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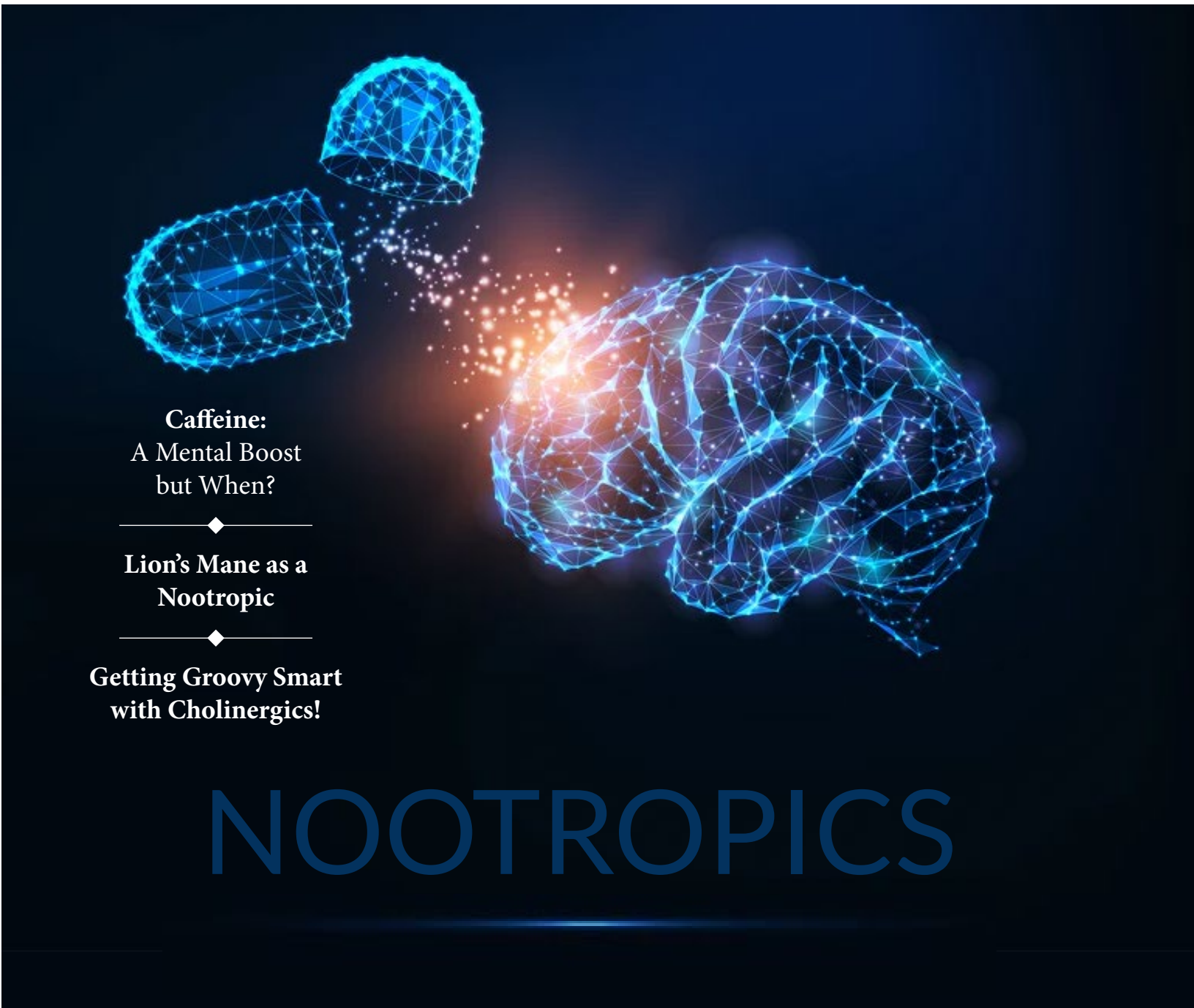

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SPORTSRXNEWS
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Pharmacist Athlete Contributors

MISSION STATEMENT

THE PURPOSE

Brandon K. Welch, Pharm.D.
Founder of Pharmacy Athlete

The Sports Pharmacy magazine exists to empower a community of pharmacist professionals to optimize their impact through disseminating evidence-based knowledge and applied science on sports performance supplements and nutrition. Pharmacists can be pivotal players in the arena of sports. They are poised to help intersect biochemistry with biomechanics and real-life science with athletic performance. Our patient athletes rely on results and we are here to deliver them in real-time.

