 2017. He is currently in the editing phase of *Let's Be Real About Reflux: Getting to the Heart of Heartburn*, a book on underlying mechanisms and the treatment of gastroesophageal reflux. Website: functionalgastroenterology.com

# Simply the Best


It's so good the FDA uses Boluoke® as the gold standard for lumbrokinase research!

Your Patients.
Your Reputation.
**Trust Nothing Less!**

## Boluoke® (lumbrokinase)

- the original lumbrokinase used in trials
- highest fibrinolytic strength on the market
- over 25 years of clinical safety/efficacy records
- does not affect INR or aPTT testing

## Hypercoagulation, a central issue in:

- conditions with a poor circulation
- growth and spread of malignant cells
- biofilm-associated chronic infections
- poor tissue healing due to hypoxia
- severe acute viral/bacterial infections

Dragon's Medical Bulletin
www.dragonsmedicalbulletin.com
Your Quick Stop for Integrated Clinical Research Updates

CRNA

**1-866-287-4986**
www.canadaRNA.com

*Boluoke® is also available through:*

Researched Nutritionals · Pro Health Network · nature 2 health · antaging-systems.com · MyP · NaturoDoc · BIORESOURCE

# Combating Depression and Anxiety with Herbal Medicines: A Case Report

by Christian del Rosario and Baljit Khamba, ND, MPH

**Abstract**

In adults with generalized anxiety disorder (GAD) and major depressive disorder (MDD), conventional treatment includes the prescriptions of benzodiazepines, selective serotonin receptor inhibitors (SSRIs), and selective serotonin norepinephrine reuptake inhibitors (SNRIs). These have clinical effectiveness in ameliorating symptoms temporarily, but long-term use is questionable due to negative side effects. The findings in this case report suggest that herbal medicine and nutraceutical supplementation can be as effective as pharmaceutical interventions without the adverse side effects in the treatment of chronic depression and anxiety in a 57-year-old female. The primary variables assessed in this case study were the scores in depression and anxiety screening questionnaires (Graph 1 and 2). Depression screening included the Patient Health Questionnaire-9 (PHQ9) and Beck Depression Index (BDI) as an objective measurement of the severity of depressive symptoms, while the severity of anxiety was objectively measured via the Generalized Anxiety Disorder-7 (GAD-7) throughout the progression of treatment. This patient's improvement in the severity of anxiety and depression symptoms suggest that herbal medicine and nutraceutical supplementation are an effective therapeutic in the treatment of depression and anxiety. Herbal medicine and nutraceutical supplementation are less toxic therapies that may produce favorable outcomes in patients with GAD or MDD. Their therapeutic action may be on a biochemical level, comparable to the mechanism of pharmaceutical drugs, by modulating protein transporters, decreasing oxidative stress and neuro-inflammation, as well as influencing brain neurotransmitter levels.

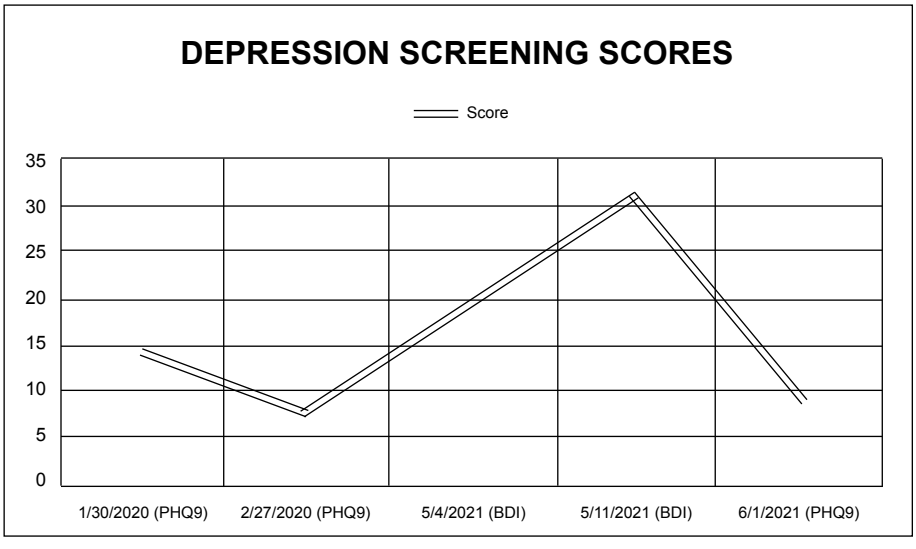
**Introduction**

Depression and anxiety can be challenging to treat considering the complex multifactorial interplay of lifestyle habits, epigenetics, psychosocial dynamics, biochemical pathways, and emotional or mental trauma. Long-term health complications, such as cancer, heart disease, or diabetes, may arise in patients with depression or anxiety as many co-present with chronic systemic low-grade inflammation, immune dysfunction, and neurochemical and hormonal imbalances.[1]

At least 8-12% of the world population experiences an episode of depression at least once in their life, while the National Institutes of Mental Health estimates that depression affects nearly 16 million people in the United States alone.[2] Patients with depression experience symptoms of depressed mood, loss of interest in daily activities, fatigue, feelings of worthlessness or guilt, diminished ability to think or concentrate, recurrent thoughts of death and weight loss or weight gain, and sleep or appetite disturbances.[2] This detrimentally impacts their quality of life, while on a larger scale contributes to substantial economic burden due to reduced work productivity.[3]

The American Psychiatric Association estimates the prevalence of anxiety disorders to be more than 25 million people in the United States.[4] Patients with anxiety disorders experience symptoms that include persistent, excessive worry, fear of objects or situations, inability to relax, tension, and recurrent panic attacks.[2] Risk factors for depression include poor performance status, while risk factors for anxiety include poor performance status, old age, and female gender.[4]

In adults with generalized anxiety disorder (GAD) and major depressive disorder (MDD), conventional treatment includes the prescriptions of benzodiazepines, selective serotonin receptor inhibitors (SSRIs), and selective serotonin norepinephrine reuptake inhibitors (SNRIs). These have clinical



effectiveness in ameliorating symptoms temporarily, but long-term use is questionable. Benzodiazepines, such as diazepam, lorazepam, or alprazolam, exert their influence as an anxiolytic via binding to gamma aminobutyric acid ($GABA_)$ receptors; thus, reducing the excitability of neurons and producing a psychologically calming effect. Caution is warranted as undesirable side effects include somnolence and cognitive impairment.[5] Fluoxetin, paroxetine, and citalopram, commonly prescribed SSRIs, act as antidepressants by selectively blocking the serotonin transporter, thereby inhibiting the reuptake of serotonin to increase neurotransmitter concentrations.[5] Drug side effects include sexual dysfunction and neuropsychiatric disorders such as suicidal tendencies and sleep dysfunction.[1]

Herbal medicine and nutraceutical supplementation are less toxic therapies that may produce favorable outcomes in patients with GAD or MDD. Their therapeutic action may be on a biochemical level, comparable to the mechanism of pharmaceutical drugs, by modulating protein transporters, decreasing oxidative stress and neuroinflammation, as well as influencing brain neurotransmitter levels.[6]

The phytochemical constituents in herbal medicine have been shown to activate one or more cellular stress response pathways to enhance the adaptive ability of cellular resistance to injury and disease.[7] Specific signal transduction pathways that are of importance in MDD and GAD include the serotonergic, noradrenergic, glutamatergic, and GABA-ergic biochemistry considering their proven role in behavior and mood.[1] Altered biochemical pathways and imbalances in neurotransmitters and hormones that regulate mood, immune response, and stress are fundamental mediators in the pathogenesis of depression and anxiety.[1] The findings in this case report suggest that herbal medicine and nutraceutical supplementation can be as effective as pharmaceutical interventions without the adverse side effects in the treatment of depression and anxiety.[2,4-6]

**Patient Presentation**

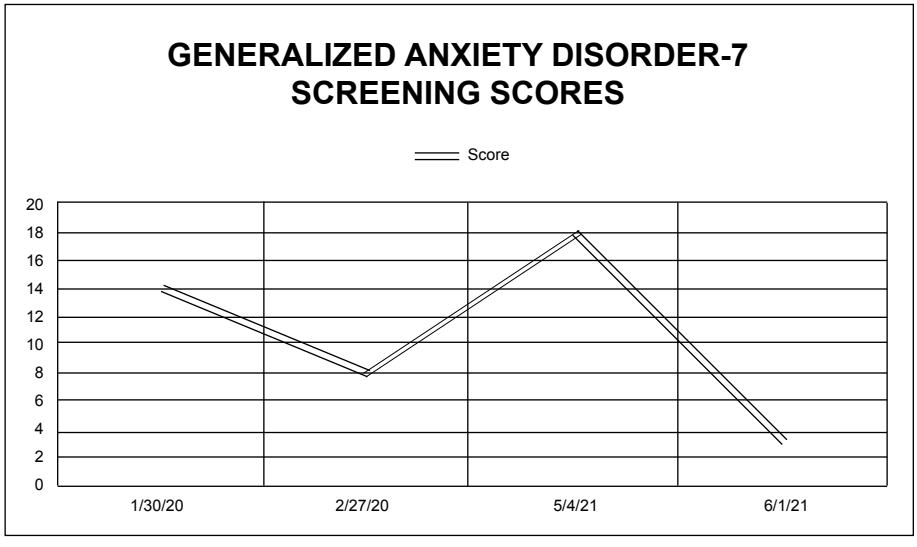
PH is a 57-year-old menopausal female who presents with a chronic history of alternating MDD and GAD. Her past medical history is significant for diverticulitis and an emergency dilation and curettage after a massive menstrual hemorrhage in 2015. Family history is significant for arthritis, diabetes, dementia, unspecified cancer, a brother who passed away from a myocardial infarct before the age of 55, as well as a history of unspecified heart disease in both maternal and paternal sides.

She was initially diagnosed with GAD and MDD on January 30, 2020 by a psychiatrist at Kaiser Permanente Hospital; however she reports that depressive symptoms began four years ago after her parents passed away abruptly due to health problems. She was the primary caretaker for her parents. She believes the chronic worry of ensuring their wellbeing while balancing her personal responsibilities took a toll on her mental health. The anxious symptoms developed shortly following depression. A PHQ9 and GAD7 in the January 30 hospital visit resulted in a score of 14 and 16, respectively indicating moderate depression and severe anxiety. The depression is characterized as severe exhaustion and decreased energy/chronic fatigue despite sleeping 11-12 hours daily, random bouts of sadness and depressed mood most of the days, diminished ability to concentrate, easy forgetfulness, and anhedonia. The anxiety is characterized as a chronic nervousness and anxious feeling, restlessness, irritability, excessive worry about responsibilities and others, in addition to a general feeling of unease. She has an associated decrease in appetite, increased agitation, and denies chest pain, palpitations, or panic attacks.

She was prescribed 75 mg of sertraline and 150 mg of bupropion daily for depression disorder and lorazepam 0.5 mg as needed for anxiety disorder. These successfully controlled her symptoms and improved her quality of life considering that a follow up PHQ9 and GAD7 on February 27, 2020, resulted in a score of 8 and 9, respectively indicating mild depression and mild anxiety. However, she discontinued one year later due to bothersome side effects, particularly an increase in confusion and memory loss, and severe fatigue. In addition, she noted an exacerbation of depressive and anxiety symptoms after discontinuing, which is most likely a withdrawal and rebound phenomena that typically follows cessation of chronic antidepressant use. In February 2021, she began menopause, further exacerbating depression and anxiety symptoms.

Her stressors that may be contributing to the etiology of her mood disorder include the abrupt loss of close family members, the loss of her job during the pandemic, and the detrimental impact of ➤

**Nutraceutical and herbal medicine can be just as effective as conventional pharmaceuticals for treating depression and anxiety.**



➤

social isolation on mental and emotional wellbeing.

Other obstacles to cure include high daily stress rated 8/10 on average, non-restorative sleep, and a sub-optimal diet that is lacking in key micronutrients and fiber. She is a former four-pack/year tobacco smoker who quit in 2004. She quit drinking alcohol in 2016. She currently uses marijuana at night to help with sleep. Daily physical activity includes one hour of cardiovascular exercise.

She was not judged to be a suicidal risk and denies suicidal ideation, intent, and plan. Despite the various hardships she must overcome, she continues to exhibit resilience and a desire for change in all visits thus far.

**Assessment**

On examination, PH was well groomed, in no distress, and presented with a calm mood. Her speech was normal, while her affect was mildly depressed. She was not judged to be a suicidal risk. Despite the hardships she has been facing, she exhibited resilience and a strong desire for change. She had an elevated blood pressure of 150/82 mm Hg and a body-mass index (weight in pounds divided by the square of the height in meters) at 31.3. All other vitals and physical exams were within normal limits.

The primary variables assessed in this case study were the scores in depression and anxiety screening questionnaires (Graph 1 and 2). Depression screening included the Patient Health Questionnaire-9 (PHQ9) and Beck Depression Index (BDI) as an objective measurement of the severity of depressive symptoms, while the severity of anxiety was objectively measured via the Generalized Anxiety Disorder-7 (GAD-7) throughout the progression of treatment.

Laboratory analysis was obtained to evaluate for physiological etiologies of depression or anxiety. A CBC revealed a moderately elevated fasting blood glucose and hemoglobin A1c. A CMP

**Table 1: Timeline of Recommended Care**

| Date | Visit Assessment | Treatment |
|---|---|---|
| 05/04/21 | PH presents with chronic, alternating anxiety and depression. The depression and anxiety symptoms alternate in severity. The anxiety symptoms seem to be the most troublesome, with a GAD-7 and BDI assessment indicating severe anxiety and a mild mood disturbance, respectively. | **Intervention name:** Lavela WS 1265 Brand: Integrative Therapeutics<br>Ingredients: 80 mg English Lavender (*Lavendula angustifolia*)<br>Dosing regimen: 1 softgel per oral daily with meals<br><br>**Intervention name:** Ashwaghanda Brand: Pure Encapsulations<br>Ingredients: 500 mg Ashwaganda (*Withania somnifera*) root extract<br>Dosing regimen: 1 softgel per oral daily with meals<br><br>Diet diary for 1 week recording food intake, mood changes, bowel movements<br><br>Diagnostic analysis (CBC, CMP, Thyroid panel, Lipid panel, Hormone panel, B12, HbA1c, FBG) |
| 05/11/21 | Follow-up: PH reports a significant exacerbation in depression symptom severity, specifically increased sadness, difficulty concentrating and increased confusion, and fatigue. A BDI indicates severe depression. | **Intervention name:** Super DHA Liquid Brand: Genestra<br>Ingredients: 1200 mg DHA, 260 mg EPA<br>Dosing regimen: 1 tsp daily per oral with meals<br><br>**Intervention name:** HMF Neuro Brand: Genestra<br>Ingredients: probiotic consortium 12 billion, *Lactobacillus acidophilus, Bifidobacterium bifidum, Bifidobacterium animalis subsp.* Lactis, *Lactobacillus rhamnosus,* L-glutamine<br>Dosing regimen: 2 capsules per oral at night away from food<br><br>**Intervention name:** Neurologix Brand: Integrative Therapeutics<br>Ingredients: 5 mg Vitamin B6 (as pyridoxal-5'-phosphate)<br>250 mg Neumentix spearmint (*Mentha spicata*) leaf extract<br>250 mg Citicoline Cognizin brand, Saffron (*Crocus sativus L.*) Stigma Extract<br>Dosing regimen: 2 capsules per oral daily with food<br><br>**Herbal tincture for Depression & Anxiety:**<br>*Bacopa monniera* (Coastal waterhyssop), dry herb 45 ml<br>*Eleutherococcus senticosus* (Siberian ginseng), dry root 35 ml<br>*Passiflora incarnata* (Passionflower), dry herb 20 ml<br>*Crataegus species.* (Hawthorne berry), dry berry 10 ml<br>*Rosmarinus officinalis* (Rosemary), dry leaf 10 ml<br>Sig: two ml three times daily |
| 06/01/21 | PH presents with a joyful affect and rates her health as very great. She noted a significant improvement in her overall quality of life and was recently hired for a new job at a senior care facility. She reports her mental and emotional state is getting better and her stress levels have decreased as she began implementing self-care techniques such as spending time in nature, journaling, mindfulness, and daily physical exercise.<br><br>A GAD-7 score of 3 and PHQ-9 score of 9 indicate mild anxiety and mild depression, respectively. | Continue previous treatment protocol<br>Mediterranean diet recommendation<br>Sleep hygiene education |

revealed high alkaline phosphatase. A lipid panel was performed considering her extensive family history of cardiovascular disease. It showed high LDL, high cholesterol:HDL ratio, high triglyceride, and low HDL. A hormone panel revealed low total testosterone and low dihydrotestosterone. She also had low vitamin D.

**Treatment**

The goal of treatment was to stabilize mood and reduce symptoms of anxiety and depression to improve overall quality of life using natural therapeutics. Initial treatment recommendations included beginning a Mediterranean diet that included vitamins and nutrients to support optimal neurotransmitter synthesis and an increase in fiber intake to reduce risk for cardiovascular disease and diabetes.[8] She was prescribed a daily regimen of herbal medicine and nutraceutical supplementation indicated for its anxiolytic and antidepressant properties (Tables 2 and 3).

**Discussion**

The main objective of this case study was to share the clinical efficacy of herbal medicine and nutraceutical supplementation on the clinical course of MDD and GAD. PH's improvement in the severity of anxiety and depression symptoms suggest that herbal medicine and nutraceutical supplementation are an effective therapeutic in the treatment of depression and anxiety. The patient has undergone conventional pharmaceutical therapy using antidepressants and benzodiazepines; however, the side effects were too significant to continue long-term.

A review of literature presents potential mechanisms of action and supports use of botanicals in the treatment of depression and anxiety.

Supplementation that targets common nutritional deficiencies in depression and anxiety in conjunction with phytochemicals that support optimal neurotransmitter synthesis and stress responses may reduce the severity of depression and anxiety symptoms.[4] In addition, the safety concerns, potential for abuse, and severity of adverse side effects in many frequently prescribed antidepressant and anti-anxiety pharmaceuticals compel the need for physicians to carefully evaluate the benefits and risks when prescribing these to patients, and more importantly consider the inclusion of progressive natural therapeutics. The use of herbal medicine in the prevention and treatment of various diseases, especially mental health illness, has been a long-standing tradition in many cultures throughout the world noted by centuries of anecdotal evidence as well as a growing body of scientific research.

In a study comparing the efficacy of a six-week protocol of Silexan to lorazepam in adults with GAD found that Silexan successfully ameliorated anxiety symptoms comparably to lorazepam, indicating the therapeutic effect of lavender oil as a potent anxiolytic.[10] The therapeutic efficacy of lavender essential oil as an anxiolytic and anti-depressant may be due to its antagonistic affinity for the glutamate NMDA-receptor in a dose dependent manner, in addition to the binding of the serotonin transporter.[5] The monoterpenes linalool and linalyl acetate in lavender essential oil have been shown to interact with the NMDA receptor, signifying its role in the anxiolytic effects.[5] The researchers also found that in a model of neural human tissue neurotoxicity induced by hydrogen peroxide, lavender improved and protected the viability of cells subjected to oxidative stress further elucidating its potential antioxidant capacity.[5]

*Withania somnifera* (Ashwagandha) is a medical herb used for centuries as an adaptogen to help the body react

➤

**Table 2. Supplement Prescriptions**

| Intervention | Brand Name | Ingredients | Dose | Desired Therapeutic Action |
|---|---|---|---|---|
| Lavela WS 1265 | Integrative Therapeutics | 80 mg English Lavender (*Lavendula angustifolia*) essential oil | 1 capsule twice daily | Improve quality of sleep[9]<br>Improve mental and physical health[9]<br>Decrease anxiety severity[10] |
| Ashwaghanda | Pure Encapsulations | 500 mg Ashwaganda (*Withania somnifera*) root extract | 1 capsule per oral daily | Adaptogen[11] |
| Super DHA Liquid | Genestra | 1200 mg DHA<br>260 mg EPA | 1 teaspoon per oral daily with food | Decrease systemic inflammation contributing to neurocognitive inflammation[12]<br>Modulate overactive hypothalamic-pituitary-adrenal axis contributing to anxiety[12] |
| HMF Neuro Probiotics | Genestra | probiotic consortium 12 billion: *Lactobacillus acidophilus, Bifidobacterium bifidum, Bifidobacterium animalis* subsp. Lactis, *Lactobacillus rhamnosus,* L-glutamine | 2 capsules per oral at night away from food | Relieve depressive symptoms via modulating immune function and decreasing inflammation[13] |
| Neurologix | Integrative Therapeutics | 5 mg Vitamin B6 (as pyridoxal-5'-phosphate)<br>250 mg Neumentix spearmint (*Mentha spicata*) leaf extract<br>250 mg Citicoline Cognizin brand, Saffron (*Crocus sativus* L.) Stigma Extract | 2 capsules per oral daily with food | Antidepressant[2]<br>Anxiolytic[2]<br>Antioxidant[2]<br>Anticarcinogenic[2]<br>Neuroprotective[2]<br>Cardioprotective[2] |

➤

to stress in an optimal and effective manner. In a double-blind, randomized, placebo-controlled trial of 64 subjects with a history of chronic stress, they found that the group treated with 300 mg of Ashwagandha root extract twice daily for 60 days exhibited a significant reduction in stress-assessment scores with substantially reduced serum cortisol levels.[11]

Saffron, a renowned spice derived from the flower *Crocus sativus* has been studied and shown to exert clinically significant antidepressant and anxiolytic properties for the treatment of mild-to-moderate depression and GAD, with its effects being comparable to conventional antidepressant drugs such as fluoxetine and imipramine.[2] Saffron may exert its neuroprotective and antidepressant action by increasing cyclic adenosine monophosphate response element binding protein and brain-derived neurotrophic factor (BDNF) levels in the hippocampus.[2] BDNF, a growth factor that promotes cell survival, differentiation, and death of neuronal populations, have been shown to be significantly lower in depressed patients compared with healthy controls.[2] Moreover, psychopharmacological actions of saffron include inhibition of monoamine reuptake, such as serotonin, dopamine, and noradrenaline, similar to SSRIs or SNRIs, inhibition of monoamine oxidase, and GABAergic effects.[6]

*Bacopa monnieri,* a South Asian native plant, is traditionally used in Ayurvedic medicine for its gentle but potent cognitive enhancing benefits. Randomized controlled trials in healthy middle-aged to elderly adults indicate that extracts of Bacopa can improve speed of information processing and decision-making time, working memory, and produce anxiolytic effects following long-term supplementation of 3-4 months.[15]

*Eleutherococcus senticosus* is used primarily for its adaptogenic properties that optimize the body's response to environmental or physical stressors. The major active constituents – triterpene saponins, caffeoylquinic acids, flavonoids, and polysaccharides – have been shown to penetrate the blood brain barrier in mice and exert direct influence on neuron-related bioactivity, most notably, exerting axonal growth activity in amyloid β-induced degeneration models, and ultimately enhancing memory function.[20]

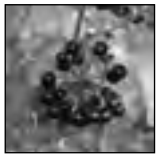
In a study by Ngan and Conduit, a traditional tea preparation of passionflower taken before bedtime led to improvements in sleep quality.[4] Extracts of passionflower have been found to produce statistically significant improvements in anxiety scores without sedation as well as improvements in cognitive function.[4] Its mechanism as an anxiolytic is attributed to its alkaloid constituents and affinity for GABA receptors, in which positive allosteric modulation elicits behavioral anxiolytic effects similar to those of diazepam in an in vitro study using mice.[21]

*Crataegus spp.* (hawthorne berry) is widely studied for its cardioprotective properties as an herbal medicine in treating cardiovascular patients; however, its neuroprotective benefits are worth exploring. A novel study conducted by Lim *et. al.,* found that hawthorne berry extracts display antidepressant-like effects in mice showing depressive-like behaviors.[17] Their findings indicate that hawthorne extracts could ameliorate depressive behavior by protecting against glial activation and oxidative stress.[17]

*Rosmarinus officinalis* (rosemary) is used therapeutically for its neuropharmacological properties in headaches, insomnia, and depression and may exhibit anti-inflammatory, antimicrobial, anti-oxidant, anti-tumorigenic, antinociceptive, and neuro-protective properties.[18] In a 14-day behavioral study of mice, administration of rosemary extract reduced anhedonic-like behavior and hyperactivity similar to fluoxetine, while interactions with the dopaminergic pathway via activation of dopamine receptors is suggested as a potential mechanism for antidepressant properties.[18]

The importance of the gut-brain axis in mental health is elucidated through nutraceutical and dietary interventions that lead to positive patient outcomes. Current meta-analyses of omega-3

**Table 3: Herbal Tincture**

| Image | Latin name | mL | Desired Therapeutic Actions |
|---|---|---|---|
|  | *Bacopa monnieri* | 45 | Enhance cognitive performance[14]<br>Improve working memory[15] |
|  | *Eleutherococcus senticosus* | 30 | Alleviate stress and improve stress response[16]<br>Enhance cognitive function[16] |
|  | *Passiflora incarnata* | 20 | Improve sleep quality[4]<br>Decrease anxiety symptom severity[4]<br>Enhance cognitive function[4] |
|  | *Crataegus species* | 10 | Antidepressant[17]<br>Antioxidant[17] |
|  | *Rosmarinus officinalis* | 10 | Antidepressant[18]<br>Improve memory performance[19]<br>Reduce anxiety and depression scores[19]<br>Improve sleep quality[19] |

supplementation in depression report comparable effects to that of conventional antidepressants, which may be due partly to findings of reduced omega-3 blood serum levels in patients with depression.[12] Deficits in omega-3 fatty acid uptake lead to lipid signaling abnormalities and increases in arachidonic acid, thereby increasing systemic inflammation and most likely contributing to neurocognitive inflammation.[12]

Immunoregulation and neuroendrocrine pathways are influenced by the communication between the gut microbiome and brain via cytokine production, activation of inflammatory pathways and optimal immune responses, in addition to neurotransmitter synthesis and availability.[13] A randomized, placebo-controlled, double-blind study conducted by Kazemi *et. al.,* evaluated an intervention of probiotics in patients diagnosed with MDD and found that BDI scores were significantly decreased by the end of the study in the probiotic group compared to placebo.[22] In addition, there was a significant decrease in the kynurenine/tryptophan ratio, thus increasing the availability of tryptophan for the synthesis of serotonin and mitigating possible deficiencies that contribute to the development of depression and anxiety.[22] Many studies indicate the probiotics *B. longum, L. acidophilus, L. casei, Clostridium butyricum, L. rhamnosus, L. bulgarigus, B. breve,* and *L. helveticus,* relieves depressive symptoms, most likely by regulating overactive immune responses and decreasing inflammation levels via the gut-brain axis.[13]

**Conclusion**

The growing body of scientific research elucidating the clinical effectiveness and psychopharmacology of herbal medicine and nutraceuticals for the treatment of depression and anxiety disorder is promising and hopeful. Understanding the biochemical pathways that impact neurotransmitter metabolism and neurocognitive function is the basis of an integrative approach that addresses the connection between physical health and emotional wellbeing.

Considering that nutraceutical and herbal medicine is cheaper, safer, but can be just as effective as conventional pharmaceutical interventions, it is necessary to consider including these natural treatments in an integrative approach to patients with depression and anxiety.

It is important to note that in any case of mental illness or disease, we must always treat the whole person. In conjunction with natural treatments; ensuring the wellness of mind and spirit is paramount in successful outcomes.

