# PANHANDLE HEALTH

A QUARTERLY PUBLICATION OF THE POTTER-RANDALL COUNTY MEDICAL SOCIETY

WINTER 2023 | VOL 33 | NO.1


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**On The Cover:** ***Canyon Road Christmas*** by Marsha Clements


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# President's Message:
## Medicine: A Science and an Art

***by Nicole Lopez, MD, FAAFP***

In medical school, I was taught that medicine is both an art and science. Over 20 years of practice, I have certainly found that to be true. In residency, we were taught how to use evidence-based medicine to provide the highest standard of care, but there is always research to be done for answers that we do not know yet. Years of practice have helped me develop a collaborative style of care between myself and patients. As a family physician, I try to focus on the patient as a whole rather than a single organ or system. I tell my patients, I can't just cut off your head and treat that! As anyone who has had GI upset before a Board exam can attest, the mind definitely affects the body!

Webster's dictionary defines alternative medicine as any of various systems of healing or treating disease that are not included in the traditional curricula taught in medical schools. Integrative medicine is medicine that integrates therapies of alternative medicine with those practiced by traditional medical practitioners. As one of my colleagues wrote, "good medicine is based in good science. It is inquiry-driven and open to new paradigms. Alongside the concept of treatment, the broader concepts of health promotion and prevention are paramount." As scientists, it is important to have an open-mind and continue to do our own research, striving to learn and grow each day.

Did you know that the Texas Medical Association's website offers free access to its members to the medical literature and is available through the TMA Knowledge website? It is extremely user-friendly and uses Publication Finder and links to Pubmed as well as the EBSCO Alternative Health Watch. This is a reliable source to search the literature about the types of alternative medications and products our patients are using, to help us make informed decisions about their medical care. The TMA also offers free CME for members, including courses for opiate prescribing and human sex-trafficking required for our licensure.

As we close out 2022, our Potter Randall County Medical Alliance will once again be participating in the Hard Hats for Little Heads Program sponsored by a grant from the TMA Foundation. Last year, I had the opportunity to participate in this community event, and it was such a blessing to help others and see the joy on the children's faces as we fit them for new helmets to keep them safe. With the holidays just around the corner, I hope that you and your loved ones stay safe this holiday season.

### Yes, I Would Like To Contribute To The Potter-Randall County Medical Society Endowment Fund

The endowment fund was established in 1981 to promote the advancement of general education in medical science in Potter and Randall counties through discussion groups, forums, panel lectures, and similar programs. It is the hope of the society that, through the endowment fund, the work of our physicians will be continued by increased public awareness and understanding of the advances in medical science.

We are happy to accept memorials and/or honorariums. Notification of gift is sent immediately. Amount remains confidential. Your contribution is tax deductible. Please make checks payable to Potter-Randall County Medical Society, and send to PRCMS, 1721 Hagy, Amarillo, Texas 79106.

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# Executive Director's Message

***by Cindy Barnard, Executive Director***

Complementary and alternative medicine (CAM) is an approach to medical care that combines conventional medicine with CAM practices that have been shown through science to be safe and effective. Massage, acupuncture, tai chi, medical marijuana, green tea, hyperbaric oxygen treatment and a host of other treatments are among complementary and alternative medical practices. Medical treatments used instead of mainstream therapies are often referred to as ³alternative² or CAM. Again, complementary and alternative medical practices are used instead of or with traditional (mainstream) therapies. This issue of Panhandle Health describes just some of the specific complementary and alternative medical practices.

As the year ends, I want to thank the 2022 Board of Directors for their service and dedication to our Society. Under the leadership of our President, Dr. Evelyn Sbar, your Society has worked diligently, despite the continuation of Covid. The following physicians deserve an enormous thank you for their support:

EXECUTIVE COMMITTEE 2022: President, Evelyn Sbar MD, President-Elect, Nicole Lopez MD, Secretary-Treasurer, Tetyana Vasylyeva MD, and Past President, Neil Veggeberg MD.

TMA DELEGATES: Rodney B. Young MD, Daniel Hendrick MD, Robert Gerald, MD, Evelyn Sbarims, MD, Neil Veggeberg MD and Tetyana Vasylyeva MD.

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COMMITTEE CHAIRMEN: Retired Physicians, Mitch Jones MD & Richard McKay MD, Panhandle Health Editor, Steve Urban MD, Physician Health & Wellness, Robin Martinez MD, and Potter Randall County Medical Alliance President 2022, Tricia Schneiderjan,

Another thank you goes to the 2022 Panhandle Health Editorial Board led by Steve Urban MD. Members of the Editorial Board are Steve Urban MD (Copy Editor), Rouzbeh Kordestani MD, Paul Tullar MD, Skye McLaurin-Jiang MD, Sheryl Williams MD, Scott Milton MD, Marge Weis PhD, Elaine Bruno DO (Resident), and Basek Basbayraktar MD (Resident). Special thanks to Carol Hill and Shanna James from the Amarillo Health Department.

A final thank you goes to our "Circle of Friends" for their continued financial support and generosity. Their commitment is absolutely essential to the success of all of our events. They are Amarillo National Bank, Baptist Community Services, Neely, Craig & Walton Insurance Agency, Texas Medical Association Insurance Trust, Texas Medical Liability Trust, Happy State Bank, ColorArt Amarillo, Daryl Curtis, CLU, CHFC, Physicians Financial Partners, Boxwell Brothers Funeral Home, and Leslie Massey, Farmers Insurance Agency.

Their abiding confidence and encouragement continues to fuel us throughout our journey, and we remain grateful to all of you.



**Our Next Issue Of *Panhandle Health* Features:**

**Human Trafficking**

# Guest Editor's Message

***by Marge Weis, PhD.***

The market for nutritional supplements is very large, including more than 1700 businesses, for a total value estimated at more than $37 billion. The market niche is poorly regulated with regard to demonstrating efficacy, and, to some extent, safety. A number of products tout their verification by U.S. Pharmacopoeia (USP), without mention of what that means. A maker of a particular supplement submits a list of ingredients, and USP merely verifies that that list is accurate. There is no assurance that the product will perform as claimed, or even that the product is safe if used as directed.

Verification of product safety and efficacy is the function of the Food and Drug Administration (FDA), but FDA verification is not required to market "natural products", those products produced that contain naturally occurring compounds such as herbal preparations. This has allowed marketers to exploit the perception that "natural products" are in some manner superior to synthetic or semi-synthetic (and demonstrably efficacious) compounds.

Consequently, "natural product" marketing success relies, at least in part, on consumer ignorance, opening the door for predatory marketing practices. Compounding the issue, the establishment of the National Institute of Complementary and Alternative Medicine (originally the Office of Alternative Medicine) in 1991 has lent a veneer of respectability to "natural product" marketing. In no area have these predatory marketing practices had more insidious consequences than in those products claiming to preserve cognitive function.

Our population is aging, and the fear of cognitive decline and dementia is very real, and rightfully so. This fear has been exploited by a number of supplement marketers. However, even a cursory examination of these products reveals very little that is supported by clinical evidence, but a great deal that indicates that these products are very profitable for the marketer.

Many "brain health" supplements include B vitamins, phosphatidyl serine, DHA (docosahexaenoic acid, 22 carbon Ω-6) , etc. While no two appear to have the same formulation, the products are remarkably expensive, with an average cost per dose of about $0.81, but no demonstrated efficacy. Two widely-advertised formulations contain either apoaequorin or coffee cherry extract.

Apoaequorin is a 196 amino acid protein (about 24,000 dalton molecular weight). The "brain health supplement" which includes apoaequorin is administered by mouth. As the digestive tract is home to a large number of proteolytic enzymes, it is unlikely that any apoaequorin escapes the gut and enters the circulation. In the unlikely event that some of a dose can make it to the circulatory system, it is virtually unthinkable that a molecule of that size could find its way past the blood brain barrier. A clinical trial sponsored by the manufacturer is cited as evidence of efficacy. Individuals (n=218) with self-reported memory concerns were randomly assigned to apoaequorin (10 mg/day) or a placebo for 90 days. Their cognitive performance was evaluated at baseline and after treatment. The treatment group showed a statistically significant improvement in cognitive performance as compared to baseline. However, that improvement was no better than that observed with placebo. The apoaequorin-containing supplement also contains 50 µg calciferol (Vitamin D3), and costs approximately $1.25 per capsule. In contrast, vitamin D3 tablets (125 µg) are readily available for as little as $0.08 each.

Coffee cherry extract (CCE) is a preparation of the whole coffee berry. Data in healthy adults suggest that CCE may increase brain derived neurotrophic factor (BDNF). Decline in plasma BDNF has been noted in cognitive impairment, but I have been unable to find studies indicating that increasing BDNF alone will increase cognitive function in dementia. The hypothetical active principle in CCE has not been identified, so that it is not possible to speculate on a

mechanism of action, if any. The CCE "brain health" preparation also contains, in addition to 100 mg of CCE, 100 mg soybean derived phosphatidyl serine (PS). While PS is an important brain phospholipid, it is doubtful that orally administered PS can survive the trip through the gut, which is home to multiple lipases and phospholipases. The cost of the CCE/PS formulation is about $1.49 per capsule. In contrast, PS capsules (400 mg) can be acquired for as little as $0.13 each.

In this issue of Panhandle Health, our contributors will look at the science behind the current interest in complementary and alternative medicine. Many of our authors work at the Jerry H. Hodge School of Pharmacy at Texas Tech Health Sciences Center and will bring the critical scrutiny that we teach our clinical pharmacists and graduate students to bear on these issues. Several of our contributors are medical doctors who deal with patients who use these products on a daily basis. While some promising products that are still under study (e.g., cannabinoids, psychedelics) are discussed, our contributors look at these topics through the critical lens of accepted scientific practice. We hope that you will enjoy and profit from this critical (and somewhat skeptical) approach to these common clinical topics.

# Message from the Potter-Randall County Medical Alliance

***by Tricia Schniederjan, President***

Our TMAA President Libby White from Lubbock put together a fantastic regional meeting for us here in Amarillo. The speakers were great and we all learned so much from them. It's inspired us to get busy, and one thing I realized is that we need better communication. The first thing we are doing to improve this is to create a newsletter that will come to your email quarterly. Look for Volume 1 to arrive soon!

On December 17th at Palo Duro High School, we will be joining up with the Northside Toy Drive for our Hard Hats for Little Heads event. Bike helmets will be fitted and given away to the children of Amarillo in need. If you would like to volunteer please email me at tschnied@gmail.com and look for a signup in an upcoming email. You do not need to be an alliance member to help. Helpful older children can come with you to volunteer as well.

Save the Date! On February 9th at 6pm, the Alliance is hosting a dinner party at the Amarillo Club. We will enjoy a delicious 4 course meal with wine pairings. You do not want to miss it! Any physician groups who'd like to sponsor a table, please contact me and I can get you the information.

Membership renewals have been sent. If you didn't receive one, you can renew online. Visit www.texmedalliance.org in order to do so. You can also choose to automatically renew yourself every year so that you don't have to worry about doing it anymore. If you haven't been a member for a few years, now is the time to join us again.

Finally, I'd like to thank Rachel and Ryan McKenna for hosting the fabulous Medicine and Margaritas party. We all had so much fun and really appreciate it. What a wonderful group we had! I look forward to seeing everyone at one of the many upcoming events. Thanks everyone!

# Medical Marijuana

*by Thomas W. Hale, R.Ph., Ph.D. Department of Pediatrics and InfantRisk Center, TTUHSC (Amarillo)*

Few plants are as controversial as cannabis. Used by societies for more than 6000 years, it was cultivated not only for its medical use, but also for fiber, food and oil content. But because of its well-known psychoactive properties, in recent years it has largely been excluded from research by restrictive national laws (1). Over the past 25 years, however, attitudes toward cannabis have evolved from forbidden and hazardous, to decriminalized, to useful and partially legalized. In 1999, the Gallup Poll published that 36% of U.S. population supported legalized marijuana (2). In 2015 approximately 58% supported legalization. Legalization of marijuana has extended across the USA, with at least 37 states now permitting medical use, and 19 states allowing full recreational use. Despite these changes, the classification of marijuana as a Schedule 1 controlled substance by the Federal Government has severely restricted clinical research of this product and made it too difficult to do these studies. Thus, the literature is filled with poorly designed studies, sophisticated surveys, and frank hysteria about this old product.

Over the last 25 years, some of the bias against cannabis has changed due to limited research suggesting that several chemical components present in cannabis may actually have beneficial effects in various diseases. In essence, the field is now largely concerned with what new syndrome we can treat with cannabis products. The recent FDA approval of a cannabinol (CBD) product to treat severe infantile seizure disorders was a major development. Data on tetrahydrocannabinol (THC) now suggests some efficacy in treatment of chronic pain, anxiety disorders, nausea and vomiting due to cancer chemotherapy, and numerous other potential uses. These small changes have now awakened an interest in the use of cannabis products in other conditions. However, the marketplace, which is largely unregulated, is flooded with hundreds of strains of the marijuana plant with no clear understanding of the uses of these varied strains. These products are not regulated by the FDA nor are quality control standards well established (3). Thus it is still the "wild west" in the cannabis world.

Cannabis products exist in various forms, including dried plant, gummies, crushed flower heads, leaves, and hash oils. These can be ingested orally, inhaled, or applied topically. While there are hundreds of components in cannabis, the most commonly studied components are delta-9-THC (THC) and cannabidiol (CBD). At maturity, the cannabis plant is often inverted so the oil (containing THC) can flow downward to the bud and tips of the plant, where the THC content can become extraordinarily high. Thus, while marijuana leaves used many years ago contained 2.5% THC, today's buds average about 15% and some have upwards of 34% THC. Aside from the flower, users can now buy marijuana edibles, topicals, tinctures, and concentrates.

THC is responsible for most of the psychoactive properties of the plant, while CBD is largely non-psychoactive and commonly used for chronic pain and for pediatric seizure disorders. While the concentration of THC in the plant has risen enormously in today's products, this does not necessarily mean that the clinical dose commonly used today is correspondingly higher. Many users dose to effect, thereby using much smaller quantities of raw but highly potent cannabis. Thus, the clinical dose transferred is really up to the individual user, which is highly variable. Three prescription cannabinoids presently on the US market include: Marinol (dronabinol), Cesamet (nabilone), and Epidiolex (CBD) in the US. Nabilone is virtually identical to delta-9-THC and dronabinol is pure delta-9-THC.

THC is the main psychoactive component in the cannabis plant and binds to both CB1R and CB2R receptors in the brain and peripheral sites, producing dose- and time-dependent stimulatory, hallucinogenic, euphoric and sedative effects, control of pain, and even ophthalmic changes such as mydriasis. The physiologic effects of cannabis are almost entirely derived from its cannabinoid content. While there are hundreds of phytocannabinoids present in the plant, currently delta-9-THC and cannabidiol (CBD) are the most recognized and studied components of the cannabis plant. In the past two decades, cannabis plants have been genetically modified to produce a much higher content of THC or conversely CBD. It is often misconstrued that current users use much higher "doses". This is not necessarily true. While users in 1975 smoked cigarettes containing 0.6 grams of 3.7% THC, current users usually smoke only 0.1 gram of cannabis that might contain up to 23% THC to attain the same high. Both of these mixtures provide about 22 mg of THC.

Cannabidiol (CBD) is a non-psychoactive phytocannabinoid commonly found in cannabis products. It has a high affinity for CB2R receptors in the periphery, and it exhibits multiple therapeutic uses including control of seizure disorders, a neuroprotective property, anxiolytic, antipsychotic, anti-inflammatory and other properties. While often reported, not all these properties are well studied or even supported in the literature. That said, several randomized control trials using a purified form of CBD have demonstrated significant improvement in seizure frequency in pediatric patients with various treatment-refractory seizures such as Dravet and Lennox-Gastaut syndromes (4).

**AVERAGE DOSE:**

The average dose is highly variable and depends largely on the amount of cannabis consumed and the content of THC in the cannabis product. In general, the dose of THC ranges from 10-30 mg, but this is highly variable and primarily depends on the method of consumption as well as the plant product itself. Only about 20-37%

of THC in a joint is inhaled and the rest is lost to pyrolysis from the smoldering end of the joint or exhaled by the smoker. Even if 20-37% is inhaled, far less than half of this is systemically absorbed in the lungs. With cannabis, the only thing that can be controlled is the amount of the product smoked or ingested.

**CANNABIS PHARMACOKINETICS:**

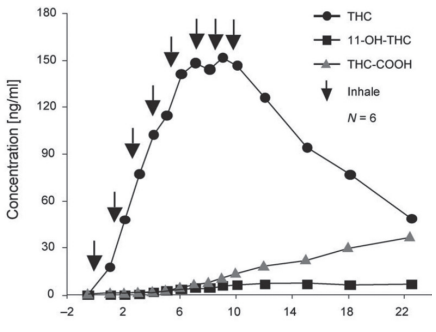
THC is highly lipid soluble, highly protein bound, and has a volume of distribution of 2.5-3.5 L/Kg. While THC passes into the CNS rapidly following smoking (Figure 1), its plasma half-life is fleeting, and rapidly redistributes to the liver and adipose tissue within an hour. Subsequently, it leaks out of adipose tissue over weeks of time, generally in picogram quantities. Unfortunately, the small leakage of THC from adipose tissue is commonly mistaken for recent use. Plasma levels following smoking are thousands of times higher than plasma levels just a few hours after smoking. Following inhalation, plasma levels reach a peak in approximately 6 minutes and dissipate rapidly by 22 minutes (Fig 1) (5). The rate of inhaled absorption of THC is highly variable and ranges in humans from 2-56% and is entirely dependent on how the product is smoked or ingested, how deep the individual inhales the smoke, and the individual type of cannabis product used. THC rapidly enters the plasma compartment, then the CNS compartment, and then just as quickly is redistributed to liver and adipose tissues where it stays for long periods. Because of hemoconcentration (of THC) by the kidneys, individual subjects may be urine screen-positive for up to a month, while almost no THC content is measurable in the plasma compartment. Positive urine screens only mean that the individual ingested THC sometime in the last month. They may or may not necessarily correlate with recent use or level of cognitive function.

**ENDOCANNABINOID SYSTEM AND RETROGRADE INHIBITION:**

Approximately 25 years ago, the endocannabinoid nervous system was discovered. While we have long known about the sympathetic and parasympathetic nervous systems, THC apparently acts at unusual sites in the postsynaptic receptor. THC and CBD are catorgorized as 'retrograde' inhibitors of the sympathetic and parasympathetic nervous system. They act to reduce firing of the sympathetic system in reducing pain and potentially seizures. The two primary endogenous inhibitors of the endocannabinoid system in the human are anandamide and 2-arachidonyl glycerol. These neurotransmitters are high in abundance in nervous tissues and act to suppress firing of presynaptic sympathetic neurons. Theoretically, cannabinoids such as THC and cannabidiol (CBD) act on postsynaptic receptor sites (CB1R and CB2R) to release anandamide or 2-Arachidonyl glycerol that then suppress presynaptic activation of the neuron, thus reducing pain, seizures, and other syndromes. The physiologic effects of cannabis are almost entirely derived from its cannabinoid content. While there are hundreds of phytocannabinoids present in the plant, at present, delta-9-THC and cannabidiol (CBD) are the two most recognized and studied components of the cannabis plant.

While there are a number of recognized cannabis receptors, CB1R and CB2R are considered the most important clinically. CB1R is a G-protein coupled receptor that inhibits the release of neurotransmitters such as norepinephrine, dopamine, serotonin, and acetylcholine from the presynaptic receptors. CB1R receptors are found in high density in the hippocampus, cerebellum, basal ganglia, and cerebral cortex. Cannabis activity in these regions of the brain is known to alter cognitive and motor function. CB2R receptors are localized more in peripheral tissues such as the spleen, bones, joints, and muscle tissue, in the peripheral immune system, and in glial cells. While THC is more commonly used for its psychotomimetic properties, CBD is almost exclusively used for peripheral pain or specific seizure disorders, due to its anti-inflammatory, pain-relieving and anti-epileptic properties.

**Figure 1. Mean (N=6) plasma concentration of THC, 11-OH-THC, and THC-COOH during smoking of a single cannabis cigarette (3.55% THC). Arrows(↓) indicate one inhalation or puff on the canabis cigarette. Reprinted and adapted with permission by Springer-Verlag, 'Handbook of Experimental Pharmacology', 2002, p.660, Fig.1.**




**CLINICAL USES OF THC AND CBD:**

**ANXIETY DISORDERS**

Cannabis abuse is much higher in individuals with mental illness, including schizophrenia, anxiety, mood and personality disorders, and post-traumatic stress disorder. While many surveys report the primary reason individuals use cannabis is to treat anxiety, 89% of individuals apparently use cannabis for other mental or physical health symptoms as well, including depression, gastrointestinal symptoms, chronic pain, acute cancer pain and posttraumatic stress disorder (6). Presently, there are limited or no data to suggest that cannabis products are significantly beneficial in many psychiatric or mood disorders, including anxiety disorders. And in some cases (such as schizophrenia), it may be detrimental. Still, many users surveyed suggest that anxiety is the reason they use cannabis.