> Where Pharmacists unlock biochemistry to intersect with biomechanics to optimize patient-athlete performance
>
> Brandon K. Welch, PharmD.

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Brandon Welch, PharmD
NASM-CWC (Expected December 2022)

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Caffeine
A Mental Boost but When?

By Dr. Matthew Liaw, Pharm.D.

AUTHOR BIO:

Matthew Liaw is a pharmacist with ten years of service to Navajo people at Crownpoint Healthcare. He is also an amateur distance runner specializing in the 10k, half-marathon, and marathon. As a pharmacist, he has led a medication error subcommittee, run a pain management clinic, and led an antimicrobial stewardship program. The runner in him is a scientist who enjoys repeating physiology trials to see how valid they are for his training. Some of his favorite moments at the UNM physiology lab include testing how shoes affect running economy, testing the impact of an extended interval block, and comparing methods of body fat testing. His dream is to bring his expertise in pharmacy and passion for running together and become a sports pharmacist.

Introduction

It is 5am. I wake up, prepare breakfast, and brew a mug of coffee. I plan on running about an hour after waking up. After finishing my coffee, I feel awakened. About twenty minutes later, I feel excited and eager to complete my hard workout. During my run, I feel focused and energized. Are these true effects or do I simply believe my coffee habit provide these benefits? These feelings are a handful of cognitive benefits that lead many to use it as a performance enhancer and a lifestyle routine.

Caffeine is considered one of the most popular ergogenic aids among athletes. A national survey in 2014 of college athletes suggested caffeine may be the 5th most popular supplement.[1] However, when combined with energy drinks and shots, it takes second place in popularity. Another survey of the military showed 40.5% of men and 35.5% of women report using supplements containing caffeine. In addition, caffeine is socially acceptable and provided in many work places to increase alertness, reduce the slowing of reaction time throughout the day, and reduce work accidents.[2] While it is used in endurance sport as a physiological enhancer there are many sports that can potentially benefit from its cognitive effects.

How Does it Work?

Caffeine is a stimulant with three mechanisms. First, it mobilizes intracellular calcium. Second, it inhibits phosphodiesterases. Finally, it is an adenosine receptor antagonist that enhances the release of neurotransmitters. This final mechanism is typically associated with its cognitive effects. By blocking adenosine, neurotransmitters like glutamate, serotonin, acetylcholine, noradrenaline, and dopamine are released more frequently.

For the improvement of cognition, low to moderate (40mg to 300mg) doses are typically used.[4] In addition, doses at or greater than 200mg or 3mg/kg are often used as an ergogenic aid in exercise. After ingestion, peak concentrations are usually reached within an hour. Absorption can be slowed with a meal or increased by using buccal formulations like a gum. After absorption, caffeine will have a 3-to-5-hour half-life in the body. This allows caffeine to exert a prolonged effect as it circulates throughout the body.

What Does it Do?

One reason why people use caffeine is to improve vigilance. This is the ability to sustain performance on lengthy, tedious tasks. For example, a study using two 200mg does of caffeine spaced 4 hours apart was shown to maintain cognitive performance for 9-hour mission tasks.[5] It has also been shown to improve lane-tracking in sleep restricted people performing a 2-hour drive.[6] This effect appears consistent irrespective of rested state.4 However, there are few studies that investigated the effects on vigilance in sport.

Attention is the ability to focus and select important details while suppressing less important information. People will often turn to caffeine to improve attention at work, for study, and to maintain focus due to poor sleep. When cyclists were subjected to attentional tests after consuming caffeine and performing an endurance

exercise, they were found to have a faster Stroop time test.[7] This was confirmed in a follow up experiment where participants on caffeine have quicker reaction times without sacrificing accuracy.[8] However, not all studies showed a benefit with caffeine. One study done on rugby players did not detect a difference on the Stroop test between the caffeine and placebo group.[7] This might suggest that the benefits of caffeine on attention can be different based on the type of sport.

Reaction time is how fast a person reacts. This is broken into simple reaction time (how fast one reacts to a single stimulus) and choice reaction time (how fast one identifies and responds to multiple stimuli). A meta-analysis done by Calvo and colleagues did not find significant differences in both simple and choice reaction times.[7] One study performed on experienced football (soccer) players did find improvements both simple and choice reaction times.[9] For the average population, caffeine has demonstrated improvements in reaction time and additional research and more work could be done to shed light on different types of athletes.[4]

Another reason people take caffeine is to improve memory. While memory is boosted with exercise, there is little information on whether caffeine improves short and long-term memory in sport. Investigations in both athletes and the average population are inconclusive on the benefits of caffeine in short-term memory.[4,7] However, there may be benefits in long-term memory for the habitual caffeine consumer.[4]

Research on executive function will usually investigate inhibitory control to see if one can control their impulses. Currently, there is no evidence suggesting caffeine improves inhibitory control in sport.[7] There is debate as to whether higher doses of caffeine are needed to see a benefit in this cognitive function. Unfortunately, studies on the greater population in this area are few and inconclusive.