**References**


1. Ménard C, Hodes GE, Russo SJ. Pathogenesis of depression: Insights from human and rodent studies. *Neuroscience*. 2016;321:138-162.
2. Shafiee M, et al. Saffron in the treatment of depression, anxiety and other mental disorders: Current evidence and potential mechanisms of action. *J Affect Disord*. 2018;227:330-337.
3. Greenberg PE, et al. The economic burden of adults with major depressive disorder in the United States (2005 and 2010). *J Clin Psychiatry*. 2015;76(2):155-162.
4. Yeung KS, et al. Herbal medicine for depression and anxiety: A systematic review with assessment of potential psycho-oncologic relevance. *Phytother Res*. 2018;32(5):865-891.
5. López V, et al. Exploring Pharmacological Mechanisms of Lavender (*Lavandula angustifolia*) Essential Oil on Central Nervous System Targets. *Front Pharmacol*. 2017;8:280. Published 2017 May 19.
6. Sarris J, et al. Herbal medicine for depression, anxiety and insomnia: a review of psychopharmacology and clinical evidence. *Eur Neuropsychopharmacol*. 2011;21(12):841-860.
7. Lee J, et al. Adaptive cellular stress pathways as therapeutic targets of dietary phytochemicals: focus on the nervous system. *Pharmacol Rev*. 2014;66(3):815-868.
8. Soliman GA. Dietary Fiber, Atherosclerosis, and Cardiovascular Disease. *Nutrients*. 2019;11(5):1155. Published 2019 May 23.
9. Kasper S, et al. Silexan, an orally administered Lavandula oil preparation, is effective in the treatment of 'subsyndromal' anxiety disorder: a randomized, double-blind, placebo controlled trial. *Int Clin Psychopharmacol*. 2010;25(5):277-287.
10. Woelk H, Schläfke S. A multi-center, double-blind, randomised study of the Lavender oil preparation Silexan in comparison to Lorazepam for generalized anxiety disorder. *Phytomedicine*. 2010;17(2):94-99.
11. Chandrasekhar K, Kapoor J, Anishetty S. A prospective, randomized double-blind, placebo-controlled study of safety and efficacy of a high-concentration full-spectrum extract of ashwagandha root in reducing stress and anxiety in adults. *Indian J Psychol Med*. 2012;34(3):255-262.
12. Ross BM. Omega-3 polyunsaturated fatty acids and anxiety disorders. *Prostaglandins Leukot Essent Fatty Acids*. 2009;81(5-6):309-312.
13. Smith KS, et al. Psychobiotics as treatment for anxiety, depression, and related symptoms: a systematic review [published online ahead of print, 2019 Dec 20]. *Nutr Neurosci*. 2019;1-15.
14. Calabrese C, et al. Effects of a standardized Bacopa monnieri extract on cognitive performance, anxiety, and depression in the elderly: a randomized, double-blind, placebo-controlled trial. *J Altern Complement Med*. 2008;14(6):707-713.
15. Downey LA, et al. An acute, double-blind, placebo-controlled crossover study of 320 mg and 640 mg doses of a special extract of Bacopa monnieri (CDRI 08) on sustained cognitive performance. *Phytother Res*. 2013;27(9):1407-1413.
16. Tohda C, et al. Combined Treatment with Two Water Extracts of *Eleutherococcus senticosus* Leaf and Rhizome of *Drynaria fortunei* Enhances Cognitive Function: A Placebo-Controlled, Randomized, Double-Blind Study in Healthy Adults. *Nutrients*. 2020;12(2):303. Published 2020 Jan 23.
17. Lim DW, et al. Chlorogenic Acid from Hawthorn Berry (Crataegus pinnatifida Fruit) Prevents Stress Hormone-Induced Depressive Behavior, through Monoamine Oxidase B-Reactive Oxygen Species Signaling in Hippocampal Astrocytes of Mice [published online ahead of print, 2018 Jun 12]. *Mol Nutr Food Res*. 2018;e1800029.
18. Ghasemzadeh Rahbardar M, Hosseinzadeh H. Therapeutic effects of rosemary (*Rosmarinus officinalis* L.) and its active constituents on nervous system disorders. *Iran J Basic Med Sci*. 2020;23(9):1100-1112.
19. Nematolahi P, et al. Effects of Rosmarinus officinalis L. on memory performance, anxiety, depression, and sleep quality in university students: A randomized clinical trial. *Complement Ther Clin Pract*. 2018;30:24-28.
20. Yamauchi Y, et al. Memory Enhancement by Oral Administration of Extract of *Eleutherococcus senticosus* Leaves and Active Compounds Transferred in the Brain. *Nutrients*. 2019;11(5):1142. Published 2019 May 22.
21. Savage K, Firth J, Stough C, Sarris J. GABA-modulating phytomedicines for anxiety: A systematic review of preclinical and clinical evidence. *Phytother Res*. 2018;32(1):3-18.
22. Kazemi A, et al. Effect of probiotic and prebiotic vs placebo on psychological outcomes in patients with major depressive disorder: A randomized clinical trial. *Clin Nutr*. 2019;38(2):522-528.


◆


Christian del Rosario is a fourth-year Doctoral Candidate for Naturopathic Medicine at Bastyr University California. He achieved his undergraduate from the University of California-Irvine having studied biological sciences as a pre-med student. While obtaining his undergrad, Christian worked in several settings and start-ups that allowed him to start his career in healthcare, beginning as an intern at Hoag Memorial Hospital and employed by BHH Respite Care as a therapist for kids with autism spectrum disorder.

His interest in science, the human body, and its inherent self-healing process led him to explore the various fields within medicine and ultimately led him to study naturopathic medicine. A defining experience was training alongside physicians and witnessing the breakthrough power of regenerative medicine and anti-aging aesthetics in which he has obtained several certifications. Christian also has extensive clinical training in regenerative medicine, functional medicine, and anti-aging treatments through a preceptorship with the renowned Dr Rahi, MD, in Beverly Hills. To further his studies, after taking the medical board exams, Christian intends to obtain a fellowship in anti-aging and stem cell therapy.



Baljit Khamba, ND, MPH, is a graduate of the Canadian College of Naturopathic Medicine and is currently completing her Doctorate in Education at the University of Western Ontario. She is a board member of the American Association of Naturopathic Physicians (AANP) and an alumni of both York University (H.BSc) and Lakehead University (MPH).

Dr. Khamba is Chair of Clinical Sciences, clinical supervisor, and an assistant professor at Bastyr University. She has been successfully instructing and mentoring students for the past five years in a variety of different programs, such as naturopathic medicine, Master of Counselling Psychology, and Doctor of Acupuncture and Oriental Medicine. Integrative medicine, clinical research, and motivational-based teaching are factors that Dr. Khamba holds in high regard. She has published in a number of journals, newsletters and disseminated research findings in conferences globally.

Dr. Khamba has practiced in clinics in Toronto, Edmonton and San Diego. She approaches care using a holistic perspective and integrates the philosophies of naturopathic medicine to empower patients through their health goals. Dr. Khamba is also an active member of the community, speaking at conferences, and various media often discussing her own journey through breast cancer and her use of integrative medicine.

# Mind-Body Applications of Essential Oils: A Case Study of Anxiety

by Sarah A. LoBisco, ND, IFMCP

**Essential Oils for Enhanced Treatment Outcomes**

Essential oils are a passion of mine… and of the mind. Plentiful animal and in-vitro studies, along with many accumulating human trials have shown their ability to *simultaneously* modulate emotions, brain wave patterns, neurochemistry, physiology, and biochemistry. This is an amazing feat not often seen with conventionally based applications.[1-25]

Due to their multifaceted properties, essential oils bridge the link between the mind and body. They are synergistic with many integrative and conventional treatments based on their influence on one's mindset, mood, and biology. Various types of studies have demonstrated essential oils' ability to modulate emotional patterns and promote mindfulness, as they enhance outcomes by removing psychological blocks to healing. [1-2,5-6,12-25] I have found them to be extremely helpful in assisting clients to break through the fears, struggles, and setbacks that often arise when moving forward to create a new reality as a healed individual.

In previous articles in this journal, I have reviewed the cellular mechanistic pathways, emotional and cognitive processing effects, and functional applications of essential oils.[1-2] These intricate particulars may have left the reader appreciative of essential oils' prowess yet desiring more concise examples on how they could implement them into their clinical practice.

For this reason, in this article, I will be moving away from emphasizing the theoretical. Rather, I wish to demonstrate how I incorporate essential oils into my practice through a case study. I will provide this as an example on how they can be incorporated into any holistic and integrative treatment approach.

I have aimed to exclude extraneous particulars of other interventions and details on lab work for the case. This was intentional to focus more succinctly on essential oils as an imperative intervention.

As with any functional or naturopathic doctor, it is rare to have a sole modality for any complex issue. This holds true for essential oils. Therefore, before I discuss the case, I will review a few important and practical considerations any practitioner or consumer should be aware of when implementing essential oils with other healing protocols.

**Considerations for Clinical Use of Essential Oils**

*Address the Root Cause.* As I mentioned in my previous article, "Exploring the Complexities and Caveats of Safe Internal Use of Essential Oils for Pain: Highlighting Intestinal Discomfort, Part 2," "[b]efore selecting a therapeutic modality of any kind, it is important to address the underlying cause and use a naturopathic and functional medicine approach to address it."[2]

Understanding one's full health history, pertinent labs, and assessing any triggers, mediators, and antecedents of the current health issue is imperative to fully address any disease process or symptom.

Although many consumers are using essential oils for general health, as practitioners we have the capability to boost their efficacy for our clientele. This can be accomplished by selecting an essential oil in a category that addresses the causative factors and complements our other interventions.

For example, lavender often works well for anxiety and sleep,[6,14] yet if someone hates the smell of lavender flowers it will result in a more jarring reaction than a calming one. Perhaps in this case, we have done our due diligence and understand that the underlying issue for this person's anxiety is based on an inability to focus and lack of energy, not a nervous system hyperarousal.

In this scenario, along with considering appropriate hormonal, neurotransmitter, digestive, oxidative stress, mitochondrial, and lifestyle support, we may be apt for selecting peppermint essential oil. This oil would help to alleviate the lethargy and cognitive fatigue that manifests into this type of anxiousness. [3-6]

You just can't get that preciseness from general consumer training, right!?

*Be Aware of Biochemical Individuality and Essential Oils Properties.* As noted above, aromas possess qualities that are pleasing or displeasing to an individual based on their prior associations of that

smell. Beyond this, everyone's unique biochemical and microbiome signature interacts with the hundreds of different molecules in one drop of essential oil. This means responses may vary.[1]

Based on this individual variability, some may do better with different essential oils in a category. This "matching game" makes essential oils an art and science. For example, if someone is not responding to lavender, other calming oils to consider include the following:

- Citrus oils, such as lemon, lime, and orange, which are soothing to the mind, boost mood, and enhance focus;
- Bergamot, which calms anxiety, assists with inflammation, and can abate nervous system overwhelm.[15-17]

Most essential oil companies have a basic "starter kit" that contains some of the most popular essential oils. You can use them to guide you in selecting which oils you may wish to begin working with. They also provide blends in the kit that are self-explanatory. I like "Stress Relief" and "Peaceful" blends.

I also offer a free database of essential oils that reviews the properties of single oils and contains various uses of essential oils in specific health categories. These articles offer scientific reviews, consumer tips, and applications. They can be found at https://dr-lobisco.com/essential-oils-database.

Biochemical individuality makes using essential oils empowering because patients must participate in their healthcare and be mindful on how different essential oils impact their wellbeing and symptoms.

The good news is that essential oils are very forgiving based on their synergism and overall makeup. Rather than acting solely on one chemical pathway or cascade using one isolated compound, for the most part, generalized, positive effects are often observed.[1-26] This means that even if an essential oil isn't an exact match, it will likely still produce a beneficial effect.

*You Don't Have to Start Off Being an Expert, But Be Mindful of the Basics*. Overall, essential oils are extraordinarily safe and exit the body quite quickly with no negative effects on the microbiome.[1-2] Still, there are some general safety things to be aware of.

As a rule, it is good to space essential oils away from medications, about 1-2 hours, and monitor effects as you would with any other intervention.[1-2]

If you are not comfortable with internal usage of essential oils, start with topical applications. About 2-4 drops twice a day, diluted in about 1 tsp of an organic fatty oil, is a good place to start. This is based on a 2-5% dilution rate. (Please see my previous article, "Exploring the Complexities and Caveats of Safe Internal Use of Essential Oils for Pain: Highlighting Intestinal Discomfort, Part 2," for more details on dilution ratios.) Begin with just 1-2 drops in this carrier oil base if one is new to essential oils.

When assessing for feedback, listen to your patient, believe them, and learn from them about their experience with all essential oils.

*Quality Counts*. Quality matters… a lot. Just as with supplements, you won't get as good results from essential oils labeled as "organic, pure" essential oil as you would from essential oils that are third-party tested for active constituents and have extensive quality and manufacturing standards. Unfortunately, standards and quality are not monitored with essential oils in the United States so one truly has to get to know their supplier and do their homework.

You can read more about this and see examples of tests that a manufacturer may require to ensure quality in "Exploring the Complexities and Caveats of Safe Internal Use of Essential Oils for Pain: Highlighting Intestinal Discomfort, Part 1."[2] I also have articles for quality on my database.

Now we are ready for the case study.

**Annie's Courageous Story**

One of my clients, "Annie," came to me because she was unsuccessfully "coping" with anxious feelings. She was very concerned with the repercussions. Lately she noticed she was drinking more than she wanted to and felt that the effects of her "off mood" and wine intake were impacting her, her career, and her family. Annie found that she wasn't engaging as much as she'd like to with her husband and two small children, aged five and nine years old.

Annie's sleep had been poor, with some late-night awakenings that she attributed to stress with subsequent rumination. She also noted she wasn't as focused and productive at work. She admitted that she may be using alcohol to soothe uncomfortable feelings. She was hoping to find an alternative to calm her down so she could stop reaching for wine at the end of every day.

**Even if an essential oil isn't an exact match, it will likely still produce a beneficial effect.**

Annie had been experiencing extreme anxiety for over a year now but reported that she had always had a nervous disposition since childhood. Last year she had been prescribed antidepressants and benzodiazepines by her primary care doctor. At that time, she felt her anxiety was at a point that it was taking over her life. The antidepressant, Effexor, caused her to be more "jittery" and the benzodiazepine made her feel "out of it." She was also nervous of their side effects and feared getting dependent on them. Annie was aware she could not mix them with alcohol.

Annie's open-minded physician suggested that Annie try some "natural, herbal support," because they weren't getting anywhere. Annie remained determined to find safe relief and sought me out after she spoke with a friend who was a current client.

Annie and I had an instant connection. She courageously opened up to me about her past history, which contained some trauma. We discussed how her exposure to her mom's excess prenatal stress hormones, in combination with her genetics and turbulent childhood, set her up to be more vulnerable to the stressors of life. I explained to her how some of her symptoms were likely linked to prenatal and adverse childhood

➤

➤

events. These contributed to her more sensitive and "nervous predisposition" and they may put her at greater risk for physical health imbalances if not addressed.[27]

I told Annie I didn't think we would get very far if we couldn't calm down her brain and allow for her nervous system and adrenal glands to relax a bit from excreting excess stress hormones. I suggested several mind-body options, including yoga, breathing exercises, Emotional Freedom Technique (EFT), and HeartMath to assist her in processing and dealing with her emotions constructively.[27-28] I also suggested she seek out cognitive behavioral therapy.

Annie rarely reached out for support or took downtime for herself. I explained to her that self-care and supportive relationships were important components in healing. I also emphasized how isolation and loneliness can put her more at risk for mental and physical health ramifications.[29-30]

To effectively support Annie's mind, body, and emotions through her changes, I introduced her to essential oils.[1-25, 30-31] We discussed the instantaneous shift in her mood that could occur with a single inhalation and the additive impact of the volatile compounds in plants.[1-2]

Annie was grateful for all the information and felt hopeful.

**Essential Oils Formulations for Annie**

The following are the essential oils mixtures I suggested for Annie within two visits.

*An essential oil blend that included 1-2 drops each of ylang ylang, lavender, and orange oil.* This blend would be supportive in modulating nervous system tone and assisting with promoting a calm, cheerful mood.

Ylang ylang was used because it has been studied to enhance the parasympathetic nervous system and modulate heart rate, which is often impacted by stress and anxiety. Its aroma is thought to induce feelings of confidence and self-esteem,[20-22] which is something that I felt would benefit Annie.

Lavender is the "universal oil" for calming the nerves, assisting with anxiety, and addressing sleep issues.[1-2,5-6,14]

Orange oil is uplifting to the mood, assists with focus, and has many wellness benefits due to its high limonene content.[13-14] Note: citrus oils can be photosensitizing so only apply them to areas that are not exposed to direct sunlight.[32-33]

Application: Annie was instructed to inhale the oil blend from the cup of her hand and apply it twice a day over her heart. The oils were to be mixed in 1 tsp of organic coconut or jojoba oil.

Note: If Annie had sensitive skin, she could bypass her chest and apply the oils to the bottoms of her feet first. The bottoms of the feet are the least sensitive area of the body and a good place to start if someone has sensitive skin. Essential oils are lipid soluble and do enter circulation topically, regardless of where they are applied.[1-2]

*Joyful oil blend from my favorite manufacturer that could be diffused in her home daily for 3-8 hours.*

The Joyful blend contains many oils that fit well with Annie's symptom picture:

- Bergamot peel oil (Furocoumarin-free) to soothe anxiety and support the mind-body.[15-17]
- Ylang ylang flower for balancing the cardiovascular and nervous systems.[20-22]
- Rose Geranium flower oil for its hormonal and mood balancing properties.[19,34]
- Lemon peel oil which has a refreshing scent that invigorates.[23-24]
- Coriander seed oil which contains compounds that have been found to be calming and promote a positive mind-gut connection.[35-36]
- Tangerine peel oil, another citrus oil to promote happiness and focus.[23-24]
- Jasmine oil which has been shown to balance the brain's electrophysiology and calm stress.[12]
- Roman chamomile flower oil to enhance calmness of the mind and support overall health.[37-38]
- Palmarosa oil for general overall wellness enhancement.[39]
- Rose flower oil to inspire romance, connection, joy, and healthy hormonal output.[19,34,40-41]

Application: I suggested an atomizer diffuser, which keeps all essential oil compounds intact. The directions were to place 8-10 drops of the Joyful blend a day in the diffuser and to fill it with filtered or distilled water. It could be run on intermittent speed for 3-8 hours a day.

Finally, we also discovered that Annie's estrogen and serotonin levels needed support based on her serum blood markers and a urinary metabolite panel she had previously done with her open-minded primary care doctor.

Along with nutrition to support her borderline low iron levels and B12 (high Methylmalonic Acid, MMA), and herbals to balance her stress response (Bacopa and Eleuthero), we added another oil blend.

*The last blend contained 2 parts clary sage and geranium to 1 part neroli.* Clary sage has been shown in a small trial to modulate cortisol and serotonin.[18]

Geranium has been shown to help balance the mood and in one small trial it impacted estrogen levels favorably. [19]

Neroli is a beautiful scent that has an anxiety relieving effect. A small trial concluded it assisted with anxiety-induced crack withdrawal.[23-25]Although Annie didn't have cocaine issues, the modulating of anxiety-based substance use was important

Applications: I asked Annie to apply this blend to her ankles in her preferred organic carrier oil in the morning and in the evening. The ankles are an area that I was taught by holistic healers to have benefit for hormonal issues. I was not able to substantiate this claim, but I have followed it with good results.

**Annie's Wellness Protocol Instructions**

I told Annie to start with the essential oils, calming procedures, and sleep hygiene. After noticing any changes, in a week, she could introduce the herbals and nutritional support one at a time. This spacing allowed Annie to experience how each intervention separately had a subtle or powerful impact.

I also encouraged her to eat at regular intervals to balance her blood sugar and combine a good quality protein, fat, and carbohydrate with every meal to prevent hypoglycemic dips. Annie was not someone in which dietary restriction would serve.

Annie checked-in a few times within the next few months to discuss progress, work out stumbling blocks, and assist with implementation.

**The Six-Month Follow Up**

When Annie returned a few months later, she had nourished her body and mind and had more fully, gained awareness of the mind-body connection. When given natural alternatives to manage stress and anxiety, she had stopped drinking regularly. She was able to honor her emotions without needing to suppress them!

Today, she can have an occasional wine and stop after one. She uses her mind-body practices to help her stay centered and soothed. She will not go anywhere without applying her oils. She especially noted positive effects from the Joyful and "Happy Hormone" blend. Annie discovered a side benefit as well. She noticed straight away that diffusing that combination of oils in the Joyful blend not only uplifted her, but also her whole household.

She is now living a happier, calmer life. This is reward enough, but there was a bonus…she gave me flowers from the garden she started!

**Concluding Remarks**

Prescribing an antidepressant or treating Annie's drinking as an "addiction" would have missed the mark in this case. Here is an example of someone who lacked self-care resources and was using a substance to sooth hypersensitivity to stress hormones and an endocrine imbalance.

When given a mood balancing medication that also increased norepinephrine, it made symptoms worse.

In this case, we looked at the root cause, addressed the imbalances, and gave her new tools to help her navigate her emotions in a more constructive way. Essential oils were key factors to this transformation that assisted with her psychology as we modulated her physiology.

In a few months, Annie and I will likely adjust her essential oils formulations, as I like to change oils as one's biological and emotional health shifts. In the meantime, Annie and I are thrilled with how well she's doing.

This is just one example of why I feel essential oils are my "secret sauce" to better patient outcomes and happier clients.

◆

**References are available online at www.townsendletter.com.**

Sarah Lobisco, ND, IFMCP is a graduate of the University of Bridgeport's College of Naturopathic Medicine (UBCNM). She is licensed in Vermont as a naturopathic doctor and has earned her certification in functional medicine through the Institute of Functional Medicine (IFM). Dr. LoBisco also holds a Bachelor of Psychology from State University of New York at Geneseo and an Applied Kinesiology certification.

She is a speaker on integrative health, has several publications, and does independent contracting for companies regarding supplements, nutraceuticals, essential oils, and medical foods. Dr. LoBisco currently incorporates her training as a naturopathic doctor and functional medicine practitioner through writing, teaching, private practice, and through her independent contracting work. She maintains her private wellness consultation practice through virtual consultations. Dr. LoBisco also enjoys continuing to educate and empower her readers through her blogs and social media. Her recent blog can be found at dr-lobisco.com.

This article is reprinted from *NeuroRegulation*: Peper E, Harvey R, Cuellar Y, Membrila C. (2022). Reduce anxiety. *NeuroRegulation*, *9*(2), 91–97. https://doi.org/10.15540/nr.9.2.91 https://www.neuroregulation.org/article/view/22815/14575

# Reduce Anxiety[1]

## by Erik Peper, PhD, Richard Harvey, PhD, Yanneth Cuellar, and Catalina Membrila

### San Francisco State University

**Abstract**

More than half of college students self-report some kind of anxiety and depression. This study reports how a university course that incorporated structured self-experience practices may reduce symptoms of self-reported anxiety associated with college stress and strain. 98 college junior and senior students were enrolled in a Holistic Health class that focused on 'whole-person' Holistic Health curriculum and included the exploration of psychobiology of stress, the role of posture, and the psychophysiology of respiration. The class included daily self-practices of awareness of stress, muscle relaxation, diaphragmatic breathing and posture awareness. The students were instructed to apply these techniques whenever they become aware of, or experienced, sensations of stress or dysfunctional breathing during the day. After five weeks of practice, the students self-reported a 73% reduction in anxiety, 68% reduction in stress, 27% reduction in neck and shoulder discomfort, 26% reduction in abdominal discomfort; 18% of abdominal discomfort and 16% reduction in menstrual cramps. We recommend that schools incorporated a 'whole-persons' self-care approach within their curriculum to teach students skills to prevent and reduce anxiety and stress and therapists teach these skills before beginning bio/neurofeedback.

1. Correspondence should be addressed to: Erik Peper, PhD, Institute for Holistic Healing Studies/Department of Recreation, Parks, Tourism and Holistic Health, San Francisco State University, 1600 Holloway Avenue, San Francisco, CA 94132
COVID-19 mailing address: 2236 Derby Street, Berkeley, CA 94705
Email: epeper@sfsu.edu
web: www.biofeedbackhealth.org
blog: www.peperperspective.com

More than half of college students now self-report some kind of anxiety (Coakley et al., 2021). Before the COVID-19 pandemic nearly one-third of students had or developed moderate or severe anxiety or depression while being at college (Adams et al., 2021). The pandemic accelerated a trend of increasing anxiety that was already occurring. "*The prevalence of major depressive disorder among graduate and professional students is two times higher in 2020 compared to 2019 and the prevalence of generalized anxiety disorder is 1.5 times higher than in 2019*" as reported by Chirikov et al (2020) from the UC Berkeley SERU Consortium Reports.

In an anonymous survey during the first day of a spring semester class, 59% of the students reported feeling tired, dreading their day, being distracted, lacking mental clarity and had difficulty concentrating. Unsurprisingly, these are some of the same symptoms corresponding with the prevalence of anxiety and depression, other types of stress and strain observed in college students as reported by Beiter et al. (2015).

The increases in symptoms of stress and strain, such as in anxiety, has both short- and long-term performance and health consequences. Severe anxiety reduces cognitive functioning and is a risk factor for early dementia many years after students leave college (Bierman et al., 2005; Richmond-Rakerd et al, 2022). Chronic severe anxiety also increases the risk of many kinds of co-morbid health issues, listed here alphabetically, such as asthma, arthritis, back/neck problems, chronic headaches, diabetes, heart disease, hypertension, pain, obesity, and ulcers (Bhattacharya et al., 2014; Kang et al, 2017).

The most used medical treatment approaches for anxiety are various

**Table 1. Typical Uses for Sedating Medications**

| Trade Name | Duration | Generic Name | Typical Use depending on dose |
|---|---|---|---|
| Ativan | longer | Lorazepam | Anxiety, Seizures, Anesthesia |
| Centrax | longer | Prazepam | Anxiety, Insomnia |
| Dalamane | shorter | Flurazepam | Insomnia |
| Doral | longer | Quazepam | Insomnia, Anxiety |
| Halcion | shorter | Triazolam | Insomnia |
| Klonopin | longer | Clonazepam | Seizures, Panic |
| Librium | longer | Chlordiasepoxide | Anxiety, Alcohol Withdrawal |
| ProSom | shorter | Estazolam | Insomnia |
| Restoril | shorter | Temazepam | Insomnia |
| Serex | longer | Oxazepam | Anxiety, Insomnia |
| Tranxene | longer | Clorazepate | Anxiety, Insomnia, Seizures |
| Valium | longer | Diazepam | Anxiety, Seizures, Anexthesia, Restless Leg |
| Versed | shorter | Midazolam | Anesthesia |
| Xanax | longer | Alprazolam | Anxiety |

pharmaceutical drugs (Kaczkurkin & Foa, 2015). These anti-anxiety drugs are sedative medications (e.g. benzodiazepines; Bushnell et al., 2017). Unfortunately, side effects of sedating medications like benzodiazepines include drowsiness, irritability, dizziness, memory and attention problems, and physical dependence (Crane, 2013; Peppin et al., 2020; Shader & Greenblatt, 1993; Shri, 2012). Note that the most typical uses for sedating medications (arranged alphabetically by trade name) are for issues relating to anxiety and insomnia (Table 1).

Sedating medications (benzodiazepines) are restricted under the Controlled Substances Act under Schedule IV. The most common prescription medications for anxiety are trade named Valium, Xanax, Halcion (short acting), Ativan and Klonopin. Benzodiazepines may have toxic or fatal interactions when combined with alcohol, barbiturates, and other non-benzodiazepine/non-barbiturate sleeping pills such as Zolpidem (Ambien), Eszopicione (Lunesta), Zopicione (Somnol) and Zaleplon (Sonata).

Because benzodiazepine medications work by enhancing the effects of a neurotransmitter that slows down nervous system excitability and regulation of muscle tone (e.g. Gamma-Amino Butyric Acid or GABA; Toosi et al., 2017), it is plausible that many behavioral techniques that influence anxiety may also influence regulation of neurotransmitters that slow down regulation of muscle tone and nervous system excitability (Bandelow et al., 2015).

The most commonly used non-medical treatment approaches for anxiety are Cognitive-Behavioral Therapy (CBT) techniques based upon the assumption that anxiety is primarily a disorder in thinking which then influence the symptoms and behaviors associated with anxiety (Marker, et al., 2018; Smits, et al., 2008). In an oversimplification, the primary treatment intervention by CBT practitioners focuses on changing thoughts which co-occur with behaviors and physical measures of psychophysiology .

Prior research (cf. Peper, Harvey & Hamiel, 2019) suggests transforming 'hopeless, helpless, depressive' thoughts into 'empowering' thoughts, has enhanced efficacy when a person first shifts to an upright posture, and then begins slow diaphragmatic breathing, before finally reframing their hopeless/helpless/negative thoughts into empowering/positive thoughts. Participants were able to reframe stressful memories much more easily when in an upright posture compared to a slouched posture. Those who incorporated posture-plus-reframing reported a relevant reduction in negative thoughts and self-reported anxiety compared to those with no posture change while attempting to reframe their thoughts. Whereas the relationship between postural changes (e.g. 'power poses') and hormones associated with dominance or submission (e.g. testosterone levels) is still under investigation (Korner et al., 2020; Metzler et al., 2019), it has been proposed that 'power poses,' such as those poses practiced in various Yoga traditions, may act on the body by enhancing the inhibitory neurotransmitter GABA (Streeter, et al., 2018). As suggested by Peper, Harvey and Lin (2019b) as well as Streeter, et al., (2020), behavioral strategies that enhance attention, influence posture, as well as regulate breathing, all have a positive effect on emotions and behaviors.