**SCHIZOPHRENIA:**

The chronic use of cannabis products may be closely associated with an increase in the development of psychotic illness. An increased risk of severe psychosis has been correlated with higher and sustained doses of THC. Individuals using such doses are 2-4 times more likely to develop schizophrenic psychosis. An odds ratio of 3.90 (95% CI 2.84 to 5.34) was correlated with the risk of schizophrenia and other psychosis-related outcomes, particularly among high-dose users (7).

**CHRONIC NEUROPATHIC PAIN:**

Unfortunately, the current medical treatments for chronic neuropathic pain provide benefit for only a few people, with adverse effects that largely outweigh the benefits. Hence, the use of cannabis to treat neuropathic pain is increasing, despite only minimal scientific support. Various cannabis products have been recommended for all types of pain, particularly neuropathic pain. A recent well-documented study in 1750 patients from 16 individual studies suggests some efficacy of cannabis in controlling chronic pain (8). These studies included both oral and inhaled products. All cannabis-based

products pooled together were better than placebo in reducing chronic pain intensity.

However, the literature is highly conflicted. Other studies suggest that inhaled cannabis products were only moderately effective in reducing chronic non-cancer pain. At present, CBD is largely used for chronic pain, whereas THC is used for acute pain, for poor appetite following cancer chemotherapy, and for its euphoric effects.

**SEIZURE DISORDERS:**

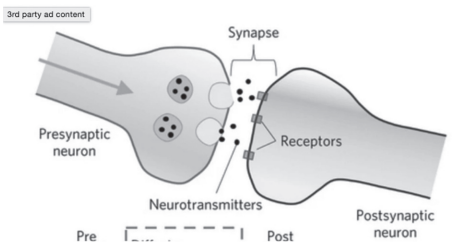
Currently there is significant interest in the use of the non-intoxicating cannabidiol (CBD) in the treatment of certain seizure disorders. Cannabis-derived cannabinoids apparently have neuromodulator activity. New CBD products have been approved by the FDA for the treatment of various forms of pediatric seizure disorders, such as Lennox-Gastuat and Dravet syndromes. More typical seizure disorders do not seem to respond to cannabis products. The mechanism of CBD's control of these disorders is unknown, but may be due to a reduction of inflammation, prevention of neuronal loss, stimulation of neurogenesis, or its effect on antioxidant formation (9). Data from one meta-analysis indicated that CBD reduced seizure frequency in patients with intractable seizures from Lennox-Gastuat and Dravet syndrome (10).

**NAUSEA AND VOMITING:**

The use of THC and CBD have been modestly studied in the treatment of nausea and vomiting.

In one review of 79 trials (6462 participants) who were treated with THC, CBD, and numerous other antinauseant drugs such as prochlorperazine, etc., all studies suggested a slightly greater benefit from the addition of cannabinoids.

**Figure 2. Retrograde Inhibition by endocannabinoids on presynaptic neurotransmitters.**




In particluar, patient response was better with cannabinoids (dronabinol or nabiximols) than placebo (OR, 3.82 [95% CI, 1.55-9.42]) (11).

Limited evidence suggests that cannabis-based therapy with both THC plus CBD may be far more beneficial than either alone. In one recent study, the combination of THC and CBD together produced far better control of chemotherapy-induced nausea and vomiting. Eighty three percent of the patients receiving combination therapy preferred the combination product (12).

**CONCLUSIONS:**

At present, modest evidence suggests that cannabinoids may be useful in some syndromes, including chronic pain, spasticity, some seizure disorders, and perhaps nausea and vomiting. There are unsubstantiated claims that THC might be useful in treatment of PTSD, but this has not yet been supported by other studies. The use of CBD for pediatric seizures is modestly supported by some research, although the doses employed are incredibly high and the benefit modest.

At this time, both the amount of research published and its quality are generally poor. Most of this is due to two main factors: 1. the federal government's scheduling of THC and CBD as schedule 1 significantly inhibits the study of cannabis products in humans in the USA, and 2. the quality and content of THC/CBD in cannabis products varies enormously. Even the products available from government stocks are much less potent than that commonly available on the streets. Unfortunately, most of the studies of cannabis are surveys, with only limited hard-core scientific studies in patients. Until researchers can attain access to good standardized products, and until we can carry out extensive human trials directly with different forms of cannabis, the usefulness of cannabis in treating human pathology will continue to be unresolved.

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**AUTHOR BIOGRAPHY**


*Dr. Thomas Hale, R.Ph., Ph.D. graduated from pharmacy school and received a Ph.D. in Pharmacology and Toxicology from the University of Kansas. Dr. Hale is currently associated with the Texas Tech University School of Medicine (Amarillo), Department of Pediatrics, and is currently director both of the Clinical Research Unit and of the InfantRisk Center. He is a recipient of the Grover Murray Distinguished Professorship at TTUHSC.*

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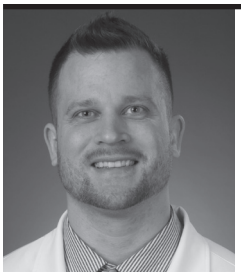

# Tripping Through Time:
## The Past, Present, & Future of Psychedelics

***by Alex Collins, MBA, Amy Stark, MD***

Psychedelic – a word that, for most, conjures the Technicolor world of the 1960s. But more recently, psychedelics are having a renaissance in the psychiatric world, with many hoping that they will provide relief to those who have failed to respond to conventional treatment options. According to the National Institute of Health, nearly 53 million adults in the United States live with a mental illness (1). The treatment approach to mental illness has come a long way since the time of asylums, insulin coma therapy, lobotomies, and Franz Anton Mesmer's animal magnetism. Today, treatment is often multifaceted, including the possibility of various psychotherapies, a long list of pharmaceutical agents, and biomedical treatments such as transcranial magnetic stimulation and electroconvulsive therapy. However, there remains a need for novel treatment approaches, since a significant percentage of patients (20-60%, depending on the specific diagnosis) do not adequately responded to current options (2).

Enter psychedelic medicine…

The term "psychedelic" was first coined by psychiatrist Dr. Humphrey Osmond in 1957 (3). It is an umbrella term for substances that can induce alterations in perception, mood, and affect via the brain's serotonergic, dopaminergic, glutaminergic, and noradrenergic pathways. The term classically includes substances like lysergic acid diethylamide (LSD), mescaline, and psilocybin (4-6). Psychedelics have been used for centuries for various purposes ranging from religious and spiritual rituals to recreational use. Despite their long history, they only officially entered the world of medical research in the early 20th century. The initial interest in psychedelics was focused on their psychotomimetic effects: researchers used psychedelics to produce temporary mental states similar to psychosis in an attempt to better understand the underlying biology (7). Although this psychotomimetic theory was an inadequate model as it failed to recreate the lack of insight which is one of the hallmarks of psychosis, it did lead to the exploration of the use of psychedelics as adjuncts to psychotherapy. In the 1950s, biological psychiatry slowly gained popularity, and many studies showed promising results regarding the use of psychedelics to treat various mental health conditions. In fact, in the 1950s and 1960s, more than 1000 articles were published on the use of psychedelics to treat psychiatric illness (3, 8).

Unfortunately, as psychedelic research became more popular, the recreational use of these substances also gained unanticipated popularity and became associated with the counter-culture movement and political activism during the 1960s. This partly led to President Richard Nixon's "War on Drugs" (3). During the decades to come, psychedelics were placed on the Schedule I drug list one after the other, meaning they officially had no safe and accepted medical use in the United States, thus making it nearly impossible to receive federal funds for clinical trials investigating their therapeutic use. In retrospect, the combined effect of the Drug Amendments of 1962 and the Controlled Substances Act of 1970 halted psychedelic research for decades (7). The War on Drugs has also played an important role in the public's negative perception of these substances. For decades, the government's propaganda focused only on the dangers of psychedelic drugs without mentioning their potential benefits as pharmacological agents. This negative perception likely played a role in delaying psychedelics from becoming pharmaceutical agents in the United States, since the US Drug Enforcement Administration only allowed psychedelic research to resume starting in 1990 (9).

Today, psychedelic research is booming, as an increasing number of universities and medical facilities participate in studies examining the therapeutic efficacy and safety of psychedelics in clinical settings. Their findings, although with limitations, have been compelling. This information has trickled down to medical professionals and the general lay population, making it ever more difficult to ignore the therapeutic potential of psychedelic substances.

The hallucinogenic effect of all classic psychedelic substances is thought to be a result of interaction with the serotonin (5HT) 2A receptor via full or partial agonism (10, 11). Psilocybin, the active ingredient of "magic mushrooms", is an entheogen psychedelic that has been associated with recreational use throughout history. Interestingly, the action of psilocybin at the 5HT 2A receptors is similar to selective serotonin reuptake inhibitor (SSRI) medications, which are widely accepted first-line treatment options for depression and anxiety (10). A thought-provoking study published in 2021 in the New England Journal of Medicine compared psilocybin to escitalopram, an SSRI frequently used to treat depression, and found no significant difference between the two drugs (12). Of course, the study has limitations, including a small sample size and brief duration of treatment with escitalopram (which has a delayed therapeutic action). Even more recently, a study published in JAMA Psychiatry this year showed that patients with alcohol use disorder (AUD) who were treated with a combination of psilocybin and psychotherapy had a significant

reduction in heavy drinking days compared to an active placebo and psychotherapy control (13). Although there are limitations to this study as well, its results provide empirical support for continued studies of psilocybin as a treatment option for AUD, a condition for which there are currently only three US Food and Drug Administration (FDA) approved medications.

Those two studies are only some of the more recent examples of research from the last 30 years demonstrating that psilocybin-assisted psychotherapy could be a promising treatment option for substance use disorders, depression, and anxiety associated with life-threatening medical diagnoses such as cancer (14-16). Currently, psilocybin remains a Schedule I substance; however, a phase 2 trial investigating its effects on treatment-resistant depression is scheduled to be completed by early 2023 (17). Depending on the results of this study, there soon may be sufficient evidence for the FDA to approve psilocybin to treat some of the aforementioned conditions in the next five years.

Another promising psychedelic is 3,4-Methylenedioxymethamphetamine (MDMA), the main ingredient of the well-known club drug ecstasy. In clinical settings, MDMA-assisted psychotherapy allows clinicians to create an environment where patients can freely imagine a world where they live free from their trauma. In such a setting, patients can better confront emotionally distressing memories (3, 18). A phase 3 trial recently concluded that MDMA-assisted therapy is a highly effective treatment option for people suffering from post-traumatic stress disorder (PTSD). (3, 19). This means that the FDA approval for MDMA might be at our doorstep--even sooner than for psilocybin.

While not a classic psychedelic like MDMA or psilocybin, ketamine (technically a dissociative anesthetic) has also been a topic of discussion as a novel treatment for psychiatric illnesses. Ketamine is a Schedule III substance that has been approved and used as an anesthetic since the 1970s (20). Due to its legal status as an FDA-approved anesthetic, securing funds and conducting studies to explore its therapeutic potential in psychiatric illnesses have been a less rigorous journey. In recent decades, multiple studies have demonstrated ketamine's potential as an antidepressant. It is hypothesized that its antidepressant properties are due to its antagonistic effects on N-methyl-D-aspartate (NMDA) receptors (21). This led to intranasal esketamine becoming the first psychedelic approved by the FDA for treatment-resistant depression in 2019 (6).

As exciting as the therapeutic potential of psychedelics appears, it is important to note that they are not panaceas. More appropriately, with continued study, they have the potential to join healthcare providers' armamentarium of treatment options. As with other pharmaceutical agents, treatment with psychedelic drugs will carry potential side effects and risks; thus, it will be imperative that they are used under the supervision of a healthcare provider. Additionally, enthusiasm must be tempered with reasonable consideration of the limitations of the existing evidence. This includes small study sizes, sample selection (including participants with positive experiences with prior psychedelic use) that might bias results, and difficulty in truly blinding even with active placebos given the unique experience of psychedelics.

As the evidence base and popularity of psychedelics grow, it is crucial to create an environment in which studies and unbiased regulatory reviews can be conducted to continually increase the safety and efficacy of psychedelics as they make their way into clinical medicine. One major step in creating such an environment is to remove psychedelics from their Schedule I status. This would allow more federal funds to support these research projects, instead of relying on private donors. Using federal funds could also make clinical trials more accessible to minorities, thus making the findings more generalizable to all cultural and ethnic groups (22). Lastly, creating evidence-based clinical guidelines would make it more likely for clinicians to prescribe these novel drugs and increase the likelihood that private and government health insurance would cover them as viable treatment options for psychiatric patients.

As we look to the future, having an open mind about the therapeutic possibilities of these substances is needed. These treatments are coming, and our patients will be asking about them. Ironically, if you need help opening your mind, you might want to explore to see if psychedelic-assisted psychotherapy is right for you!

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*Amy Stark, M.D. is board certified in both general and addiction psychiatry. Upon earning her medical degree from the Texas Tech University Health Sciences Center, Dr. Stark completed residency in general psychiatry at the Mayo Clinic, followed by a fellowship in addiction psychiatry at Yale. Dr. Stark's areas of expertise and professional interests include opioid use disorder and medication assisted treatment; alcohol use disorder; and psychiatry for specialty populations, including perinatal women, professionals with substance use disorder and the LGBTQIA community. She is currently an Associate Professor of Psychiatry at the Texas Tech University Health Sciences Center School of Medicine in Amarillo.*

*Alex Collins moved to the United States from Hungary at age 21 and pursued a degree in neuroscience from the University of Texas at Dallas. In 2020, he started medical school at Texas Tech University Health Science Center, earned his master's degree in business administration as part of Tech's MD/MBA dual program, and is currently a third-year medical student in Amarillo. Alex is passionate about mental health, medical research, and providing care for underserved communities. In his free time, he volunteers at free clinics in West Texas, coordinates the Complexities of Sex Trafficking elective at Tech, and stays active with weightlifting and snowboarding.*

*In Memoriam*

## Dr. Bang Wan, Internist

Died February 27, 2022 at the age of 67.

*He was a member of Potter Randall County Medical Society for 16 years.*

POTTER RANDALL COUNTY MEDICAL SOCIETY

# CAM Products and Drug Interactions

*by Oluwatoni Makinde and Becky Mahan, PharmD*

## INTRODUCTION

Complementary & Alternative Medicine (CAM) products are often perceived as safe due to their easy accessibility on store shelves or online. Additionally, a common misconception about these products is "if it comes from nature, it must be good for you and unproblematic". While CAM products may have some proposed benefits in chronic conditions, they can interact with other medications. Drug interactions involve at least two components: one of the components is a drug while the other component could be food, natural medicine, beverage, or another drug. There are three broad outcomes of drug interactions: decreased efficacy, increased toxicity, or no effect. These interactions can ultimately lead to mild or potentially even life-threatening situations. As health care providers, it is important that we ask patients what CAM products they may be taking in addition to prescribed medications at every visit to evaluate these interactions. This article will discuss established drug interactions with some CAM products--berberine, red yeast rice, garlic, Coenzyme Q10, and aloe--to illustrate the extent of such interactions.

## BERBERINE

Berberine is an alkaloid: a basic, naturally-occurring compound found in different plants. In some studies, berberine has been shown to reduce blood glucose and cholesterol levels in patients with diabetes and dyslipidemia, respectively (1). It may also be beneficial in polycystic ovary syndrome (PCOS). Based on berberine's mechanism of increasing insulin sensitivity, it can increase hypoglycemia risk. As expected, berberine may have additive or synergistic effects with insulin and other antidiabetic medications like sulfonylureas. Sulfonylureas enhance insulin release. For those close to blood glucose goals already or experiencing hypoglycemic episodes, this combination would potentially be unsafe. Berberine also has sedative effects. This effect can be detrimental to susceptible populations such as older adults. Generally, elderly patients are on more medications than the average younger adult. So, there is a higher probability of drug interactions. Berberine is a known inhibitor of metabolic pathways that can lead to higher concentrations of antiplatelet agents and anticoagulants, increasing bleeding risk. The frequency of cardiac comorbidities in patients with diabetes provides an additional reason a health care provider would want to know their patient is taking this supplement.

## RED YEAST RICE

Red yeast rice (RYR) is a natural product that contains monacolin K, which is identical to lovastatin, a drug used for hyperlipidemia (1). Therefore, it can exhibit the same benefits, adverse effects, and even drug interactions. Due to this structural resemblance, red yeast rice should not be used with other statins. If used together, the patient will be at a higher risk for muscle and liver toxicities. Niacin and gemfibrozil are other lipid-lowering medications that can be used as combination therapies with statins. They can increase the risk for muscle toxicity whether the patient is taking lovastatin or RYR. In some cases, it is necessary to discontinue either red yeast rice or the interacting drugs. In other cases, lowering the dose of red yeast rice may be sufficient. Not all RYR supplements are made equal. There can be varying levels of monacolin K (lovastatin) and other ingredients in different RYR formulations. These other components may also interact with certain drugs. For instance, inappropriate fermentation of red yeast rice can lead to the formation of citrinin (2). Citrinin is a toxin that can bind to albumin (3). Many medications are albumin-bound and, in some cases, this binding serves as a safety mechanism to prevent dangerously-elevated drug concentration in the blood. So, when there is a disruption in albumin binding as seen with citrinin, drug concentration and side effects increase.

## GARLIC

Garlic is commonly used as a seasoning and flavoring agent. Garlic appears to have many benefits in conditions ranging from dyslipidemia to fatty liver disease. Despite these benefits, garlic can negatively interact with many life-saving medications. Whether garlic is ingested raw or swallowed as a capsule, there is a

possibility that it may interact with certain medications. One study showed that the plasma concentration of saquinavir is lower in the presence of garlic supplementation (4). Saquinavir is a protease inhibitor that serves as an antiretroviral agent. It reduces viral load in people with HIV. It is unknown whether garlic would reduce the concentration and efficacy of other protease inhibitors. Garlic may decrease the efficacy of antibacterial agents as well. An example is isoniazid, an antitubercular agent. A study was conducted on rabbits receiving isoniazid who later ingested garlic extract (5). The investigators compared the bioavailability of isoniazid at baseline and after garlic consumption. They found that garlic may reduce the absorption and bioavailability of isoniazid. While this study was done on animals, the results may apply to humans. It is important to monitor patients who are taking garlic with their isoniazid. HIV and tuberculosis are infections needing adequate treatment in a timely fashion. Any delay or disruption in treatment could have undesirable outcomes for these patients.

**COENZYME Q10**

Coenzyme Q10 (CoQ10) is an antioxidant naturally present in cells. It can also be supplemented through external means. It protects cells against free radicals. Low levels of CoQ10 are associated with heart disease and with statin use, so CoQ10 supplements are sometimes used to improve cardiac function in heart failure, to reduce myopathy associated with statin use, and even to reduce the risk of developing certain cancers (although the latter is yet to be adequately proven). However, CoQ10's effects can oppose the actions of some chemotherapeutic agents. For example, cyclophosphamide produces free radicals to destroy cancer cells. Cells respond to cyclophosphamide's actions by utilizing CoQ10. When CoQ10 stores are depleted, cells are damaged. Replenishing the stores with supplements may prevent further damage to non-cancerous cells; however, this may counter the beneficial effects of cyclophosphamide. Mechanistically, CoQ10 may reduce the anti-tumor effects of cyclophosphamide. One trial investigated this theory in patients treated with chemotherapy, including cyclophosphamide (6). The results suggest that antioxidants may predispose patients to cancer recurrence. Patients with cancer should be individually assessed. Healthcare providers should weigh the benefits and risks before recommending CoQ10 supplements in a patient undergoing chemotherapy.

**ALOE**

Aloe is known for its dermatologic, antidiabetic, and laxative effects. Prolonged use of oral aloe can cause diarrhea and vomiting which can result in hypokalemia and other electrolyte abnormalities (7). The co-administration of aloe with diuretics or stimulant laxatives can amplify the hypokalemic effects. Potassium level also affects digoxin actions. Hyperkalemia would attenuate digoxin's effect, while hypokalemia as seen with aloe would increase toxicity. Digoxin toxicity can manifest as nausea, vomiting, visual disturbances, and cardiac arrhythmias. Therefore, chronic use of aloe is not recommended in patients taking digoxin. For cases when a patient is still on aloe, it may be beneficial to monitor digoxin levels frequently. Warfarin is another medication whose effects must be closely monitored. It is an anticoagulant known for its interactions with many drugs and food. International Normalized Ratio (INR) measures warfarin's efficacy by estimating the time it takes blood to clot. The higher the INR, the higher the bleeding risk. INR can fluctuate due to different factors including supplement use. Aloe is no exception. The diarrheal effect of aloe can increase INR and bleeding risk when used with warfarin. So, if a patient has an unexplained increase in INR, it may be helpful to assess their CAM use.