Many athletes will use caffeine to improve their mood and resist fatigue. These are subjective measures and are measured with scales. The research is consistent in that ratings of pleasure and arousal are higher after caffeine use compared to placebo.[7] When measuring rate of perceived exertion (RPE), caffeine did not appear to reduce these values compared to placebo even when duration is increased.[10]

Final Thoughts

For a non-pharmaceutical drug, caffeine is well studied. In addition to the benefits to physiologic performance, it has also demonstrated beneficial effects in attention and accuracy. There may be benefits in reaction time, but further study may be needed in sports. Limited information is present supporting its benefits in short-term memory and executive function. Caffeine consistently increases feelings of vigor, pleasure, and arousal. However, more information is needed to determine if there is a benefit to mental fatigue. A major confounder with these analyses is that there are many different types of sports and each can benefit from caffeine in different ways. The benefits can potentially be greater in activities that demand greater attention. When taken at appropriate doses, the supplement is generally safe for one to enjoy, improve an activity, and power through the day.

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Creatine

Beyond the Brawn and Into the Brain!

By Sean Casey, RD, CSCS

AUTHORS BIO:

Sean Casey RD CSCS is a registered dietitian, movement coach and member of the Evolve Wellness Science Team at Hometown Pharmacy of Wisconsin. He specializes in sports nutrition, nutraceuticals, and proactive care.

Quick Hit Summary

Creatine's role in enhancing physical performance is well documented. Interestingly, its performance enhancing benefits may extend beyond the muscle and into the brain. Although, research is mixed, it appears to enhance brain function during cognitively challenging task as well as potentially support memory, with this latter effect being most evident in older individuals. Additional lines of research indicate that creatine may also support mood. Although more research is needed to determine optimal dosing strategies, based on currently available research, supplementing with 20 grams (g) of creatine per day (d) for 1 week, followed by 5-10g/d thereafter may be an effective strategy to enhance brain function.

Creatine – It's more than just a muscle builder!

Creatine – when you hear this, what pops into your mind? Power? Speed? Strength? If you answered 'yes' to any of these, it'd make sense as creatine is one of the most widely researched ergogenic supplements. Its impact on strength, power and speed as well as safety are well documented in scientific literature; with earliest reports of use in elite level sport dating back >50 years ago.[1-3]

Going beyond its role in skeletal muscle, emerging research also indicates that creatine supplementation may hold great promise in supporting the brain. For instance, as discussed in Issue No. 3 of Sport Pharmacy Magazine, creatine supplementation has been shown to support traumatic brain injury recovery.[4] Additional research indicates that creatine may enhance cognitive function as well as support mood.

In this article, we will examine these latter brain health benefits; More specifically, we'll review clinical research on creatine's ability to enhance cognitive function as well as improve mood.

A Mechanistic Rationale

The brain is a highly energetic organ. Despite making up only 2% of the average person's body mass, on average, it's responsible for 20% of an individual's resting metabolism.[5] With respect to cost to run relative to space (i.e. energy relative mass), you can think of powering the brain like renting property on New York Time Square – it's expensive!

When called upon to do a mentally challenging task, specific regions of the brain experience increased blood flow to deliver oxygen and glucose to the brain. [6] However, this increase in blood flow occurs a few seconds following the initial stimulus. Additionally, local glucose levels also dip.

It's during this time period of reduced nutrient delivery where the brain appears to rely on the hydrolysis of phosphocreatine to regenerate ATP and energy availability. [6] Thus, similar to what is seen in skeletal muscle, by saturating the brain's phosphocreatine levels, the theoretical potential exists for creatine supplementation to enhance brain function.

It's ability to increase brain's energy reserves also explains its theoretical role in supporting mood. Disruptions in brain energetics appear to play a role in the development and maintenance of depression as evidenced in human neuroimaging, genetics, epidemiology, and animal studies.[7]

It should be noted that many of the studies examining the effects of creatine on depression have been open label in nature. Thus, more placebo controlled randomized control trials are needed to assess what, if any role, the placebo effect has on the observed results.