Simplifying a complex relationship between mechanisms involving GABA, testosterone and anxiety behaviors can be difficult; however regulation of GABA has been associated with lowered anxiety in humans and animals (e.g. Lowery-Gionta, et al., 2018; Smith, et al., 2017; Thayer, 2006). There are strategies to reduce anxiety that focus on breathing and posture change. At the same time, there are many other factors that may contribute to the onset or maintenance of anxiety such as social isolation, economic insecurity, etc. In addition, low glucose levels can increase irritability and may lower the threshold of experiencing anxiety or impulsive behavior (Barr, Peper, & Swatzyna, 2019; Brad et al, 2014). This is often labeled as being "hangry" (MacCormack & Lindquist, 2019). Thus, changing a high glycemic diet to a low glycemic diet may reduce the somatic discomfort (which can be interpreted as anxiety) triggered by low glucose levels. In addition, people are also sitting more and more in front of screens. In this position, they tend to breathe quicker and more shallowly in their chest.

**As a result of my practice, I felt my anxiety decrease as well as it reduced my menstrual cramps. I felt very calm and felt my anxiety at ease especially on the days where my anxiety was eating me alive.** – College senior

Shallow, rapid breathing tends to reduce the partial pressure of carbon dioxide (pCO2) which has normal values between 35 to 45 mmHg. Reduced pCO2 contributes to subclinical hyperventilation which could be interpreted as a symptom of anxiety (Lum, 1981; Wilhelm et al., 2001; Du Pasquier et al, 2020). Experimentally, the body sensations that co-occur with experiences of anxiety can be evoked by instructing a person to sequentially exhale about 70% of their inhaled air, continuously for 30 seconds. After 30 seconds, participants report a significant increase in self-reported anxiety (Peper & MacHose, 1993). During the period of the COVID-19 pandemic when college students spent many hours sitting in front of a computer screen with 'shallow breathing' and having hopeless, helpless thoughts from the pandemic may all be cofactors that contribute to the self-reported increases in anxiety symptoms.

To reduce symptoms related to anxiety and discomfort in college students, McGrady and Moss (2013) suggested that self-regulation and stress management approaches could be offered as the initial treatment/teaching strategy in health care instead of first

➤

➤

offering medication. Another useful approach to reduce sympathetic arousal and optimize health in college students is breathing awareness and retraining as described by Gilbert (2003).

The purpose of this report is to describe how a university course curriculum that incorporated structured self-experience practices may reduce symptoms of self-reported anxiety associated with college stress and strain (Peper, Miceli, & Harvey, 2016). For several decades starting in 1976, up to 180 undergraduates have enrolled in a three-unit Holistic Health class on stress management and self-healing (Klein & Peper, 2013). Students in the class are assigned self-healing projects using techniques that focus on awareness of stress, 'dynamic regeneration,' stress reduction imagery for healing, and other behavioral change techniques adapted from the book, *Make Health Happen* (Peper, Gibney & Holt, 2002). At the end of the semester, 4 out of 5 of students (82%) self-reported that they were 'mostly successful' in achieving their self-healing goals. Students have consistently reported achieving positive benefits such as increasing physical fitness; improving diets; and reducing symptoms of anxiety, depression, and pain; eliminating eczema; and, even reducing substance abuse (Peper et al., 2003; Bier et al., 2005; Peper et al., 2014). This survey explores the change in self-reported anxiety, stress and other somatic symptoms after practicing 'whole-person' Holistic Health stress management program that included the exploration of psychobiology of stress, the role of posture, psychophysiology of respiration, and daily self-practices.

**When I changed back to slower diaphragmatic breathing, I was more aware of the negative emotions and I was able to reduce the stress and anxiety I was feeling with the deep diaphragmatic breath.** – College junior

**Method**

*Participants*: 98 college junior and senior students enrolled in a holistic health class for the experimental group. At the same time 12 students in another class served as controls. As a report about an effort to improve the quality of a classroom activity, this report of findings was exempted from Institutional Review Board oversight.

*Procedure:* Students were enrolled in a Holistic Health class that focused on the psychobiology of stress, the role of posture, and the psychophysiology of respiration. For five weeks, the class included didactic presentations along with guidance for daily self-practice in paced-breathing and posture awareness while sitting or using a computer.

*Didactic lecture content.* Didactic class presentations on the psychophysiology of stress, how mind emotions impact body, how body affect mind and emotions, and how posture impacts health (Sapolsky, 2004). It included discussions about the physiology of breathing and how a constricted waist tends to cause the person to breathe more in their chest (the cause of neurasthemia) and how the fight/flight response may trigger chest breathing, breath holding and/or shallow breathing.

The lectures include short experiential practices of the body-mind connections such as imagining a lemon to increase salivation, the effect of slouched versus erect posture on evoking positive/empowering or hopeless/helpless/powerless/defeated thoughts, and the effect of sequential 70% exhalation for 30 seconds on increasing anxiety (Peper, Gibney, & Holt, 2002; Tsai, Peper, & Lin, 2016; Peper, Lin, Harvey, & Perez, 2017; Peper & MacHose, 1993).

*Daily self-practice.* Students were assigned daily self-practices focusing on skill mastery (e.g gradually building to 20 minutes of practices daily) and implementing the skills during their daily life. Students recorded their experiences after their practice. At the end of the week, they reviewed their own log and summarized their observations (benefits, difficulties), then met in small groups to discuss their experiences and extract common themes. These daily practices included the following:

**Figure 1. Self-report of decrease in symptoms after practice integrated stress management and diaphragmatic breathing**

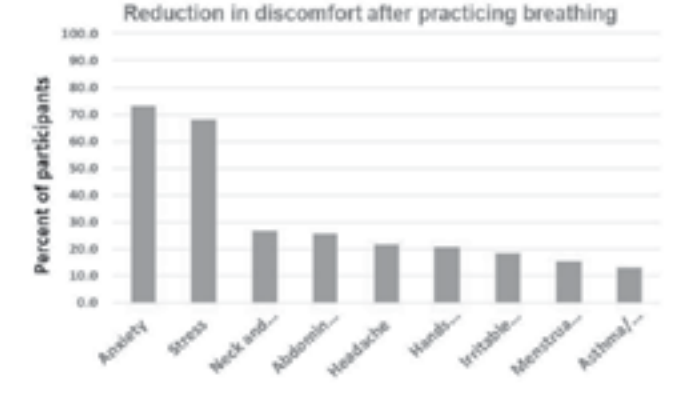
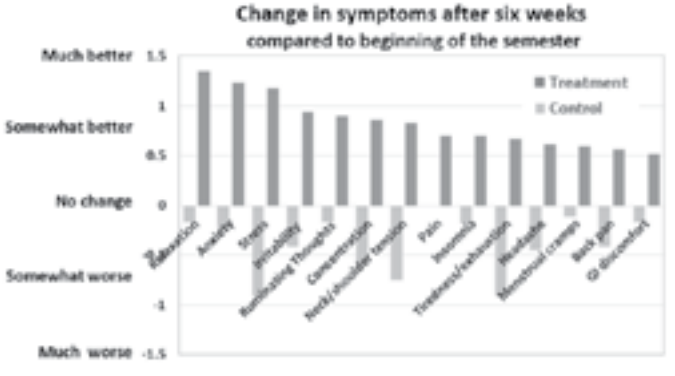



**Figure 2. Self-report of how symptoms changed when looking back to the beginning of the semester for the treatment and control group.**



- Awareness of stress by monitoring their reactions to daily stressors.
- Practicing dynamic relaxation for 20 minutes a day and then observe and inhibit bracing pattern during the day.
- Changing 'energy drain and energy gains.' Students observed what events reduced or increased their subjective energy and were instructed to implemented changes in their behavior to decrease events that reduced their energy and increased behaviors that increase their energy.
- Creating a 'memory of wholeness' which consisted of evoking a past memory when they felt healthy and well. They would relax and then recall and evoke this memory.
- Practicing effortless breathing. Students practiced slow diaphragmatic abdominal breathing at approximately 6 breaths-per-minute pace, for 10-20 minutes per day. Even more importantly, each time they become aware during the day of dysfunctional breathing pattern (e.g., breath-holding, shallow chest breathing or, gasping), they would change to an erect power posture and shift to slower diaphragmatic breathing.

After five weeks students filled out an anonymous survey in which they rated the change in anxiety and other symptoms as compared to the beginning of the semester. The control group filled out the same questionnaire.

*Result.* It will come as no surprise that the majority of students reported improvement. 73% reported a reduction in anxiety and 68% reported a reduction in stress. In addition, they reported decreases in their symptoms of stress, neck and shoulder, abdominal discomfort, headaches, irritable bowel/acid reflux, menstrual cramps as shown in Figure 1.

The control group did not report a decrease in symptoms instead they reported a slight increase in anxiety, stress and somatic symptoms as shown in Figure 2. In addition, although not assessed on the symptom questionnaire, most students anecdotally reported an increase in mental clarity and concentration that improved their study habits. As one student noted: "Now that I breathe properly, I have less mental fog and feel less overwhelmed and more relaxed. My shoulders don't feel tense, and my muscles are not as achy at the end of the day."

**Discussion**

Almost all students were surprised how beneficial these easily learned practices were to reduce their symptoms of anxiety along with other symptoms of depression, stresses and strains while other students not in this class informally reported an increase in anxiety and somatic symptoms. Arguably the most important skill students learned was to interrupt their individual stress responses throughout the day, including shifting to diaphragmatic breathing. The more they practiced during the day, the more benefits they reported in reducing their symptoms. In summary, the major factors that contributed to the students' improvement were:

- Learning through self-mastery as an education approach versus clinical treatment.
- Generalizing the skill into daily life and activities. Practicing the skill during the day in which, the cue of a stress reaction triggered the person to shift to an upright position and breathe slowly which would reduce their sympathetic activation.
- Interrupting escalating sympathetic arousal. Responding with an intervention reduced the sense of being overwhelmed and unable to cope by the participant performing an active task.
- Redirecting attention and thoughts away from the anxiety trigger to a positive task of diaphragmatic breathing.
- Increasing heart rate variability through slower breathing which enhanced sympathetic parasympathetic balance.
- Reducing subclinical hyperventilation by breathing slower and thereby increasing pC02.
- Increasing social support by meeting in small groups. The class discussion group normalized the anxiety experiences.
- Providing hope. The class lectures and assigned readings and videos provide hope since students read case reports and watched videos of other students who had had reversed their chronic disorders such as irritable bowel disease, acid reflux, psoriasis with behavioral interventions.

## Reduce Anxiety

Although the study lacked a systematic control group and is only based upon self-report (e.g. correlated), this approach represents an economical non-pharmaceutical approach to reduce anxiety. The stress management strategies referred to may not resolve anxiety for everyone. By practicing and implementing these skills the moment the student comes aware of, or experiences symptoms of stress (sloughing shallow breathing or breath holding, neck and shoulder tension, etc.), they reduce the development of symptoms and enhance health. Nevertheless, we recommend that schools implement this non-pharmacological educational approach into the classroom to reduce anxiety and stress related disorders and therapists teach this approach first before beginning bio/neurofeedback.

To quote another student "I noticed that breathing helped tremendously with my anxiety. I was able to feel okay without having that dreadful feeling stay in my chest and I felt it escape in my exhales. I also felt that I was able to breathe deeper and relax better altogether. It was therapeutic, I felt more present, aware, and energized."

**Author Disclosure**
Authors have no grants, financial interests, or conflicts to disclose

◆

**References are available online at www.townsendletter.com.**

# Helping the Distressed Clinician by Identifying and Treating Burnout


## by Jonathan E. Prousky, ND, MSc, MA, RP

### Professor, Chief Naturopathic Medical Officer
### Canadian College of Naturopathic Medicine



**Abstract**

The focus of this article is on clinician burnout, which is characterized by emotional exhaustion, depersonalization, and diminished personal accomplishment. One goal is to provide a comprehensive but brief overview on burnout, including its prevalence among physicians in the United States and Canada, the ways it was impacted by the COVID-19 pandemic, relevant neurobiological and neurochemical associations, its relationship to depression, the known drivers, and diagnosis. Another goal is to review specific evidence-based interventions that have the potential to attenuate chronic stress and burnout, and which may help to prevent burnout altogether. The timing is urgent for such interventions with the goal of enhancing resilience, so clinicians recover from burnout and do not become repeat burnout customers.


**Introduction**

Neil Young is credited with saying in one of his brilliant songs, "It's better to burn out than to fade away." Though this may have some value and cachet in the world of rock and roll, no clinician would tell anyone that their burnout was preferable over a contented and productive working experience. Burnout is a brutal psychological syndrome consisting of exhaustion, cynicism, and workplace inefficiency.[1] A state of exhaustion is characterized by feeling "overextended and depleted of one's emotional and physical resources."[1] Cynicism refers to a "negative, callous, or excessively detached response to various aspects of the job."[1] Inefficiency refers to feeling incompetent at work with an associated "lack of achievement."[1] An updated definition of burnout has since renamed the three aforementioned key dimensions to that of emotional exhaustion, depersonalization, and diminished personal accomplishment.[2]

Burnout is clinically significant due to all sorts of cascading effects that result from this uncomfortable, detached, and exhausted way of existing within one's place of work. Clinicians care deeply about their work, usually involving some combination of training and/or mentoring students and fellow professionals, and most importantly, caring for patients. When burnout makes its presence known, it becomes nearly impossible to shoulder the burdens of work and patient needs amidst the unending demands of trying to stay afloat while the ship (i.e., the burned-out clinician) is literally sinking in despair, or has unfortunately sunk.

This paper reviews the prevalence, neurobiology, neurochemistry, drivers (i.e., causes and consequences), diagnosis, and management of burnout as it relates to clinicians. Most of the burnout research cited in this paper comes from studies on physicians, and/or is related to the work that physicians do.

**Prevalence**

Evidence suggests that burnout is a unique clinician experience resulting from multiple influences (i.e., both positive and negative) that emanate from the workplace environment.[3] The highest rates of physician burnout in the United States (US) happen among emergency medicine physicians, with the lowest rates among physicians working in preventive medicine/occupational medicine.[3] The overall mean rate of burnout (i.e., as assessed by having 1 symptom of burnout, such as scoring high in emotional exhaustion or scoring high in depersonalization as per the 2-item Maslach Burnout Inventory/MBI) among US physicians increased from 45.5% in 2011 to 54.4% in 2014.[4] During this same timeframe, physician satisfaction from work-life balance (WLB) declined from 48.5% in 2011 to 40.9% in 2014.[4] By contrast, when burnout was assessed among employed nonphysicians in the US, the overall mean rate of burnout was 28.6% in 2011 and 28.4% in 2014.[4] WLB among employed nonphysicians in the US increased from 55.1% in 2011 to 61.3% in 2014.[4]

More recent data has shown that the mean rate of burnout among physicians (i.e., as assessed by having 1 symptom of burnout as noted earlier) decreased to 38.2% in 2020 compared to 43.9% in 2017, 54.4% in 2014, and 45.5% in 2011.[5] This same 2020 dataset showed that satisfaction from work-life integration (WLI), a reengineered term to describe WLB, was 46.1% among physicians.[5] Based on these results, the mean burnout rate among US physicians compared to the general population is markedly greater, while WLI (or WLB) is markedly lower.

In Canada, the 2018 Canadian Medical Association National Physician Health Survey aggregated data from different residency and medical specialties and different settings (e.g., hospital, private office/clinic, academic, and administrative/corporate office).[6] The same burnout assessment tool that was used to generate the US data – i.e., the

2-item MBI – was also used to assess burnout among Canadian physicians. Unlike the US data, the Canadian data did not compare physician burnout and WLI to that of employed nonphysicians in Canada. In aggregate, the overall physician burnout rate was 30%. The report showed that some 32% of females and 27% of males met criteria for burnout. Some 38% of residents met criteria for burnout compared to 29% of physicians. The highest rates of burnout were among physicians in family medicine/general practice (32%) with the lowest rates among physicians holding administrative positions (19%). Similarly, physicians working in administrative/corporate offices had the lowest rates of burnout (25%) whereas physicians working in their own private offices/clinics had the highest rates of burnout (31%).

How did the global COVID-19 pandemic influence burnout? The US data showed that in the first 6-9 months of the pandemic, the mean rate of physician burnout decreased and WLI increased compared to prior years.[5] However, physicians working in specific areas in the US that were considered geographic hot spots early in the pandemic experienced acute stress, as documented in several studies (see p.502 for the specific studies).[5] The drivers of increased occupational stress during this time period included high case volumes, working outside of one's specialty, providing care without adequate personal protective equipment, and managing patients before effective COVID-19 treatments had been established.[5] In fact, symptoms of burnout – namely, emotional exhaustion and depersonalization – among US physicians working in medical specialties directly impacted by the pandemic "did not improve…even as these measures of burnout improved for physicians as a whole."[5] In fact, the rates of burnout during the first year of the pandemic increased over time among 4 of 5 US frontline medical specialties, with the most significant increases among hospitalists and primary care respondents.[7]

In Canada, preliminary data from a survey by the Canadian Medical Association conducted in November 2021 showed that "more than half of physicians and medical learners (53%) have experienced high levels of burnout."[8] This same report noted that almost half of Canadian physicians (46%) have considered reducing their workload in the next two years, which would have considerable impacts upon the Canadian healthcare system already burdened by access to care issues. The same survey found that 59% of physicians indicated that their mental health worsened since the pandemic began due to increased workload, lack of WLI, abrupt policy/process changes, as well as other issues. The survey also noted that some 47% of physicians reported reduced levels of social wellbeing. In the Province of Ontario, a survey of physicians identified that 29% reported high levels of burnout prior to the pandemic.[9] By March 2021, the same survey noted that the rate of burnout increased to 34.6% among Ontario physicians.

For some physicians, the pandemic increased a sense of meaning and purpose in their work, which had attenuating effects on burnout during the early stages of the pandemic.[5] For other physicians, however, the pandemic not only caused burnout but also moral injury.[10] Moral injury happens when events directly infringe upon physicians' moral convictions, such as what happens when managing medical decisions in the unfamiliar territory of a pandemic. Physicians had to tell loved ones that they couldn't attend the bedside of their dying relatives or attend the births of new relatives. Physicians had to endure considerable stress by determining who would receive life-saving treatments and, for non-COVID patients, having life threatening conditions in whom care would be delayed. These types of moral injuries added considerable psychological burdens to physicians who never could have imagined facing these types of restrictions and complications in the delivery of the medical care they provide.

**Neurobiology**

There seems to be a strong association between chronic stress and burnout. Chronic stress broadly refers to "ongoing demands that threaten to exceed the resources of an individual in areas of life such as family, marriage, parenting, work, health, housing, and finances."[11] Chronic stress invokes a "pathological state that is caused by prolonged activation of the normal acute physiological stress response, which can wreak havoc on immune, metabolic, and cardiovascular systems."[12] Burnout invokes a similar pathological state characterized by dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and immune function.[13] Burnout appears to be a consequence of chronic stress that is particular to one's job and work environment. It has been described as a "cumulative stress reaction to ongoing occupational stressors."[1]

**Allostasis refers to biological adjustments that allow an individual to adapt to particular challenges.**

When experiencing burnout, a person's allostatic systems would be persistently activated. Allostasis, coined by Sterling and Eyer,[14] refers to biological adjustments that allow an individual to adapt to particular challenges that happen over the lifespan. Adapting to such challenges demands the synchronous though non-linear activation of many different physiological processes, such as neural, neuroendocrine, and neuroendocrine-immune mechanisms.[15] Allostasis begins in the brain and happens or is instigated by how an individual perceives and interprets any given situation. Allostasis is about adaptation, but the physiological adaptations may not ensure survival because they can become deleterious over time and cause irreversible damage. Thus, each person's allostatic responses are unique and depend on (1) "how the individual perceives and interprets the situation" and (2) "the condition of the body itself."[15]

Allostatic load (AL) represents a state when the aforementioned physiological adaptations become deleterious, as happens from repeated allostatic responses during stressful situations.[16] This happens when an allostatic system fails to habituate to the recurrence of the same stressor, fails to shut off following overwhelming stress, and/or whose response is deficient resulting in heightened activation of other, normal counter-regulatory systems.[15,17] If, for example, an individual perceives something as chronically stressful and has not been able to habituate to it (i.e., they lack adequate proactive planning skills and

➤

➤

psychological buffers), then they won't be able to shut-off their allostatic response, and this would likely accelerate brain aging and organ pathology. Additionally, if the condition of the body itself is further challenged by poor physical health and an unstable physiology, the individual would be more vulnerable to AL, which sets in motion problems such as hypertension, obesity, diabetes, atherosclerosis, inflammation, exaggerated autoimmune responses, neuronal atrophy and even neuronal death.[15] Allostatic overload (AO) is accordingly an extension of AL, and describes the result of allostatic responses that lead to irreversible damage to body organ systems (i.e., pathology), and/or mental disorders (i.e., diagnosable mental illness). Burnout ought to be considered a specific and persistent work-related state associated with AL and AO, with accompanying psychological distress signals of emotional exhaustion, depersonalization, and diminished personal accomplishment.

Neurobiologically, when an individual is faced with uncertainty arising from chronic stress and has not been able to habituate to a persistent stressor (or a persistent set of chronic stresses), specific areas of the prefrontal cortex (PFC) activate the anterior cingulate cortex (ACC).[18] The ACC "assesses the degree of uncertainty about whether future outcomes are uncertain."[18] The PFC "governs high-order reasoning, social cognition, and complex decision-making, including the integration, ceptualization, and critical evaluation of information."[19] In situations when the degree of uncertainty about future events cannot be reconciled, the PFC activation of the ACC triggers the amygdala – to initiate a stress response – followed by the release of norepinephrine.[18] This leads to a hypervigilant state, and the simultaneous activation of the sympathetic nervous system, leading to increased glucose for energy utilization due to the high metabolic demands of the brain. There is also activation of the HPA axis leading to increased cortisol output, which plays a vital role in synaptic plasticity and learning after stress.[18] The released cortisol passes through the blood-brain-barrier and binds to glucocorticoid receptors in the amygdala, hippocampus, and PFC.[18]

Activation of these neurobiological processes leads to feelings of threat and loss of control, concomitant with damaging alterations to brain architecture within the amygdala, hippocampus, and PFC. Specifically, the neuronal dendrites housed within the hippocampus and PFC shrink, become shorter and less branched, and these changes result in diminished synaptic output.[17] These changes further compromise an individual's "capabilities for nuanced cognitive function, memory and self-regulation."[17] The same type of chronic stress causes an expansion of dendrites and increased synaptic input to an area of the amygdala known as the basolateral amygdala, which results in heightened anxiety, aggressiveness, and vigilance.[17] These changes result in more bottom-up control via the ACC-amygdala complex, and compromised emotional regulation since the PFC is unable to exert effective top-down control.[18]

The neurobiology of burnout appears to be similar to the neurobiology of chronic stress. In an article on physician distress and burnout, Amsten and Shanafelt review various neurobiological implications.[19] They described how significant fatigue (e.g., from sleep deprivation) and uncontrollable stress severely impacts the functionality of the PFC, with a corresponding weakening of its higher-order functions, rendering the PFC to go "offline." They noted an association between sleep deprivation and "impairments in PFC metabolic and physiologic activity correlating with cognitive deficits." They also noted that uncontrollable stress leads to high levels of norepinephrine and dopamine being released within the brain, which diminishes PFC function, subsequently impairing cognitive functions, and causing the PFC synaptic connections to atrophy. On the other hand, the high levels of norepinephrine and dopamine that get released in situations of uncontrollable stress, strengthen (i.e., expand) the synaptic connections of the amygdala, striatum, and brain stem, which undermines emotional regulation. When there is effective top-down control, the PFC can sustain important work-related tasks by inhibiting the stress response and maintaining an optimal neurochemical environment. However, when the PFC goes offline, as suspected in burnout, the ensuing PFC dysfunction results in poor top-down control, and an increased probability for medical error and/or unprofessional (i.e., more disinhibited) behavior (Table 1).

**Neurochemistry**

A comprehensive 2019 narrative review was unable to show consistent HPA axis findings – i.e., involving measures such as the cortisol awakening response, morning cortisol, diurnal cortisol variation, daytime/evening cortisol, 24-hour urinary free cortisol, and others – among individuals with burnout (for further information, refer to "Table 1 Summary of HPA axis findings in clinical and non-clinical burnout," p. R151).[20] Testing that assesses how individuals with burnout respond to acute stress might eventually yield more convincing and stable neurochemical differences as opposed to measuring "resting state hormonal levels."[20] Similarly, studies that evaluated burnout and immune function were unable to find reproducible and discernable patterns of clinically relevant immune system changes among individuals with burnout.[20]

A couple of studies are worth discussing, however, since the results suggest that some neurochemical findings could be predictive of burnout, and relate to clinically significant burnout symptoms. In terms of burnout prediction, a study

**Table 1.** Burnout and the Consequences of Dysfunctional PFC Top-Down Control
*Adapted from: Arnsten, A., & Shanafelt, T. (2021, p.766).[19]

| *PFC Dysfunction* | *Consequences* |
|---|---|
| Forgetful, limited "concrete" thinking | Increased probability for medical error |
| Poor concentration, disorganized | Challenges when managing complex tasks |
| Diminished decision-making | Poor patient care, medical errors |
| Limited insight, poor judgment, and impaired moral conscience | Lack of professionalism |
| Reduced empathy and compassion fatigue | Communication problems with patients and coworkers |
| Diminished optimism and drive | Cynicism and reduced work engagement |
| Reduced self-regulation and increased disinhibition | Greater chances of acting unprofessionally toward others |

assessed hair cortisol changes among 372 adult healthcare workers from Quebec, Canada.[21] The participants completed questionnaires, such as the 2-item MBI, and other questionnaires that evaluated anxiety, depression, and PTSD symptoms. The participants were also sent validated instructions to self-collect hair samples that were used to measure cortisol. From the 6 cm samples of hair that was collected, it was possible to calculate the relative changes in cortisol 3 months before the COVID-19 pandemic and three months after the COVID-19 pandemic started. From a sample of 367 healthcare workers, 50.4% had symptoms of burnout, as defined by emotional exhaustion or depersonalization. The hair cortisol increased at the start of the pandemic (i.e., with a median relative change of 29%; p<0.0001), with 2.6 times more odds of burnout (p=0.002), and resulting in 59.6% of healthcare workers having burnout at that time. There were no associations between changes in hair cortisol and symptoms of PTSD, anxiety, and depression. The results of this study showed that changes in hair cortisol was predictive of burnout at three months among healthcare workers after the onset of the COVID-19 pandemic. With respect to clinical applicability, the results supported the use of hair cortisol as a possible screening tool to identify clinicians at high-risk for burnout when confronted with a significant stressor (or set of stressors).

Here is an important study that evaluated the relationship between brain-derived neurotrophic factor (BDNF) and burnout.[22] BDNF is an essential neurotrophic factor found in the human brain and participates in a myriad of functions, such as neuronal growth and proliferation, synaptic neurotransmission, and neuroplasticity.[23] The study compared 37 participants with burnout and 35 healthy controls.[22] Many different samples of various analytes (i.e., serum cortisol, serum BDNF, and others) were taken to assess HPA axis function between the different groups. Statistically significant differences were found between the means level of serum BDNF in both groups (p=0.005), such that the burnout group had a lower mean serum BDNF level (88.66±18.15 pg/ml) than the healthy controls (102.18±20.92 pg/ml). The results showed associations between burnout and emotional exhaustion (p=0.05), depersonalization (p=0.005), and depression p=0.025). In fact, depression (odd's ratio: 0.722; p<0.001) was the most salient factor in distinguishing the burnout participants from the healthy controls. Serum BDNF levels correlated negatively with emotional exhaustion (r=-.268; p=0.026) and depersonalization (r=-.333; p=0.005), and correlated positively with personal accomplishment (r=.293; p=0.015). Based on these results, it was proposed that stress may downregulate the production of BDNF within the hippocampus and reduce the amount produced, which would increase the vulnerability for neuronal damage to take place along with increased clinical symptoms of burnout. In other words, the "low BDNF levels in burnout might be related to the concentration-memory problems and mood symptoms often observed in burnout syndrome."[22]

Could hair cortisol measurements and serum BDNF levels be used to assess and/or predict burnout? I believe there is some utility in measuring these neurochemical biomarkers when managing patients at risk, or patients suspected of having burnout. If, for example, a patient presents with significant occupational stress, but they appear to be coping sufficiently, measuring hair cortisol and BDNF could serve as helpful baseline metrics, which then could be remeasured over time as treatment is instituted to encourage allostasis, and to safeguard against burnout. Alternatively, if a patient presents with burnout, capturing measurements of hair cortisol and serum BDNF could be helpful in determining how biologically impacted the patient is. In this situation, the hair cortisol would likely be increased and the serum BDNF likely decreased, which would be modifiable and potentially reversible with effective treatment.