**CONCLUSION**

Some CAM products are used in their raw forms, and some are present as capsules, oils, or gummies. The actions and drug interactions between these formulations can vary. They can be negligible or significant. When in doubt, ask a pharmacist or seek out medically sound information before starting any natural product.

For health care professionals: while performing a medication review or initiating a new medication, it is important to inquire about supplements, vitamins, and herbs.

For patients: ask your physician or pharmacist before starting any supplements if you are already on medications or vice versa.

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| CAM Product | Interacting Drugs | Effects of Interaction |
|---|---|---|
| Berberine | Sulfonylureas (e.g., glipizide, glyburide) | Hypoglycemia |
| | CNS depressants | Increased sedation |
| Red Yeast Rice | Statins | Enhanced myotoxicity and hepatotoxicity |
| | Niacin and gemfibrozil | Increase myotoxicity |
| | Citrinin and albumin-bound medications | Increase drug toxicity - side effects would vary with the medication |
| Garlic | Isoniazid | Increased tuberculosis bacterial load |
| | Protease inhibitors | Increased HIV viral load |
| Aloe | Diuretics | Enhanced hypokalemia |
| | Stimulant laxatives | Enhanced hypokalemia |
| | Digoxin (via hypokalemia) | Arrhythmias, nausea/vomiting, halo vision |
| Coenzyme Q10 | Chemotherapeutic agents (e.g., cyclophosphamide) | Ineffective tumor eradication |

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**AUTHOR BIOGRAPHIES**

*Becky Mahan, PharmD, BCGP, BCACP, FASCP is an assistant professor of pharmacy practice in the geriatrics division at TTUHSC Jerry H. Hodge School of Pharmacy. An alumna of Butler University, she completed a community-practice residency with Penobscot Community Health Care and a Geriatric Pharmacotherapy Residency with TTUHSC/VA-North Texas. She maintains a clinical practice site at Hendrick Housecalls, a hospital-affiliated home health agency, focused on improving patient safety through the care transitions process and at home.*

*Oluwatoni Makinde was born and raised in Nigeria. Growing up, she was fascinated by the mechanisms of different medications. She is currently a fourth-year Doctor of Pharmacy candidate at TTUHSC Jerry H. Hodge School of Pharmacy. She is passionate about individualizing medication regimens and hopes to be a compounding or geriatric pharmacist someday. In her spare time, she enjoys sewing and catching up on TV shows.*


# PANHANDLE HEALTH

**A Publication of the Potter-Randall County Medical Society**

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# History of Natural Products in Drug Discovery & Development

*by Anna Kochanowska Karamyan Pharm D and Quentin Smith, Ph D, Department of Pharmaceutical Sciences School of Pharmacy, TTUHSC*

## INTRODUCTION

Natural products have served as the cornerstone of traditional medicines from the dawn of human history (1). Some of the oldest written documents from Mesopotamia (2600 BCE) and China (1100 BCE) list recipes for over 1000 nature-derived treatments. Archeological evidence points to plant use by humans in paleomedicine for over 60,000 years (2). The best-known example is the use of opium poppies, which the ancients called "God's own medicine," for pain control and diarrhea (5,000 BCE, Samaria). Equally well-known in the ancient world was the use of willow (salix) for fevers and flu (salicylic acid, Egypt, 3,000 BCE) (3). Over two thirds of nature-derived medicines were of plant origin, but we have prominent examples from fungal, insect, animal and ocean-derived sources. Ocean-based products will be a focus of the second part of this manuscript.

Over time, knowledge of specimen collection and compounding evolved into the profession of pharmacy. Traditional medicines and herbal remedies still serve important roles for many people across the world, particularly in developing countries. However, in the last 200 years, there has been a revolution in science and medicine, creating the modern discipline of pharmacology. This review will provide a short overview of this transformation and will outline how natural products continue to be important drug leads to this day.

## CHEMISTRY TRANSFORMATION

The growth of scientific knowledge in the West from the 1500-1800s fueled the growth and advancement of chemistry as a modern science. By the early 1800s, a number of chemical substances within the body had been isolated and synthesized from simple building block precursor molecules. This challenged age-old beliefs that life was based upon special "vital" sources. In the new view, life was seen to function through chemicals and chemical reactions that could be isolated, studied and understood by rational minds. In 1805, the German pharmacist Friedrich Sertürner extracted the active principle from opium and showed that it was ~8 times more potent than the original opium plant product. This is believed to be the first isolation of an active drug from a plant. The new product was named "morphine" after the Greek god for dreams (Morpheus).

Morphine's isolation led to an explosion of new drug products for the treatment of a range of maladies. Additional opiate congeners of morphine, including codeine and thebaine, were isolated and marketed as medical treatments. Furthermore, using the same technology, a range of natural product agents for a variety of ailments were isolated in the 1880's. These included quinine for fever, colchicine for gout, stimulants (e.g., caffeine, cocaine) to improve energy and activity, and a wide range of nervous system active agents (e.g., pilocarpine, atropine, muscarine, nicotine, amphetamine, and many others), just to name a few. The revolution supplied the medical cabinet of practicing doctors with an array of pure compounds that could be accurately dosed. Soon, chemists began to modify the chemical structures of natural product compounds to create a range of new chemical derivatives, each with differing profiles of activity. One of the first of these was a great success – the creation of acetylsalicylic acid (aspirin) from salicylate by the German scientist Felix Hoffmann of Bayer Pharmaceuticals. Aspirin was far more tolerable to the stomach than salicylate and became the first international blockbuster drug, with sales skyrocketing during the great flu epidemic of 1918. Hoffmann similarly acetylated morphine to create heroin, which was thought initially to be superior to morphine in activity and adverse effect profile. Unfortunately, heroin, unlike aspirin, was not a success and soon led to development of tolerance and addiction. In general, however, the combination of natural products and chemistry was a great success, leading ultimately to the creation of the modern pharmaceutical industry by the 1950s.

*In Memoriam*

Dr. Charles Seward, Rheumatologist

Died April 7, 2022 at the age of 81.

*He was a member of Potter Randall County Medical Society for 50 years.*

POTTER RANDALL COUNTY MEDICAL SOCIETY

## MODERN ZAUBERKUGELN ("MAGIC BULLETS")

The first entirely "new" chemical drug produced with no input from natural products was the antibiotic Salvarsan. This drug was identified by careful screening of over 1,000 agents. Paul Ehrlich's lab identified Salvarsan, the 606th test candidate, as having the best activity with least adverse effects of any in the screen. Salvarsan was moved forward to human clinical testing and soon became a major success. Ehrlich termed these new active agents as "Zauberkugeln ("Magic Bullets") from the famous 1821 Weber opera ''Der Freischutz" (The Marksman or Sharpshooter), in which the main character - the marksman - is in competition to be the best shot. The marksman is so focused on winning the match that he sells his soul for a handful of special "magic bullets" that always hit their intended target. It turns out that, in reality, one time out of six the new bullets miss and go astray. Because of this, an errant bullet kills the marksman's fiancé. The story has much to teach us about life. Ehrlich chose the term "magic bullets" because he needed chemical agents that acted selectively to go to where the disease was and to act specifically to make the patient better. Yet, Ehrlich knew that even "magic bullets" would occasionally have unintended side effects and lead to detrimental outcomes, as later occurred with Salvarsan. Ehrlich was sued for adverse effects of Salvarsan and died of a stroke following a major trial (at which he was acquitted).

The modern pharmaceutical drug development industry is a mixture of new drug synthesis and screening as well as preparation of drugs where possible from natural products (4). Most new drugs presently are "small molecular weight agents (<1,000 Daltons)," to allow ready drug absorption, distribution, and elimination and to reduce unwanted side effects. In addition, over the last 50 years, protein, peptide, and oligonucleotide-based drugs have been developed in increasing numbers for therapy of human diseases (5). The peptide insulin was one of the most important initial peptide drugs in this category. Now, this drug category is termed "Biologics" and (including monoclonal antibodies as well as antibody-drug conjugates) makes up 15-30% of new drugs approved annually by the FDA. For example, in 2020, the FDA approved a total of 53 new agents, split between 40 small molecule drugs and 13 Biologics (6). Fig.1 shows the contributions for each class for that year. Natural products (including chemically-modified natural products) constituted 8 of the 40 new chemical entities (20%) and 15% overall of new drugs for the year. This matches with data over the past 5 years (2017-2021; averaging 8 per year), 10 years (2010 – 2019; 7 per year), and 40 years (1980-2019; 9 per year) as compiled by two separate groups (4, 6). Natural products have maintained their position within the lineup for the past 40 years; their potential remains, as only about 15% of potential species on earth have been screened and much more remains to be learned about life and disease.

**Table 1: Catalog of New Natural Product Drugs 2020-2021 From Plants, Animals, Microbes**

| Compound | Drug name | Source | Indication | Year approved |
|---|---|---|---|---|
| Artesunate | ArtesunateTM | Artemisinins, derivatives from "qinghao," or sweet wormwood plant (Artemisia annua) | Malaria | May 2020 |
| Lactitol | Importal, Pizensy | Cow's milk lactose that is chemically converted to the polyol | Food sweetener and osmotic laxative | Feb 2020 |
| Clascoterone | Winlevi, Breezula | Chemically modified animal sterol | Androgen receptor antagonist; treatment of acne and hair loss | Aug 2020 |
| Decitabine Cedazuridine Combination | Inqovi | Combination nucleoside metabolic inhibitor and cytidine deaminase inhibitor, derived from nucleoside antimetabolites | Treatment of adults with myelodysplastic syndromes (MDS) and chronic myelomonocytic leukemia (CMML) | July 2020 |
| Remdesivir | Veklury | Nucleotide prodrug developed from viral nucleoside library | Used for the treatment of COVID-19 | Oct 2020 |
| Samidorphan | Lybalvi | Opioid antagonist taken with antipsychotic olanzapine to control schizophrenia. Chemically modified morphine from opium plant. | Used to prevent weight gain from antipsychotic drug treatment | May 2021 |
| Maribavir | LivtencityTM | Ribose antiviral drug effective against cytomegalovirus. | Used to treat post-transplant cytomegalovirus | Nov 2021 |
| Ibrexafungerp | Brexafemme | Triterpenoid antifungal drug that inhibits glucan synthase for cell wall synthesis. Used to treat vaginal yeast infections | Used to treat vaginal yeast infections | June 2021 |

## NATURAL PRODUCT -BASED NEW DRUGS: 2020-21

Table 1 presents most of the natural product drugs approved over the past two years (2020 and 2021) focusing on plant, animal or microbial origin (7, 8).

Focused bioprospecting among life forms beyond the plant kingdom may be a solution to maintain the natural product pipeline. This includes bacteria and fungi as well as insect and oceanic life specimens. Interestingly, a 2011 PNAS paper reported that plant species generating biologically active products cluster

into only about 2% (n=144) of 6,763 plant families (9). In line with this, 80% of federally approved natural product drugs and 67% of clinical trial test agents are derived from only 47 drug-prolific plant families. Thus, focused bioprospecting of the highest activity plant families may be the wisest natural product screening strategy for the future. Similarly, greater attention should be given to projects expanding screening of microbial, insect, oceanic, and extremophile species, which in the past contributed less than one quarter of all natural product approved agents.

**MARINE NATURAL PRODUCTS**

For centuries, nature has been an abundant source of new medicines. By the end of twentieth century, natural products and compounds derived and inspired by them accounted for about 80% of all drugs. And while most of drugs derived from natural sources come from terrestrial organisms and plants, the marine environment has also been recognized as a great source of novel compounds possessing a wide array of biological activities. Exciting breakthroughs from aquatic life forms are expanded upon below.

Oceans cover about 70% of the earth's surface and are home to a very diverse group of organisms producing a plethora of chemical compounds. Systematic investigation of marine natural products started in 1970s and was driven by the fact that terrestrial organisms have been quite well explored in the search of potential new drug leads. Funding agencies expanded their programs and made it possible for many natural product chemists to start looking for new medications under water. This process led to the isolation, purification, and characterization of over 28,500 marine natural products by the end of 2016 (10). Many studies have highlighted the unique structural scaffolds of these compounds. Most marine natural products discovered to date are characterized by cytotoxic and anti-tumor activity. This is not surprising, as these chemicals are typically used for defense against predators that could otherwise easily destroy sessile (or very slowly moving) marine invertebrates. Other metabolites, including indole alkaloids, share structural similarities with neurotransmitters and endogenous amines, potentially sharing also their targets in the human brain. This might be yet another defense strategy: to act upon brain receptors (serotonin, anybody?) in order to confuse the predator and avoid being eaten. Additionally, many marine natural products have also shown potential as immunosuppressive, anti-viral, anti-inflammatory, anti-nociceptive, and anti-fungal agents. It is also worth noting that a number of these chemicals are produced not by the invertebrates themselves, but rather by symbiotic microorganisms colonizing sponges, tunicates, and mollusks (11). This is actually great news because many of these marine metabolites are found in very small quantities, and scaling up their collection often proves challenging and can be problematic from ecological point of view. With symbiotic microorganisms being the source of these chemicals, it is now possible to scale up production by growing the microbes or identifying the microbial genes responsible for synthesis and inserting them into *E.coli* or other organisms well-known to scientists.

According to the Midwestern University Marine Pharmacology data base (13), there are 15 marine natural product drugs or medications derived from those chemicals currently approved

**Table 2: Drugs of Marine Origin**

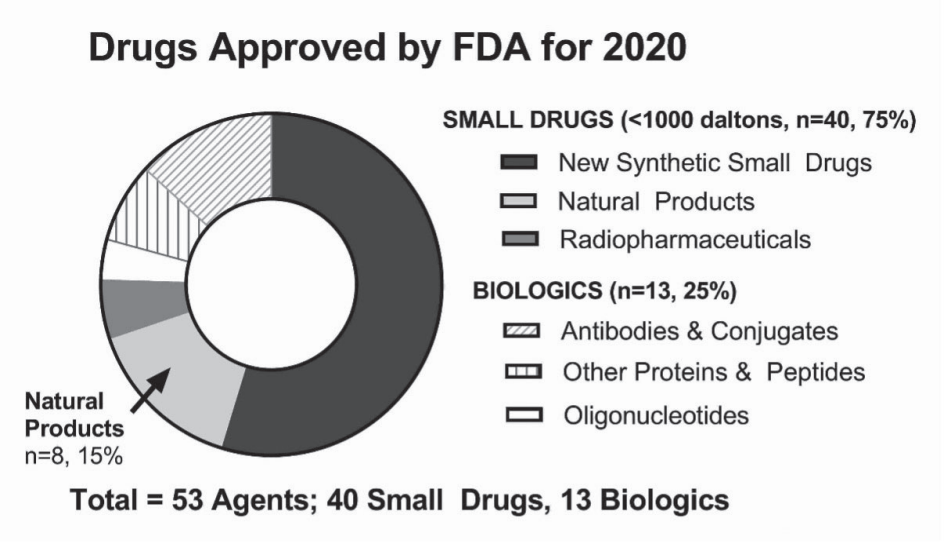
| Compound | Drug name | Source | Indication | Year approved |
|---|---|---|---|---|
| Cytarabine | Cytosar-U ® | Sponge Cryptotheca crypta | Leukemia | 1969 |
| Vidarabine* | Vira-A® | Sponge Tethya crypta | Antiviral (Herpes virus) (currently discontinued) | 1976 |
| Ziconotide | Prialt® | Cone snail Conus magus | Pain | 2004 |
| Omega-3-acid ethyl ester | Lovaza® | Fish | Hypertriglyceridemia | 2004 |
| Eribulin mesylate | Halaven® | Sponge Halichondria okadai | Metastatic breast cancer | 2010 |
| Brentuximab vedotin | Adcetris® | Mollusk/cyanobacterium Dolabella auricularia | Anaplastic large T-cell systemic malignant lymphoma, Hodgkin's disease | 2011 |
| Eicosapentaenoic acid ethyl ester | Vascepa® | Fish | Hypertriglyceridemia | 2012 |
| Omega-3 carboxylic acid | Epanova® | Fish | Hypertriglyceridemia | 2014 |
| Trabectedin | Yondelis® | Tunicate Ecteinascidia turbinata | Soft Tissue Sarcoma and Ovarian Cancer | 2015 |
| Plitidepsin | Aplidin® | Tunicate Aplidium albicans | Multiple Myeloma, Leukemia, Lymphoma | 2018 |
| Polatuzumab vedotin | Polivy TM | Mollusk/cyanobacterium Dolabella auricularia | Non-Hodgkin lymphoma, Chronic lymphocytic leukemia, Lymphoma, B-Cell lymphoma | 2019 |
| Enfortumab vedotin-ejfv | PADCEVTM | Mollusk/cyanobacterium Dolabella auricularia | Metastatic urothelial cancer | 2019 |
| Lurbinectedin | ZepzelcaTM | Tunicate Ecteinascidia turbinata | Metastatic Small Cell Lung Cancer | 2020 |
| Belantamab mafodotin-blmf | BlenrepTM | Mollusk/cyanobacterium Dolabella auricularia | Relapsed/refractory multiple myeloma | 2020 |
| Tisotumab vedotin-tftv | TIVDAKTM | Mollusk/cyanobacterium | Metastatic cervical cancer | 2021 |
| Panobinostat | FarydakTM | Sponge Psammaplin aplysilla | Multiple myeloma | 2022 |

for medical use. The first marine derived drug, cytarabine (Cytosar-U ®), modeled after spongothymidine, a nucleoside isolated from a sponge, was approved in 1969. Table 2 below shows currently approved marine drugs. It is noteworthy that, after initially slow process of marine-origin drug approval, in the last three years (2019-2022) we have witnessed approval of six new marine drugs, showing increasing potential of these medications.

In addition to the drugs already approved, a number of marine natural products and medicines derived from them are in the clinical pipeline: seventeen are in Phase 1, eight in Phase 2, and four in Phase 3 (12).

The early days of marine natural product discovery focused on easily accessible organisms in mostly warm waters. Slowly, the interest switched to deeper and colder areas, including sampling of the ocean floor. Technical advances have made it possible to reach the very deep parts of the oceans; more sensitive nuclear magnetic resonance instruments allowed determination of the structures of compounds isolated in tiny quantities. Considering that only about 5% of the seas and oceans have been explored so far, the field of marine pharmacology is still in its infancy and has a tremendous potential to provide novel drug leads to help humans fight many diseases, including different types of cancers.

Fig 1. New drugs approved in 2020 by the FDA broken down in to categories between small drugs and biologics. Data taken from (6).