Creatine & Cognition – What does the Research Show?

The first clinical trial to examine the effects of creatine on cognitive function was completed by Watanabe et al in 2002. In their study, the research team examined the effects of creatine supplementation (8g/d for 5 days) vs. placebo on the study subjects ability to perform a mentally fatiguing mathematical calculations. For reference, the study was completed in a healthy young population with a mean age of 24 years old.[8] When comparing pre and post intervention results, it was found that those supplementing with creatine performed significantly better vs. baseline scores. In contrast, no changes were observed in the placebo group.

Positive effects of creatine supplementation on cognitive processing were also observed by Rae et al.[9] In their cross-over designed study, 27 vegetarian and 18 vegan participants consumed 5g of creatine or a placebo daily for a period of 6 weeks. Following a 6 week washout period, subjects received the opposite treatment. In comparing results from a battery of cognitive tests following the creatine supplementation portion of the trial, it was found that participants experienced significantly improved working memory and intelligence scores. No significant changes were observed while consuming the placebo.

More recently, Samadi and colleagues found enhanced brain function in young, healthy military personnel following creatine supplementation . In their study, 20 male individuals were assigned to one of two groups which consumed beta-alanine for a period of 4 weeks + 1 week of high dose creatine (~ 0.14g/lb bodyweight) or beta-alanine + placebo.10 Using the Serial Sevens test to assess cognitive function, it was found that the creatine group experienced a small, but statistically significant, improvement in scores, whereas no changes were observed in those receiving beta-alanine+ placebo.

Positive nootropic effects of creatine supplementation have been observed in older populations as well. In a 2022 meta-analysis completed by Prokopidis et al., which reviewed 10 studies, it was found that creatine supplementation improved various indices of memory with greater effect sizes in older (66-77 years) vs. younger individuals (11-31 years).[11]

It should be noted, although many studies have shown creatine to hold nootropic benefits, a few studies have reported a lack of positive effect with supplementation.[12] The discrepancies in study outcomes may be the result of genetic differences, assessment tools, dietary factors and/or other reasons.

Collectively, looking at research to date, most studies showing benefit have used

between 5-20 grams of creatine daily for a period of 7 days to 6 weeks. As it relates to the brain, more research is needed to determine if daily doses of 20g/day are needed or if daily dosing of 5-10g/day are equally effective at supporting brain function over time.

Creatine & Depression – What does the Research Show?

Along with potentially enhancing one's brain power during cognitively demanding task, creatine may also support mood. As aforementioned, multiple lines of research indicate that abnormal brain energetics may contribute to depression.[7]

To the knowledge of this author, nine studies have been published examining the effects of creatine supplementation on depression and/or other mood related disorders.[13-21] Of these studies, seven appeared to show beneficial effects of creatine on various indices of mood.[13,14,16,18-21] Effective doses of creatine appear to be ~ 5g/day.

It should be noted that many of the studies examining the effects of creatine on depression have been open label in nature. Thus, more placebo controlled randomized control trials are needed to assess what, if any role, the placebo effect has on the observed results. Additionally, a majority of the trials to date have only been completed in females, limiting generalizability over to males.

Wrapping Things Up

As discussed in this article, the effects of creatine appear to extend far beyond just that of physical performance. Indeed, it appears that creatine holds promise for those looking to enhance mood and cognitive performance.

However, more research is needed to determine optimal creatine dosing protocols for brain health. Additionally, more clinical trials are required to establish which individuals are most likely to receive nootropic benefits from creatine consumption.

Until this research is completed, based on current literature, one may receive nootropic benefit from creatine supplementation by consuming a loading dose of 20g/d for 1 week followed by 5-10g/day thereafter.

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The Pharmacogenomics of Caffeine

By Dr. Kristal Potter, Capt, USAFR, BSC, PharmD

AUTHOR BIO:

Dr. Kristal Potter received her B.S. in Neuroscience from Florida Atlantic University and her Pharm.D. from the University of South Florida Taneja College of Pharmacy. After graduating she served as a pharmacist in the United States Air Force at Cannon Air Force Base, where she was the Pharmacy and Therapeutics Committee Chair and championed several patient education programs. She is passionate about holistic approaches to healthcare and inspiring the next generation of pharmacy leaders. Dr. Potter currently serves as an Assistant Professor at the Larkin University College of Pharmacy and as an Air Force Reserve Pharmacist for Davis-Monthan Air Force Base.