**Is Burnout a Specific Form of Depression?**

In an editorial by Meier, the similarities between burnout and depression were described.[24] He noted that measures of burnout correlate strongly with measures of depression. An earlier cited study in this paper showed associations between burnout and emotional exhaustion, depersonalization, and depression.[22] Given the fact that there is strong overlap between burnout and depression, some researchers have put forth the argument that burnout should be redefined as occupational depression.[25] One of the main reasons for this consideration comes from data on a construct known as negative affect (NA). NA "refers to emotions experienced as unpleasant or aversive."[24] Thus, "burnout is NA situated in the workplace, experienced as a result of chronic stress."[24] In a review of studies spanning several decades, correlations between NA and burnout/depression yielded an overall effect size of 0.492, and among people that were older and had worked for longer periods of time, the effect size increased to 0.535.[26]

There are also neurobiological and neurochemical similarities between major depressive disorder (MDD) and burnout. In MDD, chronic stress leads to impairment in PFC function, an overactivated amygdala resulting in more fear-based or bottom-up control, and a concomitant downgrading of hippocampal functioning.[27] Some of the common features of MDD, such as neurocognitive impairment, withdrawing from aversive environments, and anhedonia are linked to these brain circuit issues.[27] Likewise, in burnout there is PFC dysfunction, neurocognitive impairment, and strengthened fear-based synaptic connections.[19] In MDD, chronic stress results in low levels of serum BDNF due to hippocampal alterations.[23] In burnout, chronic stress also leads to low levels of serum BDNF presumed to result from hippocampal alterations.[22] Though burnout will continue to be studied as a separate psychological syndrome from depression, it seems very likely and probable that it could be understood as a unique form of depression that happens or is situated within the work environment (Table 2).

**The Drivers and Consequences of Burnout**

The symptoms of burnout mentioned earlier – i.e., emotional exhaustion, ➤

**Table 2.** Similarities between Burnout and Depression

| | *Burnout* | *MDD* |
|---|---|---|
| Personality | ↑ NA | ↑ NA |
| Neurobiology | ↓ PFC Function | ↓ PFC Function |
| | ↑ Amygdala Activity | ↑ Amygdala Activity |
| Neurochemistry | ↓ Serum BDNF | ↓ Serum BDNF |

depersonalization, and diminished personal accomplishment – result mostly from the clinician's chronically stressful work environment, and less from the personal characteristics of the individual clinician.[28] In the subsections below, the more salient drivers and consequences of burnout are described and have also been summarized in Table 3.

*Occupational Factors.* Physicians that work more than 50 hours per week were noted to be at the highest risk of burnout, while working over 40 hours per week also increases the risk of burnout.[28] When physicians spend less than 20% of their time on activities that they deem most meaningful, the rate of burnout almost doubles.[28] This latter point refers to an "imbalance between time spent on satisfying and less satisfying aspects of work."[2]

Other occupational factors include a lack of control concerning work conditions and decision-making; time pressures linked to physicians' perceptions that productivity is what they are valued for; and a "chaotic and inefficient work environment" forcing physicians to be overburdened by clerical and other tedious tasks.[3] These factors result in a loss of autonomy for physicians, along with more micromanaged practices; all of which are major causes of burnout.[3]

In addition to loss of autonomy, the term "asymmetrical rewards" happens when productivity is more valued than quality of care.[3] When physicians do the work that is expected of them, they receive very little positive feedback for doing their jobs. However, when mistakes happen, even serious mistakes in which a patient is harmed, the "negative consequences are immediate, painful, and expensive."[3] As is generally known, bad outcomes become the subject of analysis at morbidity and mortality conferences.[3] In some instances, public reporting (i.e., due to regulation) may be necessary, which can result in malpractice lawsuits, obscuring and in some cases obliterating a physician's "consistent record of high-quality performance."[3]

With micromanaged practices, as noted above, every decision a physician makes has to be weighed against available limited resources (i.e., "opportunity costs").[3] This type of decision making process results in "cognitive scarcity" – which undermines cognitive performance while also increasing burnout – i.e., as happens when physicians need to place the goals of healthcare organizations over the needs of patients.[3] When the goals of the healthcare organization force physicians "to constantly consider the opportunity costs of each of the hundreds of clinical decisions made each day for their patients" this will invariably "consume their available time and lessen their ability to solve problems for their patients."[3]

Management of the electronic health record (EHR) also contributes significantly to burnout,[2] largely due to the negative impacts arising from regulatory compliance and reimbursement requirements.[28] The EHR consumes a significant proportion of a physician's time during the day (i.e., consuming 49.2% of daily time in one study,[29] and more than half of their workday in another study[30]). The EHR also consumes time outside of regular clinic hours (i.e., 1-2 hours in one study,[29] and 1.4 hours in another study[30]).

Another occupational factor that drives burnout is that of insufficient sleep. Close to 50% of physicians report that long working hours result in inadequate sleep.[28] This contributes to burnout by reducing energy reserves and activating the HPA axis resulting in increased amounts of stress.[28]

All of the aforementioned occupational factors lead to significant challenges with WLI noted earlier. This contributes to physicians being more unhappy compared to the general population.[2] Women physicians are more likely to be adversely impacted by WLI problems, most notably in the early stages of their career.[2]

*Medical Culture.* There are several salient factors, particular to the medical culture, that seem to play a role in burnout. One factor is that of presenteeism since taking any time away from work is seen as detrimental to colleagues and patients.[28] Another factor involves hiding weaknesses since any illness – whether physical or mental – are problems that physicians will often keep private though they usually "continue to work at less than their full capacity or find other ways to hide their illness."[28] Above all, maladaptive behaviors are embedded in medical culture and get reinforced during medical education, and in healthcare organizations through what has been called the "hidden curriculum."[2] This is an implicit way of modeling maladaptive behaviors – i.e., even unprofessional and unethical behaviors – that get perpetuated and passed on during the early years of medical training and beyond.[2]

Another shift in medical culture that has influenced burnout is that of evidence-based medicine (EBM). EBM is a factor in burnout among seasoned physicians whose work may be discredited by relying on "intuition and unsystematic clinical experience."[28] In fact, medical knowledge doubles every 73 days, making it very stressful for all physicians regardless of clinical experience to keep pace "with the rapidly changing medical literature and new technologies."[3] This adds considerable stress to the work that physicians do because the public demands them to "have the latest knowledge at their fingertips, to be able to reliably offer them the best treatment, and never make mistakes."[3]

*Interpersonal Factors.* The sheer challenges associated with gaining acceptance into medical school, then completing the rigorous education, residency training and beyond has created an emblematic "survival of the fittest" way of life.[28] This leads to competitiveness that can be subtle or inconsequential, or can evolve to outright bullying. Some 40% of physicians have reported bullying between colleagues of the same rank, or between colleagues of different ranks.[28] Regrettably, bullying has had more detrimental impacts upon female physicians and has links to burnout and suicidal thoughts (e.g., as noted in a study of female surgical residents[31]), and maybe even suicide itself. There may be associations between burnout and female suicides due to accumulated stress that results when they have been mistreated, humiliated, and intimidated.[28]

*Personal Factors.* Most physicians that seek out a career in medicine have perfectionistic traits, a keen sense of responsibility, and are usually altruistic.[28] Perfectionism can lead to micromanagement, inadequate delegation, and marked self-criticism, which is often associated with anxiety, depression, and burnout.[28] Altruism or a selfless "hero mentality,"[2] though noble, can become pathologic for some physicians that consistently "go beyond the call of duty."[28] This additional burden of feeling responsible can result in

negative outcomes for both patients and "even the physicians themselves."[28]

There is also something known as "second victim syndrome" that happens to physicians when an unexpected or even an expected adverse patient outcome happens.[28] Some physicians also have greater proximity to death and dying compared to other physicians, which can result in "secondary traumatization," compassion fatigue, added stress, and burnout.[2] Whether work results in "second victim syndrome" or "secondary traumatization," these experiences can lead to a myriad of symptoms, such as fatigue, sleep problems, increased heart rate, and ongoing suffering, as well as adverse personal and professional consequences.[28]

**Diagnosing Burnout**

To determine if a patient has burnout, a comprehensive history of their work-related stress is necessary. When asking about their work environment, perform an inventory of all the different factors (as noted earlier) that could be causing their stress levels to increase. Learning about their eating, sleep schedule, work and personal relationships, exercise type and frequency, and even bowel function are all important. Completing a mental status evaluation is essential since symptoms of anxiety and depression are often comorbid with burnout.[32-34] Inquiring about how they have been coping – what resources have been accessed (e.g., employee assistance programs), what treatments they are currently taking or have tried (e.g., prescribed medications, natural health products), and what therapeutic lifestyle choices (TLCs) they have or are engaged in (e.g., exercise, diet, and meditation) – are all important.

It is preferable that some type of validated burnout questionnaire/instrument is used to quantify burnout symptoms, including the frequency and/or severity. A simple method to use could be the 2-item MBI that was described earlier. This 2-item method addresses the domains of emotional exhaustion and depersonalization, compares very well to the full MBI, and has essentially the same ability to identify burnout.[35] For emotional exhaustion and depersonalization, the questions that are asked include "I feel burned out from my work" and "I have become more callous toward people since I took this job," respectively. Each domain-associated question is then scored on a seven-point Likert scale (0-6). If the score is greater than 3 for any of the questions, meaning that the frequency is at least once each week or more, this meets the definition of burnout.[36]

As an alternative, the Oldenburg Burnout Inventory (OLBI) could be used, as it is also psychometrically validated.[37] This scale evaluates two dimensions of burnout, i.e., exhaustion and disengagement, and can be used in any setting regardless of occupation. There is also a "Burnout Self-Test" that assesses burnout more informally. This test has not been psychometrically validated and should not be used as a diagnostic tool.[38] It may still provide useful information when working with patients that seem vulnerable to burnout.

In terms of finalizing the diagnosis, referring to the definition of burnout, as described in the 11th Revision of the International Classification of Diseases (ICD-11), may prove to be helpful.[39] Though it is not considered a medical condition, burnout is found within the chapter, "Factors influencing health status or contact with health services," and is defined as "a syndrome conceptualized as resulting from chronic workplace stress that has not been successfully managed." The ICD-11 characterizes burnout by the following three dimensions: Feelings of energy depletion or exhaustion; Increased mental distance from one's job, or feelings of negativism or cynicism; and reduced professional efficacy. It must specifically refer to "phenomena in the occupational context and should not be applied to describe experiences in other areas of life." The clinician should review all of the information gathered, including scores on any burnout questionnaire/instrument, and integrate the ICD-11 criteria, when considering a diagnosis of burnout.

**Management of Burnout**

There is much that healthcare organizations can do to lessen the triggers of burnout and reduce its overall incidence. The reader is recommended to review these specific references for more information on what can be done from a macro, or systems-wide level to mitigate and manage burnout.[3,28,40,41] My own experience has unfortunately revealed that most organizations do very little to mitigate burnout other than offering help through employee assistance programs, perhaps free weekly meditation (or free access to meditation apps), or other services. I can certainly appreciate the complexity, costs, and challenges required to restructure healthcare organizations to realistically attenuate burnout. I suspect that the short-term challenges and associated costs would be high, but the long-term organizational gains would be potentially tremendous. As such, the focus of this section will be on what individual clinicians can tangibly do to help themselves when confronted with a chronically stressful work environment. It is rather obvious that to assist with chronic work stress, eating well, getting plenty of exercise, taking sufficient breaks, proper WLI, and sufficient sleep would be necessary. All clinicians are fully aware that these work modifications and TLCs are essential when moderating stress and mitigating burnout. Less well known are specific treatments that have been shown in clinical studies to attenuate chronic stress (i.e., a known precursor to burnout) and to even target some specific symptoms of burnout.

**Micronutrient Treatment Options**

Chronic stress adversely impacts micronutrient concentrations, leading to micronutrient depletion, for the following reasons:

1. Redistribution of micronutrients from tissues and organs to blood, or vice versa;

➤

**Table 3.** Drivers and Consequences of Burnout

| *Factors* | *Consequences* |
|---|---|
| Occupational | • Time pressures<br>• Less satisfying work<br>• Asymmetrical rewards<br>• Cognitive scarcity<br>• EHR demands<br>• Insufficient sleep |
| Medical Culture | • Presenteeism<br>• Hiding weaknesses<br>• Maladaptive behaviors<br>• EBM demands<br>• Expectations of knowing/keeping up with the latest information |
| Interpersonal | • Survival of the fittest way of life<br>• Competitiveness<br>• Bullying |
| Personal | • Perfectionism<br>• Selfless hero mentality<br>• Second victim syndrome<br>• Secondary traumatization |

➤

2. Increased oxidative stress and inflammation;
3. Increased urination and sweating;
4. Increased cortisol output via its impact on aldosterone levels leading to changes in the urinary excretion of electrolytes and minerals; and
5. Appetite changes due to reduced intake.[42]

According to the "Triage Theory," when there is moderate shortage of micronutrients (i.e., as described above from chronic stress), the body will conserve the vitamin/mineral-dependent "proteins/enzymes that are essential for survival and reproduction."[43] As a result, the proteins/enzymes that are required to ensure long-term health are essentially rendered insufficient, which results in vulnerability toward disease, stress-related problems and brain dysfunction.

To lessen these adverse effects, at-risk clinicians or clinicians experiencing burnout, ought to consider taking B-complex vitamins with additional micronutrients (i.e., 500 mg of vitamin C, 100 mg of calcium, 100 mg of magnesium, and 10 mg of zinc) based on positive findings from several clinical studies.[44-48] Some of the known brain mechanisms of B-complex vitamins include improved brain energy metabolism, increased production of monoamine neurotransmitters (i.e., serotonin, dopamine, and norepinephrine), increased production of gamma aminobutyric acid (GABA) and acetylcholine, and reductions in the rate of brain atrophy.[49,50] Some of the known brain mechanisms of calcium, magnesium, and zinc include the release of neurotransmitters, augmented chemical signaling between cells, the production of adenosine triphosphate, active transport of ions across cell membranes, regulation of gene expression, and maintenance of normal neuronal cell function.[49] Some of the relevant brain mechanisms of vitamin C (ascorbic acid) include the reduction of oxygen free radicals, and modulation of glutamatergic function.[51]

The actual doses of the B-complex vitamins with additional micronutrients was very modest (i.e., low by therapeutic standards) in all these studies.[44-48] The formulation that was used in two of the cited studies consisted of the following: B1 (15 mg); B2 (15 mg); niacinamide (50 mg); pantothenic acid (23 mg); B6 (10 mg); biotin (150 µg); folic acid (400 µg); B12 (10 µg); C (500 mg); calcium (100 mg); magnesium (100 mg); and zinc (10 mg).[44,46] Another cited study used the same formulation, but without zinc, and with double the amount of vitamin C (1000 mg).[45] One of the formulations studied was more unique since it included B-complex vitamins, vitamins E and C, choline, inositol, lecithin, and modest doses of herbal medicines (i.e., 250 mg of *Avena sativa* and 100 mg of *Passiflora incarnata*).[47] Overall, the evidence from these clinical studies showed that the oral use of B-complex vitamins – i.e., with additional micronutrients as specified above, and with the addition of herbal medicines in one cited study – lower symptoms of anxiety, depression, and perceived stress (or related parameters) while also increasing general wellbeing (or related parameters).[44-48] None of the trials noted any worrisome or concerning adverse effects associated with these B-complex formulations.

Therapeutic doses of vitamin C, ranging from 1-3 grams daily, may also attenuate some of the effects of chronic stress. One randomized clinical trial on healthy adults allocated 3 grams of sustained-release vitamin C or placebo over the course of 14 days.[52] As would be expected, the plasma level of vitamin C increased among the subjects taking the vitamin and not the subjects taking placebo. The plasma vitamin C level at the end of the trial, "but not pre-trial was associated with reduced stress reactivity of systolic blood pressure, diastolic blood pressure, and subjective stress, and with greater salivary cortisol recovery." Another randomized placebo-controlled trial administered 1000 mg of vitamin C or placebo to 142 female graduate students.[51] The study showed that vitamin C possessed acute anxiolytic effects. In both of the cited studies, no adverse effects were attributed to the use of vitamin C.

Broad spectrum minerals and vitamins (BSMV), in daily doses much higher than a one-a-day multiple vitamin and mineral supplement, have been shown in a couple of clinical studies to attenuate the effects of chronic stress resulting from natural disasters.[53,54] Though the psychological effects of burnout may not be fully comparable to the psychological effects resulting from natural disasters, it would seem probable that treatment shown to benefit people affected by natural disasters would also benefit those affected by burnout. In one study people having been through the trauma and stress following an earthquake were given one capsule/day of B-complex vitamins plus additional micronutrients, or four capsules/day of BSMV, or eight capsules/day of BSMV for 28 days.[53] All the treatment groups showed favorable effects upon a broad array of symptoms when compared to changes from baseline to four weeks. The BSMV group (4 capsules/day) had the most notable clinical benefits on the various clinical rating scales compared to the other groups. Specifically, people taking four capsules/day of BSMV experienced the greatest reductions in symptoms of depression, anxiety, and stress. Comparatively, people taking four capsules/day of BSMV also experienced less perceived stress, and greater reductions in avoidant and arousal symptoms. Some 5% of all people given treatment experienced adverse effects. The BSMV group that took eight capsules/day had the largest number of adverse effects, such as constipation, sleep disruption, and gastrointestinal disturbances. None of the adverse effects were considered serious and the compliance was extremely high (i.e., 92% or higher) during the trial.

In the second study, a similar design was used to assess psychological distress following a natural disaster, but the duration was six weeks.[54] Unlike the other study, the groups evaluated included people taking four capsules/day of BSMV, 1000 IU of vitamin D3, and one capsule daily of a B-complex vitamins plus additional micronutrients (as described earlier). The B-complex vitamins plus additional micronutrients and the vitamin D3 groups lowered a broad array of symptoms when comparing changes from baseline to six months. People taking B-complex vitamins plus additional micronutrients had more notable clinical effects compared to those just taking vitamin D3. Similar to the findings noted in the other study, people taking four capsules/day of BSMV experienced greater reductions in symptoms of depression, anxiety, and stress. They also experienced more marked reductions in intrusive and arousal symptoms. The average compliance among all the treatment groups was 93%. With respect to treatment-emergent adverse effects,

no differences were found across all the treatment groups, and none were considered serious.

The use of BSMV to treat neuropsychiatric disorders, including chronic stress, has evolved considerably since the early 2000s. Several key review articles have documented the brain mechanisms positively impacted by the broad spectrum micronutrient (or "multinutrient") approach.[55,56] In a 2013 review article, the following brain mechanisms were highlighted as viable explanations for the observed positive effects on brain function: (1) providing sufficient micronutrients to assist enzymes "with drastically reduced activity" to become "so supersaturated with the necessary cofactors that near-normal function is restored;" (2) maintaining optimal homocysteine levels to ensure proper cellular function; (3) improved energy metabolism of neuronal and glial cells via the production of ATP and augmented mitochondrial function; and (4) moderating the effects of gastrointestinal inflammation and/or gut sensitivities.[55] In a more recent 2021 review, similar brain mechanisms were noted as the reasons for beneficial clinical outcomes when using BSMV, but with the addition of offering protection from environmental toxins, especially those that adversely impact brain health.[56]

Table 4 lists the different micronutrient options to moderate the adverse effects of chronic stress. These treatments would presumably help to prevent and/or treat burnout since burnout is an adverse outcome when chronic occupational stress becomes unmanageable.

**Herbal Medicine Treatment Options**

There are only a couple of well-studied herbal medicines that I believe have been shown to attenuate many of the negative impacts of chronic stress. This will not be an exhaustive review, but rather a few notable studies will be highlighted as a way in which to demonstrate the clinical plausibility of the chosen herbal medicines. It could also be argued that the chosen herbal medicines, including the cited studies, are too sparse and represent just a tiny sample of other clinically plausible herbal medicines to manage chronic stress and burnout. Given the paucity of available evidence, I maintain that only two herbal medicines currently possess sufficient evidence as treatment options for chronic stress and burnout.

*Rhodiola rosea* extract (RRE) ought to be considered since it normalizes the release of stress hormones (i.e., cortisol) while augmenting the production of ATP synthesis in mitochondria.[57] It also possesses monoamine oxidase-A (MAO-A) and MAO-B inhibition, which suggests a mechanism underlying its antidepressant, anxiolytic, and activating properties.[58] It has been the subject of an open-label trial involving patients with symptoms of burnout (400 mg/day; 12 weeks),[59] and a randomized clinical trial assessing patients with stress-related fatigue (576 mg/day; 28 days).[60] Though RRE has been safely combined with selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs),[61]and more recently in combination with sertraline,[62] there are case reports of patients experiencing concerning cardiovascular adverse effects when combined with paroxetine,[63] and escitalopram.[64]

In the burnout study, RRE was able to lower specific burnout symptoms of depersonalization and emotional exhaustion (all with p values <0.001) despite the fact that the actual amount of symptom lowering does not seem to be clinically meaningful.[59] However, the more clinically meaningful and statistically significant improvements (all with p values <0.001) over the 12 weeks involved sub-scores of the Perceived Stress Questionnaire (PSQ) related to fatigue, harassment, irritability, lack of joy, overload, tension, and worries. Similarly, in the Multidimensional Mood State Questionnaire (MDMQ), there were clinically meaningful and statistically significant improvements (all with p values <0.001) over the 12 weeks in sub-scores of alertness, tiredness, calmness, restlessness, good mood, and bad mood. Some noted adverse effects possibly related to RRE during the study included head pressure, lightheadedness, nausea, feeling irritated, and eye swelling. The actual calculated overall incidence of adverse effects per observation day, however, was extremely low at 0.015.

In the stress-related fatigue study, RRE attenuated the cortisol awakening response, improved symptoms of burnout (as per the Pines' Burnout Scale; p=0.047), physical health (as per the 36-Item Short Form Survey Instrument; p=0.056), and various aspects of mental performance (i.e., involving attention and stable work pace; some measures were statistically significant).[60] No serious or concerning adverse effects were attributed to the use of RRE in this study. Based on the results of these two studies, RRE represents an herbal medicine that could help assuage numerous psychological symptoms associated with burnout, as well as the physical and emotional exhaustion that often accompanies this psychological syndrome.

The next herbal medicine to consider is Ashwagandha (AG). Mechanistically, AG has a high affinity for GABA receptors and possesses GABA mimetic properties.[65,66] It also modulates cortisol (i.e., lowers serum cortisol).[67-69] It has been the subject of clinical studies involving stressed healthy adults taking the following daily doses: 600 mg for 60 days (5% withanolides, 30 mg);[67] 250 mg and 600 mg for 8 weeks (5% withanolides, 12.5 mg and 30 mg, respectively);[68] and 240 mg for 60 days (35% withanolides, 84 mg).[69] AG can be combined with all classes of psychiatric medications, but caution is warranted when combined with benzodiazepines, and/or insomnia medications ("Z-drugs") such as eszopiclone, zaleplon, and zolpidem.

In terms of how AG impacts biochemistry, physiology, and organ function several important publications are worth discussing. In a safety study, 600 mg/day of AG was given to healthy ➤

**Table 4.** Micronutrient Options

| *Treatment Options* | *Suggested Daily Dose* |
|---|---|
| B-complex 50 or 100 (with 100 mg of calcium, 100 mg of magnesium, and 10 mg of zinc) | 1 pill (Note: any B-complex 50 or 100 supplement would exceed the majority of the B-vitamin doses used in the cited clinical studies) |
| Vitamin C | 500-3000 mg (Note: timed-release formulation recommended) |
| BSMV | 4 pills (Note: the recommended product should approximate the doses and ingredients that were used in the cited clinical studies) |

➤

volunteers for eight weeks.[70] No adverse effects were noted in the AG and placebo groups. Hematological and chemistry parameters remained within the acceptable range at baseline and after the eight weeks of AG. No significant changes were noted for the hematological and other parameters (including thyroid hormones) when comparing the AG and placebo groups. No adverse effects were also reported during this study.

A study evaluated the impact of AG upon subclinical hypothyroid adult patients (n=50).[71] Twenty-five patients received AG (600 mg/day), and 25 received placebo over the course of eight weeks. The efficacy variables were serum thyroid stimulating hormone (TSH), serum triiodothyronine (T3), and thyroxine (T4) levels. Eight weeks of AG treatment improved serum TSH ($p < 0.001$), T3 ($p = 0.0031$), and T4 ($p = 0.0096$) levels significantly compared to placebo. AG treatment effectively normalized the serum thyroid indices during the treatment period in a significant manner (time-effects: TSH [$p < 0.001$], T3 [$p < 0.001$], and T4 [$p < 0.001$]). One patient in the AG group reported adverse effects that were mild and temporary. I have given AG to several patients taking thyroid replacement therapy, and none of them experienced adverse effects or changes in their thyroid status even with the addition of AG to L-thyroxine treatment.

Unfortunately, rare liver abnormalities have been attributed to the use of AG. In a report, five cases of liver injury were connected to the use of AG.[72] The mean age of the patients was 43 years with a range of 21-62 years of age. Three of the patients were male. All five patients developed liver-related symptoms 2-12 weeks into AG treatment that consisted of jaundice, nausea, lethargy, pruritus, and abdominal discomfort. The liver injury was determined to be cholestatic or mixed, and the pruritus and hyperbilirubinemia was prolonged (i.e., lasting 5-20 weeks). None of the patients succumbed to hepatic failure, and the liver tests normalized "within 1-5 months in four patients." One patient was lost to follow-up.

In my own clinical practice, I have had one case in which a patient developed elevated levels of aspartate aminotransferase, alanine transaminase, and alkaline phosphatase, and also some hematological abnormalities (i.e., decreased platelets, lymphocytes, and monocytes). None of the liver function elevations or hematological decreases were serious, and the patient did not develop any liver-related symptoms. All of the lab abnormalities normalized within one month of stopping the AG. I do provide this information, as part of informed consent, when recommending AG to patients. I offer monitoring of liver function as an option, but most patients feel fine without such clinical vigilance once they understand that instances of liver injury are extremely rare.

Therapeutically, the results of several trials have established efficacy when using AG to lessen the psychological impacts of chronic stress. In all the studies, adverse effects were insignificant, or were very mild and clinically indistinguishable from those attributed to placebo.[67-69] In the 2012 study, healthy subjects with chronic stress demonstrated the following clinical improvements when taking AG for 60 days over placebo (all with p values<0.0001):

- Perceived Stress Scale (PSS) reduced by a mean of -9.1 points compared to a mean of -1.4 points among subjects in the placebo group;
- General Health Questionnaire reduced by a mean of -24.6 points compared to a mean of -0.7 points among subjects in the placebo group; and
- Depression Anxiety Stress Scales (DASS) reduced by a mean of -39.3 points compared to a mean of -2.8 points among subjects in the placebo group.[67]

In the 2019 study, the results were also very favorable. Over the course of eight weeks, the stressed healthy subjects taking the higher daily dose of AG (600 mg) demonstrated the following clinical improvements (i.e., all with p values <0.001):

- PSS - the AG group went from a mean (standard deviation) of 22.95 (1.57) at baseline to a mean of 14.15 (2.62) compared to the placebo group that went from a mean of 22.70 (2.17) at baseline to a mean of 16.63 (3.13); and
- Hamilton Anxiety Rating Scale (HAMA) – the AG group went from a mean of 24.10 (3.21) at baseline to a mean of 20.15 (3.66) compared to the placebo group that went from a mean of 23.32 (3.09) at baseline to a mean of 21.42 (3.27).[68]

In another 2019 study, the results were once again clinically favorable toward AG over placebo (i.e., between group comparisons) but did not reach the same statistical significance as the other noted studies. Over the course of 60 days, the stressed healthy subjects taking AG demonstrated the following clinical improvements in the HAMA and DASS rating scales (i.e., p values of 0.40 and 0.96, respectively):

- HAMA - the 240 mg/day AG group went from a mean (standard deviation) of 10.27 (0.59) at baseline to a mean of 6.07 (0.38) compared to the placebo group that went from mean of 9.73 (0.54) at baseline to a mean of 7.37 (0.41); and
- DASS - the 240 mg/day AG group went from mean of 16.83 (1.00) at baseline to mean of 11.77 (0.86) compared to placebo group that went from mean of 16.40 (1.06) at baseline to mean of 14.73.[69]

The mean serum cortisol measurements from all three studies showed clinically meaningful changes (i.e., decreases) from baseline as a result of AG administration (Table 5). The reduction in cortisol in all these studies suggest that AG possesses a moderating effect on HPA axis activity in stressed healthy adults. Even though multiple mechanisms have been purported to account for AG's therapeutic effects,[69] I believe its affinity for GABA receptors and having GABA mimetic properties (as noted earlier) may be one of the key ways in which AG moderates HPA axis activity in response to ongoing stressors.