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**AUTHOR BIOGRAPHIES**

*Dr. Anna Karamyan graduated from the Medical University of Lublin, Poland with a Master of Sciences of Pharmacy (MPharm) in 2005. After that, she completed a Ph.D program at the University of Mississippi and received her doctorate in Pharmaceutical Sciences with emphasis in Pharmacognosy. She joined TTUHSC School of Pharmacy in 2010 and is currently an adjunct associate professor in the Department of Pharmaceutical Sciences.*

*Dr. Quentin Smith is Professor of Pharmaceutical Sciences at TTUHSC Jerry H. Hodge School of Pharmacy in Amarillo and has worked on drug development for >40 years. He came to Texas Tech to help with the startup of the Pharmacy School.*

# Spotlight on New Members

***The following were approved for membership on January 19, 2022:***

***REGULAR MEMBERSHIP:***

***PAY, ADRIAN P., M.D.***
(INTERNAL MEDICINE)
*6700 W. 9th, Amarillo TX 79106. Graduated from University of Kansas School of Medicine, Kansas City KS 1995. Internship and Residency at University of Iowa, Iowa City IA 1996-1998.*

***WALLEY, ROBERT DAVID, D.O.***
(PULMONOLOGY/PULMONOLGY/CRITICAL CARE)
*6700 W. 9th, Amarillo TX 79106. Graduated from William Carey University College of Osteopathic Medicine,Hattiesburg MS 2015. Residency at Largo Medical Center, Largo FL 2015-2018.*

***TRANSFER MEMBERSHIP:***

***GALLAGHER, JENNIFER, M.D.***
(OPHALMOLOGY)
*7411 Wallace Blvd., Amarillo TX 79106. Transfer from San Antonio TX. Graduated from Texas Tech University Health Science Center, Lubbock TX 2015.Internship at Ochsner Clinical Foundation, New Orleans LA 2015-2016. Residency at Louisiana State University, New Orleans LA 2016-2019. Fellowship at University of Texas San Antonio, San Antonio TX2019-2021*

***The following were approved for membership on March 22, 2022:***

***FIRST YEAR MEMBERSHIP:***

***BIGGS, SARAH, M.D.***
(ALLERGY & IMMUNOLOGY)
*1900 S. Coulter, #D, Amarillo TX 79106. Graduated from University of Texas Medical Branch, Galveston TX 2017. Residency at University of Texas Medical Branch, Galveston TX 2017-2020 (Internal Medicine). Fellowship at Medical College of Georgia at Augusta University, Augusta GA 2020-2022.*

***REGULAR MEMBERSHIP:***

***ARMOUR, ALEXANDER WOOLF, D.O.***
(CARDIOLOGY)
*6200 W. I40, Amarillo TX 79106. Graduated from Chicago College of Osteopathic Medicine, Midwestern University, Chicago IL 2008. Residency at Lutheran General, Park Ridge IL 2008-2011. Fellowship at Plaza Medical Center, Fort Worth TX 2011-2014(Cardiology). Fellowship at Plaza Medical Center, Fort Worth TX 2014-2015 (Interventional Cardiology).*

***BASSE, DAVID RYAN, M.D.***
(INTERNAL MEDICINE)
*9055 Spur 591, Neal Unit, TTUHS, Amarillo TX79107. Graduated from University of Texas Medical Branch, Galveston TX 1995. Internship and Residency at Texas Tech University Health Science Center, Amarillo TX 1995-1998.*

***KIANI, RAJA, M.D.***
(PSYCHIATRY)
*1400 Wallace Blvd., #106, Amarillo TX 79106. Graduated from Aga Khan Medical College, Aga Khan University, Karachi, Pakistan 2011. Residency at Tulane University, New Orleans LA 2016-2021 (Triple Board-:Pediatrics, Psychiatry, Child and Adolescent Psychiatry).*

***KIM, SANG TAE CALEB, D.O.***
(FAMILY MEDICINE)
*1500 Coulter, #6, Amarillo TX 79106. Graduatedfrom Chicago College of Osteopathic Medicine, Midwestern University, Chicago IL 1995. Residency at Carle Foundation Hospital, Urbana IL 1995-1998.*

***NGUYEN, QUE VU, M.D.***
(PSYCHIATRY/PEDIATRICS)
*1400 Coulter, Amarillo TX 79106. Texas Tech University Health Sciences Center, Managed Care. Graduated from Medical & Pharmaceutical University,Ho Chi Minh City, Vietnam 1971. Residency at Oklahoma University, Norman OK 1989/1991(Psychiatry). Internship at University of Texas School of Medicine, Houston TX, 1987-1989 (Psychiatry).Clinical Instructor for Texas Tech Medical School, Amarillo TX.*

***PASTON, MICHAEL, M.D.***
(OCCUPATIONAL MEDICINE)
*Box 30020, JCDC N1.109, Amarillo TX 79120.Graduated from State University of New York Health Science Center, Syracuse College of Medicine,Syracuse NY 1993. Residency at USAF School of Aerospace Medicine, San Antonio TX 1998-2000 (Aerospace/OSC Medicine). Internship at Syracuse University, Syracuse NY 1993-1994 (OB/GYN). Residency at Harvard University, Boston MA 1997-1998.*

***SBAR, ALAN DAVID, M.D.***
(GENERAL SURGEON)
*1400 Coulter, Amarillo TX 79106. Graduated from George Washington University School of Medicine & Health Sciences, Washington DC 1996. Residency with U.S. Army, San Antonio TX 1996-2002 (General Surgery).*

***The following were approved for membership on May 17, 2022:***

***REGULAR MEMBERSHIP:***

***DE RIESE, JOHANNES, M.D.***
**(**ANESTHESIOLOGY)
*1600 Wallace, Amarillo TX 79106. Graduated from Texas Tech University Health Science Center, Lubbock TX 2010. Residency at Scott and White Memorial Hospital, Temple TX 2010-2014.*

***LIU, HANLIN, M.D.***
(OCCUPATIONAL MEDICINE)
*JCDC N1 U.S. Highway 60 & FM 2373, Amarillo TX 79120. Graduated from Shandong Medical University, Jinan/Shandong, China 1982. Internship at UTHSCSA, San Antonio TX 1999-2000 (General Surgery). Residency at UTMB, Galveston TX 2000-2002(Occupational & Environmental Medicine).*

***SOLIMAN, BASEM GAMAL A., M.D.***
(GENERAL SURGERY)
*1400 Coulter, #2100 Surgery, Amarillo TX79106. Graduated from Asyut University FAC of Medicine, Asyut, Egypt 2007. Fellowship at Cleveland Clinic, Cleveland OH 2014-2016 (Transplant Research Fellowship). Internship at Cleveland Clinic, Cleveland OH 2016-2017 (General Surgery). Residency at Houston Methodist Hospital, Houston TX 2017-2019(General Surgery).*

***The following were approved for membership on July 19, 2022:***

***FIRST YEAR MEMBERSHIP:***

***MANCHESTER, CAMERON, M.D.***
(DIAGNOSTIC RADIOLOGY)
*1901 Medi Park, #2050, Amarillo TX 79106. Graduated from University of Texas Medical Branch, Galveston TX 2016. Surgical Resident at Brookdale University Hospital and Medical Center, Brooklyn NY, 2016-2017. Residency - at Integris Health, Oklahoma City, OK. Atrium Health Wake Forest, Winston Salem, NC 2021-2022, Neuroradiology.*

***REGULAR MEMBERSHIP:***

***WILSON, JOANNA, D.O.***
(INTERNAL MEDICINE)
*Amarillo Diagnostic Clinic, 6700 W. 9th, Amarillo TX 79106. Graduated from University of North Texas Health Science Center, Fort Worth, TX 2001, (D.O.) Internship and Residency at University of Texas Southwestern St. Paul University Hospital, Dallas TX 2001-2004 (IM).*

***The following were approved for membership on September 20, 2022:***

***REGULAR MEMBERSHIP:***

***BAZZAZ, OMAR, M.D.***
(INTERNAL MEDICINE)
*6010 Amarillo Boulevard, Amarillo TX 79106 Graduated from University of Baghdad, College of Medicine, Baghdad Iraq 2006. Internship and Residency at Texas Tech University Health and Science Center, Amarillo TX 2014-2017*

***KNIGHT, LAUREN L., M.D.***
(FAMILYMEDICINE)
*1600 Wallace Boulevard, Amarillo TX 79106 Graduated from St. George¹s University School of Medicine, St. George¹s, Grenada 2017. Internship and Residency at Texas Tech University Health Science Center 2017-2021*

***PARAT, SUMESH, M.D. PD***
(PEDIATRICS)
*1400 S. Coulter, Amarillo TX 79106 Graduated from Government Medical College, Kerala University for Health and Sciences, Kozhikode(Calicut, Kerala, India 1999. Residency at Metrohealth Medical Center, Case Western, Cleveland, Ohio 2009-2912. Fellowship at Metrohealth Medical Center, Case Western, Cleveland, Ohio 2012-2015 (Neonatal/Perinatal Medicine)*

***TRANSFER MEMBERSHIP:***

***UNDERWOOD, LAUREN, M.D.***
(UROLOGY)
*1900 MediPark, Amarillo TX 79106 Transfer from HarrisCounty TX (Houston) Graduated from Louisiana State University School of Medicine, Shreveport, Louisiana 2012. Residency at Texas Tech University Health Sciences Center, Lubbock TX 2012-2017*

***VOWELS, TRAVIS J., M.D. GS/VS***
(GENERALSURGERY/VASCULAR SURGERY)
*6 Medical Drive, Amarillo TX 79106 Transfer from Harris County TX (Houston) Graduated from McGovern Medical School at University of Texas Health Science Center at Houston, Houston TX 2016. Residency/ Fellowship at Houston Methodist, Houston TX 2016-2022*

***The following were approved for membership on November 15, 2022:***

***REGULAR MEMBERSHIP:***

***COSGROVE, AMY M.D.***
(FAMILY MEDICINE)
*P.O. Box 50924, Amarillo TX 79159 Graduated from Texas Tech University Health Science Center, Lubbock TX 2010. Residency at John Peter Smith Hospital 2013 (completed).*

***McLAURIN-JIANG, SKYLER M.D.***
(PEDIATRICS)
*7802 Continental, Amarillo TX 79119 Graduated from Texas Tech University Health Science Center, Lubbock TX 2014. Residency at Texas Tech University Health Science Center, Lubbock TX 2017 (completed).*

***WILHELM, SETH M.D.***
FAMILY MEDICINE (FM)
*2001 S. Coulter, #2001, Amarillo TX Graduated from Texas Tech University Health Science Center, Lubbock TX2013. Residency at Texas Tech University Health Science Center, Amarillo TX 2013 -2016.*

***TRANSFER MEMBERSHIP:***

***THETFORD, DAVID D.O.***
FAMILY MEDICINE
*275 Casino Drive, Amarillo TX 79118. Transfer fromDallam-Hartley-Sherman-Moore County Medical Society Graduated from Oklahoma College of Osteopathic Medicine and Surgery, Tulsa OK 1993. Internship and Residency at Presbyterian St. Luke Hospital, Denver CO 1993-1996.*

# Vitamins B, C, D, & Zinc:

## Is there evidence to support their Supplementation?

*by Sweta Mishra PharmD. Candidate 2023, Akosua Boateng MBA, PharmD. Candidate 2023, Emily Eddy PharmD, MSLD, BCACP Texas Tech University Health Sciences Center, Jerry H. Hodge School of Pharmacy*

**Introduction**

The overuse of vitamin supplements is common among adults in the United States. In fact, vitamin and mineral supplement sales were estimated to cost about $14.3 billion in the United States in 2014 (1). Although a healthy lifestyle and a balanced diet provide the nutritional requirements of the body, the public demand for supplement products continues to increase. It is a common belief that vitamin supplementation prevents certain outcomes such as cardiovascular disease or improves overall health. Ironically, the individuals who choose to use vitamin supplementation are typically those who live healthy lifestyles, and instead are at risk of exceeding the daily recommended vitamin intake and accruing a hefty cost burden. In this article, the benefits of vitamin B, C, D, and zinc supplementation will be weighed against the risks of exceeding recommended daily requirements and the associated cost burden.

**Vitamin C** (ascorbic acid) is an antioxidant present in citrus fruits, peppers, tomatoes, and leafy greens. Vitamin C is often considered an "immune booster" that can help fight infections and prevent cardiovascular events. However, the data does not support the use of vitamin C for this indication. One study showed there was no significant reduction in the incidence of upper respiratory tract infections in those receiving vitamin C daily (RR 1.01, 95% CI 0.70-1.46) (2). Another study found there was no significant risk reduction with vitamin C and major cardiovascular events after an 8-year follow-up (HR, 1.01; 95% CI, 0.90-1.13) (3). Instead, overuse of vitamin C exceeding 2 g/day can lead to nausea, vomiting and can increase cases of gout. The market value of a 75-day supply of vitamin C is approximately $20, equating to about $100 for a year's supply (4). The cost burden exceeds the benefits to support the use of this product. Additionally, the use of vitamin C can increase the risk of interactions with other medications such as warfarin. Over-the-counter products often go underreported by patients and may not always be documented by healthcare providers, increasing the risk of drug-drug interactions.

**Vitamin B complex**, a mixture of water-soluble vitamins, consists of thiamin, riboflavin, niacin, pantothenic acid, pyridoxine, biotin, folate, and cyanocobalamin. Pyridoxine (vitamin B6), folate (vitamin B9), and cyanocobalamin (vitamin B12) are known to lower homocysteine levels. Since higher levels of homocysteine are associated with abnormal endothelial function, thrombogenesis, and cognitive decline, studies have been conducted to evaluate the association these may have on cardiovascular health and cognitive impairment. One study showed that, despite lowered homocysteine levels, the use of B6, B9, and B12 did not show a significant reduction in cardiovascular events after a 7-year follow-up (RR, 1.03; 95% CI, 0.9-1.19) (5). Another study showed a lack of benefit in the use of vitamin B12 and vitamin B9 in preventing cognitive decline (6). After 2 years, the results did not show a significant difference between the supplemental group and placebo group for executive function (-0.03; 95% CI -0.19- 0.13). Vitamin B12 injections cost approximately $90/30 day supply (4), equating to approximately $1000/yr in expenses. With the available evidence, the cost burden largely outweighs the benefit seen with supplementation in this case.

One common use of **vitamin B6 (pyridoxine)** has been seen in pregnancy, in the treatment of nausea and vomiting. The data DOES support the use of pyridoxine in this case as it significantly reduces nausea and vomiting in pregnant women who receive a combination pill containing delayed-release doxylamine succinate 10 mg plus pyridoxine hydrochloride 10 mg compared to placebo (-4.8 ± 2.7 vs −3.9 ± 2.6; P = .006)(7). A 30-day supply would amount to approximately $60 (4). This price may seem high; however, the cost burden weighed against the increase in quality of life for pregnant women must be considered. In the study mentioned earlier, 48.9% of the participants wished to continue receiving doxylamine succinate 10 mg- pyridoxine hydrochloride 10 mg formulation compared to 32.8% of participants in the placebo group (P=0.009) for symptom relief (7).

**Vitamin D**, a fat-soluble vitamin, is a micronutrient obtained from foods we consume or naturally from the sun. Vitamin D toxicity is unlikely to occur from diet or sun exposure but can occur from supplement intake. A daily maximum of 2000 IU or less is recommended unless under supervision by a medical provider. Vitamin D toxicity causes hypercalcemia and can be associated with symptoms such as anorexia, weight loss, irregular heartbeat, and hardening of blood vessels. Since vitamin D is important for bone health, researchers have conducted studies to evaluate whether vitamin D supplementation would reduce the risk of fractures. However, a study with a 5-year follow-up showed no significant reduction in fractures between those receiving vitamin D supplementation or placebo (HR, 0.98; 95% CI 0.89-1.08) (8).

Vitamin D over the counter is approximately $5-10 for 100 tablets; however, with the lack of benefit in healthy populations, the cost-to-benefit ratio remains high(4).

**Zinc (Zn)**, an essential trace element present in our body, is involved in many facets of cellular metabolism. Zinc-binding proteins (especially metallothioneins) are protective in situations of stress and exposure to toxic metals, infections, and low Zn intake (9). The recommended daily dietary intake of Zn is 8 mg in females and 11 mg in males (10). Most patients will reach the daily recommended intake of zinc from their diet through foods such as meat, seafood, poultry, eggs, dairy products and cereals fortified with Zn. Zn absorption depends on the amount of protein in the diet, putting vegetarians, vegans or people on restricted diets at higher risk of Zn deficiency. Unless patients are in a high-risk category for Zn deficiency, Zn supplementation is not necessary to meet the daily requirements. Additionally, Zn is present in many multivitamins, so separate Zn supplementation is not necessary if the patient is already receiving a daily multivitamin. The price of Zn over the counter is approximately $5-10/100 tablets (4). The benefits of supplementation only outweigh the costs for those at high risk of deficiency.

The use of vitamin supplementation in the hopes of promoting general well-being and preventing disease occurs despite evidence from the literature showing a lack of benefit for many vitamins and supplements. A healthy lifestyle and a well-balanced diet can supply a patient with most if not all of the vitamins needed to maintain optimal health. Additional vitamin supplementation can increase the risks of potential adverse effects or drug interactions and increase the cost burden on the patient if not taken correctly. It is important for healthcare providers to consistently inquire patients about over-the-counter products, educate them, then counsel patients on the cost/benefits/risks associated with vitamin use.

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**PRIMARY AUTHOR**


*Sweta Mishra is a fourth-year pharmacy student at Texas Tech University Jerry H. Hodge School of Pharmacy in Dallas. Her professional interests include academia, ambulatory care, and oncology. She hopes to complete a PGY-1 residency upon graduation from pharmacy school.*


**CORRESPONDING AUTHORS**


*Akosua G. Boateng is a fourth-year pharmacy student at the Texas Tech Jerry H. Hodge School of Pharmacy in Dallas. She has over 10 years of experience as a business analyst; her areas of interest after pharmacy school include pharmacy informatics and specialty pharmacy. After graduation, she hopes to work as a pharmacist and then apply to a pharmacy informatics fellowship program.*

*Emily Eddy, PharmD, MSLD, BCACP is an Assistant faculty member at Texas Tech Jerry H. Hodge School of Pharmacy. She also practices at the North Texas VA as an ambulatory care pharmacist. She has been with Texas Tech for two years after completing her PGY-2 residency in ambulatory care and academia.*

# Neuromodulation devices in migraine or cluster headache:

## Adjunctive Therapy for Unmet Treatment Needs

*by Evelyn Sbar MD, Levi S, Campbell PharmD, Duren M. Ready MD*

Sometimes the cure is worse than the disease." – Yiddish Proverb

### INTRODUCTION

In 2006, the European Headache Foundation and the World Headache Alliance named migraine the "forgotten epidemic." (1). This chronic paroxysmal disorder has incapacitating neurological symptoms. It is typically an inherited disorder characterized by neurologic, sensory, autonomic, cognitive, and gastrointestinal symptoms (2). This disease affects 39 million people in the US alone, and 1 billion individuals worldwide (3). It is the 3rd most prevalent illness across the globe; with peak prevalence between 25 and 55 years of age. Since it affects the most productive years of an individual's life (4), migraine is the number one cause of disability under the age 50 (5). Migraine disability is a public health issue with serious social and economic ramifications. Both absenteeism and presenteeism ("I'm here but I'm not") costs are estimated to be as high as 36 billion dollars annually in the United States (3). In 2015, chronic migraine costs exceeded $5.4 billion, and suffers spent over $41 billion in total on migraine associated care (3).

### MIGRAINE AND CLUSTER HEADACHE: MANAGEMENT CHALLENGES

While migraine patients experience varying levels of frequency, severity and disability related to their attacks, severity does not always guide treatment. As migraine frequency increases, so does the need for effective and tolerable prophylaxis. We know that chronic treatments are generally associated with poor adherence (less than 80% of medication is taken as prescribed) and that this often results in poor outcomes (6). Persistence refers to the time in which a patient remains on a prescribed treatment after starting therapy (7). Both adherence and persistence to pharmacological preventative agents for migraine treatment have been shown to be below acceptable level within six months (8). When compared with placebo, active interventions were discontinued primarily due to poor efficacy and side effects.

Cluster headaches are another debilitating primary headache disorder, frequently occurring multiple times a day (2). Treatment options are somewhat limited for cluster headache, and the only agents with Level A evidence (meaning established as effective by The American Headache Society) are: parenteral sumatriptan, zolmitriptan nasal spray, and oxygen (9). Parenteral sumatriptan with or without 100% oxygen has evidence that supports its use in improving headache response (9). However, parenteral sumatriptan can only be used twice daily despite the number of attacks, is expensive, and is contraindicated in individuals with heart disease or uncontrolled hypertension (9). An alternative treatment to subcutaneous sumatriptan is zolmitriptan nasal spray up to 10 mg, which is effective in improving headache response with potential problems being unpleasant taste and nasal cavity discomfort. Oxygen given at a rate of 10 to 15 liters per minute via non-rebreather mask can also be used for acute treatment, but is rarely covered by insurers and is cumbersome to haul around for patient convenience (10).

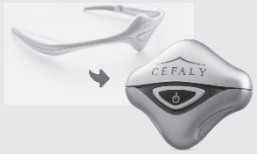
### NON-PHARMACOLOGICAL NEUROMODULATION AS ADJUNCTIVE THERAPY FOR UNMET TREATMENT NEEDS

Neuromodulation devices offer an alternative for individuals interested in effective nonpharmacological interventions. Five devices are approved by the United States Food and Drug Administration (FDA) for migraine: supraorbital transcutaneous neurostimulation (CEFALY®), single pulse transcranial magnetic stimulation (Savi Dual®), transcutaneous vagus nerve stimulation (gammaCore™), remote electrical stimulation (Nerivio®) and combined occipital and trigeminal nerve stimulation (Relivion®). (11-13). For a side-by-side comparison of the 5 neuromodulation devives, please refer to Table 1 below. There are some distinct advantages of neuromodulation devices over traditional pharmacological options, including favorable safety and side effect profiles. This makes them attractive additions to the migraine toolbox. The main contraindications to usage of neuromodulation devices are implanted devices (e.g., cardiac pacemakers or cochlear implants).

### CEFALY® (SUPRAORBITAL TRANSCUTANEOUS NEUROSTIMULATION)

One of the first devices receiving FDA clearance was the CEFALY® device, a supraorbital transcutaneous neurostimulator (STNS) designed to desensitize the trigeminal nerve. CEFALY® is approved for use in individuals over 18 years of age with acute migraine with or without aura and for prevention of episodic migraine (14). An initial migraine preventive trial using daily 30-minute stimulation for 90 days with STNS did not meet its primary end point, but did have 50% response rate of 38.1% (15). An open-label trial in chronic migraine prevention with 58 patients treated with CEFALY® 20 minutes a day for 3 months found that the frequency of headache days decreased by -3.12 days (-16.21%, $p < 0.001$) and that acute medication intake decreased from 26.33 to 18.22 (-30.81%, $p < 0.001$) during month 3 of treatment (16). A multi-cen-

**Table 1. Overview of Available Neuromodulation Devices Approved for use in the United States**

| Device | Manufacturer | Approved Indications | Mechanism of Action | Unique qualities | Approximate Cost^ |
|---|---|---|---|---|---|
| **CEFALY®**  | CEFALY technology | ≥ 18 years of age with acute migraine with or without aura and prevention of episodic migraine | Supraorbital transcutaneous neurostimulation | Does not require a prescription.<br>First available over-the-counter product for acute and preventative treatment of migraine.<br>Covered under VA benefits. | **Device:** $514<br>**Electrodes:** $25 to $33 per 3 pack |
| **Savi Dual®**  | Aruene Corp - eNeura | ≥ 12 years of age and older for acute and prophylactic treatment of migraines. | Single pulse transcranial magnetic stimulator | Requires a prescription<br>Device may only be rented, not outright purchased | $350 per 3 months, |
| **gammaCore™**  | electroCore | ≥ 12 years of age and older for acute and preventative migraine treatment AND for episodic cluster HA | Transcutaneous vagus nerve stimulation | Requires a prescription<br>Has cluster HA indication<br>Has COVID-19 EUA for asthma-related dyspnea<br>Covered under VA benefits. | $450 for 3 months, 30 stimulations per month. Refills via RFID card. |
| **Nerivio®**  | Theranica | ≥ 12 years of age and older for acute migraine treatment of episodic or chronic migraine | Remote electrical stimulation | Requires a prescription<br>Applied to the arm and controlled with smart phone<br>Individuals may utilize FSA or HSAs for payment | $599 for twelve 45 minutes simulations. Patient savings plan available. |
| **Relivion®**  | Neurolief | ≥ 18 years of age and older for acute migraine treatment of episodic migraine | Combined occipital and trigeminal nerve stimulation | Only non-invasive multi-channel neuromodulation technology for the treatment of acute migraine | Not available |

^ Pricing and trade-in information accurate as of November 14, 2022.
Veterans Affairs = VA; headache = HA; Emergency Use Authorization = EUA; Radiofrequency identification = RFID
Flexible Spending Account = FSA; Health Savings Account = HSA
CEFALY® image available at: *https://cdn.ziftrshop.com/zw7nebe4ks/upgrade-hero-trimmed@2x.png*
sTMS mini® image available at: *https://www.migrainetrust.org/wp-content/uploads/2020/09/sTMS1.jpg*
gammaCore™ image available at: *https://www.medicaldesignandoutsourcing.com/wp-content/uploads/2016/05/gammaCore-S-Product-With-Caps-1-.jpg*
Nerivio® image available at: *https://assets.migraineagain.com/wp-content/uploads/2019/11/NM_gray_01.png*
Relivion® image available at: *https://1au3b422k9zdqzddw3my51gg-wpengine.netdna-ssl.com/wp-content/uploads/sites/7/2021/03/Relivion-neurorelief-600x400.jpg*

ter, double-blind, acute migraine STNS trial with 106 patients showed a 1-hour reduction in pain intensity of 3.46 on a visual analog scale in the treatment group, compared to 1.78 in the sham group ($p < 0.0001$). Similar statistically significant results were seen in the subgroup of migraine without aura, but not in the migraine with aura subgroup (17).

The new generation CEFALY Dual® has an ACUTE (abortive) 60 minute setting as well as a 20 minute daily PREVENT (preventative) setting (18). This model is powered by a rechargeable lithium battery, has intensity control settings and is much more compact than the first model. The original C1 CEFALY® device can be traded in for the newer model and a $75 rebate (19). It is recommended to complete the preventative cycle at night, as mild sedative effects have been noted with the use of the device. CEFALY® originally was only available by prescription, but it is now the first available over-the-counter product for acute and preventative treatment

of migraine in the United States (14). As of the time of this writing, the device sells for $514. A well-cared for electrode pad will last a month. Refills are available for around $25 for 3 standard electrode pads or $33 for hypoallergenic/blue gel electrodes (20). CEFALY® offers a 60-day risk-free trial and is fully covered under VA benefits (18, 21).

### SAVI DUAL® (SINGLE PULSE TRANSCRANIAL MAGNETIC STIMULATION)

The single pulse transcranial magnetic stimulator (sTMS) Savi Dual® is indicated for the acute and prophylactic treatment of migraine headaches in adolescents age 12 and older and in adults (22). sTMS induces a current to the underlying cerebral cortex and is capable of modulating neuronal excitability and firing, thus interrupting the cortical spreading depression pathology for migraine headache (23). A 2010 randomized, sham-controlled, parallel-group, double-blinded study of 164 patients encouraged patients use sTMS as soon after aura onset as possible (but within one hour), using two magnetic pulses (24). This study found that 39% of sTMS patients were free of pain at 2 hours (compared to 22% in the sham group). Subsequently, an open label, multicenter, prospective observational investigation in 263 patients with chronic migraine used four pulses twice daily with an additional 3 pulses up to 3 times a day as needed for prevention (25). The baseline headache frequency was 9.06 days; after 3 months of treatment patients had 2.75 fewer headache days, with a 50% response rate of 46%. Acute daily medication use was reduced by 2.93 days. The most common adverse event was light headedness, tingling, and tinnitus (25). The Savi Dual® is a rented device and requires a prescription. As of the time of this writing, November 14, 2022, the cost is $350 per 3 months with two months initial device trial free (22).

### GAMMACORE™ (TRANSCUTANEOUS VAGUS NERVE STIMULATION)

The transcutaneous (non-invasive) vagus nerve stimulation (nVNS) device known as gammaCore™ is approved for use in adolescents 12 to 17 years and adults for the preventive treatment of migraine and cluster headache and for the acute treatment of pain associated with migraine and episodic cluster headache (26). It is thought to work by inhibiting brain structures that produce serotonin and norepinephrine and that are involved in central desensitization (23). The treatment protocols varied in the studies, but mainly consisted of a series of bilateral (migraine) and unilateral (cluster) stimulations lasting 120 seconds and variably repeated. Several of the studies failed to meet their primary end points, but the overall findings were sufficient to gain FDA approval. Post hoc analysis showed significant effects in treatment-adherent patients (27). During the COVID-19 pandemic, gammaCore™ also received Emergency Use Authorization (EUA) to treat patients with known or suspected COVID-19 who were experiencing exacerbation of asthma-related dyspnea and reduced airflow (28). The most common side effects were application site discomfort and nasopharyngitis. The gammaCore™ device requires a prescription. At the time of this writing, November 14, 2022, the cost is $450 for 3 months of therapy, which is subject to factors such as co-pay and insurance. This provides for 30 stimulations per month (29). Refills are done via a radiofrequency identification (RFID) card held over the device to load next month's therapy onto the device. The gammaCore™ is contracted for sale at the VA and Department of Defense, and there is no out-of-pocket cost to veterans.

### NERIVIO® (REMOTE ELECTRICAL STIMULATION)

The FDA recently-approved Nerivio® device uses remote electrical stimulation (REN) to activate descending pain modulation and was named a TIME Magazine invention of the year in 2019. Nerivio® is indicated for treatment of episodic or chronic migraine in individuals 12 years of age or older. It stimulates upper arm peripheral nerves to induce conditioning pain modulation--an endogenous analgesic mechanism in which conditioned stimulation inhibits pain in remote body regions (30). It is applied to the arm at the beginning of an attack and is activated with a smart phone application that also acts as a diary. The stimulation lasts for 45 minutes. A 2019 study in 252 adults found that acute treatment of migraines with REN resulted in two-hour pain freedom of 37.4% with treatment, compared to 18.4% in the sham group ($p = 0.003$). Additionally, two-hour pain relief was 66.7% with treatment, compared to 38.8% for the sham (30). Around 1.6% of the patients reported a warm sensation as an adverse effect. A post hoc analysis

demonstrated similar efficacy to triptans and superiority to NSAIDs. The device is available by prescription from a specialty pharmacy, though it can also be obtained via telehealth. The present cost is $599 for twelve 45-minute stimulations but may be covered by commercial insurance with little to no co-pay. The company offers a patient savings plan for qualified patients that may significantly lower the cost. It is covered under VA benefits. It is recyclable for free through the company. There is no return policy on this device.

**RELIVION® (COMBINED OCCIPITAL AND TRIGEMINAL NERVE STIMULATION)**

Lastly, Relivion® is a combined occipital and trigeminal nerve stimulation (COT-NS) device (31). It was recently approved by the FDA for acute treatment of episodic migraine in individuals 18 years of age or older. It is a non-invasive multi-channel brain neuromodulation system for treating neurological and neuropsychiatric disorders. It delivers stimulation to six branches of the occipital and trigeminal nerves through three adaptive channels, causing release of neurotransmitters and modulating brain pathways that control pain and mood. One prospective, randomized, double-blind, placebo-control trial in 131 patients found that 46% of patients with COT-NS achieved complete pain freedom, compared to 11.8% in the control arm. It was also better for complete freedom from most bothersome symptom within 2 hours after treatment (75% versus 46.7%), freedom from migraine symptoms at 2 hours after treatment (47.2% vs 11.1%) and pain relief 2 hours post treatment (60% vs 37%) (31). Studies are ongoing for use in depression, migraine, ADHD, and insomnia (31). Relivion® cost information is not currently available.

**CONCLUSION**

Current neuromodulation devices offer effective nonpharmacological options for patients with unmet treatment needs. They are a worthy addition to our Headache Toolbox.

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*In Memoriam*

## Dr. Richard Archer, Internist

Died in April of 2022 at the age of 88.

*He was a member of Potter Randall County Medical Society for 62 years.*

POTTER RANDALL COUNTY MEDICAL SOCIETY

*In Memoriam*

## Dr. Jack Waller, Dermatologist

Died June 2, 2022 at the age of 79.

*He was a member of Potter Randall County Medical Society for 47 years.*

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*In Memoriam*

## Dr. Donald Kuxhausen, Radiologist

Died July 9, 2022 at the age of 91.

*He was a member of Potter Randall County Medical Society for 54 years.*

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# Mineral Supplements:

## What Providers and Consumers Should Know

*by Aizelle Gaddi, PharmD Candidate 2023, An Hoang, MBA, Pharm D Candidate 2023, Alaina Van Dyke, PharmD, MBA, BCACP Texas Tech University Health Sciences Center, Jerry H. Hodge School of Pharmacy*

**INTRODUCTION**

Nutritional supplements, also called dietary supplements, are products intended to provide nutrients to the body. They are nonprescription products that can be taken without medical advice, and their use is recommended as an adjunct to a balanced diet. The popularity of nutritional supplements is continuously increasing in the United States; approximately three out of four Americans take at least one nutritional supplement on a regular basis. According to a US national health survey, the majority of participants reported that their reason for using supplements was to improve or maintain overall health. A balanced diet should provide the required amount of nutrients needed for normal function; however, there are certain instances where nutritional supplements may be required to correct deficiencies or even treat and prevent disease. The phrase "nutritional supplements" encompasses a wide variety of products including vitamins, minerals, botanicals and botanical compounds, and other related products. This article focuses on basic information on three widely used mineral supplements, calcium, magnesium, and iron, as well as the regulation of dietary supplements.

**CALCIUM**

Calcium is one of the most frequently reported supplements consumed. As a major component of bones and teeth, it is not surprising that "bone health" is almost exclusively the reported motivator for use of calcium supplements. Calcium, particularly when coupled with vitamin D, is heavily used to help with overall bone health and to prevent the fragility of bones caused by aging. Aside from bone health, calcium plays an integral role is several other biological processes including the synthesis of acetylcholine, absorption of vitamin B12, muscle contraction and relaxation, and activation of the plasma clotting cascade.

Calcium supplements are available in multiple salt formulations. The two most used formulations are calcium citrate and calcium carbonate. Both calcium carbonate and calcium citrate are efficacious, but there are slight differences. One difference is that calcium carbonate contains a higher percentage of elemental calcium (40%) compared to citrate (21%). Another difference between the two salt forms pertains to absorption. Since calcium carbonate is water insoluble and requires an acidic environment for optimal absorption, it should be taken with meals to enhance absorption. Calcium citrate, on the other hand, does not need an acidic environment and can be taken without regard to meals. The citrate salt may be preferred for those with a higher gastric pH, such as geriatric patients as well as those on chronic histamine-2 receptor antagonists or proton pump inhibitors. Lastly, optimal absorption occurs in doses of 500 mg or less, regardless of salt form; therefore, patients taking more than 500 mg should be instructed to take calcium in divided doses.

Overall efficacy of calcium supplementation can be seen in increased blood calcium levels and improvement in bone density. Despite these benefits, there are some potential risks and adverse effects that should be considered. Constipation is a common side effect, and supplementation of 3 grams or more daily can lead to renal damage and possible kidney stone formation. Some studies have shown a possible increased risk of cardiovascular disease and death in men consuming calcium supplements. Other studies have shown protective cardiovascular effects with calcium supplementation. More studies are necessary to clarify this discrepancy regarding cardiovascular risk and benefit.

**MAGNESIUM**

Similar to calcium, magnesium plays several important roles in our body. At a biomolecular level, magnesium is needed for glycolysis, protein synthesis, energy production, and active transportation of calcium and potassium ions across cell membranes. For patients taking supplemental magnesium, the main purpose is not to discover the biomolecular intricacies that magnesium plays, but for the health benefits that come with the intake of magnesium. Magnesium provides benefits to patients by supporting muscle and nerve function, maintaining heart health and blood pressure regulation, helping with energy production (i.e., ATP utilization), and supporting a healthy immune system.

Low magnesium has been reported to have many negative health outcomes including depression, hypertension, and heart disease. Patients who consume fresh, unprocessed foods regularly should not be deficient in magnesium, as all unprocessed foods contain some amount of magnesium. In general, populations that have a higher risk of magnesium deficiency include patients with gastrointestinal (GI) disorders, malabsorptive syndromes, chronic alcoholism, and drug-induced magnesium wasting.

Recommended daily allowance (RDA) of magnesium for men ages 19-51, non-pregnant women (both lactating and non-lactating), and pregnant women are 400-420 mg, 310-320 mg, and 350-360 mg, respectively. While magnesium supplements are typically safe for the general

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population to consume, high levels of magnesium can cause nausea, abdominal cramping, and diarrhea.

Severe hypermagnesemia is rare, as the kidneys work hard to get rid of excessive magnesium. However, patients with kidney impairment may have trouble filtering out excessive magnesium, which can lead to hypermagnesemia if caution is not taken. Magnesium levels between 5-12 mg/dL can lead to decreased reflexes, drowsiness, confusion, headache, constipation, and flushing. Higher values of serum magnesium, exceeding 12 mg/dL, can induce muscle paralysis, labored breathing, hypotension, arrhythmias, and even cardiorespiratory arrest and coma.

**IRON**

In addition to magnesium and calcium, iron is another popular supplement among consumers. Iron is one of the major components of hemoglobin, a protein in red blood cells that carries oxygen from the lungs to all parts of the body. Iron's benefits are many. Iron helps with general energy and focus, GI processes, and immune system support. Oral iron supplementation is generally used to treat and prevent iron deficiency anemia.

Iron deficiency usually results from blood loss (due to menstruation or hemorrhagic loss), but it can also occur from poor dietary intake or malabsorption. Iron is also lost with the shedding of skin and GI mucosal cells, and by excretion in sweat, urine, and feces. Early signs and symptoms of iron deficiency are rather vague, such as pallor and fatigue. Other signs that point toward iron-deficiency anemia are "spoon-shaped" nails, tongue soreness, angular stomatitis, dyspnea, and cold extremities.

The RDA for iron varies by age, gender, and pregnancy status. In general, non-pregnant patients need 7-15 mg of elemental iron depending on age, and patients who are pregnant should be consuming 27 mg of elemental iron daily. Like calcium, iron supplements come in different formulations containing various amounts of elemental iron. Ferrous fuma-

rate contains the highest percent of elemental iron at 33%, followed by ferrous sulfate at 20% and then ferrous gluconate at 12%. Fortunately, consumers can easily find the total amount of elemental iron listed on the Supplement Facts panel without needing to do this calculation.

As with other supplements, there is a limit to how much iron one should take. High levels of iron intake, greater than 40-45 mg per day, can lead to upset stomach, constipation, vomiting, and diarrhea. More serious side effects include gastritis and gastric ulcers. It is recommended to take iron supplements with food to help mitigate the GI side effects.

**REGULATION**

The Dietary Supplement Health and Education Act (DSHEA) of 1994 granted authority over nutritional supplements to the FDA. Under DSHEA 1994, the FDA established standards for manufacturing and labeling. As nonprescription products, supplements are not reviewed by the FDA for safety and efficacy prior to entering the market. The FDA does, however, require all nutritional supplement manufacturers, both domestic and foreign, to abide by good manufacturing practices (GMPs). Third party verification programs exist to assess and validate compliance with manufacturing standards. The United States Pharmacopeia-Dietary Supplement Verification Program (USP-DSVP) provides a seal on supplement labels which indicates adherence to GMPs. Consumers should look for seals stating "GMP certified" or "USP certified" when selecting over-the-counter nutritional products. Supplement labels must also identify the product as a supplement and include the statement, "this product is not intended to diagnose, treat, cure, or prevent any disease." While the FDA has established several standards for regulation of dietary supplements, the oversight is limited in comparison to prescription products.

**CONCLUSION**

Nutritional supplements are primarily used for a self-perceived need. With only about a quarter of consumers using supplements on the advice of a medical professional, steps need to be taken to promote safe usage. Safe supplement utilization includes purchasing products bearing the GMP or USP certified seal, taking the supplement as the label instructs, and making one's healthcare team aware of use. Supplements can be beneficial if used appropriately to help augment nutrient insufficiencies when needed. Possible dangers occur when supplements are taken incorrectly, especially in high amounts. Healthcare providers should be educated on this topic to promote safe utilization of dietary supplements as their usage continues to increase.

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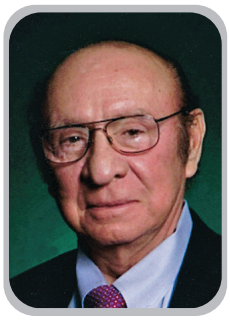
**AUTHOR BIOGRAPHIES**


*Aizelle Ann Gaddi is an Abilene native who graduated with a degree in chemistry and sociology from The University of Texas at Austin. She returned to her West Texas roots to attend pharmacy school at TTUHSC Jerry H. Hodge School of Pharmacy where she is currently a fourth year Doctor of Pharmacy candidate. She is passionate about healthcare access and hopes to be a community or ambulatory care pharmacist in the future.*

*An Hoang is currently a fourth year student at TTUHSC Jerry H. Hodge School of Pharmacy. An found his passion for pharmacy when he first started working as a pharmacy technician. During his free time, An likes to catch up on news in football, play chess, and dabble with the stock market.*

*Alaina Van Dyke is an Assistant Professor in the Department of Pharmacy Practice at TTUHSC Jerry H. Hodge School of Pharmacy. She completed her PharmD and MBA at Samford University McWhorter School of Pharmacy in Birmingham, Alabama. Dr. Van Dyke is a board-certified ambulatory care pharmacist and practices at the Fort Worth VA Outpatient Clinic. Her professional interests include chronic disease management through lifestyle medicine, health and wellness, and pharmacy experiential education.*


*In Memoriam*



Dr. Gregorio Matos-Serrano, General Surgeon

Died August 29, 2022 at the age of 88.

*He was a member of Potter Randall County Medical Society for 48 years.*

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# When Too Much is Too Much : the Story of Hypervitaminosis

*by David Vineyard, JD, MD, FACOG*

Beriberi, Rickets, Scurvy, Pellagra: all exotic names from the history of medicine. Recognition of these deficiency conditions let to the identification of the nutritional components which they reflected, and the field of "vital amines"--later shortened to "vitamins"--was born! It is an unfortunate characteristic of human nature, however, to believe that "more" of any good thing is by definition "better." The consumption of vitamins seems to be widely accepted as healthful. Fortune Business Insights quotes the worldwide vitamin and supplement market at $129.6 billion USD in 2021. Is there a danger in consuming large quantities of the micronutrients that we refer to as "vitamins?" Other articles in this issue will address the benefits of micronutrients at accepted levels, while this article will explore the dangers of ingesting these compounds in excess.