Table 6 lists the different herbal medicine options to moderate the adverse effects of chronic stress, and to prevent and/or treat burnout.

**TLCs**

My own clinical work has taught me that recovery from burnout is much like recovery from depression: It will take time and patience for the burned-out clinician, which may mean months or even a couple years, to return to an acceptable baseline. The danger for the recovered clinician is returning to the same job and the same circumstances that were largely responsible for causing burnout to happen in the first place. Most recovered clinicians have to be willing to change how they work and to seriously moderate their work-related triggers, if they want to protect themselves from becoming a repeat burnout customer.

First, foundational supports are needed to bring balance to an overactive and depleted nervous system. This involves some combination of a healthy diet, good sleep, regular exercise, meditation, psychotherapy, and social support.[73,74] All of these foundational supports (i.e., in combination) moderate cortisol and inflammatory cytokines, lessen HPA axis activity, increase PFC functioning, increase serum levels of BDNF, and encourage synaptic plasticity. All of these treatments aim to improve self-care. Workshops dedicated to improving self-care have been shown to lower depersonalization, one of burnout's main symptoms.[75] Clinicians ought to consider adding cognitive behavioral therapy (CBT), as part of their ongoing psychotherapy treatment. CBT can improve emotional exhaustion, another one of burnout's key symptoms.[76]

Second, since self-blame and shame tend to coexist with burnout, it is recommended that some form of mindfulness self-compassion (MSC) be used to augment emotional flexibility and regulation. Many studies and systematic reviews have been done on this approach to help with burnout and related problems. For example, the results of a study on MSC and mindfulness-based stress reduction given to health professionals (i.e., mostly physicians) working at six different Spanish National Health Systems teaching units showed improvements in both mindfulness and self-compassion, with the positive effects being sustained when measured three months after the intervention.[77] In a systematic review on MSC for nurses, the results showed "medium-to-large effect sizes for self-compassion, traumatic stress, burnout, stress and compassion satisfaction," and "high intervention adherence (mean=86%) in the included studies."[78]

To augment MSC, I typically review its three components with clinicians based on the work of Drs. Neff and Germer.[79] The three components include: (A) Self-kindness (i.e., talking to ourselves as a good friend would); (B) Common humanity (i.e., that all of us are flawed, works in progress, and that suffering is normal and part of one's daily experience of living); and (C) Mindfulness (i.e., acknowledging feelings in the moment without over-identifying with them, and without letting them embody or engulf who we are). There are many ways of encouraging this approach when feeling the ill-effects of chronic stress and burnout, but in its most elemental form, clinicians could practice in the manner described below:

> Jonathan, right now you are feeling overwhelmed and exhausted. It is OK to feel this way, as we all experience moments or times when things are just too much to manage. I want you to know that despite the challenges you face at this moment, you can get through this, and I am here to support you.

To improve the positive benefits of this brief MSC exercise, clinicians can then give their arm a gentle squeeze, place a hand on their heart, or provide some other type of reassuring touch. By giving ourselves physical support, we are "tapping into the mammalian caregiving system" and "triggering the release of oxytocin."[80] This will "increase feelings of trust, calm, safety, generosity, and connectedness and also facilitate the ability to feel warmth and compassion for ourselves."[80] This needs to be practiced several times each day – i.e., whenever emotions feel overwhelming – for it to have durable therapeutic effects over time.

Third, it is essential for clinicians to not only remember, but to relearn and reclaim the meaning they once derived from the work they do. Burnout is antithetical to meaning, since meaning from work cannot happen when burnout happens. The most influential scholar on the subject of meaning was that of Viktor E. Frankl, MD, PhD.[81,82] Even though the experience of burnout is not proximate to having survived the Holocaust, his seminal work on meaning and suffering can be generalized to all circumstances a person faces, including that of burnout. Meaning is embedded in our biology, and so finding meaning (or reclaiming) meaning demands the simple but essential self-reflective remembrance that work was once fulfilling and life affirming.[82] Doing so is not easy and may require help from a qualified psychotherapist, but there are apparently three main avenues by which suffering clinicians can arrive at meaning once again. The first and most obvious is by "doing a deed."[82] When clinicians feel the satisfaction of helping someone again, even with all of its complexity and nuance, they can begin to feel the positive momentum and fulfillment of being in the service of others.

Another way in which to encourage meaning is by "experiencing something or encountering someone; in other words, meaning can be found not only in work but also in love."[82] There is nothing short-sighted or pedantic about experiencing love and having love in one's life. Much too often, I am saddened by the sacrifices most clinicians make by forsaking love for the important clinical work they do. Burned-out clinicians both cause and experience resentment by weakening the integrity of relationships with the people they love. Work, especially when burnout happens, becomes a one-sided affair anchored to the external world ➤

**Table 5.** Changes in Mean Serum Cortisol Levels

| | *2012 Study (60 days; p=0.002) - 600 mg/day[67]* | *2019 Study (8 weeks; p<0.0001) - 600 mg/day[68]* | *2019 Study (60 days; p<0.001) - 240 mg/day[69]* |
|---|---|---|---|
| AG - Baseline; ug/dL (standard deviation) | 15.7 (3.2) | 16.12 (3.97) | 14.15 (0.94) |
| AG - End of Study; ug/dL (standard deviation) | 11.3 (3.7) | 10.86 (3.80) | 10.84 (1.04) |
| Placebo - Baseline; ug/dL (standard deviation) | 15.6 (3.3) | 16.15 (4.80) | 14.00 (0.94) |
| Placebo - End of Study; ug/dL (standard deviation) | 14.4 (3.2) | 15.52 (4.57) | 14.07 (1.04) |

**Table 6.** Herbal Medicine Options

| *Treatment Options* | *Suggested Daily Dose* |
|---|---|
| RRE | 400-600 mg (minimum of 3% total rosavins and 1% salidroside per pill) |
| AG | 600 mg (the daily amount of withanolides should be 30 mg; dose of withanolides could be increased to approximately 84 mg if necessary) |

➤

of achievement at the expense of love, which is the "ultimate and the highest goal to which man can aspire."[82] When we feel bereft of everything (i.e., as happens in burnout), it is ultimately the experience of love that provides much needed sustenance. Just as clinicians must recommit to finding work meaningful and satisfying once again, they must recommit even more to strengthening the intimate connections they have with the people they love. The security and strength derived from renewed commitments to salient love relationships provide essential buffering and resilience against burnout. Clinicians need meaningful work, but more importantly they need supportive and meaningful relationships to return home to each and every day.

As we finalize the discussion on meaning, it is important to recognize that if the external circumstances of a clinician's work may not change (i.e., like "the helpless victim of a hopeless situation"), then it is possible for the clinician to rise above themself, grow beyond themself, and by so doing can change themself.[82] All clinicians can "turn a personal tragedy into a triumph."[82] This may be the most complicated and counterintuitive way in which to help the burned-out clinician. This shift in attitude does not suggest or make the contention that "suffering is indispensable to the discovery of meaning;" rather, it simply means that meaning is available in spite of unavoidable suffering.[82] If the suffering that caused the burnout to happen in the first place is avoidable, then the right thing to do would be to remove the cause since unnecessary suffering in such a case would be "masochistic rather then heroic."[82] However, in situations when suffering is not avoidable (i.e., as in many work circumstances), clinicians can choose their attitude towards such unchangeable situations, and turn their suffering (and burnout) into an achievement. When all else fails, sometimes it is a consistent shift in attitude that will help the most.

In addition to MSC and building meaning, the final component to helping burnout is simply time, and allowing sufficient time to heal. Regrettably, most clinicians do not have the luxury of taking some type of short-term leave when burnout happens. If they did, they would likely want to attend a specialized facility that focuses on treating burnout. A six-week inpatient program on a "burnout ward" provided individual CBT, group therapies, activating body therapies (e.g., yoga and physical exercise), regenerative individual therapies (e.g., massage and ear acupuncture), resources activating therapies (e.g., music and art), and job coaching (if necessary).[83] There was a reduction in symptoms and also increases in BDNF following the inpatient program. Since this type of approach is unavailable to most clinicians, they can maximize the time they do have by improving the odds of a better outcome. They can do this by creating their own comprehensive weekly program to combat burnout. Therapeutic change and recovery won't happen fast but can be significantly improved by securing the right support and regularly engaging in several of the healing modalities (as noted above), or other healing modalities, such as dance, martial arts, theater, and drumming – activities that enhance joy, meaning, and purpose in life.

**Conclusion**

Burnout is an "epidemic phenomenon" that is real and difficult to avoid for most clinicians.[28] There is a high prevalence of burnout among physicians (and likely, most clinicians) with correspondingly reduced amounts of WLI. Burnout results from chronic work-related stress that overwhelms allostatic systems, causing heightened HPA axis activity and damage arising from AL/AO. These effects change neurobiology, resulting in an underfunctioning PFC and an overfunctioning (i.e., over responsive) amygdala. These changes are associated with low levels of serum BDNF and increased NA. The unfortunate outcome of burnout involves more medical errors and/or behavioral consequences resulting from disinhibition. Since organizations seldom do more than provide a few helpful services/resources to lessen the impacts of chronic work-related stress, the onus is on individual clinicians to find a way forward whether they are heading towards burnout, or have been diagnosed with it.

Micronutrient and/or herbal (botanical) treatment options can assuage some of the devastating effects of chronic stress and may reduce symptoms of burnout. These treatments may even delay the onset of burnout or prevent burnout if they are started well in advance of work-related stress. TLCs are also vital in preventing and recovering from burnout, which involve foundational support, MSC, finding (or reclaiming) the meaning of work, and taking the time needed to implement a comprehensive anti-burnout strategy involving several healing modalities.

Even though our current understanding of burnout has increased considerably, including its prevalence and diagnosis, for medicine and all of healthcare to fulfill its mission, clinicians need to be better supported so they can effectively treat patients and do their important work without being demoralized in the process. All stakeholders in healthcare ought to be very concerned about the current state of affairs and should continuously find opportunities to develop and implement effective strategies, such as those identified in this paper, to better support clinicians and minimize burnout.

Dr. Jonathan Prousky (ND, Bastyr University, 1998; MSc, University of London, 2008; MA, Yorkville University, 2016; RP, College of Registered Psychotherapists of Ontario, 2020) holds the positions of Professor and Chief Naturopathic Medical Officer at the Canadian College of Naturopathic Medicine. His primary responsibility is ensuring the delivery of safe and effective naturopathic medical care to patients, as well as ensuring the safety and effectiveness of the medical training in the naturopathic program. His clinical practice focus is primarily on the evaluation and management of mental health problems. He has spent over 20 years advocating for patients that wish to receive integrative care to assist with their mental health.

Website: www.jonathanprouskynd.com

**Burnout Assessment Links**

1. **Burnout Self-Test (informal assessment tool; free):** https://www.mindtools.com/pages/article/newTCS_08.htm
2. **Maslach Burnout Inventory (MBI; license required):** https://www.mindgarden.com/117-maslach-burnout-inventory-mbi
3. **Oldenburg Burnout Inventory (OLBI; free):** https://www.mdapp.co/oldenburg-burnout-inventory-olbi-calculator-606/

◆

**References are available online at www.townsendletter.com.**

# The results are *in*

NOW CLINICALLY RESEARCHED

## Clinical research [1] demonstrated support for:

- Working and episodic memory*
- Cortisol and IL-6 biomarkers*
- Attention and reaction-time*
- Mood and mental well-being*


Learn more

[1] *Clinical research has been completed and is in process of peer-review submission.*

**ResearchedNutritionals.com/BDNF-Essentials**

Researched Nutritionals® solutions for life

800.755.3402 • Info@ResearchedNutritionals.com • ResearchedNutritionals.com | Available only through healthcare professionals.

**These statements have not been evaluated by the Food and Drug Administration. These products are not intended to diagnose, treat, cure, or prevent any disease.*

# The Brain: Effects of Molds and Mycotoxins

## by Andrew W. Campbell, MD

Your brain is who you are. Your brain makes your personality, your character, your ability to be happy and enjoy life, your emotions, your ability to learn and how quickly or slowly, your daily actions and reactions, how and what interests you, all of these and much more. Your brain's health is essential to your well-being. Duly, your brain is well protected: it is the only organ almost completely surrounded by bone: the skull. No other organ is so guarded: not the heart, nor the kidneys, nor the liver. The weight of the brain is approximately 3 pounds, or about 2% of our body weight, yet consumes 30% of our glucose and 20% of our calories. There are 400 miles of blood vessels, mainly capillaries, to bring oxygen and nutrients to the 100 billion neurons that make up the brain.[1,2] Each neuron has 1,000 synaptic connections. The visual cortex has 12,000 connections per neuron, and the prefrontal cortex, 80,000 synapses per neuron. This part of the brain is where executive functions take place, where we decide our long-term goals, plan for the future, develop our personality expressions and our social behavior, and control of certain parts of speech. It is where we determine between good and bad, future consequences of what we are currently doing.[2-8] This part of the brain is missing in many politicians.

One of the most vital parts of the brain is the blood-brain barrier (BBB). It is a highly specialized brain endothelial structure. The BBB separates components of the blood from neurons. The BBB limits the entry of plasma components, red blood cells, and leukocytes into the brain. Approximately 98% of small molecule drugs and all large molecule neurotherapeutics, e.g., recombinant peptides, proteins, are normally excluded from the brain. The intact BBB is a major obstacle for the development of pharmaceutical drugs for central nervous system (CNS) disorders.[2]

According to the World Health Organization, diseases caused by mycotoxins are many and mycotoxins are known as the "Great Masquerader" of the 21st century due to their ability to present in patients a number of nonspecific clinical signs and symptoms and not routinely suspected by the medical establishment.[9] Many patients get misdiagnosed with chronic Lyme disease, chronic fatigue syndrome, fibromyalgia, or eventually psychiatric disorders such as adjustment disorder, depression, and others.[10]

Mycotoxins are known to adversely affect the blood-brain barrier. Several mycotoxins, including satratoxin, T-2 toxin, gliotoxin, deoxynivalenol (DON), and ochratoxin, are known to be able to penetrate the intact BBB by altering permeability and induce oxidative stress responses, including reactive oxygen species (ROS) generation, lipid peroxidation, and protein carbonyl formation.[11] DON directly affects brain neurons and glial cells after passing through the BBB and affects the vitality and function of astrocytes and microglia.[12] DON induces neuronal cell apoptosis via mitochondrial apoptosis pathways. This mycotoxin induces inflammation of the central nervous system, increasing the expression of proinflammatory molecules. T-2 toxin is able to accumulate in the brain.[12,14] Gliotoxin (GTX) is capable of injuring and killing microglial cells, astrocytes, and oligodendrocytes.[15] Glutathione, a popular supplement used by many who treat mold- and mycotoxin-affected patients, is known to increase the toxicity of gliotoxin.[15-17]

The breaking down of the BBB, allowing mycotoxins into the brain, is linked to several diseases and disorders, such as autism spectrum disorder (ASD), multiple sclerosis (MS), Alzheimer's disease (AD), and amyotrophic lateral sclerosis (ALS), better known as Lou Gehrig's disease.[1]

The overwhelming medical and scientific evidence show that it is the brain and nervous tissues that are first affected by mycotoxins. Serum antibodies to mycotoxin antibodies bind to human tissue, including neural tissues such as myelin, triggering demyelination in the brain and peripheral nervous system. This demyelination includes sensory and motor neurons or both, as demonstrated in a study of 119 patients with confirmed exposure to molds and mycotoxins. All participants tested positive for serum antibodies to mycotoxins. The study concluded that all 119 patients tested positive for serum antibodies to mycotoxins and to neural tissues such as myelin.[18]

Studies from university medical centers, including some controlled studies, have shown a clear link between mycotoxins, including ochratoxin, and the effects on the brain leading up to ASD. In a study of 172 children with ASD and 61 controls, there were statistically significant differences comparing mycotoxin serum antibody levels between the two groups, with the ASD group showing elevated mycotoxins serum antibodies. In an ensuing study on ASD, these researchers linked ASD

to ochratoxin A. In another study, Tufts University School of Medicine found evidence implicating mycotoxins in the pathogenesis of ASD. These included the secretion of pro-inflammatory cytokines from mast cells. They concluded: "… exposure to mold and mycotoxins can affect the nervous system, directly or through immune cell activation, thus contributing to neurodevelopmental disorders such as autism spectrum disorder." A subsequent study by the same institution a year later confirmed these important and essential findings.[19-22]

Multiple sclerosis (MS) is one of the most frequent and severe demyelinating neurological diseases, mainly affecting young people, eventually leading to their becoming disabled. Initially, it was believed that the viruses or genetics were involved as causative agents. However, studies from Rutgers University Medical Center and others have demonstrated that gliotoxin is a common trigger of MS.[23-25]

In a study on AD, Bredesen found three subtypes of AD: type 1 (inflammatory), type 2 (non-inflammatory or atrophic), and type 3 (cortical). He reported that type 3 AD can be due as the result of exposure to mycotoxins.[26] In a later study examining why Finland has the highest rate of dementia in the world, the authors linked factors such as the environment and a climate that is both very cold and humid. They found that this resulted in homes frequently harboring molds that produced neurotoxic mycotoxins.[27] Other researchers found that the mycotoxins ochratoxin A (OTA) caused cell death due to loss of mitochondrial membrane potential, indicating that OTA is neurotoxic at very low concentrations and contributes to the development of AD and Parkinson's disease. Another study showed the effects of OTA resulting in demyelination and neurodegenerative disorders. OTA also causes neurotoxicity through mitochondria-dependent cell death in brain astrocytes.[28-30]

**The overwhelming medical and scientific evidence show that it is the brain and nervous tissues that are first affected by mycotoxins.**

The most common form of motor neuron disease in an adult is ALS. The well-known scientist from Cambridge University, Dr. Stephen Hawkins, suffered from this devastating disease. ALS is a progressive and fatal disease, with 5-10% being linked to genetic mutations. Patients suffer a progressive loss of motor neurons in the brain stem and spinal cord, resulting in muscle weakness, twitching, muscle wasting, cramps and stiffness of arms and/or legs, problems with speech and/or swallowing or breathing. Neuroinflammation is commonly found in the majority of ALS patients. A recent review study showed how mycotoxins significantly increase glutamate production, stimulating TDP-43 translocation, and provide a link between mycotoxins and one of the molecular and histologic hallmarks of sporadic ALS.[31] Another study showed ➤

➤

how the mycotoxin verrucarin increased the spontaneous release of glutamate by 1300%.[32-33]

Brain-related symptoms are many and varied. A good review of these is in the chapter "Mold and Mycotoxins: Effects on the Neurological and Immune Systems in Humans."[18] That same chapter gives which testing methods were found to be most accurate, namely serum antibody testing for mycotoxins and also molds, use of nerve conduction velocities for detecting demyelination, and the use of serum testing for antibodies to myelin and other nerve tissues. Several recent studies link chronic fatigue syndrome, fibromyalgia, postural orthostatic tachycardia syndrome (POTS), dysautonomia, and others to the exposure to mycotoxins.[34] These are due to the effects of mycotoxins on the brain.

In addressing some misconceptions, studies have shown that OTA levels in urine are found in healthy persons worldwide and represent the mycotoxins from foods consumed that day. Indeed, another study showed that urine samples show day-to-day variations in mycotoxin intake. Additionally, while urinary excretion normally indicates recent mycotoxin intake from food, serum measurements indicate exposure to mycotoxins from an indoor mold growth environment.[35,36] The majority of the studies discussed above used serum antibody testing for mycotoxins and mold issues in patients.

Lastly, in reading this publication, we can see that mycotoxins, by causing dysregulation of mitochondria via various effects, cause cell death. It is therefore clear that cells, including fat cells, cannot store mycotoxins for these reasons.

In treating patients suffering from the effects of molds and mycotoxins, it is vital to follow the first rule of toxicology: get the patient away from the toxin or the toxin away from the patient. This is probably the most difficult part as testing a home or workplace for molds is not standardized in the United States: different companies will give different readings for the same indoor space. Treatment must be individualized: one cannot give the same treatment to a 22-year-old woman weighing 110 pounds and to a 55-year-old man weighing 220 pounds. There are several published studies and textbook chapters that clearly demonstrate the best treatments for the different diseases and disorders caused by molds and mycotoxins. The basic principle of identifying the cause, then removing the cause, and finally repairing the damage holds as the best way to proceed.

Andrew W. Campbell, MD, was medical director of the Medical Center for Immune and Toxic Disorders in Houston for 20 years. He has published over 90 studies in peer-reviewed medical journals and chapters in medical textbooks, and has received awards from many national and international organizations. He is Editor-in-Chief of Alternative Therapies in Health and Medicine, Advances in Mind-Body Medicine, and Microbiology Research.

## References


1. Campbell AW, Decena K. The Brain and Mycotoxins. *Altern Ther Health Med*. 2020 Nov; 26(6) 8-11.
2. Zlokovic, Berislav V. The blood-brain barrier in health and chronic neurodegenerative disorders. *Neuron* vol. 57,2 (2008): 178-201.
3. Elisabeth Murray, Steven Wise, Kim Grahatle. Chapter 1: The History of Memory Systems." In: *The Evolution of Memory Systems: Ancestors, Anatomy, and Adaptations* (1st ed.). Oxford University Press. 2016;pp. 22–24.
4. Miller EK, Freedman DJ, Wallis JD (August 2002). The prefrontal cortex: categories, concepts and cognition. Philosophical Transactions of the Royal Society of London. Series B, *Biological Sciences*. **357** (1424): 1123–36.
5. DeYoung CG, et al. (June 2010). Testing predictions from personality neuroscience. Brain structure and the big five. *Psychological Science*. June 2010;21 (6): 820–8.
6. Yang Y, Raine A (November 2009). Prefrontal structural and functional brain imaging findings in antisocial, violent, and psychopathic individuals: a meta-analysis. *Psychiatry Research*. **174** (2): 81–8.
7. Gabrieli JD, Poldrack RA, Desmond JE (February 1998). The role of left prefrontal cortex in language and memory. Proceedings of the National Academy of Sciences of the United States of America. **95** (3): 906–13.
8. Baldauf, D.; Desimone, R. (2014-04-25). Neural Mechanisms of Object-Based Attention. Science. **344** (6182): 424–427.
9. Mycotoxins - World Health Organization www.who.int\ceh\capacity\mycotoxins
10. Campbell, AW. Lyme Disease and Mycotoxicosis: How to Differentiate Between the Two. *Altern Ther Health Med*. 2019 Jul;25(4):8-10.
11. Nguyen, Vu Thu Thuy et al. The role of mycotoxins in neurodegenerative diseases: current state of the art and future perspectives of research. *Biological chemistry* vol. 403,1 3-26. 27 Aug. 2021.
12. Zhang, Jiajia et al. The neurotoxicity of trichothecenes T-2 toxin and deoxynivalenol (DON): Current status and future perspectives. *Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association* vol. 145 (2020): 111676.
13. Park, Sunwoo et al. Ochratoxin A exerts neurotoxicity in human astrocytes through mitochondria-dependent apoptosis and intracellular calcium overload. *Toxicology letters* vol. 313 (2019): 42-49.
14. Dai, Chongshan et al. T-2 toxin neurotoxicity: role of oxidative stress and mitochondrial dysfunction. *Archives of toxicology* vol. 93,11 (2019): 3041-3056.
15. Fraga-Silva TFC, Mimura LAN, Leite LCT, Borim PA, Ishikawa LLW, Venturini J, Arruda MSP, Sartori A. Gliotoxin Aggravates Experimental Autoimmune Encephalomyelitis by Triggering Neuroinflammation. Toxins (Basel). 2019 Jul 26;11(8):443.
16. Axelsson, V et al. Glutathione intensifies gliotoxin-induced cytotoxicity in human neuroblastoma SH-SY5Y cells. *Cell biology and toxicology* vol. 22,2 (2006): 127-36.
17. Axelsson, V et al. Gliotoxin induces caspase-dependent neurite degeneration and calpain-mediated general cytotoxicity in differentiated human neuroblastoma SH-SY5Y cells. *Biochemical and biophysical research communications* vol. 345,3 (2006): 1068-74.
18. Campbell AW.; Thrasher JD.; Gray MR.; Vojdani A.: Chapter: "Mold and Mycotoxins: Effects on the Neurological and Immune Systems in Humans." *Adv Appl Microbiol* (Volume 55). David C. Straus., (ed.), Published by Elsevier Inc., 2004.
19. De Santis B, Raggi ME, Moretti G, et al. Study on the Association among Mycotoxins and other Variables in Children with Autism. *Toxins* (Basel). 2017;9(7):203. Published 2017 Jun 29.
20. De Santis B, Brera C, Mezzelani A, et al. Role of mycotoxins in the pathobiology of autism: A first evidence. *Nutr Neurosci*. 2019;22(2):132-144.
21. Ratnaseelan AM, Tsilioni I, Theoharides TC. Effects of Mycotoxins on Neuropsychiatric Symptoms and Immune Processes. *Clin Ther*. 2018;40(6):903-917.
22. Theoharides TC, Kavalioti M, Martinotti R. Factors adversely influencing neuro-development. *J Biol Regul Homeost Agents*. 2019;33(6):1663-1667.
23. Campbell AW.: Autoimmunity and the Gut. Autoimmune Diseases; (2014), Special Issue: Environmental Triggers and Autoimmunity; Autoimmune Dis. 2014:152428.
24. Purzycki CB, Shain DH. Fungal toxins and multiple sclerosis: a compelling connection. *Brain Res Bull*. 2010;82(1-2):4-6.
25. Ménard A, Amouri R, et al. A gliotoxic factor and multiple sclerosis. *J Neurol Sci*. 1998 Feb 5;154(2):209-21.
26. Bredesen DE. Inhalational Alzheimer's disease: an unrecognized - and treatable - epidemic. *Aging* (Albany NY). 2016;8(2):304-313.
27. Eiser AR. Why does Finland have the highest dementia mortality rate? Environmental factors may be generalizable. *Brain Res*. 2017;1671:14-17.
28. Zhang X, et al. Ochratoxin A induces apoptosis in neuronal cells. *Genes Nutr*. 2009;4(1):41-48.
29. von Tobel JS, et al. Repeated exposure to Ochratoxin A generates a neuroinflammatory response, characterized by neurodegenerative M1 microglial phenotype. *Neurotoxicology*. 2014;44:61-70.
30. Park S, Lim W, You S, Song G. Ochratoxin A exerts neurotoxicity in human astrocytes through mitochondria-dependent apoptosis and intracellular calcium overload. *Toxicol Lett*. 2019;313:42-49.
31. French, Peter W et al. Fungal Neurotoxins and Sporadic Amyotrophic Lateral Sclerosis. *Neurotoxicity research* vol. 35,4 (2019): 969-980.
32. French PW, Ludowyke R, Guillemin GJ. Fungal Neurotoxins and Sporadic Amyotrophic Lateral Sclerosis. *Neurotox Res*. 2019;35(4):969-980.
33. Bradford, H F et al. Changes in transmitter release patterns in vitro induced by tremorgenic mycotoxins. *Journal of environmental pathology, toxicology and oncology: official organ of the International Society for Environmental Toxicology and Cancer* vol. 10,1-2 (1990): 17-30.
34. Tuuminen T, et al. Dysregulation of the Autonomous Nervous System in Patients with Advanced Sick Building Syndrome. *J Otolaryngol Neurotol Res*, 2021;4(1): 97-111.
35. Alvito, Paula, and Luís Pereira-da-Silva. Mycotoxin Exposure during the First 1000 Days of Life and Its Impact on Children's Health: A Clinical Overview. *Toxins* vol. 14,3 189. 4 Mar. 2022,
36. Peraica, Maja et al. Mycotoxicoses in children. *Arhiv za higijenu rada i toksikologiju* vol. 65,4 (2014): 347-63.