Vitamins are typically categorized as water-soluble or fat-soluble. Vitamins are absorbed in a number of ways, some by both active transport and passive diffusion. Their storage in the human body also is varied, with vitamin A and vitamin B12 stored in amounts sufficient for a year or more, while others, such as folate and thiamine, may be depleted within weeks. Furthermore, just as the effect of deficiencies varies, the effect of excess doses can span from no adverse effect to death at the other end of the spectrum.

**WATER-SOLUBLE VITAMINS**

No toxic effects of vitamin B1 (thiamine), B2 (riboflavin), B5 (pantothenic acid), B9 (folate) or biotin have been reported.

The effects of excess amounts of **vitamin B3 (niacin)** range from flushing, commonly seen at doses used to treat hyperlipidemia, to pruritis, hives, nausea, vomiting, abdominal pain, constipation and elevation of aminotransferase levels; glucose intolerance, macular edema and macular cysts; myopathy—and most seriously to hepatitis, with the most severe cases requiring liver transplantation. Interestingly, no toxicity has been reported from niacin derived from food sources.

Excess amounts of **vitamin B6 (pyridoxine)** may cause dermatoses, photosensitivity, dizziness, nausea and peripheral neuropathy that can be so severe as to prevent ambulation. As noted above with niacin, no adverse effects have been reported from pyridoxine derived solely from food sources.

Although **vitamin B12 (cobalamin)** is often used in high therapeutic doses, it has been reported to cause acne and rosacea, symptoms which resolve upon cessation of treatment.

Although **vitamin C (ascorbic acid)** is popularly regarded as an essential treatment for every condition from the common cold and Covid-19 to cardiovascular disease and cancer, no evidence supports its role in disease prevention. Excess amounts may cause false-negative stool guaiac test results, nausea, vomiting, diarrhea and bloating, as well as elevated levels of ALT, LDH, uric acid and oxalate--and thus may be implicated in cases of gout, oxalate kidney stones, and hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency.

Excess amounts of **choline** may cause hypotension, cholinergic sweating, diarrhea, salivation and a fishy body odor.

**FAT-SOLUBLE VITAMINS**

**Vitamin A toxicity** can be serious and even fatal. **Acute toxicity** results in nausea, vomiting, vertigo, blurry vision, drowsiness, malaise and recurrent vomiting. **Chronic toxicity** can cause ataxia, vertigo, alopecia, dry skin, exfoliative dermatitis, cheilosis, glossitis, amenorrhea, hyperlipidemia, hepatotoxicity, bone and muscle pain, visual impairments, hypercalcemia, lymph node enlargement, hyperlipidemia, amenorrhea, features of pseudotumor cerebri with increased intracranial pressure and papilledema, liver fibrosis with portal hypertension and bone demineralization, vertigo, diplopia, and seizures. Both acute and chronic vitamin A toxicity may cause death. Hypervitaminosis A is a known **teratogen** and for a pregnant female can result in spontaneous abortion or congenital malformations including craniofacial abnormalities (e.g., microcephaly) and cardiac anomalies. Only preformed vitamin A has these effects. High doses of carotenoids from food, however, may cause carotenemia, with yellowing of the skin.

**Vitamin D** is more accurately classified as a hormone rather than a vitamin, since it is produced in the human body as a result of sunlight exposure. Toxic levels only occur with supplementation or replacement therapy, and are the result of hypercalcemia: acutely causing confusion, polyuria, polydipsia, anorexia, vomiting and muscle weakness, and chronically leading to nephrocalcinosis, bone demineralization and pain.

**Vitamin E** supplementation may cause nausea, flatulence, and diarrhea. Since it may reduce platelet aggregation and interfere with vitamin K metabolism, it can result in increased bleeding, partic-

ularly for persons also taking aspirin or an anticoagulant.

Toxicity from dietary sources of **vitamin K** has not been reported. However, high doses of vitamin K can impair the action of oral anticoagulants such as warfarin, and thus should be used with caution by that population. Vitamin K is administered to newborns to prevent vitamin K deficiency bleeding. The form of vitamin K used for this treatment (1 mg of phytonadione) has not been associated with toxicity for the newborn, but menadione, a water-soluble precursor to vitamin K, has been known to cause hemolytic anemia, hyperbilirubinemia, jaundice and kernicterus.

The sentence "Only small amounts of these substances are needed for carrying out essential biochemical reactions" comes straight from Harrison's Principles of Internal Medicine. A review of the numerous adverse effects of the over-supplementation of vitamins should be sufficient to reinforce the message that "more is not always better" when it comes to medication. All physicians and medical providers should reiterate this message to our patients. Refraining from megadoses of vitamins will prevent everything from fishy body odor, acne and flushing to fulminant hepatitis and death--and will save money in the process.

**AUTHOR BIOGRAPHY**

*David D. Vineyard, JD, MD, FACOG, serves as Associate Professor in the Department of Obstetrics & Gynecology at Texas Tech-Amarillo. Dr. Vineyard graduated from the University of Texas Southwestern Medical School, then completed residency training in Obstetrics & Gynecology at Scott & White in Temple, Texas. He is board certified in Obstetrics & Gynecology, and was in private practice until joining the faculty of Texas Tech in 2020. Prior to attending medical school, he graduated from The University of Texas School of Law and practiced law in Dallas.*

# Vitamins, Supplements, and Alternative Treatments in Pregnancy

***by Paige Phillips MD & Makena Shields MD, Department of Obstetrics & Gynecology, TTUHSC, Amarillo***

Vitamins, supplements, and alternative treatments have always had a presence in prenatal care. Prenatal vitamins became popular in the 1970's with the addition of folic acid to their ingredient list and are now globally recommended despite a lack of conclusive evidence for their use. On the other hand, some prenatal supplements, like folic acid and iron, are well-studied and widely used during and outside of pregnancy. Questions regarding alternative treatments for common pregnancy-related symptoms frequently arise during prenatal counseling, and the clinician's familiarity with these topics can only benefit patients. Correlations are seen between certain limited nutrients and pregnancy outcomes; however, difficulties arise when executing research in pregnancy, and many questions remain. Regardless, enhancing maternal nutrition during pregnancy with prenatal vitamins, folic acid, vitamin B6, and iron remains standard practice.

Pregnancy requires modification of maternal nutritional needs to promote normal fetal growth and development. Maternal nutritional status is an important modifiable risk factor that should not be overlooked when counseling a patient at any stage in their reproductive journey. While it is known that the requirement for nearly all micronutrients increases during pregnancy (1), there are limitations to the available data that should be noted. Prenatal vitamins, folic acid, iron, and vitamin B6 are among the most commonly recommended nutrient supplementations, and while the use of these supplements is based on expert consensus and observational studies, a lack of high-quality research limits the strength of these recommendations.

Regarding prenatal vitamins, there is a variation in recommendations due to the lack of high-quality evidence surrounding the effectiveness of micronutrient supplementation in well-nourished pregnant women living in high-income countries like the United States (1). However, even in these high-income countries, a shift toward inferior-quality diets has been observed in recent years. This shift has resulted in increased incidence of inadequate vitamin intake during pregnancy (2) and will likely continue to support the practice of maternal nutritional modification during pregnancy.

Micronutrient intake recommendations during pregnancy are based on observational studies and expert consensus. The overwhelming body of evidence supports an association between maternal diet and maternal/offspring wellbeing (1). Supplementation with folic acid and iron is associated with multiple positive birth outcomes, and a meta-analysis published in the American Journal of Obstetrics and Gynecology observed decreased rates of small for gestational age neonates and defects of the neural tube, cardiovascular system, and urinary tract (1). No changes were seen in the primary outcome, preterm birth rates, however. It should also be noted that none of the studies reviewed in this analysis compared the use of multivitamins to the use of folic acid and iron, and the only outcome with at least a moderate degree of clinical evidence was the occurence of neural tube defects (2). Prenatal vitamins remain the standard to provide adequate micronutrient intake during preconception and pregnancy (1). There are no negative outcomes associated with prenatal vitamin use in the recommended dosage (1,2); therefore, routine use of prenatal vitamins can be recommended even in high-income countries—though due to the lack of high-quality evidence,

this should be done with caution. As with many guidelines focused on the care of pregnant patients, more research involving randomized trials and large cohort studies are necessary.

Iron is a vital micronutrient involved in fetal brain development, placental maturation, and increasing maternal red blood cell mass (3). Iron requirement increases during pregnancy, and, with iron-deficiency being the most prevalent single-nutrient deficiency in the world (3), the importance of preconception and prenatal counseling on the benefits of supplementation are obvious. Not all prenatal vitamins contain iron, and many pregnant patients do not realize the importance of iron supplementation. Iron deficiency anemia in pregnancy is associated with poor prenatal outcomes including preterm delivery, low birth weight, and perinatal mortality. It is well known that pregnant patients are routinely screened for anemia in the first and third trimesters, with treatment being iron supplementation in addition to prenatal vitamins; however, there is some evidence that iron supplementation should be recommended to all pregnant individuals, not just those who are anemic. Low-dose iron supplementation in non-anemic pregnant patients enhances hematologic parameters and is not associated with harm, although it has not been proven to affect perinatal outcomes (3). The U.S. Preventive Services Task Force concluded that there was insufficient evidence to make a recommendation; however, the American College of Obstetricians and Gynecologists recommend that low-dose iron supplementation be initiated in the first trimester (3).

After cardiac malformations, neural tube defects are the next most common major congenital anomaly in the world (4). Neural tube defects pose a significant public health problem and are unique in that primary prevention is possible. The correlation between folic acid supplementation and decreased nonsyndromic neural tube defects is well established, and studies report up to a 70% reduction in both first occurrence and recurrence with proper supplementation (4). Evidence supports the efficacy of both folic acid supplementation and dietary fortification in reducing the prevalence of neural tube defects. In 1998, the United States began mandatory fortification of flour with folic acid, which led to the reduction of neural tube defects by 19% (4). The MRC Vitamin Study led to the recommendation that all women of child-bearing age supplement a minimum of 400 mcg of folic acid as well as consuming a folate-rich diet (4). The U.S. Preventive Task Force and other governing bodies continue to uphold this recommendation. Neural tube defects occur in early pregnancy, often before women realize they are pregnant, making it imperative to discuss folic acid supplementation during well-woman visits and preconception counseling. Prenatal vitamins became popular when their formulations began to include this recommended dose of folic acid, and the presence of this specific micronutrient continues to support the use of prenatal vitamins by women around the world.

More than 50% of patients report experiencing nausea and vomiting during pregnancy (5), so the presence of a slew of alternative treatments promising relief is not surprising. Prenatal vitamins are thought to reduce vomiting (1), though it is unclear whether this is due to optimized nutritional status, increased vitamin B6 levels, or both. Most women have heard that ingesting ginger can decrease nausea, and this has proven true in limited trials; however, while safe in pregnancy, there is no solid evidence that ginger reduces vomiting (5). A better studied treatment for nausea and vomiting in pregnancy is Vitamin B6. Vitamin B6 with or without doxylamine is considered first-line pharmacotherapy for nausea and vomiting in pregnancy (5). Of historical significance, the combination of vitamin B6 and doxylamine was prescribed to over a quarter of pregnant women in the United States during its availability (5); however, production was discontinued when initial studies suggested an association between this combination and birth defects. Because of this, a decline in the use of prescription antiemetics during pregnancy was seen. It is now accepted that vitamin B6 in combination with doxylamine is non-teratogenic (5), and the use of antiemetics including this combination have continued to increase.

The use of vitamins, supplements, and alternative treatments have a long history in association with pregnancy and prenatal care and will continue to be discussed and investigated. The clinician's understanding of the benefits, risks, and alternatives of these practices can provide guidance to a patient in their reproductive journey in a safe and patient-centered direction. While there is evidence to support the use of supplementation of prenatal vitamins, iron, folic acid, and vitamin B6 in pregnancy and the quality of the research varies, there is sufficient evidence to suggest benefits with little to no harm. The lack of high-quality research should encourage caution and curiosity when counseling patients on the use of these vitamins, supplements, and treatments.

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**AUTHOR BIOGRAPHIES**

*Dr. Paige Phillips was born and raised in Nebraska but is so excited to call Texas her new home! She and her husband are newlyweds and enjoy traveling, movie nights, wine tasting, and playing with their new puppy, Murphy. Dr. Phillips is passionate about Ob/Gyn because of its fast-pace, surgical training, and opportunity for women's advocacy. She has always enjoyed writing and hopes to continue honing this skill throughout her career.*

*Dr. Makena Shields is currently an Ob/Gyn intern at Texas Tech Health Science Center. She was raised in Amarillo, Tx and, after attending medical school in Virginia, she is happy to be home to finish her training! She and husband Andrew have two beautiful daughters, Everleigh and Emersyn.*

# Hyperbaric Oxygen (HBO) Therapy:
## Its History, Use, Clinical Indications and Controversies

*by Rouzbeh K. Kordestani, MD, MPH*

### THE DEFINITION OF HYPERBARIC OXYGEN THERAPY

Hyperbaric Oxygen Therapy (HBOT) is categorized as the use of increased oxygen for the treatment of disease processes. Specifically, HBOT advocates the inhalation of near-100% medical grade oxygen at pressures greater than 1 atmosphere (1ATA) in a pressure environment/capsule/container designed for the safe delivery of such a treatment.

The intent of HBOT is to use increased oxygen delivery to help augment the perfusion and oxygenation of tissues. It is hoped that, with increased oxygen delivery and tension in the tissues, the physiological benefits of oxygen can be supplemented.

### INDICATIONS FOR HBOT

Studies have demonstrated that HBOT provides clinical benefit in a myriad of disease processes. In the medical literature, there are 14 proven indications for the use of HBOT. These include treatment for: 1. Air or gas embolism; 2. Carbon monoxide poisoning; 3. Clostridial myositis and myonecrosis (gas gangrene); 4. Crush injury, compartment syndrome and other acute traumatic ischemic syndromes; 5. Decompression sickness; 6. Arterial insufficiency; 7. Severe anemia; 8. Intracranial abscesses; 9. Necrotizing soft tissue infections; 10. Osteomyelitis (refractory); 11. Delayed radiation injury (soft tissue and bony necrosis); 12. Compromised grafts or flaps; 13. Acute thermal burn injury; and 14. Idiopathic sudden sensorineural hearing loss;

As the list shows, there is a great deal of variability in the clinical setting for which HBOT is now indicated. In most of these settings, the benefit of HBOT is based on the increased oxygen tension in the local tissues. With the increased perfusion in the local tissues, there is a decreased chance of ischemia and ischemic injury. In cases such as compartment syndrome or crushing traumatic injuries, the local tissues are under stress. This results in decreased local oxygen tension. This ischemia in turn causes the formation of by-products that only do more damage when perfusion is restored (reperfusion injury). With HBOT, this transient ischemic condition is alleviated, and the local tissues are saved from the initial ischemia as well as the subsequent reperfusion injury. In the infectious disease setting, data demonstrate significant physiological benefits of HBOT when used early. In settings such as clostridial soft tissue infections, HBOT use increases local oxygen tissue perfusion and the local infiltration of neutrophils. Since *Clostridium* is an anaerobic organism, this tends to stem the disease progress. Also, HBOT use actually decreases the release of the bacterial exotoxins that are known to cause the rapid progression of disease in fasciitis or myonecrosis cases. In doing so, HBOT prevents the progression of the disease and ameliorates local tissue destruction.

### ISSUES AND COMPLICATIONS OF HBOT

The use of HBOT, although effective, does come with certain complications and concerns. The use of high concentration oxygen at high atmospheric pressures can infuse the body with oxygen radicals. These free radicals can themselves cause tissue damage. The medical literature is well-versed in the presence of oxygen radicals and their deleterious effects on tissues and organ systems. Any prolonged HBOT is fraught with concerns about this type of excessive exposure. Along with the chemical toxicity of oxygen, the actual mechanical application/administration of HBOT can cause pneumothorax or to the ear/barotrauma. Neither one of these complications can be taken lightly. A more severe issue with HBOT is the Paul Bert Effect. This phenomenon has been documented in prolonged HBOT therapy patients. The Paul Bert Effect occurs when patients undergoing HBOT develop seizures. These clinical seizures bring to light transient but clinically significant functional and behavioral changes. The Paul Bert Effect is rarely predictable and is always a risk when HBOT is used.

### NEW APPROACHES AND POSSIBLE CONTROVERSIES

More recently, HBOT has been combined with radiation therapy for the treatment of a multitude of cancers. These include breast, prostate, cervical and colorectal cancers. It is reasoned that, in certain cancers, the tumor burden may affect the local tissues and cause transient hypoxia. In this hypoxic state, the regular cells fare poorly, while the cancer cells continue to grow. A combination of HBOT and radiation produces beneficial effects in these patient populations, as the increased oxygen tension along with the radiation therapy blocks downstream tumor effectors. This therapeutic combination inhibits tumor progression and growth and helps to restore the local humoral/cellular immune function. Studies are actively being completed analyzing the applications of this type of combination intervention using both HBOT and radiation.

While the combination of radiation and HBOT is slowly gaining favor, other uses of HBOT are not as clear-cut. In view of recent studies demonstrating the wide range of benefits of HBO therapy in clinical applications, some investigators have taken it upon themselves to

try to use HBOT for more controversial and unestablished indications. A case in point is a series of studies that have recently been published showing beneficial effects of HBO therapy on patients with chronic brain injury, cerebral palsy and even mild head/brain injury. The use of HBO therapy in these cases may produce some benefit. However, critics are quick to point out that the benefits are mild at best. Moreover, these same critics have pointed out that, in some cases, the benefits of HBO therapy can be shown by simply breathing oxygen under normal atmospheric pressure. Because of this, more randomized controlled trials have been advocated before any additional formalized indications for HBO therapy are approved.

## NORMOBARIC OXYGEN AND WOUND HEALING

Along with concerns about unproven indications for HBO use, the use of normal oxygen therapy (normobaric oxygen therapy--NBOT) for wound healing has evoked significant concerns. As HBOT has been proven to increase wound healing and local tissue oxygenation, it has become popular to use "oxygen" in offices for healing of wound care issues, either with minor surgical procedures or with more chronic surgical wound issues. Unfortunately, many of these offices or clinical settings do not use HBOT properly and/or do not have access to HBOT tanks. Instead, normal oxygen breathing is used. In these scenarios, data has already shown that healing is unaffected without reaching the prescribed 1 ATA as seen in therapeutic HBOT use. Without reaching this pressure, there is no proof of increased perfusion in the local tissues, and so any healing benefits that may be noted with HBOT do not apply. However, because post operative wound healing is needed in many clinical settings, the use of NBOT is very much in vogue. Unfortunately, these recent practices have not shown any increased healing benefit. In this arena, again, more effective trials are needed to show the benefit or lack of benefit of this newly prescribed type of oxygen use.

## CONCLUSION

Hyperbaric Oxygen Therapy (HBOT) has been in use for over a century now. Early on, its benefits were anecdotal. As more data became available, its use was restricted, due to concerns about oxygen free radicals and toxicity. However, as the years have gone on and as standards have been established for its use, its effectiveness has been proven again and again. As of now, fourteen different clinical indications exist for HBOT. As more clinical data are made available, it is likely that additional clinical uses will be found and advocated. As its benefits are more clearly demonstrated, it is hoped that in the future HBOT will be more readily and geographically available for use, across a wider breadth of patients.

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*Rouzbeh K. Kordestani attended undergraduate school at the University of California at Berkeley. He went to medical school at Tulane in New Orleans and did general surgery residency at UCLA and the University of California at San Francisco. He completed a plastic surgery residency at the University of Oklahoma and has practiced plastic surgery in Amarillo since 2004. He has served on the editorial board of Panhandle Health for 13 years and was editor-in-chief of our journal in 2009 and 2010.*

Ortiz

# Non-opioid Therapeutics for Chronic Pain

*by Yuma T. Ortiz, Nadezhda German, Ph D, Nakia Duncan, Pharm D, Jenny L. Wilkerson, Ph D From the Department of Pharmacodynamics, University of Florida, the Department of Pharmaceutical Sciences, TTUHSC (Amarillo), and the Department of Pharmacy Practice, TTUHSC (Dallas)*

Wilkerson

## INTRODUCTION

Opioids have been the standard for chronic pain management and many times as used as monotherapy. The opioid crisis highlighted not only opioid misuse and abuse but also the underutilization of adjuvant agents or non-opioid analgesic options. Recently there is a push to ensure that pain is being treated using the best mechanistic approach. This best approach may include combination therapy of both opioids, non-opioids, and other multimodal interventions. Here we will highlight gabapentinoids, selective norepinephrine reuptake inhibitors (SNRIs), and corticosteroids for chronic pain management. This article will also discuss the current state of the science behind cannabis use for chronic pain treatment and how cannabis may or may not augment opioid analgesia for chronic pain management.

## GABAPENTINOIDS

Gabapentinoids, such as gabapentin and pregabalin, are anticonvulsants that inhibit calcium channels, specifically the alpha-2-delta-1 subunit. They are used to treat various neuropathic conditions including post-herpetic neuralgia (PHN), post-stroke pain, post-amputation pain, diabetic peripheral neuropathy (DPN), fibromyalgia, etc. (1, 2). Due to the opioid crisis, there has been a sharp increase in the use of this class for the management of both neuropathic and non-neuropathic chronic pain such as chronic low back pain and sciatica. Gabapentin and pregabalin have long been used to treat the aforementioned conditions; however, a large portion of the use is off-label for gabapentin. The most recent Cochrane reviews of gabapentin and pregabalin showed that the number needed to treat (NNT) for major pain relief (> 50%) was 6.9 for patients with PHN and 5.9 for patients with DPN (3-5). While many may benefit from the gabapentinoids, many patients suffer from adverse effects such as somnolence, drowsiness, peripheral edema, weight gain, etc. Fear of these side effects may also leave individuals suboptimally treated, especially when using pregabalin. To ensure maximum clinical benefit with the fewest side effects, experts recommend starting low and going slow. Additionally, it is recommended to implement asymmetric dosing titrations; increasing the larger dose in the evening to avoid the sedating effects of this class (6). Typical dosing for gabapentin ranges 300-3600 mg/day and for pregabalin from 25-600mg/day, with the lower end reserved for initiation, older adults, and renally impaired individuals (7).

## SEROTONIN AND NOREPINEPHRINE REUPTAKE INHIBITORS

The mechanism for the beneficial effect of antidepressants in chronic pain is not fully known; however, these medications work through inhibition of neurotransmitters (8). Serotonin and norepinephrine reuptake inhibitors (SNRIs) specifically block reuptake of norepinephrine and 5-HT and are relatively free of muscarinic, cholinergic, histaminic, and alpha-adrenergic receptor activity (9). SNRIs such as venlafaxine and duloxetine provide a wide range of analgesic benefit and are the most widely used treatments for neuropathic pain (2). Venlafaxine is typically dosed between 75-225 mg for neuropathic pain. At higher doses, however, there has been an increase in hypertensive episodes, and therefore its role may be limited in patients with uncontrolled hypertension. On the other hand, duloxetine does not have a similar effect on blood pressure. Duloxetine is used at doses 60-120 mg for various neuropathies, with lower doses used in patients with renal insufficiency (7).

## CORTICOSTEROIDS

Corticosteroids inhibit the action of phospholipase, preventing the formation of arachidonic acid and subsequent inflammatory mediators (10). Corticosteroids are divided into two groups, mineralocorticoids and glucocorticoids; the latter is used for the treatment of pain. Glucocorticoids may cause fluid retention, bone demineralization, impaired glucose metabolism and changes in mood/nervousness. Caution is recommended for use in patients with heart failure, diabetes, and osteoporosis. Side effects are increased with systemic formulations as opposed to locoregional preparations. Therefore, ideally, corticosteroids are given as an injection for musculoskeletal and peripheral neurological conditions. Injections are given to the intra- articular space, trigger point, ligament, peritendon region, perineural region, and epidural space (10). Dose frequency of injection varies based on indication and patient specific variables.

## CANNABIS/CANNABINOIDS

Cannabis-related therapeutic actions are, in part, the result of its main compounds, Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC acts at two identified cannabinoid receptors, both of which are G protein-coupled receptors. Cannabinoid 1 receptors (CB1R) appear in high densities among presynaptic neurons within the central nervous system (CNS), (particularly among GABAergic interneurons) and on peripheral neurons, as well as on astrocytes and oligodendrocytes (11-13). The behavioral effects of cannabinoid consumption, termed as 'cannabimimetic' behavioral effects, are

mediated by neuronal CB1R (14-16). CB1Rs are found throughout the CNS in pain relevant regions such as afferent nerve fibers (17, 18), spinal cord interneurons (19), trigeminal sensory neurons (20), and neurons within the periaqueductal grey (21). As for the periphery, CB1Rs are observed on peripheral nociceptors (22) and the dorsal root ganglia (17). CB1Rs are also associated with anti-inflammatory mechanisms, contributing to therapeutic prospects of CB1R agonists (22, 23). CB2 receptors (CB2Rs) are expressed by immune cells including microglia, astrocytes, oligodendrocytes (24-26), and discrete neuronal populations (27) within the brainstem (28) and the hippocampus (29). Unlike CB1R agonism, CB2R agonism does not result in the cannabimimetic effects observed with CB1R agonists, but still produces anti-inflammatory signaling cascades (30). THC is a non-selective CB1R/CB2R agonist. Dronabinol is a clinically approved synthetic THC formulation.

The therapeutic actions of CBD are generally attributed to non-CB1R/ CB2R activity, including partial agonist activity at the 5-HT1A receptor (31, 32). Serotonin 5-HT1A receptors are G protein-coupled receptors (33-35). 5-HT1A receptors are expressed in areas relevant to pain signaling and transmission such as primary afferent neurons, peripheral terminals, astrocytes, oligodendrocytes, and microglia (36-38). Nabiximols is a clinically approved THC + CBD formulation.

## PRECLINICAL CHRONIC PAIN STUDIES

By themselves, both CBD and THC exert analgesic effects in numerous chronic pain animal models, such as surgically induced nerve injury and chemotherapy induced neuropathy (39-41). In models of either surgically induced nerve injury (42, 43) or chemotherapy induced neuropathy (32), 1:1 THC + CBD combinations exhibited greater efficacy at low doses that were ineffective with either THC or CBD alone.

## CLINICAL CHRONIC PAIN STUDIES

In a double-blind placebo-controlled study using multiple sclerosis patients experiencing chronic neuropathic pain, THC (dronabinol), taken orally up to a maximum dose of 15.9 mg over 16 weeks, decreased patient reported pain measurements (44). Both acute and repeated whole cannabis use alleviated chronic pain while improving patient quality of life (45, 46). In an open label, long-term efficacy and safety portion of this clinical trial, patients reported a decrease in pain intensity and few serious adverse effects (44). Nabiximols clinical trials report relief from chronic pain in a number of conditions including multiple sclerosis (47-49), peripheral neuropathy (50) and cancer (51-53). A clinical trial with nabiximols in patients experiencing chronic pain associated with late-stage cancer observed a 15.5% improvement in patient-reported perceptions of pain (53). An identical companion study to this clinical trial once again observed similar improvements with nabiximols (51). It should be noted that patient pools utilized cohorts from both the United States and Eastern Europe, with significant improvements in pain relief compared to placebo among American patients and general improvements among Eastern Europeans, though these effects were not significant compared to placebo in Eastern European cohorts (51, 53). In these studies, the Eastern European cohort was sicker than the American cohort, suggesting that patient selection criteria may have contributed to divergent study findings. Additionally, nabiximols administration met several secondary endpoints associated with quality of life, which, as suggested by the authors, may indicate therapeutic utility in cancer pain as an adjuvant therapeutic with a low opioid dose (53).

## OPIOID AND CANNABINOID INTERACTIONS

Clinical pain research suggests that medicinal cannabis or cannabinoids for chronic pain treatment may yield opioid-sparing effects, a major consideration given the interest in minimizing opioid use. Studies utilizing smoked or oral medicinal cannabis among habitual opioid using, chronic pain patient cohorts observed improvements in quality of life, pain, and opioid prescription cessation (54, 55). Indeed, following six months of opioid/cannabis cotreatment, prescribed morphine use was found to have dropped significantly compared to baseline usage among patients with chronic pain, with reductions observed after three months of opioid/cannabis cotreatment (56). Similar reductions in prescribed opioid use were also observed over a 21-month period with 83.8% of patients (N=37) reporting reduced prescribed daily opioid dosage and 40.5% of patients ceasing opioid prescriptions altogether (57).

## DISCUSSION

Preclinical and clinical research utilizing cannabinoids for chronic pain management suggest therapeutic utility and tolerability either alone or in combina-

tion with current therapeutics. There still exists a wide gap between the purported and anecdotal medicinal cannabis uses and specific therapeutic indications irrefutably supported by strong scientific evidence.

Abbreviations: Cannabidiol (CBD); cannabinoid 1 receptor (CB1R); cannabinoid 2 receptor (CB2R); central nervous system (CNS); Food and Drug Administration (FDA); Selective Serotonin Reuptake Inhibitors (SSRIs); serotonin 1a (5-HT1A); Δ9-tetrahydrocannabinol (THC)

## CONFLICT OF INTEREST

The authors declare that an absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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A Complete biobliography can be requested from www.prcms.com

## AUTHOR BIOGRAPHIES

*Dr. Jenny Wilkerson has been an Assistant Professor in the Department of Pharmaceutical Sciences within the Jerry H. Hodge School of Pharmacy, TTUHSC since December 2021. Dr. Wilkerson, originally from the Kansas City, Missouri area, received her Bachelor of Science degree in cellular/ molecular biology from Northwest Missouri State University, and her Ph.D. in biomedical sciences from the University of New Mexico School of Medicine's department of neurosciences. Dr. Wilkerson then completed a postdoctoral fellowship at Virginia Commonwealth University in the department of pharmacology and toxicology, where she was the recipient of the competitive Ruth L. Kirschstein F32 Individual National Research Service Award. She then joined the University of Florida College of Pharmacy's department of pharmacodynamics as a research track faculty member until November 2021. Her research interests broadly encompass the involvement of the immune system in preclinical models of pathological pain and neurodegeneration, with an emphasis on endogenous cannabinoid (endocannabinoid) system modulation. Additionally,*

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*she studies the adjunct administration of experimental preclinical compounds to produce enhanced analgesic opioid effects, with diminished drug abuse liability. Outside of science, Dr. Wilkerson's interests include travel and spending time with her family.*

*Yuma Ortiz is a current graduate student of the University of Florida where the majority of his work focuses on neuropathic pain. Current research interests involve neuropathic pain resulting from chemotherapy and cancer, as well natural products such as kratom, and cannabinoids for treating such pain. Other interests of his include aging and associated neurodegenerative diseases including Parkinson Disease and Alzheimer disease.*

*Nakia Duncan, Pharm.D. BCGP, BCPS is an Associate Professor of Geriatric Pharmacy Practice at the Texas Tech University HSC Jerry H. Hodge School of Pharmacy on the Dallas/Fort Worth campus with an affiliated practice with UT Southwestern. There she focuses on pain management and supportive care on the palliative care team. Her practice and research interests include pain and palliative care management of older adults. She is the author several peer-reviewed publications and has been asked to speak on various geriatrics-focused topics at both local and national meetings. She is a member of the Society of Pain and Palliative Care pharmacist severing on their research and education committees.*

*Nadezhda (Nadia) German is a tenured associate professor at the Texas Tech University Health Sciences Center (TTUHSC). She received her Ph.D. with an emphasis in Medicinal Chemistry at the University of Iowa, working with Dr. Robert Kerns. Her current research focuses on developing molecules with two different biological activities: the ability to modulate GPCRs and kill cancer cells. Her work is funded by the NIH and seed grants from various foundations.*

## *In Memoriam*

### Dr. Ruth Pilco-Jaber, Internist and Nephrologist

Died October 12, 2022 at the age of 66.

*She was a member of Potter Randall County Medical Society for 25 years.*

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German

# Non-opioid therapeutics for acute pain

*by Yuma T. Ortiz, Nadezhda German, PhD, Nakia Duncan, Pharm D, Jenny L. Wilkerson, Ph D. From the Department of Pharmacodynamics, University of Florida, the Department of Pharmaceutical Sciences, TTUHSC (Amarillo), and the Department of Pharmacy Practice, TTUHSC (Dallas)*

Duncan

## INTRODUCTION

Opioids are used frequently for the management of acute pain due to their effectiveness. However, they are not always necessary and may pose more risks than benefits. The opioid crisis has highlighted not only opioid misuse/abuse, but also the underutilization of adjuvant agents or non-opioid analgesic options for acute pain. Here we will highlight non-steroidal anti-inflammatory drugs (NSAIDs) as a 1st line treatment approach for acute pain. Due to anecdotal claims that cannabis can treat pain, many patients are increasingly turning to cannabis use for acute pain treatment. This article will discuss current NSAID uses for acute pain, including acute post-surgical pain. This article will also discuss the current state of the science behind cannabis use for acute pain treatment and how cannabis may or may not augment acute opioid-induced analgesia.

## NSAIDS

NSAIDs can be separated into two categories: non-selective cyclooxygenase-1 and cyclooxygenase-2 (COX 1 and COX 2) inhibitors and selective COX 2 inhibitors. They are available in oral, intramuscular, ophthalmic, and topical preparations(1). NSAIDs are ideal for treating acute pain due to the natural inflammation that occurs with injury. Since they target inflammation, they effectively reduce swelling, and hence the pain caused by muscle strain or sprain. In these cases, NSAIDs may be more effective than opioids. NSAIDs are used frequently for post-operative pain. A study with post-orthopedic surgery patients showed that patients using NSAIDs had more effective pain relief and required less rescue (opioid) analgesics (2, 3). Unfortunately, NSAIDs are not without side effects. Gastrointestinal effects include dyspepsia, bleeding, peptic ulcer disease, perforation, renal impairment through sodium and water retention, and increased cardiovascular risks, including hypertension, myocardial infarction, stroke, and death (1). Therefore, limiting use to the lowest effective dose for the least amount of time is recommended. In addition, combination therapies are being explored to increase the effectiveness of existing NSAIDs and to reduce side effects associated with their use. A recent analysis of clinical trials conducted in the United States from 01/01/2015 to 10/29/2022 (4) shows that 24 clinical studies have been initiated to evaluate NSAIDs, with nine being completed. Most of the conducted studies assess the efficacy of existing NSAIDs in different modalities of acute pain (Fig 1) and the effectiveness of new combinations, including diazepam/naproxen (NCT02646124), orphenadrine/naproxen and methocarbamol/naproxen (NCT02665286).

## CANNABIS/CANNABINOIDS

Cannabis-related therapeutic actions are, in part, the result of its main compounds, Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC acts at two identified cannabinoid receptors, both of which are G protein-coupled receptors. Cannabinoid 1 receptors (CB1R) appear in high densities among presynaptic neurons within the central nervous system (CNS), (particularly among GABAergic interneurons), in peripheral neurons and on astrocytes and oligodendrocytes (5-7). The behavioral effects of cannabinoid consumption, termed as 'cannabimimetic' behavioral effects, are mediated by neuronal CB1R (8-10). CB1R are found throughout the CNS in pain relevant regions such as afferent nerve fibers (11, 12), spinal cord interneurons (13), trigeminal sensory neurons (14), and neurons within the periaqueductal grey (15). As for the periphery, CB1Rs are observed on peripheral nociceptors (16) and the dorsal root ganglia (17). CB1Rs are also associated with anti-inflammatory mechanisms, contributing to therapeutic prospects of CB1R agonists (18, 19). CB2 receptors (CB2Rs) are expressed by immune cells including microglia, astrocytes, oligodendrocytes (18, 20, 21) and discrete neuronal populations (22) within the brainstem (23) and the hippocampus (24). Unlike CB1R agonism, CB2R agonism does not result in the cannabimimetic effects observed with CB1R agonists, while still producing anti-inflammatory signaling cascades (25). THC is a non-selective CB1R/CB2R agonist. Dronabinol is a clinically approved synthetic THC formulation.

The therapeutic actions of CBD are generally attributed to non-CB1R/ CB2R activity, including partial agonist activity at the 5-HT1A receptor (26, 27). Serotonin 5-HT1A receptors are G protein-coupled receptors (28, 29). 5-HT1A receptors are expressed in areas relevant to pain signaling and transmission such as primary afferent neurons, peripheral terminals, astrocytes, oligodendrocytes, and microglia (30-32).

Despite numerous preclinical studies with animals, definitive clinical studies in humans demonstrating irrevocable proof that cannabis is an effective acute pain analgesic remains elusive (33). In a small double-blinded, placebo-controlled, crossover design clinical study, oral CBD had no effect on muscle damage markers or muscle soreness in exercised untrained men (34). A recent double-blind, placebo

controlled clinical study in an emergency room setting found that orally administered CBD was equal to placebo and did not adequately control acute non-traumatic low back pain (35). In another recent Phase 2 clinical study, dronabinol, a cannabinoid agent used for the treatment of chemotherapy-induced nausea and vomiting, was evaluated in the settings of acute pain following traumatic injury (NCT03928015). However, this study was terminated due to the lack of participants.

Although these clinical studies suggest CBD may not be a frontline analgesic for acute pain, further clinical studies examining various route of administration and dosing strategies are needed. Additionally, it is unknown if the other compounds in medicinal cannabis may yield enhanced utility of these cannabinoids in clinical pain management settings.

## OPIOID AND CANNABINOID INTERACTIONS

The ability of medical cannabis to augment the analgesic potency of opioids without additional enhancement of opioid associated side effects is an area of growing research interest. Recent clinical trials yield mixed results. A study in healthy subjects reported THC (dronabinol, max 10 mg) had no consistent dose-effect relationship with the opioid agonist hydromorphone in acute pain measures, though significant analgesia in acute pain with hydromorphone and 2.5 mg dronabinol compared to placebo was observed (36). A clinical trial utilizing healthy cannabis smokers found that the combination of oxycodone (2.5 mg) and cannabis (cigarettes, 5.6% THC) was not able to provide analgesia in measures of acute pain but did increase abuse-related subjective effects, although it did increase pain thresholds and tolerance (37). This discrepancy may be due to the contributing pharmacological effects of the other compounds found in cannabis rather than THC alone, though more work is needed to explore the complex pharmacology between cannabinoids and opioids.

## MEDICINAL CHEMISTRY APPROACHES TO SAFER MEDICINE

One approach to creating pain medicines with a safer profile is to develop synthetic analogs of CBD and endogenous CBs with the optimized pharmacological profile. For example, to eliminate unwanted side effects of CB receptor agonists, new generations of CB1 ligands with limited blood-brain barrier (BBB) permeability have been designed to work peripherally (38, 39). Because CBD has been shown to act via GRP35 and GRP18, these orphan receptors have been used to develop of safer ligands for pain treatment (40). Additional strategies include the development of enzyme inhibitors to prevent the degradation of endogenous CBs. For example, it was shown that an inhibitor of monoacylglycerol lipase increases levels of 2-arachidonoyl-sn-glycerol (2-AG) and reduces the clinical severity of multiple sclerosis in mice (41).

The discovery of new NSAIDs analogs focuses on reduction in cardiovascular toxicities associated with COX-2 inhibition (42). One of the approaches is to convert selective COX-2 inhibitors to dual-acting agents with an additional activity at the pain-related target. For example, a hybrid small molecule with activities as NSAID and carbonic anhydrase inhibitor was shown to be more efficacious in the rheumatoid arthritis model (Sprague-Dawley rats) compared to ibuprofen (43).

## DISCUSSION

This review of current and past studies finds that preclinical research indicates therapeutic potential for cannabis, THC, and CBD mediated through either CB1R, CB2R, 5-HT1A, or a variable combination of these receptors. Clinical research utilizing cannabinoids for acute pain management suggest tolerability either alone or in combination with current therapeutics. However, additional clinical studies are required to clarify these therapeutic indications before definitive declarations can be made. There still exists a wide gap between the purported and anecdotal medicinal cannabis uses

and specific therapeutic indications irrefutably supported by strong scientific evidence. One possible explanation for this disparity may lie in the complex pharmacological nature of cannabis.

Abbreviations: 2-Arachidonoyl-sn-Glycerol (2-AG); Blood-Brain Barrier (BBB), Cannabidiol (CBD); cannabinoid 1 receptor (CB1R); cannabinoid 2 receptor (CB2R); central nervous system (CNS); Food and Drug Administration (FDA); Non-steroidal Anti-Inflammatory Drugs (NSAIDs); serotonin 1a (5-HT1A); Δ9-tetrahydrocannabinol (THC)

**CONFLICT OF INTEREST**

The authors declare that an absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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*In Memoriam*

## Dr. Jesus "Jesse" Benitez, Internist

Died October 19, 2022 at the age of 63.