◆

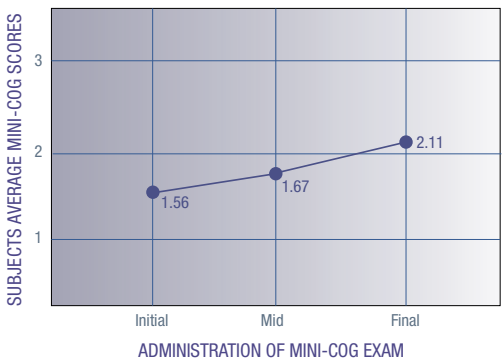
# Grow Your Practice Treating Neuro-Cog Diseases and TBI

Firefly™ LIGHT THERAPY

## Quickly Decrease Cognitive Decline and Increase Function

Exciting data from our clinical study and patient reports indicate that Firefly Light Therapy™ can do just that. Patients noted better balance, mobility, and relief in as little as one treatment and cognitive ability increased by over 30% in just 10, 10 minute treatments. For millions of people suffering from Neuro-Cog Disorders and the practitioners trying to help them, Firefly therapy is a game changer.

Firefly Light Therapy was invented by Maurice Bales and co-developed by his son, Dr. Martin Bales. Dr. Bales is a full-time practitioner who has used Firefly for more than 16,000 visits, serving as many as 25 patients a day! Referrals have more than doubled his patient base in just one year.




## Hear What Patients and Practitioners Are Saying:

"My partner was rapidly descending into the fog of Alzheimer's. The Firefly treatments combined with a mostly plant-based Ketogenic diet have resulted in changes that are frankly, miraculous. His gait, mood, sense of humor, and comprehension have markedly improved. We love the Firefly!"

Thank you,
Angela & Family

"Our Acupuncture practice added Firefly Light Therapy for pathogens, pain, and neurological conditions. We have seen remarkable results. The Firefly Light device is truly a valuable asset to any clinic that enjoys the latest cutting-edge therapy."

Betty Woo, L.Ac.
Radiant Wellness &
Acupuncture Center

Bales™ Photonics

**For pricing, testimonials, & info visit balesphotonics.com or lori@balesphotonics.com for sales.**

# Medically Integrated Electrophysiology for the Assessment and Treatment of Cognitive Impairment and Memory Loss

by Andrew Wong, MD, FACP,[1] Tedra James, MA, MS,[1] and David Hagedorn, PhD, BCN[2]

**Early Detection Conundrum.**

Physicians are uniquely charged to effectively determine the cause of patient complaints and to do so early in the course of the potential disease to maximize convalescence. This is especially salient for the growing number of patients presenting with memory loss.[1] When patients present with hindered mental capacity to perform daily activities, the physician needs a rapid, easy-to-use, low-cost, non-invasive, and sensitive test. Electroencephalography (EEG) using digital analysis and event-related potentials (ERPs) supported by international medical research meet this clinical need for a non-invasive and office-based option for brain function assessment. The added advantage of this functional measure is that it can better guide brain-computer interface therapies that are increasingly showing remarkable safety and efficacy.

**Brain Mapping Biomarkers.**

A hallmark symptom of dementia, affective, and cognitive disorders is memory loss. Because memory loss is common to several conditions, the benefits of tests that aid differential diagnosis are essential. Until recently, most medical providers have relied on self-report or caregiver-report questionnaires and occasionally some effort-based computerized testing to determine a diagnosis. Even when applied optimally, these assessments often fall short in detecting early or less severe disease presentations to include subjective cognitive impairment (SCI). While more complex, the alternative or adjunct use of functional biomarkers recorded with quantitative electroencephalography (qEEG) produces greater sensitivity and more recently improved specificity so that doctors can gauge condition severity and target functional neuro-biological networks from which the memory dysfunctions supervene.

The brain's capacity for normal productive function relies heavily on a complex array of interconnected networks that facilitate communication within and across brain structures. Therefore, to understand and influence brain function, particularly memory, there is a need to isolate key functional biomarkers. Four major electrophysiology measurement categories relevant to memory function are: 1) thalamic generated alpha frequency (posterior peak alpha frequency); 2) slow-wave frequency band dominance by brain region (i.e., delta, theta); 3) the P300b component of event-related potentials; and 4) brain structure (Brodmann Areas) scoring against a gender- and age-normed reference group.

In recent years, additional EEG devices from the US and abroad have reached the general medicine market. Some devices new to the market still lack attention to aseptic techniques (e.g., helmet designs, non-removable scalp sensors). Other instruments are not medical-grade, only utilize a limited number of scalp EEG sensor locations, or do not correlate with the international standards of scalp electrode placement. There are advantages and disadvantages to each design. Still, some critical features to look for in utilizing qEEG for patient care include finding companies with a proven track record in the medical market that are ISO and FDA-compliant, are easy to use, and have excellent clinical support and protocols. The eVox System® (Evoke Neuroscience, Inc.) is one such example used by the US Military across all service branches because of its all-inclusive electrophysiology assessment features, automated data analysis, technical support, and integrated HRV and EEG biofeedback. With modern digital analysis and machine learning, memory dysfunction biomarkers are faster and easier to obtain at a low cost, translating into a lower patient burden during a general medical care appointment.[2]

**Peak Alpha Frequency.**

The alpha frequency band (8 – 12Hz), the most dominant EEG frequency found in the brain, is a good measure of information processing capacity. One might even describe this function as the most salient feature of memory.[3] Peak alpha frequency detected from the parietal and occipital scalp locations reflects thalamic functioning. Low posterior peak alpha frequencies (< 8Hz) are correlated with cognitive disturbances and dementia.[4,5] On the other hand, higher alpha2 power – often around 11-12 Hz – is associated with central nervous system over-arousal

1. Capital Integrative Health, Bethesda, Maryland
2. Coastal Integrative Medicine, Jacksonville, North Carolina

conditions.[6] Beyond the well-established relationship between low posterior dominant alpha rhythm peak (below 8Hz) and cognitive impairment are several alpha ratios (e.g., alpha3/alpha2) or alpha to even slower frequency (theta) ratios. These different EEG frequency band power ratios appear to offer further discrimination regarding memory loss types and disease course prediction.[7-9]

**P300b**

Memory functions and several cognitive processes within the brain can be measured using event-related potentials (ERPs).[10,11] With ERPs, one can quantify time-locked neuronal responses following presented stimuli. The time delay or latency between stimulus onset and a patient's physical response reflects processing speed. The ERP component's amplitude reflects neuronal recruitment and subsequent activation. With good reliability, longer or delayed latency measures and low amplitudes are associated with aging and dementia conditions and indicate cortical and subcortical dysfunctions.[12,13] Fundamental memory elements involve the degree of attention to a stimulus and the subsequent encoding of information for storage and retrieval. Two ERP components useful to measure these cognitive processes are P300a and P300b, respectively.[14] The P300a component is dopamine-mediated and reflects frontal working memory functions or dysfunctions. The P300b component, however, is mediated by norepinephrine and is generated in the medial temporal lobe. These two components are helpful in differential diagnosis, EEG biofeedback, other neuromodulation therapies, and tracking the disease course and effects of treatment.

**Brodmann Areas and LORETA Imaging.**

Brodmann Areas (BA) represent regions of the cortex cyto-architecturally organized into functional locations and are a well-respected and widely referenced system for brain mapping. The ability of qEEG to derive statistical scores (i.e., Z-score) on the BAs throughout the patient's brain informs the clinician of deviation from normalcy and clarifies longitudinal treatment effects. When used in parallel with imaging libraries, scalp surface EEG low-resolution brain electromagnetic tomography (LORETA, sLORETA) permits added insight to differential diagnosis and treatment effects.[15-17] For example, Alzheimer's disease presents with EEG power abnormalities more globally than frontotemporal dementia; the ability to source localize to specific brain structures, using BAs, aids the clinician in cross-correlating known brain structures that are hallmarks of particular diseases. EEG and source localization sensitivity with sLORETA allow for a helpful assessment measure when considering memory impairment etiology, personalized treatment interventions, and treatment response patterns.

**Office-Based Solutions**

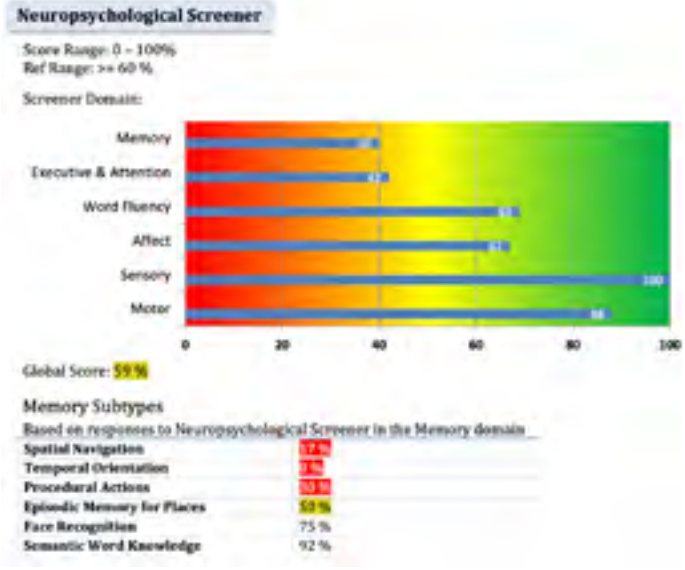
Medical office-based electroencephalography and event-related potential recording used with analysis equipment are recent advancements in general practice medicine. This patient access improvement emerged from military medicine where there was a need during the Middle East conflict to less invasively and quickly evaluate brain injury and trauma-related psychopathology. Physicians across various specialties began using this digital analysis hardware and software pioneered with the military. This first-line brain assessment approach has been easier on patients, appears to reduce imaging costs, and allows lower-income or underinsured patients greater access to functional brain-informed differential diagnosis and treatment decisions.

## Medical office-based electroencephalography and event-related potential recording are recent advancements in general practice medicine.

The FDA-registered medical equipment such as the eVox System® incorporates a portable and automated 24-channel electroencephalography (EEG) amplifier for standard 19-channel EEG and event related potentials (ERP), and 3-channel electrocardiography (ECG). EEG and ERP digital analysis with artificial intelligence algorithms have recently been sensitive and specific aids to physicians seeking to understand and track early onset dementia subtypes. Publications recently in-press and those soon to print highlight that EEG can reliably and quickly identify the major types of cognitive impairment, i.e. subjective cognitive impairment (SCI), mild cognitive impairment (MCI), and Alzheimer's disease (AD).

Here we discuss the evaluation of patients' cognitive function using the eVox System® in a primary care setting. Of note, this device is a medical grade EEG amplifier with integrated software that permits user selection of indicated tests. It also integrates heart rate variability and EEG biofeedback intervention should the assessment and clinical indications support this added therapy. Depending on their symptoms, patients in our functional medicine practice are often recommended to complete the EEG/ERP and calculated qEEG once a year. Patients receive a summary of their results and review the ➤

Figure 1. Patient with dementia's self-report neuropsychological symptoms, reporting low memory, executive function, and attention day-to-day (Case 1).



➤

comprehensive report and receive treatment recommendations with their physician.

**Case 1 – Early Dementia**

An 83-year-old patient presented to the clinic recently with a diagnosis of dementia after first receiving a diagnosis of mild cognitive impairment seven years prior. His medical history is also significant for sleep apnea and hypertension. The patient's EEG/ERP measures indeed has several markers of dementia including a peak alpha frequency of 7.60 Hz, high alpha3/alpha2 power ratio of 1.01, excess delta and theta wave activity in the front of the brain, and low self-reported memory and executive and attention functioning (Figure 1). Treatments for this patient will focus heavily on functional nutrition where he receives guidance on the Bredesen Ketoflex diet, adding sources of nitric oxide to encourage blood flow, and focusing on anti-inflammatory foods. The EEG/ERP measures will help us monitor the progression of his symptoms and brain function.

**Case 2 – Mild Cognitive Impairment**

At a routine appointment, a 66-year-old male reported forgetfulness and disorganization such as missing his highway exit on his established route. He has a family history of Alzheimer's and personal history of heart disease, hypertension, and metabolic syndrome. His qEEG report showed a peak alpha frequency (PAF) of 7.30 Hz, theta activity significantly above the population norms, and a P300b component with no defined peak (see Figure 2). The low PAF and indiscernible P300b, as mentioned above, are associated with diminished information processing abilities. The patient was referred to a neurologist for further evaluation. Here, he was diagnosed with memory impairment and with possible underlying cause of vascular inflammation, metabolic encephalopathy, and CNS hypo-perfusion. He was prescribed Ritalin and modafanil to help with his symptoms of hyper-somnolence and memory impairment. With our clinic, the patient continued acupuncture to manage inflammation-related pain and began working with our functional nutritionist to adopt lifestyle changes to decrease inflammation. He was recommended brain health supplements such as a high-quality MVI, vitamin D3, omega-3 fatty acids, CoQ10, and was encouraged to improve sleep quality and hygiene with an earlier bedtime and new mattress that decreased snoring, thus increasing oxygen supply to the brain. Other lifestyle interventions included daily walking to reduce inflammation and improve circulation to the brain.

After two years of simple-yet-effective lifestyle interventions, the patient's EEG/ERP measures showed both objective and subjective improvements in function. His PAF increased to 7.60 Hz from 7.30 Hz, demonstrating increased information processing capacity (Figure 2). Additionally, the power of his alpha3/alpha2 ratio in the occipital region decreased slightly from 0.97 to 0.95; as higher ratios are correlated with cortical atrophy of the inferior parietal lobule and worsened cognitive symptoms, the conservation of this measure is promising.[8] In addition to these neural changes, the patient's self-reported daily executive function and attention symptoms improved from 4% to 38% capacity as measured by the neuropsychological screener incorporated in the procedure. To address the

Figure 2. Patient with mild cognitive impairment's resting, eyes-closed headmaps and peak alpha frequency before (Panel A) and after (Panel B) two years of functional medicine treatment (Case 2).

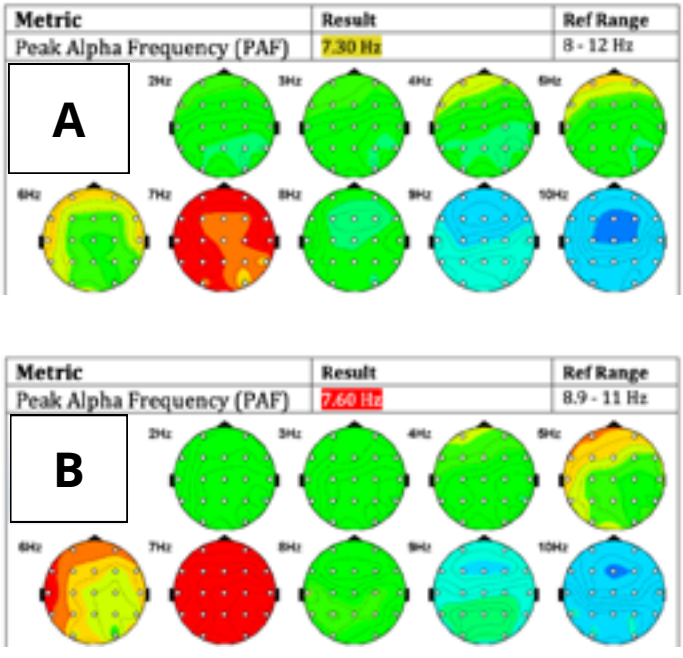
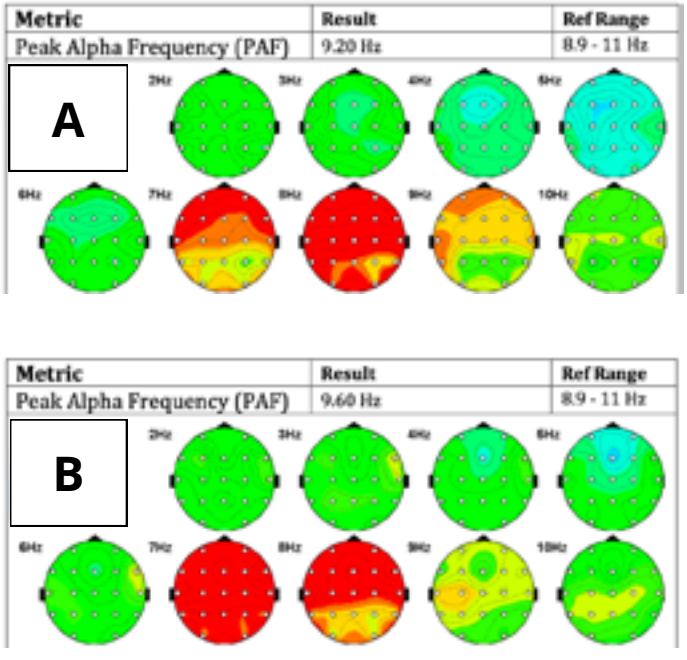



Figure 3. Patient with early dementia's resting, eyes-closed headmaps and peak alpha frequency before (Panel A) and after (Panel B) one year of functional medicine treatment (Case 2).



patient's remaining struggles with word recall, we are working on improving sleep quality with supplementation and further supporting brain health through addressing hormone balance. We hope to continue to see improvements and prevent the progression of his mild cognitive impairment.

**Case 3 - Early Dementia**

A 59-year-old female patient presented to the clinic with a diagnosis of early onset Alzheimer's that was confirmed by a glucose PET scan. She had to leave Post-It™ notes around her entire house because of her extremely compromised short-term working memory. Her history was significant for Sjogren's, POTS, chronic kidney disease, and Hashimoto's. The results of her first EEG/ERP measures contained a delayed P300b component, excess power relative to the population at 7-9 Hz at rest, and a borderline low peak alpha frequency of 9.20 Hz (Figure 3). Her treatment regimen included frequent neurocognitive screening as well as the addition of thyroid hormone replacement, low-dose naltrexone (LDN), and nitric oxide-boosting supplementation. She continued management of her POTS and chronic kidney disease through her other specialists.

Functional nutrition support included the Bredesen Ketoflex protocol, and healing gut inflammation and improving digestion via (talk to Araceli).

After 1 year of treatment, she reported improved memory. This improvement was supported by neural changes in her quantitative EEG. Significantly, her peak alpha frequency increased from 9.20 Hz to 9.60 Hz (Figure 3), suggesting improved capacity to process and retain information. Additionally, the latency of the P300b component decreased slightly from 636ms to approximately 600ms with a slight increase in power, likewise suggesting improved working memory. The patient was able to get rid of using Post-It™ notes around her house and reported less brain fog and better executive function and working memory. We continue to monitor this patient's symptoms closely and expect to see slow but steady improvement.

**EEG biofeedback**

In addition to the use of electrophysiology measures for early detection and tracking progress, these tools can guide individualized brain-computer interface (BCI) treatment interventions (EEG biofeedback or neurofeedback), both for office-based or home-based therapy (Versus®). The ability to supplement cognitive rehabilitation using EEG biofeedback avoids additional drug interaction effects. In addition, the home-use devices permit daily personal training that reduces medical costs and gives patients more autonomy over their health.

EEG biofeedback has had a history of clinical efficacy since the early 1970s. This intervention has several forms or methods of application, including real-time referenced normative database Z-score training, EEG frequency band amplitude modulation, and research-level complex fMRI guided neurofeedback.[18,19] International peer-reviewed research literature posits medium to large effect sizes, thereby making EEG biofeedback a safe and viable treatment modality in the multimodal medical management of conditions such as attention-deficit disorder,[11,20-24] pain,[25] dementia/memory loss,[19,26-35] and others.[36] With the added benefits of having no relative harm compared to other more common standard treatments, there is good reason for physicians to integrate EEG biofeedback in treating brain-related conditions.

**Conclusions**

The Alzheimer's Association 2020 facts and figures report found that 87% of primary care physicians expect to see an increase in dementia cases. This clinical population of adults with memory loss paired with the lackluster standard of care treatment results necessitates a more physiologically functional set of measures. Electrophysiology measures should aid in the determination of dementia subtype and severity and guide alternative medication and non-medication treatments. With growing trends toward personalized medical treatments enhanced by machine learning advances,[37,38] the EEG/qEEG and ERPs have become an ever more helpful office-based brain function analysis method. It is easy to use and has a relatively low cost, enough to be used routinely and frequently to track patient progress. Physicians appreciate the eVox System® as an office-based tool yielding sensitive measures to help patients see the value of treatment compliance, with additional biomarker information to support differential diagnosis and a more individualized EEG biofeedback intervention option. These advances in applied medical neuroscience, if brought out on a large-scale to the population and combined with a root-cause medicine approach, will be instrumental in preventing or even reversing the effects of cognitive impairment on the population. ◆

**References are available online at www.townsendletter.com.**

Dr. Andrew Wong is a graduate of Tufts University School of Medicine and is board-certified in internal medicine with additional training in integrative and functional medicine and medical acupuncture.

He is co-founder of Capital Integrative Health (CIH), a clinic and community in the Washington DC area focused on root causes of health and wellness, including clinical applications to improve brain health using Evoke Neuroscience's eVox QEEG system. For more information about CIH, please visit www.cihealth.org.

Dr. David Hagedorn served as a US Army medic and then went on to work in various clinical and private practice settings for over 20 years. He is experienced in clinical health psychology and neuropsychology, and serves as an international neuroscience and biofeedback expert consultant to several organizations. Dr. Hagedorn served as a teaching faculty and clinical staff member at Naval Hospital Camp Lejeune and assistant professor of military and emergency medicine and family medicine at Uniformed Services University of the Health Sciences – School of Medicine.

He is an international speaker and instructor for advanced psycho-neuro electrophysiology assessment and interventions with particular skill in the traumatic brain injury, posttraumatic stress disorder, attention deficit and hyperactivity disorders. He has authored several patents in the areas of brain computer interface and neuromodulation and lectures on transcranial magnetic stimulation (rTMS) and direct current stimulation (tDCS/tACS).

Dr. Hagedorn is licensed in several states and is board certified as an electroencephalography biofeedback practitioner with particular skill in the applications of EEG and ERP, qEEG, and brain computer interface (BCI) and portable peripheral biofeedback methods.

# Tick-Borne Relapsing Fever

## by Joseph J. Burrascano Jr., MD

Tick-borne relapsing fever (TBRF) is a surprisingly common but often overlooked infection that all practitioners that treat Lyme disease need to know about. Contrary to textbook descriptions, TBRF may present exactly as does Lyme disease; but because it is caused by a different group of *Borrelia*, Lyme disease tests probably will not detect it and you will be left with a case of "seronegative Lyme." Because there is much misinformation and the latest findings are not widely distributed, I wrote this article to shine much-needed light on this important infection.

**What Is TBRF?**

That is an excellent question because the answer can differ, depending on how you define TBRF. It has been defined by clinical presentation, by tick vector, by genetics and by serotype. However, each of these approaches has exceptions and limitations. I will go through each one in turn. Complicating matters is the broad diversity of TBRF *Borrelia* species – worldwide, eighteen species have been identified so far with at least seven known to be present in North America.

**Can TBRF Be Classified by Clinical Presentation?**

Maybe not, as we will see. Classic TBRF is described as having "recurring febrile episodes that last ~3 days and are separated by afebrile periods of ~7 days duration."[1] Each febrile episode involves a 'crisis.' "During the 'chill phase' of the crisis, patients develop very high fever (up to 106.7°F) and may become delirious, agitated, tachycardic and tachypneic. Duration is 10 to 30 minutes. This phase is followed by the 'flush phase', characterized by drenching sweats and a rapid decrease in body temperature. During the flush phase, patients may become transiently hypotensive. Overall, patients who are not treated will experience several episodes of fever before illness resolves."[1]

What causes these cycles? TBRF *Borrelia* express surface antigens that undergo cyclic variation over time due to programmed changes in expression of the genes that code for them (plasmid genes VSP and VLP). The ability to switch expression among distinct genes with the resulting change in surface antigens allows escape from an individual host's immune response and can also cause late-appearing IgM antibodies.

One would think that clinicians would not miss an illness with such an extreme presentation, but according to a recent study, this type of dramatic picture may represent a subset of cases, and a Lyme-like presentation may in fact be the more common one.

The study: 543 US patients with suspected Lyme (not TBRF) were tested for Lyme and for TBRF using advanced immunoblotting, which has the ability to differentiate these two groups. Surprisingly, despite expecting Lyme, 28% were positive for Ab to TBRF and not to Lyme!

These patients did not have the "classic" acute TBRF presentation. Clinically, they resembled Lyme patients and if this testing were not done, they either would have been diagnosed as having seronegative Lyme, or possibly would have been misdiagnosed completely. So classifying this by clinical presentation is a big mistake.

**Can TBRF Be Classified by the Tick Vector?**

Traditionally, TBRF has been defined as being carried by a group of soft ticks called collectively *Ornithodoros* ticks (however, this is not always the case). These rather remarkable ticks have a lifespan of 10 to 20 years and can endure starvation for more than five years. Once infected, these ticks remain infected for the rest of their lives. In addition, infection by at least one relapsing fever *Borrelia*, *B. turicatae*, is maintained transovarially, meaning that ticks can be born infected, do not have to take an initial blood meal to acquire the *Borrelia*, and that even larvae may transmit infection. Whether all TBRF *Borrelia* do this has not been studied.

*Ornithodoros* ticks have a unique ecology. Attached ticks are rarely seen because these ticks are rapid feeders; they remain attached for only 5 to 30 minutes and because bites are painless, they usually go unnoticed. In addition, transmission of TBRF *Borrelia* occurs within seconds of the tick bite, and the tick can feed multiple times!

These ticks do not live in the grass; they live in crevices, which can include wood cracks, leaf litter and caves, but they can also live in small- and medium-size mammal nests and dens, both indoors and outdoors, meaning that houses and out buildings can become infested.

After feeding, ticks return to their crevice, ready to emerge again, stimulated by heat – campfires, wood stoves, even from turning on your house's heat. The bottom line is that they can infect more than campers and hikers.

**Are *Ornithodoros* Ticks Easy to Identify?**

Maybe not. Soft ticks are relatively larger than hard ticks and have a rounded, swollen appearance. However, they can be almost impossible for the average person to distinguish from an engorged *Ixodes* tick, as demonstrated in these photographs:

***Ornithodoros* Ticks**


**Engorged *Ixodes***


Not only can it be difficult to tell these ticks apart, some TBRF *Borrelia* have hard tick vectors: *B. miyamotoi* – vector is *Ixodes*; *B. lonestari* – vector is *Amblyomma americanum*. In addition, there are occasional literature reports that other RF *Borrelia* were found in hard ticks in Europe. So classifying them by vector does not work.

**Can TBRF Be Classified by Their Genetic Sequences?**

This gets tricky because genetic sequencing is typically done on a specific gene – for example, the flagellin gene. However, you can also sequence other genes and even the telomere. The problem is the family tree that results looks different for each method, making precise groupings of families of *Borrelia* impossible.

**Can TBRF Be Classified by Serotyping?**

Serotyping (based on expressed surface antigens) is problematic due to antigenic variation; so to be accurate, one needs to measure multiple types of each surface antigen. This is the basis of advanced immunoblotting. In fact, before the advent of such advanced tests, many researchers gave up on trying to name each new variant and simply classified them together as "the relapsing fevers."

**Do We Need to Worry About TBRF?**

Yes!