*He was a member of Potter Randall County Medical Society for 45 years.*

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**AUTHOR BIOGRAPHIES**

*Nakia Duncan, Pharm.D. BCGP, BCPS is an Associate Professor of Geriatric Pharmacy Practice at the Texas Tech University HSC Jerry H. Hodge School of Pharmacy on the Dallas/Fort Worth campus with an affiliated practice with UT Southwestern. There she focuses on pain management and supportive care on the palliative care team. Her practice and research interests include pain and palliative care management of older adults. She is the author several peer-reviewed publications and has been asked to speak on various geriatrics-focused topics at both local and national meetings. She is a member of the Society of Pain and Palliative Care pharmacist severing on their research and education committees.*

*Nadezhda (Nadia) German is a tenured associate professor at the Texas Tech University Health Sciences Center (TTUHSC). She received her Ph.D. with an emphasis in Medicinal Chemistry at the University of Iowa, working with Dr. Robert Kerns. Her current research focuses on developing molecules with two different biological activities: the ability to modulate GPCRs and kill cancer cells. Her work is funded by the NIH and seed grants from various foundations.*

*Dr. Jenny Wilkerson has been an Assistant Professor in the Department of Pharmaceutical Sciences within the Jerry H. Hodge School of Pharmacy, TTUHSC since December 2021. Dr. Wilkerson, originally from the Kansas City, Missouri area, received her Bachelor of Science degree in cellular/ molecular biology from Northwest Missouri State University, and her Ph.D. in biomedical sciences from the University of New Mexico School of Medicine's department of neurosciences. Dr. Wilkerson then completed a postdoctoral fellowship at Virginia Commonwealth University in the department of pharmacology and toxicology, where she was the recipient of the competitive Ruth L. Kirschstein F32 Individual National Research Service Award. She then joined the University of Florida College of Pharmacy's department of pharmacodynamics as a research track faculty member until November 2021. Her research interests broadly encompass the involvement of the immune system in preclinical models of pathological pain and neurodegeneration, with an emphasis on endogenous cannabinoid (endocannabinoid) system modulation. Additionally, she studies the adjunct administration of experimental preclinical compounds to produce enhanced analgesic opioid effects, with diminished drug abuse liability. Outside of science, Dr. Wilkerson's interests include travel and spending time with her family.*

*Yuma Ortiz is a current graduate student of the University of Florida where the majority of his work focuses on neuropathic pain. Current research interests involve neuropathic pain resulting from chemotherapy and cancer, as well natural products such as kratom, and cannabinoids for treating such pain. Other interests of his include aging and associated neurodegenerative diseases including Parkinson Disease and Alzheimer disease.*

# The History of National Center for Complementary & Integrative Health (NCCIH)

*by Rouzbeh K Kordestani, MD, MPH*

**HISTORY OF NCCIH**

The Office of Alternative Medicine (OAM) was established by the United States Congress in 1991 as an adjunct of the National Institutes of Health (NIH) to probe and establish the relevance of "alternative" medicines and therapies. It was established as more and more Americans began to look for non-traditional medicines and therapies for answers. In 1998, the OAM was changed in name and breadth to the National Center for Complementary and Alternative Medicine (NCCAM). At that point, it became an official office of research and development for alternative therapies. Its budget increased from several million dollars per year to $20 M/year, and continued to grow exponentially over the next decade. By 2003, its budget had increased to $113 M/year. In December 2014, the center again changed its name, now to the National Center for Complementary and Integrative Health (NCCIH) in an attempt to fend off criticism from the scientific community about the name "alternative medicine."

**THE MISSION OF THE NCCIH AND ITS AREAS OF FOCUS**

The stated mission of the NCCIH is "to define, through rigorous scientific investigation, the usefulness and safety of complementary and alternative medicine interventions and their roles in improving health and health care."

As more Americans welcomed "alternative" medicines and therapies into their lives (>30 million American adults; roughly 10% of the population;), it was found that most of these interventions went unchallenged, without any scientific proof or merit. The original purpose of the OAM and later the NCCIH was to study these alternative therapies and to add scientific proof and evidence behind them, to assess their usefulness, efficacy and safety.

To better categorize these various therapies, the NCCIH chose to more appropriately define the terms used in the field:

Complementary—If a non-mainstream approach is used together with conventional medicine, it is considered "complementary."

Alternative—If a non-mainstream approach is used in place of conventional medicine, it is considered "alternative."

Integrative/Integrated—If a complementary approach is used in conjunction with a mainstream medical approach, it is considered "integrative/integrated."

The NCCIH chose to direct its funding into 4 areas of focus, based on the therapies and interventions that were frequently in use: 1. Biologically-based (e.g., supplements); 2. Energy medicine (e.g., electromagnetic radiation/magnets); 3. Body-based therapies (e.g., chiropractic/body manipulations), and 4. Mind/Body medicine (e.g., meditation).

With the focus of attention fixed on these 4 groupings as described, the NCCIH chose to push forward 4 clear objectives, along with its mission—1. Advancing scientific research; 2. Training complementary and alternative (CAM) researchers; 3. Sharing news and information/results about alternative/complementary/integrative health; and 4. Supporting the integration of proven CAM therapies into other avenues of medicine and intervention.

**CONTROVERSY**

Since its inception, the NCCIH (originally, OAM) has been plagued by criticisms from the scientific community. Its inception was plagued by politics from its greatest advocate, Senator Tom Harkin

from Iowa. Senator Harkin himself was a true believer in alternative therapies and wished to see them used in the more mainstream areas of health, as alternatives to traditional medical interventions. With his help, the OAM was founded. However, the entity was politically driven for decades. Many of the scientists who had tried to direct its function and purpose were systematically run out.

In 1998, Nobel Laureate Dr. Harold Varmus, the director of the NIH, came into direct conflict with Senator Harkin and his "pet" project. Dr. Varmus placed the OAM under strict control of the NIH to ensure that scientific rules were applied to the OAM. Senator Harkin responded to the director's efforts by elevating the OAM into an independent NIH center in 1998 under the new name NCCAM and out of Dr. Varmus' control.

Dr. Paul Berg, a fellow Nobel Laureate in chemistry at the NIH, commented that "quackery will always prey on the gullible and the uninformed, but we should not provide it cover from the NIH." He called the OAM/NCCAM "an embarrassment to serious scientists." Dr. Allen Bromley, another institute leader, commented to Congress that the OAM had "emerged as an undiscriminating advocate of unconventional medicine. It has bestowed the considerable prestige of the NIH on a variety of highly dubious practices, some of which clearly violate basic laws of physics and more clearly resemble witchcraft."

Years later, in 2012, the Journal of the American Medical Association (JAMA) published a widely accepted critique of the NCCAM. It noted that the NCCAM had failed in its mission in that it had not been able to produce any studies showing that complementary or alternative medicines did anything more than placebo effects. It then catalogued a myriad of studies that had shown no results whatsoever. This included a list as follows: $374,000 for a study to find the usefulness of inhaling lemon and lavender scents for wound healing; $406,000 to find if coffee enemas help pancreatic cancer; and $750,000 to find if remote prayer can cure AIDS or hasten recovery from breast reconstruction surgery. The JAMA article did point out one additional worrisome fact. It noted that the public generally ignored negative results and continued to use the complementary and integrative approaches in spite of the scientific evidence. In other words, the public continued to "believe what they want to believe, arguing that it does not matter what the data actually shows."

More recently, the institute changed its name to the NCCIH. It has new leadership from Harvard Medical School, and it is trying its utmost to adhere to its scientific purpose and its primary mission. Most of the upper echelons of the scientific community and the other divisions of the NIH, however, continue to push for its funding to be removed and for the center to be permanently closed.

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# Pediatric Posterior Reversible Encephalopathy Syndrome (PRES) Secondary to Post Streptococcal Glomerulonephritis:

## A Case Report, Literature Review, & Assessment of Treatment Modalities

*by Abdurrahman F. Kharbat, MBA, Pedro Calles, DO, Allison Ogle, DO, MBS, Tetyana L. Vasylyeva, MD, PhD, Kerrie A. Pinkney, MD, MPH.*
*From the division of neurosurgery TTUSOM (Lubbock) & the departments of family medicine & pediatrics TTUSOM (Amarillo)*

**ABSTRACT**

Posterior reversible encephalopathy syndrome (PRES) is a disorder that most commonly affects adults, and is characterized by neurologic symptoms such as encephalopathy, seizures, headaches, and visual disturbances. It usually occurs in the context of other systemic disturbances that result in hypertensive crises, such as renal failure, cytotoxic drugs, and autoimmune conditions. In children, it rarely manifests following chemotherapy induction or hematopoietic stem cell transplantation. No cases have been reported in the English literature connecting renal dysfunction and hypertensive emergency secondary to post-streptococcal glomerulonephritis (PSGN) with PRES. We present a case of an 8-year-old boy who developed a constellation of symptoms suggestive of PSGN and later developed PRES. PRES is often confirmed upon suspicion through brain MRI showing subcortical edema of various brain regions including occipital, temporal, or parietal cortices. Our patient demonstrated subcortical edema of the bilateral occipital lobes and right cerebellar hemisphere, with positive anti-streptolysin O (ASO) titers demonstrating PSGN as the likely etiology for his hypertensive emergency. Management included antihypertensive and anticonvulsant treatment, which allowed the resolution of the offending hypertensive emergency that resulted in PRES. Our case adds to the growing body of literature on PRES and describes a new etiology of pediatric PRES secondary to PSGN.

**INTRODUCTION**

Posterior reversible encephalopathy syndrome (PRES) is a syndrome characterized by reversible subcortical vasogenic edema in the brain that manifests in patients with acute neurological symptoms (i.e., seizures, encephalopathy, headache, and visual disturbances) (1-4, 6). It has been reported to occur in the setting of various systemic illnesses, such as renal failure, dramatic blood pressure fluctuations, cytotoxic drugs, autoimmune disorders, and preeclampsia or eclampsia (2, 4, 6). Pediatric PRES may occur in the setting of chemotherapy initiation for acute lymphocytic leukemia (ALL), which results in endothelial cytotoxic injury (4). Even more rarely, pediatric PRES may develop following hematopoietic stem cell transplantation (HSCT) and during prophylactic cranial irradiation (4).

Although the pathogenesis is under debate, the leading theory proposes that PRES is due to disruption in the autoregulation of cerebral perfusion, which subsequently results in the breakdown of the blood-brain barrier (1-10). This allows the extravasation of plasma and macromolecules into the brain interstitial space (4, 6). The posterior brain is particularly vulnerable to this phenomenon due to relative paucity of sympathetic innervation, which results in decreased propensity to autoregulation of blood pressure (6). This theory prevails due to the resolution of PRES symptoms clinically and radiologically following treatment of acute hypertension (6).

Clinical signs of PRES vary and are limited by a small sample of reported cases in the literature, but common symptoms include focal neurologic deficits or signs and symptoms of intracranial hypertension, including headache, nausea, vomiting, diplopia, and visual field abnormalities (4). Encephalopathy (ranging from mild confusion to deep stupor) is common, and generalized tonic-clonic seizures occur in 60-75% of patients (5-9). What is more worrisome, albeit less common, is status epilepticus, in which PRES can be the suspected etiology when bilateral occipital sharp waves are present on EEG (5-7).

Brain imaging via T2 fluid-attenuated inversion recovery sequences may demonstrate predominantly subcortical abnormal T2 signal bilaterally in the cerebellar hemispheres, watershed regions, posterior parieto-temporal regions and occipital regions (10). Imaging is often what clues clinicians in on the diagnosis of PRES and is also used to verify the resolution of this syndrome in the setting of clinical improvement (10).

**CASE PRESENTATION**

An eight-year-old, previously healthy male presented to the Emergency Department (ED) with new onset seizures. The patient had fallen and hit his head at school without any loss of consciousness (LOC). He began having severe intractable headaches, blurry vision, fever, vomiting, and nausea 3 days prior to arrival. In the ED, the patient had altered mental status (AMS) with blood pressure (BP) ranging from 192-155/132-114, followed by a witnessed focal seizure with left downward gaze. He received two doses of midazolam with loading dose of levetiracetam. A non-contrast head CT done in the ED showed no acute changes.

The patient soon became tachypneic and hypoxic, which was thought to be secondary to obstructive sleep apnea due to his large body habitus (>99th percentile). Continuous positive airway pressure (CPAP) was started. The patient had a tonic-clonic seizure lasting about 10 minutes the following morning. He received two 4 mg doses of lorazepam, then a 1000 mg dose of levetiracetam, and was

transferred to the pediatric intensive care unit. Due to continued seizures, levetiracetam was scheduled every 12 hours. Upon further questioning, the patient's parents reported a history of upper respiratory infection approximately 3 weeks before, followed by dark urine 1.5 days prior to arrival to the ED. Diagnostic labs and imaging ordered overnight began to return, with resulting studies and values seen in Tables 1 and 2.

Following results of our workup and further history from the parents, post-streptococcal glomerulonephritis (PSGN), confirmed by elevated anti-streptolysin O (ASO) titers, and severe hypertensive emergency resulting in PRES were high on the differential. The diagnosis of PRES was confirmed via axial T2 MRI without contrast demonstrating large regions of abnormal signal in both cerebral hemispheres, predominantly posteriorly in the occipito-parietal lobes, and in the right cerebellar hemisphere (Figure 1). This appearance is suggestive of posterior reversible encephalopathy syndrome (PRES).

Amlodipine 5 mg daily and IV furosemide 20 mg were initiated. Azithromycin and ceftriaxone were also started. Once the Mycoplasma IgM antibody immunoassay was determined to be negative, azithromycin was discontinued. Ophthalmology and nephrology were consulted. BP continued to be labile and significantly elevated. Labetalol was added as needed for occasional BP spikes, and amlodipine was increased to 10 mg daily. The patient's clinical encephalopathy began to resolve, but BP remained unstable. Labetalol was increased to twice daily. The patient continued to have high BP despite the highest possible dose of amlodipine and high-dose labetalol. The decision to start nicardipine drip was then made.

Respiratory failure resolved without continued hypoxia and CPAP was discontinued. BP became less labile and trended downward. The patient was then weaned off the nicardipine drip while 200 mg labetalol BID and amlodipine were continued. Enalapril 2.5 mg was added due to proteinuria and stable renal function. Enalapril was increased to 10 mg daily. Eventually, the BP was controlled with oral medications. Throughout the hospital course, careful titration of 3 antihypertensive agents slowly reduced the BP by 25% daily to prevent further neurological injury.

On hospital day 6, the patient was discharged, his BP was within normal limits, and his renal function remained stable. On discharge, the patient was counseled to maintain a sodium-restricted diet.

**Table 1**

| Study | Value | Normal Reference Range and Units |
|---|---|---|
| BNP | 980 (H) | <100 pg/mL |
| Thyroperoxidase Ab | 0.70 (WNL) | < 9 IU/mL |
| Normetanephrine, random | 180 (WNL) | 75 to 375 mcg |
| Metanephrine, random | 78 (L) | 140 to 785 mcg |
| Renin | 0.12 (L) | 0.25 – 5.82 ng/mL/hr |
| ANA | 0.3 (WNL) | > 0.00625 ratio |
| C3 | 25 (L) | 88 to 201 mg/dL |
| ASO Titer | 797 (H) | <276 IU/mL |
| Blood, UA | 3+ | None |
| CK | 62 (WNL) | 22 to 198 IU/L |
| Myoglobin, urine | 306 (H) | 0 to 85 ng/mL |
| Urine creatinine | 158.40 | Variable |
| Urine Sodium | 169 | Variable |
| Urine potassium | 90 | Variable |
| Urine protein | 1394 | Variable |
| Urine drug screen | Negative | Negative |

(H) = high, (WNL) = within normal limits, (L) = low, BNP = Brain natriuretic peptide, Ab = antibody, ANA = anti-nuclear antibody, ASO = anti-streptolysin O, CK = creatine kinase, urinary analysis = UA

**Table 2**

Laboratorial analysis demonstrating various abnormalities supporting the diagnosis of PSGN.

| Study | Findings |
|---|---|
| EEG | Abnormal study, suggestive of posteriorly maximal diffuse neuronal dysfunction and encephalopathy. |
| CXR | Bilateral lower lobe infiltrates that could be pulmonary edema or infiltrates or both. |
| Renal Ultrasound | WNL |
| Renal US with duplex | WNL |
| Transthoracic echo | WNL |
| MRI Brain | Large regions of abnormal signal in both cerebral hemispheres, predominantly posteriorly, and in the right cerebellar hemisphere. This appearance is suggestive of posterior reversible encephalopathy syndrome (PRES). |

Imaging and diagnostic studies demonstrating various indications supporting the diagnosis of PRES and ruling out other pathologies.

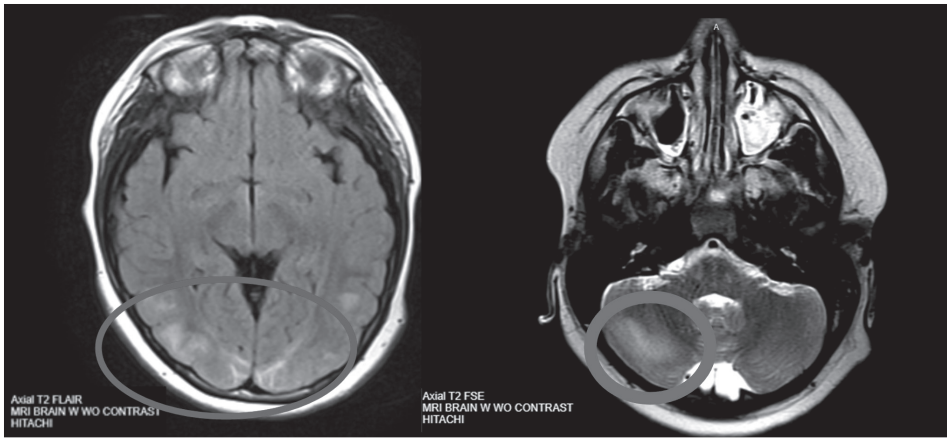


**Figure 1.** Large regions of abnormal signal in both cerebral hemispheres, predominantly posteriorly (red circle), and in the right cerebellar hemisphere (blue circle), suggestive of PRES.

## DISCUSSION

Given the irreversible sequelae of most cases of uncontrolled encephalopathy in any individual, and especially in children, the early diagnosis and appropriate treatment of PRES is of key importance in the pediatric population. Brain MRI imaging is at the forefront of the diagnostic workup and should be considered in all children with concerns of encephalopathy and a sterile CSF analysis to exclude encephalitis or /meningitis.

The treatment of PRES is supportive and consists of resolving the underlying etiology, which is often related to intracranial hypertension, disruption of the blood-brain barrier, or cytotoxic endothelial injury in the brain (1 ,4, 6). Thus, treatment often consists of initiation of antihypertensives, anticonvulsants, and withdrawal of the offending agents (in the setting of chemotherapy induction) (4).

Although the question of withdrawal of chemotherapy is a tough clinical decision to make, Norman et al present a case series describing three patients who manifested with PRES following chemotherapy induction, in whom the withdrawal of chemotherapy in conjunction with antihypertensives and anticonvulsants proved to be effective in their treatment (11). With respect to the anticonvulsants to be used, Morris et al recommend 3-12 months of seizure prophylaxis, with increased duration in patients who demonstrate EEG changes or recurrent seizures (12). Studies demonstrate that valproic acid and clonazepam are preferred over phenytoin, phenobarbital, or phenytoin, given that the first two drugs do not induce the cytochrome P450 system (13). Moreover, magnesium has been postulated to aid in the reduction of vasoconstriction in PRES, given its mechanism of competing with calcium at the cellular level as well as current studies using magnesium in the prevention of vasospasm following subarachnoid hemorrhage (14).

Our unique case adds to a growing body of literature on the rare constellation of symptoms recognized as PRES. Moreover, pediatric PRES has primarily been associated with chemotherapy induction and hematopoietic stem cell transplantation, with no cases ever reported in the English literature with PSGN as the causal agent for renal dysfunction that results in PRES.

## CONCLUSIONS

We present the first case of PSGN-associated PRES in the English literature. This case highlights some key considerations in the care of patients presenting with PRES. The importance of history taking within a workup is made evident throughout this case. The initial workup was focused on neurological symptoms, as they could relate to primary epilepsy or post-concussive syndrome, since the history of recent illness had not been made clear. A detailed history could have helped direct the workup more quickly towards the appropriate diagnosis of PRES secondary to PSGN-induced renal dysfunction and might have allowed for more efficient management of the patient. Specifically, when considering falls and seizures, it is important to always consider causation. In this case, the patient experienced an unwitnessed fall which led the initial workup to focus on the fall as a cause of the seizures. However, we now know it was more likely that an initial seizure caused that fall. Giving due consideration to alternate scenarios when starting a patient workup can increase quality of patient care.

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