"TBRF is typically considered a disease of outdoor enthusiasts and impoverished persons living in primitive conditions. However, our study suggests emergence of *B. turicatae* in metropolitan areas."[2] "Evidence indicates the endemicity of *Ornithodoros turicata* ticks in San Antonio, Dallas, and Austin, the seventh, ninth, and eleventh largest cities in the United States."[2]

"The University of Tennessee reported that in 2009, during fall hunting season, 58% of turkeys tested positive for *B. miyamotoi*."[3]

"In the USA, several species of RFB have been reported to cause disease in humans, including *B. miyamotoi, B. hermsii, B. lonestari, B. parkeri,* and *B. turicatae* …. and a fourth *Borrelia* species, *B. coriaceae*, infects ticks, although human infection has not yet been identified."[4]

**Tick-borne relapsing fever is caused by a different group of *Borrelia* than the *Borrelia* that causes Lyme.**

"TBRF has been reported in 49 of the 50 United States."[5] Worldwide Distribution: TBRF has also been reported in Central and South America; *Borrelia hispanica, B. persica,* and *B. miyamotoi* are important causes of TBRF in Europe and Asia; *B. hispanica, B. crocidurae,* and *B. duttonii* are important causes of TBRF in Africa.

**Clinical Presentations of TBRF**

As mentioned earlier, generally two types of presentation have been reported – the classic, relapsing and remitting fevers type, which may at times be confused with Rickettsias, viruses, Babesia and malaria, and the apparently more common Lyme-like presentation. However, recently many clinicians have reported that infection with *B. miyamotoi* seems to be a blend of the two; and because its vector is a hard tick, some have separated this out, calling it "*Borrelia miyamotoi* disease."

**Laboratory Testing**

Some TBRF species may be visible on blood smears, but only in the acute stage of a crisis. While insensitive, false positives can nevertheless occur, and species cannot be determined.

➤

## TBRF – Important Facts

- Transmission of RF *Borrelia* is possible within 15 seconds of tick bite.
- In Louse-borne RF (*B. recurrentis*) transmission via mucous membranes is possible. It is not known whether this can occur with other RF *Borrelia.*
- *Ornithodoros*- because of transovarial passage of *Borrelia* and its ability to survive for decades, it may serve as its own reservoir and not need to feed on an animal to acquire or maintain infection.
- Maternal-fetal passage is well recognized and can possibly result in spontaneous abortion, premature birth, and neonatal death.
- Some TBRF species are immune to complement-mediated killing.
- Acute Respiratory Distress Syndrome has been associated with *B. hermsii.*
- Prolonged QT interval has been reported with TBRF infection.

➤

PCR testing at large commercial labs is available but for *B. miyamotoi* only. IGeneX offers a PCR that is genus-specific, therefore may detect many different species of TBRF and will identify and report *B. miyamotoi* if found. However, PCRs are only sufficiently sensitive during early or acute stages of the disease and in the immunosuppressed, including very ill, late stage patients.

Serologic testing for TBRF presents several curve balls. For example, most TBRF express p41 and this can give rise to a false positive Lyme ELISA; on a Lyme western blot, a single band 41 in a suspected Lyme patient may therefore represent an unexpected TBRF infection. In addition, OspC is present in several TBRF species, another potential reason for false-positive Lyme serologies.

When doing serologic testing for TBRF, note that large commercial labs offer an IFA, but for *B. hermsii* only. You can get a GLP protein-based ELISA for *B. miyamotoi*, but this is only one protein antigen and therefore prone to false negatives; it is like having only one band to read on a western blot.

On the other hand, the best serological test is the TBRF ImmunoBlot offered by IGeneX. This method uses recombinant antigens that are specific to multiple individual species. This allows for detection of a broad array of TBRF *Borrelia* and can even identify them by species when the test is positive. The use of recombinant technology not only allows for expanded species detection, it is inherently more sensitive and more specific than ELISAs, IFAs and western blots, especially in early disease where sensitivity is 67%. Another feature of this test method is that a positive IgM, even in late disease, has a specificity of greater than 98%, meaning that a late positive IgM is unlikely to be a false positive. Significantly, the TBRF ImmunoBlot does not cross react with Lyme *Borrelia*.

Just as in Lyme, the best way to get laboratory confirmation of infection is to test using multiple methods. Here, the obvious choice is immunoblotting plus PCR. Another advantage of testing by both methods is that it may uncover immune defects; a PCR-positive patient with disseminated disease should have a positive serological response and if they do not, then immune dysfunction is suspect.

Because of the clinical similarity of TBRF to Lyme in many cases, it is imperative that TBRF testing be included in the evaluation of a suspected Lyme patient, especially one who has a history of Lyme seronegativity.

**Treating TBRF**

As far as we can tell, treatment regimens for TBRF and Lyme are similar; there are virtually no useful published studies on antibiotic susceptibility for this group of pathogens. However, it is known that TBRF can be a chronic illness, can involve the central nervous system, can involve the heart, can involve the joints, and can induce chronic fatigue. This similarity to Lyme in disease process dictates similar approaches to treating late and chronic cases.

Additional useful advice is to be careful when initiating treatment because in the classical form of TBRF, if treated during a crisis, severe Herxheimer reactions may ensue – hypotension, cardiac arrhythmias, etc. Even in the non-classical, Lyme-like presentation, unusually strong Herxheimer-like reactions can still occur.[6]

**Concluding Thoughts**

TBRF is far more common than previously recognized, geographically widespread, and can be very similar in clinical features to Lyme. Therefore, the obvious takeaway is that one must always consider and test for TBRF when evaluating a Lyme patient, especially one who has had a history of Lyme seronegativity. Laboratory confirmation with TBRF-specific ImmunoBlots and if necessary, PCR, is essential to document the diagnosis. Doing so is not only good medical practice, it will allow us, over time, to get a better feel for the presence of any important differences between these two groups of *Borrelia*, and no doubt will inform us on the best management practices.

Keep detailed records, share your info, and publish!

**References**


1. https://www.cdc.gov/relapsing-fever/clinicians/index.html
2. Bissett JD, et al. Detection of Tickborne Relapsing Fever Spirochete in Austin, Texas, USA. *Emerging Infectious Diseases*. 2018;24(11):2003-2009.
3. Kessler M, What is the Borrelia miyamotoi Infection? August 17, 2015.
4. Middelveen MJ, et al. Relapsing fever Borrelia in California: a pilot serological study. *Int J Gen Med*. 2018 Sep 21;11:373-382.2018.
5. Borreliosis (Tick-Borne Relapsing Fever) https://igenex.com/tick-talk/borreliosis-relapsing-fever-disease/
6. Dworkin MS, et al. Tick-Borne Relapsing Fever. *Infect Dis Clin N Am*. 2008;22:449–468


◆

Dr. Burrascano was raised in Montauk, New York, a small fishing village located 120 miles east of New York City. Montauk became known for a condition called "Montauk Knee," a peculiar monoarthritis, and for the occurrence of unusual "spider bites" that resembled a bullseye and responded to penicillin treatment. Later it was found that the towns in the Montauk area, which includes East Hampton New York, where Dr. Burrascano opened his medical practice in 1981, had the highest case rate of Lyme disease in the world. In addition, tick flagging assays in these towns revealed pockets in which 100% of the ticks were infected with Borrelia.

It was in this setting that Dr. Burrascano began his medical practice. Through the 1980s he saw many patients with these and other seemingly mysterious conditions. It was then that he collaborated with key colleagues including Alan MacDonald, Willi Burgdorfer, Bernard Berger, and others to work out the clinical details of Lyme disease- presentation, laboratory features, and diagnosis, and the very earliest meaningful studies on treatment. The culmination of this body of work is his now-classic monograph "Diagnostic Hints and Treatment Guidelines on Lyme Disease" which had been translated into many languages and has always been offered free of charge to all who wanted a copy. It has been suggested that this work formed the basis of the modern, currently accepted view of Lyme and related tick-borne diseases, including how difficult it can be to diagnose and treat and the wide spectrum of its potential presentations.

He was a founding member and director of both the International Lyme and Associated Diseases Society (ILADS) and its educational arm, the International Lyme and Associated Diseases Educational Foundation (ILADEF). One of the first ILADS members to host clinical clerkships, his dedication to practitioner education continues to this day through his conference presentations, webinars and writings. Dr. Burrascano closed his practice several years ago and began work in the biotech arena as a research project analyst and occasional project manager; however he still does consultancy work for business entities and fellow practitioners in the Tick-borne diseases field.

# Still the Best

## A Must Have for Kidney Function Support!


**CORDIMMUNE** ™

### The only cordyceps product that is standardized for and declares its cordycepin content

- Supports mitochondrial function and ATP production
- Modulates immune system
- Enhances athletic performance safely
- An excellent adaptogen and adrenal support
- Supports hematopoiesis
- 0.2% Cordycepin (worth over $100 per bottle)
- 0.3% Adenosine • 22% Polysaccharides

## Immune Support Beyond Just Polysaccharides!


**CORIO PSP** ™

### The most clinically researched mushroom in Japan and China

- Unmatched 38% polysaccharides
- Lessens the side effects of toxic treatments
- Raises the quality of life
- Raises the activities of NK cells and macrophages
- Increases thymus weight

*The statements herein have not been evaluated by the FDA. This product is not intended to diagnose, treat, or prevent any disease.*

CRNA

CANADA RNA BIOCHEMICAL INC.
Tel: (604) 273-2233 • **www.canadaRNA.com**

**1-866-287-4986**

# Pediatric Pearls

**by Michelle Perro, MD**

## Abdominal Pain in Children? Thinking Beyond the Gut

Abdominal pain is one of the most common pain complaints in children.[1] The diagnostic challenge in the assessment is complicated by the myriad number of potential underlying causes of the child's discomfort while differentiating acute/surgical from non-surgical conditions. The key elements in the evaluation of a child with abdominal pain rests on the tenets of thorough history taking and a careful physical examination. This is not the time for a Zoom visit!

**Horses and Zebras**

Abby is a three-year-old previously healthy girl who presented with an acute onset of abdominal pain, vomiting, and pallor. There were no historical disclosures of systemic symptoms, possible ingestions, travel, or trauma. There were three other siblings who were all well, including a younger brother in day care. (Sibling history can be very useful in sorting out potential infectious etiologies.) Abby did not have diarrhea, which would have led us down the path towards an infectious etiology. [Note: An ill child who presents with just vomiting without diarrhea requires prompt attention.] Her exam was remarkable for a lethargic-appearing child, diffuse abdominal tenderness and a very pale countenance, which is always worrisome in children.

Surgical causes first had to be considered. High on our list included intussusception and appendicitis.[2] While her history and exam were not completely aligned with either of those diagnoses, they were still both highly possible and were pursued.[3] Her laboratory data included a normal CBC with differential, metabolic panel, and urinalysis. A 20 ml/kg bolus of normal saline improved her color but not her pain. An abdominal ultrasound was normal. While awaiting a surgical consult in the ER, the child fell asleep. The ER physician did not offer her analgesics so her symptoms wouldn't be masked. (I've never seen surgical pathology masked by a dose of ibuprofen!) When she awoke an hour later, the pain had resolved and Abby was discharged from the hospital.

**No Conclusive Diagnosis**

One month later, Abby's mom called the office again since the same clinical scenario was reoccurring. This very experienced mom (an important feature in any pediatric assessment), stated that her physical appearance/complaints were a replica of the previous abdominal pain event. The child was brought in and evaluated regarding on how to proceed.

The thought of sending Abby back to the ER, repeating the work up and likely receiving the same findings seemed illogical. Clearly, there was something going on and it was my job to figure it out. Because the thought of a surgical etiology seemed less likely with a recent negative evaluation, I felt more comfortable pursuing an integrative approach and seeing if we could get to the root cause of her abdominal pain. From a homeopathic perspective, her symptoms were exacerbated by anger, better with warmth, and she was experiencing difficulty with passing her poops. I gave her a dose of *Nux vomica 30c*, repeating the dose every 10 minutes because of the acuity of her symptoms. While having her lay quietly in the office, her symptoms abated within 20 minutes after taking the *Nux vomica*. During that time, further history was obtained from mom.

There was a lot of stress happening at home with a pending separation of the parents. Additionally, there was a strong family history of gut issues and autoimmune disease. But the money question was regarding headaches. Both mom and the maternal grandmother had recurring migraine headaches.

**The Gut-Brain Connection**

Migraine is a common complaint in children, accounting for 75% of headaches in young children referred for neurological issues.[4] Of interest, 90% of children who present with migraines will have at least one parent with a history of migraines. Clinical presentations depend on age, with older children experiencing the typical symptoms as follows:

- Moderate to severe headaches, often pulsing or throbbing
  Often unilateral headaches, exacerbated with movement or activity
- Nausea
- The desire for sleep
- Photophobia, and
- Phonophobia.

However, young children/toddlers may present atypically from older children, with an ill appearance, abdominal pain, irritability, persistent crying and the desire to sleep (which often yields clinical improvement as in the case of Abby). It was the historical revelation by the mom of her history of migraines (which was not discovered initially since the focus was on ruling out a surgical pathology) that created the "lightbulb" moment.

**Conventional vs an Integrative Approach**

Although feeling confident that we were dealing with abdominal migraines, the issue of potential gut issues was still looming in the diagnostic column. There is now an epidemic of children with food allergies/intolerances, GERD, and dysregulated bowel function; so I wasn't completely sold that there couldn't also be underlying gut dysfunction that could be linked to her migraine. While practitioners often like to tie everything to one diagnosis, the experienced clinician appreciates that children are now more complicated, recognizing that other factors have created more complex challenges requiring multiple diagnoses.

Conventional medicine divides migraine treatment into two areas: Acute treatment and prevention therapeutics. I do agree with some of the recommendations, such as keeping a journal of occurrences, noting precipitating factors, dietary changes, medications/supplements and any other potential triggers. While Abby had experienced only two episodes, I decided to jump on the idea of keeping a migraine diary since this was high on the list of the likely cause of her pain. I was also concerned about her young age, the severity of her symptoms, the family history of migraines, and the stresses that were occurring in the home.[5] In an older child, I might have waited to see if there were more episodes of pain, elucidating any particular patterns or triggers.

The main approaches to the treatment of migraines in conventional medicine include the following recommendations:

- Antiemetics
- IV fluid
- Analgesics (NSAIDs and acetaminophen)
- Ergot-based medications
- Triptans.

If the child goes on to develop frequent bouts of migraines, the following prophylactic treatments are recommended:

- Beta blockers
- Antihistamines
- Tricyclic antidepressants
- Anti-epileptic drugs (valproic acid, gabapentin)
- Calcium channel blockers
- Biofeedback and relaxation training.

One might argue that with Abby having had only two episodes of abdominal pain, were we jumping the gun here towards the diagnosis of abdominal migraines? Possibly. However, when I was with the child and the mom in the room, I had a "gut" feeling that this patient was experiencing a neurologic event manifesting in her gut. It's hard to categorize that "feeling," but experienced clinicians spend years developing this sense and honing the art of clinical intuition in medical practice. I went with my gut.

**Food/Gut/Brain**

Migraine is commonly reported in patients with celiac disease and shows improvement on a gluten-free diet.[6] Whether there is a benefit to children suffering from migraines without celiac disease is not reported in the literature. However, anecdotally, there does appear to be a connection in some individuals despite the lack of research. What we do know is that a child with gluten sensitivity/intolerance may experience abdominal pain and headaches.

Abby didn't test positive for celiac disease but showed IgG antibodies on her food sensitivity testing to both gluten and dairy – very common findings in today's child. Both of those food groups were removed from her diet.

**Don't Forget Manipulative Medicine**

It is rare for one of my patients not to be referred for as assessment by a pediatric osteopathic practitioner (DO). Osteopathic manipulations can assist in a variety of health complaints and are well-tolerated in children. The hardest part is finding a DO that works with children. Abby required release of her vagal nerves as well as work on some of the abdominal muscles by a craniosacral osteopath. This required a total of two visits!

**Six Months Later**

The parents began couples therapy and the overall level of household tension was diminished. Mom reported that Abby had no further episodes of abdominal pain. We were able to avoid pharmaceuticals and Abby's clinical course never required keeping a diary. It is in situations like this where we can employ the best of conventional and integrative care. The acute pathology was adeptly ruled out and I could then pursue a holistic program. Her integrative treatment plan simply consisted of the following:

- A carefully selected homeopathic remedy
- Elimination diet
- Manipulative medicine.

**On Another Note**

The past two years have brought to light the fact that many young families and eaters have become very reliant on information generated from a medical system that receives directives from Pharma. How do we educate our patients on how to *get back* and regain control of their well-being, veering away from *pill for ill* medicine? Joni Mitchell sang it best, "…And we've got to get ourselves back to the garden…"

***Regeneration Health International*** is a newly launched website dedicated to the facilitation of a global movement and alliance, focused and committed to regenerating personal and public health.[7] Our work is based on the fundamental principles that ***food is medicine***, and that human health (mental, physical, and spiritual), are directly related to societal, environmental, and planetary health.

The team, comprised of scientists, farmers, activists, artists, physicians, and lawyers have created a ***collaboratory***, focused on a local-to-global scale, moving away from industrial agriculture and medicine, towards a solutions-based *ecohealth* model.

By *regenerating our health*, we mean the following:

- The care of and optimization of immune function
- A rebalancing of the gut microbiome
- The prevention of environmentally caused diseases, such as obesity and heart disease
- Exercise, and
- The elevation of our mental, emotional, and spiritual well-being.

Network and community outreach are some of the tools being employed, connecting to the various already established projects and organizations committed to these principals so that regenerative practices become the norm, not the alternative.

**References**


1. D'Agostino J. Common abdominal emergencies in children. *Emerg Med Clin North Am.* 2002;20:139–153
2. Kim, JS. Acute Abdominal Pain in Children. *Pediatr Gastroenterol Hepatol Nutr.* 2013 Dec; 16(4): 219–224
3. https://www.rch.org.au/clinicalguide/guideline_index/Intussusception_Guideline/
4. Tleanu, RI, et al. Treatment of Pediatric Migraine: a Review; *Maedica (Bucur).* 2016 Jun; 11(2): 136–143
5. https://migrainetrust.org/live-with-migraine/self-management/keeping-a-migraine-diary/
6. Beuthin J., et al. Gluten-Free Diet and Migraine; *Headache*; 2020 Nov;60(10):2526-2529.
7. https://www.rhi.bio


◆

# Environmental Medicine Update

**by Marianne Marchese, ND**
**www.drmarchese.com**

# The Problem with PFAS – Polyfluoroalkyl's Health Effects

**Introduction**

Perfluoroalkyl, perfluorinated chemicals (PFCs), and polyfluoroalkyl substances (PFAS) are man-made chemicals known as forever chemicals because they don't break down in the environment. Some chemicals that are in this group include perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), perfluorononanoic acid (PFNA), perfluorohexane sulfonic acid (PFHxS), and perfluorodecanoic acid (PFDA). For simplicity's sake we will refer to them in this article as PFAS. They are found in the air, soil, and water. They can accumulate up the food chain and be present in cooking and drinking water. They get into the environment from manufacturing, daily use of consumer products, and disposal of these products in landfills and incinerators. They don't break down in the environment and can remain present forever.

Everyone is exposed to PFAS throughout the day and may not even realize their presence in food, products, clothing, and cookware. They are found in the blood of people all over the world. These chemicals are linked to adverse health effects, including cancer, reproductive and hormonal effects, cardiovascular disease, elevated liver enzymes, immune disruption, and more. Environmental groups and medical organizations have called for their regulation. The American Chemistry Council states PFAS are necessary and vital and resist regulation. So, is there a problem with PFAS?

**PFAS Source of Exposure**

PFAS are used in many consumer products to make them resistant to water, oil, heat, and corrosion. The chemicals in these products then contaminate water and the soil and can accumulate up the food chain. Some examples of where PFAS can be found include the following[1,2]:

1. Non-stick pots and pans
2. Waterproof and stain-resistant clothing and shoes
3. Stain-resistant furniture, carpeting, and clothing
4. Grease-resistant food packaging found in grocery stores and takeout food (pizza boxes, paper plates, food wrappers, salad bowls, takeout containers, paper bags, food liners, baking and cooking supplies to name a few)
5. Ink used on food containers
6. Machines that make packaging
7. Paints and sealant
8. Dental floss and shampoo
9. Make-up and lipstick
10. Cleaning products
11. Firefighting foam
12. Drinking water
13. Contaminated fish
14. Fertilizer that used industrial sludge
15. Vegetables grown in or with contaminated soil, fertilizer, or water
16. Contaminated wild game such as deer

Although the amount of exposure from each source may be small, we can be exposed to more than one source at a time and these chemicals build up in our body. We know this from various organizations performing bio-monitoring studies. The Center for Disease Control has been testing for the presence of PFAS in humans since 1999. People in the US participating in the National Health and Nutrition Examination Survey (NHANES) have their blood tested for the presence of PFAS. Most recently, CDC scientists found four PFAS (PFOS, PFOA, PFHxS, and PFNA) in the serum of nearly all the people tested.[3]

Everyone is exposed to PFAS to some degree, but some more than others. It appears that lower income communities have higher amounts of PFAS in their drinking water than other communities. A recent investigation in California discovered that disadvantaged areas have increased levels of PFAS in their drinking water compared to high income communities.[4] In early 2019, California tested public water systems near PFAS sources of exposure to see if the water was contaminated. 1,300 drinking water sources in California were tested for 18 different PFAS, accounting for 3% of the state's public water sources. 65%

of the public water systems, serving over 16 million people, had high levels of PFAS. Disadvantaged communities had the highest levels in the state. California identified environmentally disadvantaged communities as those with higher rates of poverty and unemployment, higher pesticide uses in the area, and higher air pollution than the rest of the state.[4] People most at risk for having PFAS in their drinking water are those living near chemical and product manufacturing sites, airports, military bases, landfills, wastewater treatment plants, incinerators, and areas where PFAS-contaminated sludge is spread on the soil.

After drinking water contamination, food packaging is probably the next largest source of exposure. Many people have no idea that the takeout food containers, food wrapping, and packing contain PFAS. Trying to test for PFAS in food packaging is a challenge since there are thousands of PFAS and testing can only identify a few dozen. One method to test for PFAS in food products and packaging is by measuring organic fluorine; this assesses the material's total PFAS content. Denmark has recently set the limit at 20 parts per million (ppm). California is restricting the level to 100 ppm in 2023. Consumer reports published results of the testing they conducted on 118 products. 37 products had fluorine levels above 20 ppm and 22 products were above 100 ppm.[5] Paper bags contained 192.2 ppm, single use plates contained 149 ppm, and food wrappers/liners contained 59.2 ppm. Consumer Reports went on to test for organic fluorine, a measure of PFAS, in common fast food and supermarket takeout food packaging. The results are shocking. Here are a few of the findings.[5]

- Arby's bag for cookies - 457.5 ppm
- Whole Foods market container for soup - 21 ppm
- Burger Kin wrapper for Whopper - 249.7 ppm
- McDonalds bag for French fries - 250 ppm
- Panera Bread container for pizza - 82 ppm
- Nathan's Famous bag for sides - 876 ppm

Source: Toxicfreefuture.org

**PFAS Health Effects**

Since PFAS are present in the blood of over 90% of the population in the US and found in common consumer products, food, water and even found in the air, we need to understand the effects on human health. Studies show that PFAS affect men, women, and children. They have been linked to cancer, cardiovascular disease, infertility, thyroid disorders, weakened immunity, reproductive and development effects, liver disease and changes in hormones.[6] Many argue that the concentration of daily exposure is so low that PFAS present in food, products and the water may not be at a high enough dose to cause health effects. Often, they are not seen as environmentally relevant in terms of health risk. However, even those who make that argument acknowledge that there is very little information on newer PFAS that we are exposed to or their precursors and degradation products. Many studies don't take into consideration the synergistic effects of various forms and types of PFAS once in the body and the length of time these chemicals stay in the human body. In fact, there are very few studies on the safety of PFAS in small concentrations, or chronic low-dose exposure.[7]

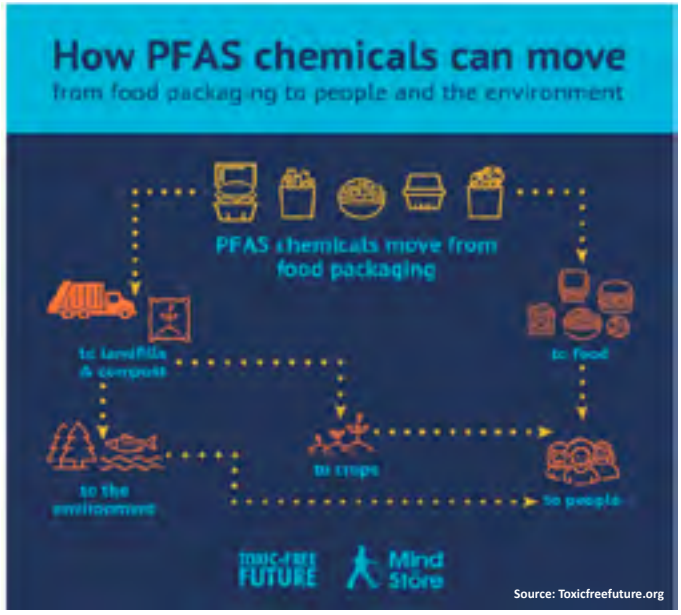
What we do know does raise concern. PFAS have a very long half-life, are difficult to excrete and tend to accumulate in the body. Hence their presence in body burden studies mentioned above. In fact, PFAS have a half-life in human blood of 3-5 years.[8] PFAS bind to blood proteins such as albumin and can be detected in blood, urine, breast milk, and plasma. They can accumulate in adipose tissue, liver, kidney, and the lungs.

The adverse health effects of PFAS have been known since the 1980s when PFAS were detected in the blood of workers who had occupational exposure. The female workers had high rates of birth defects in their offspring. Occupational exposure has also been linked to several forms of cancer such as bladder, kidney, and testicular cancer.[9] Lower dose exposure has been linked to thyroid disease, altered kidney function, high cholesterol, ulcerative colitis, altered immune systems, and adverse effects on male sperm and female ovarian function.[8] The Environmental Protection Agency acknowledges that high cholesterol is the most common adverse health effect from lower dose PFAS exposure. It appears that timing of exposure does matter. PFAS exposure *in utero* can have a negative impact on both the fetus and mother. *In utero* exposure is linked to hypertension during pregnancy, preeclampsia, and low birth weight babies.[9]

Researchers studying the health effects of PFAS are challenged by the numerous forms and mixtures, sources of exposure, geographical differences based on precipitation and wind drift, lack of an unexposed control group in the general population, various timing of exposures having different effects *in utero*, childhood, and adult years, as well as commercial laboratory testing variations.[9] Despite these challenges, there is enough data on human health to warrant concern and for health care providers to start to educate on avoidance and begin testing patients for the present of PFAS. As stated earlier, the CDC NHANES program has been testing for PFAS in the blood of the general population since 1999 and over 90% of those tested had PFAS present. The levels are declining over time most likely based on awareness and avoidance education.

**Regulation and Avoidance**

It is important that health care providers focused on preventive medicine start to educate patients on how to avoid PFAS. Patient with health conditions linked to PFAS also need to ➤



➤

implement avoidance measures at home, work, and school. It begins with testing the water that we drink and that we use for cooking. In 2009, the US Environmental Protection Agency (EPA) set a guideline for allowable levels of the PFAS chemical PFOA at 400 parts per trillion (ppt). In 2016 the agency reduced that level to 70 ppt. The EPA is currently reviewing the acceptable level of PFAS in the drinking water and will make a new proposal by the end of 2022 that will include both a non-enforceable maximum contaminant level goal and an enforceable standard as well. They will be proposing a PFAS National Drinking Water Regulation. It is important to note that real regulation will require preventing industries from contaminating our food and waterways with PFAS. In 2022 the EPA did begin steps to address PFAS contamination leaching from fluorinated containers and the EPA removed two PFAS from its Safer Chemical Ingredients list. Some states, such as California, are taking matters into their own hands by restricting PFAS in food packaging and creating tight regulating of levels of PFAS in the drinking water.[10] These are important steps but, in the meantime, people need to be educated on avoidance measures.

**Avoidance Measures**

1. Avoid non-stick cookware other than ceramic.
2. Use stainless steel, cast iron and glass cookware.
3. Avoid microwaveable popcorn bags that may be coated with PFAS.
4. Cook at home to avoid to-go containers.
5. Transfer food out of packaging as soon as you get it home to glass containers.
6. Avoid reheating food in takeout containers.
7. Avoid products, furniture, carpet, and clothing labeled as no-iron, stain-resistant, waterproof, non-stick, easy clean.
8. Test your water and report PFAS to local water regulating agencies.
9. Use a reverse osmosis or charcoal water filter for all drinking and cooking water.
10. Look for products labeled as PFAS-free.
11. Chose restaurants working to phase out PFAS from takeout containers.
12. Avoid cosmetics labeled as water-resistant or that contain "fluoro" in the ingredients.
13. Use HEPA-type air filter at home and work
14. Use a vacuum with HEPA filter
15. Continue to stay educated and informed about PFAS source of exposure, health effects and regulation

**Summary**

Perfluoroalkyl, PFCs, and polyfluoroalkyl substances (PFAS) are man-made chemicals that include perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), perfluorononanoic acid (PFNA), perfluorohexane sulfonic acid (PFHxS), and perfluorodecanoic acid (PFDA). They are present in our drinking and cooking water, food packaging and containers, cosmetics, clothing, furniture and home furnishings, indoor and outdoor air, cookware and numerous other places. The majority of people in the US are exposed to low dose PFAS—often without knowing they are exposed. Body burden studies confirm over 90% of the population has detectable levels of PFAS in the blood. These chemicals are harmful to human health even in low doses. It is vital that health care professionals consider PFAS exposure as a link to adverse health conditions, have patient test their home water for PFAS, and educate people on how to avoid PFAS in their daily life.

**References**


1. Agency for Toxic Substances and Disease Registry (ATSDR). Per-and polyfluoroalkyl Substances and Your health. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Services. www.atsdr.cdc.gov/pfas. Accessed May 31, 2022.
2. O'Brien K. Forever chemicals upended a Maine farm — and point to larger problem. *Washington Post*. April 11, 2022.
3. Center for Disease Control. per-and polyfluoroalkyl substances (PFAS) factsheet. May 2nd, 2022. https://www.cdc.gov/biomonitoring/PFAS_FactSheet.html. Accessed June 8, 2022.
4. Reade A, Lee S. CA PFAS Pollution Widespread in Disadvantaged Communities. NDRC. Aug 17, 2021. CA PFAS Pollution Widespread in Disadvantaged Communities | NRDC. Accessed June 6, 2022.
5. Loria, K. The Dangerous Chemicals in your Fast-Food Wrappers. *Consumer Reports*. May 2022. 36-43.
6. Our Current Understanding of the Human health and Environmental Risks of PFAS. Uniter States Environmental Protection Agency. March 16, 2022. https://www.EPA.gov/pfas/ Accessed June 19, 2022.
7. Sinclair GM, Long SM, Jones OAH. What are the effects of PFAS exposure at environmentally relevant concentrations? *Chemosphere*. Nov 2020;258:127340.
8. Calvert L, et al. Assessment of the emerging threat posed by perfluoroalkyl and polyluoroalkyl substances to male reproduction in humans. *Front Endocrinol (Lausanne)*. March 9, 2022;12:799043.
9. Blake BE, Fenton SE. Early life exposure to per- and polyfluroalkyl substances (PFAS) and latent health outcomes. Toxicology. Oct 2020;443:152565.
10. EPA continues to take actions to address PFAS in Commerce. March 16, 2022. https://www.epa.gov/newsreleases/ Accessed June 22, 2022.


Dr. Marianne Marchese is the author of the bestselling book *8 Weeks to Women's Wellness* about the environmental links to women's health and how to mitigate the effects from toxicants. She maintains private practice in Phoenix, Arizona, and is adjunct faculty at SCNM, teaching both environmental medicine and gynecology. She lectures throughout the US and Canada on women's health, environmental, and integrative medicine topics. Dr. Marchese recently helped develop three supplements for Priority One Vitamins. www.drmarchese.com ◆

# CALENDAR

**SEPTEMBER 24-25: OZONE THERAPY CERTIFICATION COURSE** with Dr. Bryan Rade, ND, in Halifax, Nova Scotia. Learn intravenous and intraarticular ozone therapy. Space limited to eight attendees. CONTACT: www.eastcoastnaturopathic.com.

**SEPTEMBER 30-OCTOBER 2: INTEGRATIVE DERMATOLOGY SYMPOSIUM** in Tucson, Arizona. CONTACT: https://integrativedermatologysymposium.com/

**OCTOBER 8-9: ASSOCIATION FOR THE ADVANCEMENT OF RESTORATIVE MEDICINE PEPTIDE/STEM CELL INTENSIVE** online. CONTACT: https://restorativemedicine.org/conferences/2022-peptide-course/

**OCTOBER 13-15: ASSOCIATION OF AMERICAN PHYSICIANS AND SURGEONS (AAPS) 79th ANNUAL CONFERENCE** in Springfield, Missouri. CMEs. CONTACT: https://aapsonline.org/event/oct-13-to-15-2022-aaps-79th-annual-meeting/

**OCTOBER 14-16: 12th INTERNATIONAL ADVANCED APPLICATIONS IN MEDICAL PRACTICE (AAMP) CONFERENCE – Endocrine Assessment and Treatment** in Scottsdale, Arizona, and online. CMEs available. CONTACT: https://aampconferences.com/spring-conference-2022/

**OCTOBER 15-16: NEURAL THERAPY TO ELIMINATE PAIN TRAINING COURSE** with Bryan Rade, ND, in Halifax, Nova Scotia. Learn a minimally invasive therapy to address pain. Space limited. CONTACT: www.eastcoastnaturopathic.com

**OCTOBER 22: COMMUNITY COMPOUNDING PHARMACY CONFERENCE FOR NATUROPATHIC COMMUNITY** in Portland, Oregon and as a webinar. CEs available. CONTACT: https://www.communitycmpd.com/events

**OCTOBER 27-29: A4M/MMI IV/CHELATION THERAPY** in Charleston, South Carolina. CONTACT: https://www.a4m.com/iv-chelation-therapy-symposium-a4m-october-2022.html

**OCTOBER 27-29: A4M/MMI PELLET THERAPY** in Charleston, South Carolina. CONTACT: https://www.a4m.com/pellet-therapy-a4m-october-2022.html

**OCTOBER 27-29: A4M/MMI LONGEVITY MEDICINE AND BIO-HACKING: OPTIMIZING LIFESPAN** in Charleston, South Carolina. CONTACT: https://www.a4m.com/module-viii-a4m-october-2022.html

**OCTOBER 28-29: INTERNATIONAL CONFERENCE ON PREVENTIVE MEDICINE AND INTEGRATIVE MEDICINE** in Los Angeles, California. CONTACT: https://waset.org/preventive-medicine-and-integrative-medicine-conference-in-october-2022-in-los-angeles

**OCTOBER 28-30: ACADEMY OF INTEGRATIVE HEALTH & MEDICINE CONFERENCE – People. Planet. Purpose** in San Diego, California. CONTACT: https://www.aihm.org/conference/

**OCTOBER 28-30: AzNMA NATUROPATHIC MEDICINE EDUCATION CONFERENCE** in Scottsdale. CONTACT: https://www.aznma.org/

**NOVEMBER 4-5: NEW HAMPSHIRE ASSOCIATION OF NATUROPATHIC DOCTORS CONFERENCE** in Newcastle, New Hampshire. CONTACT: https://www.nhand.org/

**NOVEMBER 5-6: OREGON ASSOCATION OF NATUROPATHIC PHYSICIANS ANNUAL CONFERENCE** in Portland, Oregon. CONTACT: https://www.oanp.org/page/AnnualConference

**NOVEMBER 12: THE WELL WOMAN CONFERENCE** – Integrative and Functional Strategies for Optimizing Women's Mental Health and Vitality online. CONTACT: https://www.psychiatryredefined.org/

**NOVEMBER 12-13: HEARTQUEST GLOBAL INTERACTIVE CONFERENCE on the Renaissance of New Healing Solutions** in Scottsdale, Arizona. CONTACT: https://www.heartquestglobalsolutions.com/nov-2022-conference

**DECEMBER 9-10: INTERNATIONAL CONFERENCE ON PREVENTIVE AND INTEGRATIVE MEDICINE** in New York City, New York. CONTACT: https://waset.org/preventive-medicine-and-integrative-medicine-conference-in-december-2022-in-new-york

**DECEMBER 9-11: A4M presents LONGEVITY FEST 2022** in Las Vegas, Nevada. CONTACT: https://www.a4m.com/longevity-fest-2022.html

**DECEMBER 9-11: A4M/MMI PEPTIDE THERAPY CERTIFICATION** in Las Vegas, Nevada. CONTACT: https://www.a4m.com/peptides-ii-a4m-december-2022.html

**DECEMBER 9-11: A4M/MMI ADVANCED ENDOCRINOLOGY: THE HORMONAL SYMPHONY (Module 1)** in Las Vegas, Nevada. CONTACT: https://www.a4m.com/module-i-a4m-december-2022.html

**DECEMBER 9-11: A4M/MMI TRIADS: A SYSTEMS BIOLOGY APPROACH (Module V)** in Las Vegas, Nevada. CONTACT: https://www.a4m.com/module-i-a4m-december-2022.html

**JANUARY 28-29, 2023: INTERNATIONAL CONFERENCE ON TRADITIONAL MEDICINE AND HERBS** in New York City, New York. CONTACT: https://waset.org/traditional-medicine-and-herbs-conference-in-january-2023-in-new-york

**APRIL 22-23: INTERNATIONAL CONFERENCE ON INTEGRATIVE MEDICINE AND NUTRITION** in New York City, New York. CONTACT: https://waset.org/integrative-medicine-and-nutrition-conference-in-april-2023-in-new-york

**JUNE 2-4: SASKATCHEWAN ASSOCIATION OF NATUROPATHIC DOCTORS HEALING SKIES CONFERENCE** in Saskatoon, Saskatchewan, Canada. CONTACT: http://www.sasknds.com/healing-skies-conference.html

**JUNE 16-18: 5th INTERNATIONAL HOMEOPATHY RESEARCH** in London, United Kingdom. CONTACT: https://www.hri-research.org/2022/07/hri-london-2023-save-the-date/

◆

# Curmudgeon's Corner

**by Jacob Schor, ND, FABNO**
**drjacobschor1@msn.com**

## Diphtheria in Maine

About two miles down our dirt road that leads toward the south end of the lake, there is a section of woods that people refer to as "the Dark Forest," an appropriate name as the trees seem larger, closer together, and more overgrown than in surrounding areas. Less light penetrates the foliage and the shadows between the trees sometimes allow one to see things that probably aren't there. Old stone walls section the forest giving evidence that the land must once have been cleared. Our neighbor Trudell, who owns much of that area, came over for lunch a few weeks back and told us a story that has lingered in my mind.

Those stone walls mark the fields of a once prosperous farm. The foundation of the original farmhouse is just off the road. According to Trudell, the man who farmed this land, along with his wife and some unknown number of children, all succumbed to diphtheria. The farmer's brother, in order to halt spread of whatever contagion led to their deaths, burnt their house to the ground. The farm was long abandoned. Trudell used a phonetic pronunciation of this disease's name, calling it 'difftheria' so it took me a moment to realize what she meant. She tells us this all happened in 1750. She is close, and possibly correct, with the date, but it is hard to believe that an old shoe she claims to have found in the ruins did belong to the original inhabitants.

The epidemic of what was called throat distemper or putrid throat swept through New England, including this part of Maine, in waves starting in 1735. Trudell's story could have occurred in 1750 or even earlier. Until vaccines were developed two hundred years later, diphtheria was a leading cause of death in our country, especially among children. The epidemic struck first in New Hampshire (NH) in May 1735, killing about 1% of that state's population. It spread south through the Massachusetts Bay Colony into Connecticut and northeast into Maine. As the epidemic ran its course, more than 5000 people died, over 75% of them were children.

The Rev. Roland Sawyer wrote in his history of the epidemic that, by 1738 in Kensington, NH, so many children had succumbed to diphtheria "there were few children left to die." Estimates of the magnitude of the epidemic vary. Most accounts are local, tallying mortality in a single township. In Kensington's cemetery, there are graves of 250 children who died of diphtheria between 1744 and 1779.

Accounts of diphtheria date back to Hippocrates. Cotton Mather recorded cases of the disease in Massachusetts in December 1659. Yet, the 1735 outbreak was more virulent than any prior outbreak. One theory suggests that a mutation in the causative bacteria had occurred and the variant was more transmissible and deadly than earlier strains, a concept we are now currently sadly familiar with. The 1735 outbreak started in Kingston, New

Hampshire, and from there spread to Hampton Falls, then to Exeter, Durham, Dover, Chester, and then to Portsmouth. From that crossroad, it spread outward from New Hampshire to Maine, Massachusetts, and Connecticut.

"Diphtheria caused over 1,000 deaths amongst the colonists between 1735-1736 alone. In New Hampshire, 90% of those deaths occurred in children under the age of 10."[1] Across New England some 5,000 people died of diphtheria between 1735 and 1740. More than 75 percent were children. Overall, it killed 22 of every 1,000 people. In New Hampshire, where it struck first and worst, 75 out of every 1,000 people died of it. The case-fatality ratio was almost 40% though few of the young survived. Afflicted children often died within three days. Roads were few and travel patterns in New England were simple enough that epidemiologists have tracked the spread in detail. Physicians had trouble agreeing on a diagnosis for the disease, calling it cynanche, angina, canker, bladders, rattles, or throat distemper.[2]

These numbers seem small in contrast to the hundreds of thousands of deaths in the waves of our modern epidemic, but we should remember how few the inhabitants were back then. In 1730 the recorded population of New Hampshire was less than 11,000.

Dr. Josiah Bartlett, who practiced in Kingston, NH, is of some interest to us. He initially adhered to the general treatment guidelines of depletion and antiphlogistic treatment. The medical standard of care back then was to treat this disease by bleeding the patient from a vein behind the tongue. Bartlett saw no benefit from this intervention during the early years of the epidemic. During subsequent waves, Bartlett instead of bleeding dosed his patients with Peruvian bark, that is, *Cinchona officinalis*. He reported in 1754 that Cinchona might relieve the disease's symptom long enough for patients to recover. Of course, this was the era when Cinchona was highly valued as a treatment for malaria. Whether or not Cinchona proved efficacious for these patients is unclear. It may have simply reduced the doctor's obligation to bleed resulting in less iatrogenic harm. Or, perhaps it did slow disease progression as Bartlett suggested. This is no longer a question that needs an answer. Effective antidotes are now available to treat diphtheria. Bartlett is far more famous as a signatory of the Declaration of Independence and for his roles in state and national politics than for promoting Cinchona.

Credit is given to the French physician Pierre Bretonneau for naming the disease in 1826, calling it *diphtérite* from the Greek word for "leather" to describe the pseudomembrane that coats the throat as a result of the disease. Bretonneau is on record for performing the first successful tracheotomy in a case of diphtheria, though his first attempts were sadly unsuccessful. This procedure involves cutting an opening in the trachea and inserting a tube to allow passage of air and removal of secretions. Another French physician, Armand

➤

➤

Trousseau, with practice, managed to achieve a survival rate of about 25% using tracheotomies.

Diphtheria is referred to as "the paradigm of toxigenic infectious disease." In 1883 Edwin Klebs, a Swiss-German pathologist, identified and described the bacterium responsible as having a club-shaped appearance. The shape led Klebs to name the bacteria, using the Greek word for club (κορυνε/koruna): *Corynebacterium diphtheriae*. In 1884, Friedrich Loeffler became the first to cultivate these *Corynebacterium diphtheriae*. The bacteria could only be grown from the nasopharyngeal cavity. Loeffler postulated that the damage to internal organs resulted from a soluble toxin.

In 1888, Roux and Yersin injected animals with sterile filtrates of *C. diphtheriae* and showed that the animals developed similar organ pathology to what was seen in humans with diphtheria, proving the existence of Loeffler' toxic protein that underlay the disease's virulence. This was the first bacterial exotoxin recognized by science. As *C. diphtheriae* colonize the upper respiratory tract, it is this toxin that injures and then destroys cells. Waste products and proteins from the dying cells form the thick gray substance over the pharynx. This pseudomembrane sticks to tissues and obstructs breathing. The toxin may also damage the heart, muscle, kidneys, liver, and other areas.



Guinea pigs and rabbits are highly susceptible to diphtheria toxin (DT) while mice and rats are resistant. This may be what gave rise to our continuing reluctance to volunteer as "guinea pigs" for laboratory experiments. The lethal dose of DT for humans is small, 0.1 µg/kg of body weight.

In 1890, von Behring and Kitasato showed that susceptible animals could be immunized by injection with graded doses of diphtheria bacilli, and that blood serum taken from these animals protected other susceptible animals from the effects of DT. This serum became known as antitoxin. A year later, in 1891, such antitoxin was used successfully to treat diphtheria in a child. The time period from the identification of the disease-causing bacteria to the introduction of antitoxin therapy for treating diphtheria was remarkably short. Perhaps even shorter was the interval to when von Behring received his Nobel Prize in 1901.

In 1909, Theobald Smith came up with the strategy of using a mixture of DT and diphtheria antitoxin together to immunize humans against diphtheria. A large-scale trial of this toxin-antitoxin vaccine was conducted in 1922 in New York City by W. H. Park and proved successful. In 1923, Ramon discovered that treating DT with formalin eliminated its toxicity while retaining its required immunogenicity. Formalin-treated DT, now called diphtheria toxoid, became the preferred vaccine against diphtheria. This diphtheria toxoid (used in combination with other vaccines) is still used for active immunization against diphtheria. The PW8 strain of *C. diphtheriae,* isolated by Park and Williams in 1896 continues to be used throughout the world to make DT for production of diphtheria toxoid for vaccine.

Given the widespread use of intubation during the current Covid pandemic, it is appropriate to mention that the technique was first introduced in 1885 by Joseph O'Dwyer as a method for rescuing young diphtheria victims from pseudomembranous suffocation. O'Dwyer died in 1898 from complications of diphtheria acquired while intubating a patient.

Widespread use of the vaccine has sharply reduced diphtheria incidence in the US and globally.

The Centers for Disease Control (CDC) recorded only 57 cases in the United States between 1980 and 1994, while the World Health Organization (WHO) reported 3,978 cases worldwide in 2006. The last major outbreak in the United States was in Seattle in 1971.

Few of us have had the misfortune of ever diagnosing diphtheria in our patients. This is a good thing, a very good thing. One can barely imagine the kind of horror described in these historical accounts. One can easily forget the depth of tragedy earlier generations lived with, except when it happened just down the road.

**References**


1. Hagen, Ashley. The Toxin-Based Diseases Common in North America during the 1600-1700s. American Society for Microbiology. July 5, 2019.
2. Caulfield, Ernest. "A History of the Terrible Epidemic, Vulgarly Called the Throat Distemper, as it occurred in His Majesty's New England Colonies Between 1735 and 1740." *Yale Journal of Biology and Medicine,* 1939 January; 11(3): p. 223, and pp. 243-245. U.S. National Library of Medicine. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2602079/pdf/yjbm00529-0057.pdf https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2602120/pdf/yjbm00530-0001.pdf


◆

➤ *continued from page 80*



contains a lot more copper than white rice. Based on this limited analysis, it would seem that Sri Lankans have abundant copper status, and are therefore less susceptible than other populations to zinc-induced copper deficiency. I also found a paper showing that zinc deficiency is quite common in Sri Lankan children, although I did not find any data for adults. Suboptimal zinc status also appears to be common in Australia, although the data are limited.

To which the author replied: "Thanks, Alan. It's a shame we don't have the money to run another randomized clinical trial to test the combination of zinc and copper. Perhaps work for someone else to do."

So, here we have a situation in which a study that was developed to answer a specific question may not have provided a clear answer to that question because the researchers were not aware of a potential problem with their study design. There are many other examples of how a better study design might have produced more useful data, although a detailed discussion of that point is beyond the scope of this editorial.

One thing that can be done to promote better research designs is to encourage researchers to publish their protocols before they actually start the study. Scientists who are interested in that particular topic can then contact the researchers to provide suggestions on how to improve the study design. Some researchers already do publish their protocols in advance, but most do not. Something else that could be done would be to create artificial-intelligence tools that could be used to identify potential problems in study designs. Clinical research is expensive and time-consuming, and it is a shame when studies fail to answer questions that might have been answerable if there had been a slight modification of the study design.

Alan R. Gaby, MD

**References**


1. Attia JR, et al. The effect of zinc supplementation on glucose homeostasis: a randomised double-blind placebo-controlled trial. *Acta Diabetol*. 2022 Apr 22 [Online ahead of print].
2. Hassel CA, et al. Impaired glucose tolerance in copper-deficient rats. *J Nutr*. 1983;113:1081-1083.
3. Fields M, et al. Impairment of glucose tolerance in copper-deficient rats: dependency on the type of dietary carbohydrate. *J Nutr*. 1984;114:393-397.
4. Klevay LM. An increase in glycosylated hemoglobin in rats deficient in copper. *Nutr Rep Int*. 1982;26:329-334.
5. Klevay LM, et al. Decreased glucose tolerance in two men during experimental copper depletion. *Nutr Rep Int*. 1986;33:371-382.
6. White HS. Inorganic elements in weighed diets of girls and young women. *J Am Diet Assoc*. 1969;55:38-43.
7. Klevay LM, et al. Evidence of dietary copper and zinc deficiencies. *JAMA*. 1979;241:1916-1918.
8. Wolf WR, et al. Daily intake of zinc and copper from self selected diets. *Fed Proc*. 1977;36:1175.
9. Klevay LM, et al. The human requirement for copper. I. Healthy men fed conventional, American diets. *Am J Clin Nutr*. 1980;33:45-50.
10. Fischer PW, et al. Effect of zinc supplementation on copper status in adult man. *Am J Clin Nutr*. 1984;40:743-746.
11. Festa MD, et al. Effect of zinc intake on copper excretion and retention in men. *Am J Clin Nutr*. 1985;41:285-292.


◆

# I'll Know My Song Well Before I Start Singing

"I'll know my song well before I start singing." Those words were written by Bob Dylan, at the end of one of his most famous songs, "A Hard Rain's A-Gonna Fall." Bob Dylan, the only songwriter in history to win the Nobel Prize in literature. I was 15 years old when I first heard that song, and those words have stayed with me ever since.

A recent correspondence I had with a medical researcher reminded me of the importance of knowing one's song well before singing it. While perusing the recent medical literature for new articles of interest, I came across a paper that examined whether zinc supplementation could improve glucose homeostasis in people with prediabetes. In that study, 98 Australian adults (aged 40-70 years) with prediabetes (defined as a hemoglobin A1c level of 5.7-6.4%) were randomly assigned to receive, in double-blind fashion, 30 mg per day of zinc or placebo for 12 months. After 12 months, compared with placebo, zinc supplementation had no significant effect on mean values for hemoglobin A1c, fasting blood glucose, or insulin resistance.[1]

I was concerned that this study had a potentially important flaw, so I sent an email to one of the authors of the study. The email read in part:

> Thank you for your contribution to the zinc/diabetes literature. My concern with the study is that it does not consider the possibility that zinc is beneficial, but that zinc-induced copper deficiency could negate the potential beneficial effect of zinc. One wonders whether a better outcome would be achieved by comparing the combination of 30 mg per day of zinc and 2 mg per day of copper with a placebo.

To support my comments, I cited the following evidence.

Rats fed a copper-deficient diet had impaired glucose tolerance[2,3] and elevated levels of glycated hemoglobin.[4] Two healthy male volunteers participating in a copper-depletion experiment had decreased glucose tolerance after consuming a diet containing 0.78 mg per day of copper for 90-120 days. Glucose tolerance improved after copper repletion (6 mg per day) and was, in fact, somewhat better than before the depletion experiment, suggesting that pre-study copper status was low.[5]

The copper content of many Western diets may be even lower than the 0.78 mg per day used in the depletion experiment. Mean daily copper intake by high school and college women was only 0.5 mg per day,[6] and the mean copper content of hospital diets was 0.76 mg per day.[7] Other studies found slightly higher amounts of copper in typical Western diets: a mean of 1.01 mg per day (range, 0.58-2.03 mg per day) in one study,[8] and a mean of 1.27 mg per day in another study.[9]

In healthy males, administration of 25 mg of zinc twice a day for six weeks resulted in a reduction in erythrocyte Zn-Cu superoxide dismutase activity, which may indicate mild copper deficiency.[10] In healthy men, increasing zinc intake to 18.5 mg per day from a lower level of intake resulted in an increase in fecal copper excretion and a reduction in copper retention.[11]

The study author replied to my email:

> Thanks for this information. It is an interesting point which we were not aware of. It may be part of the story but perhaps not the entire answer, given that a similar randomized clinical trial run in Sri Lanka (by our colleagues who collaborated on our paper) using the same dose of zinc showed a marked beneficial effect (with no copper supplementation). Is there a reason why that might be?

After finding some information about the typical diet in Sri Lanka, I wrote back to the author:

> Thank you for your reply. I can only speculate about why different results were obtained in Australia and Sri Lanka. In searching the Internet, I see that some of the dietary staples in Sri Lanka are cashews, coconut milk, and red rice. One ounce of cashews contains 622 µg of copper (which is a lot) and one cup of coconut milk contains 32% of the recommended daily intake of copper. I could not find the copper content of red rice, but red rice is apparently similar to brown rice, which

*continued on page 79* ➤

A4M MMI REDEFINING MEDICINE®

# Longevity FEST 2022

## 30TH ANNUAL WORLD CONGRESS


This year's Annual World Congress in Anti-Aging Medicine will be extraordinary in many ways, as we celebrate our past while building on the foundation of 30 years of excellence.

JOIN US!

## SPECIAL GUEST SPEAKER

Jeffrey Bland, PhD, FACN, FACB, CNS

## FEATURED SPEAKERS

Charles Brenner, PhD

Kara Fitzgerald, ND

Thierry Hertoghe, MD

Mark Houston, MD, MS, FACP, ABAARM

Gordon Lauc, PhD

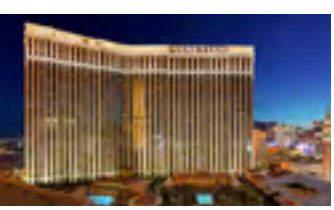
Daved Rosensweet, MD

Erika Schwartz, MD

Pamela W. Smith, MD, MPH

**As we seek to further extend longevity, how can we simultaneously help patients live longer and delay age-related health issues?**

To explore this key question, the World Congress will bring together physicians, researchers and scientists from a variety of fields including genetics, biology of aging, endocrinology, clinical psychology, physiology, and more.



## HOTEL INFORMATION

**THE VENETIAN AND PALAZZO RESORT**

3355 S. Las Vegas Blvd. Las Vegas, NV 89109

# SAVE $200

**Use coupon code Townsend 200**

**www.a4m.com**

# Truly the Best CBD: Now Two Proven Formulas!




**TruEase®:** today's best-in-class CBD product, produced under the highest ethical and quality standards, now validated as the truly superior CBD product in a newly published **Clinical Trial Study: "A Novel Self-Emulsifying Drug Delivery System (SEDDS) Based on VESIsorb® Formulation Technology Improving the Oral Bioavailability of Cannabidiol in Healthy Subjects"†**.

**TruEase® + Curcumin:** a patented, synergistic formulation with unmatched therapeutic benefits of Curcumin, Cannabidiol (CBD), Beta-caryophyllene, & Vitamin D3 powered by the VESIsorb® delivery system for maximum absorption and bioavailability and validated by the recent TruEase® Clinical Trial Study†. The active constituents in Curcumin can act as effective antioxidants against excessive free radical damage, along with support for joints, brain, and overall good health*.

TruGen3® continues the Lioon family legacy of three generations and more than a half-century of nutraceutical experience, with products produced under the highest ethical standards, available exclusively through Health Professionals. Contact us to find out how you can put our highly innovative products to work for your patients, and your practice, today.

**Contact us today for FREE SAMPLES and to find out how you can put our innovative, one-of-a-kind products to work for your patients, and your practice, today.**

**† For a complete copy of the TruEase® Clinical Trial Study, visit trugen3.com/truease.**

## Get More with TruGen3®

Direct access to **Chief Clinical Advisor Dr. Chris D. Meletis** for answers to all your CBD questions

- **VESIsorb® Technology for up to 440% more** bioavailability than ordinary CBD products†. Many Turmeric components' (including curcuminoids) fat-soluble nature can make gastronomical absorption a challenge. The VESIsorb® delivery system minimizes these challenges, better supporting the body's natural inflammatory response, as well as joint, brain and immune health.*
- **Proprietary Super Critical $CO^2$ extraction process** eliminates solvents and impurities with non-detectible THC content at < 10pm.†
- Cannabinoid profile confirmed by 3rd party Certificate of Analysis

TruGen3®

Three Generations of Truth in Nutrition

**www.trugen3.com 1-844-387-8436**