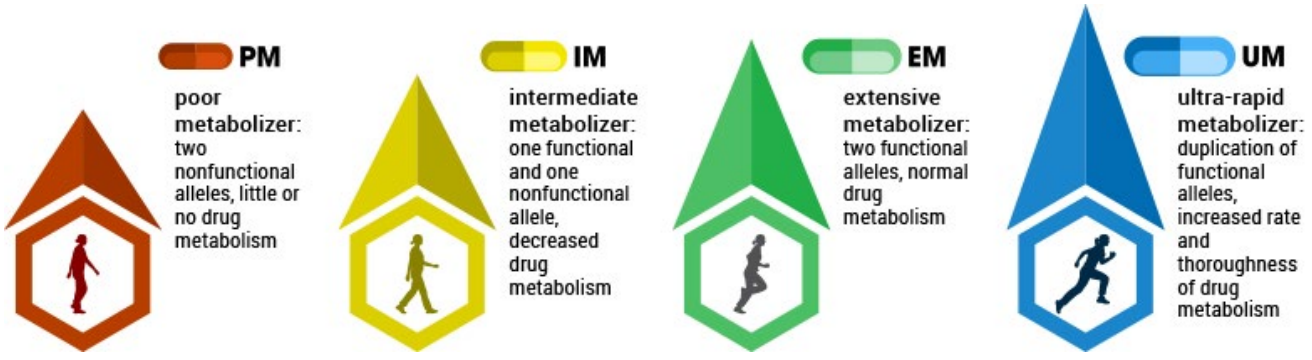
Caffeine is considered the most widely used drug in the world.[1] People love, hate, or have complete apathy towards caffeine. Some people experience anxiety or jitters after a normal cup of coffee. Some can't imagine functioning without their morning cup of joe. Others say caffeine has minimal to no effect on them. Why do people have such varied responses to this naturally occurring stimulant? Genetics may be one factor to consider.

Pharmacogenomics

Pharmacogenomics is the study of how genetic variations can affect the way people respond to medications.[2] People can inherit different alleles for the genes that code for enzymes that metabolize drugs, for receptors targeted by drugs, or for transporters that move drugs. These are just a few examples of genetic variations that can alter someone's response to a drug. Ultimately, these variations can change a drug's pharmacokinetics and pharmacodynamics.

The focus of this article will be on drug metabolizing enzymes.

Everyone inherits two alleles of a gene, one from their respective biological father and mother. The normally functioning enzyme allele is known as the "normal" or "wildtype" allele. Other variants of alleles may result in enzymes that have no function, decreased function, or increased function compared to the normal allele. The combination of inherited allele's makes up an individual's genotype. Individuals with two non-functioning alleles may experience little to no drug metabolism. Individuals with one functional and one non-functional allele may experience decreased drug metabolism. Individuals with a duplication of the normal allele or increased function alleles may experience increased drug metabolism.



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Caffeine Metabolism

Caffeine is primarily metabolized in the liver by the cytochrome-P450 1A2 (CYP1A2) enzyme.[3] Only 3% of caffeine is excreted unchanged in urine. The main route of metabolism is through N-3 demethylation to paraxanthine also known as 1,7-dimethylxanthine. Caffeine has a half-life of 4-5 hours. This can be shortened or prolonged depending on the pharmacokinetic implications of genetic variations from patient to patient.

CYP1A2 ultrarapid metabolizers may experience faster metabolism and diminished effects of caffeine relative to normal metabolizers. CYP1A2 poor metabolizers may experience slower metabolism and increased sensitivity to caffeine compared to normal metabolizers.

Insomnia

Beyond altering the pharmacokinetic properties of caffeine, some genetic variants can also alter the pharmacodynamics of caffeine. Patients with the AA genotype of the rs762551 variant of the CYP1A2 enzyme gene are more likely to experience insomnia.[6] While patients with the CC genotype may be less likely experience insomnia. Sleep is vitally important to recovery and performance in athletes. The potential of caffeine to disrupt sleep cycles and induce insomnia is something that should be considered when recommending caffeine to athletes.

Anxiety

While most differences in caffeine sensitivity are related to the CYP1A2 enzyme, some studies have identified variants in adenosine receptor genes that may be related to an individual's feelings of anxiety post caffeine consumption. Patients with the TT genotype of the rs5751876 variant of the adenosine receptor (ADORA2A) gene may be more likely to experience anxiety after caffeine consumption.[4,5] While patients with the CC genotype may be less likely to experience anxiety. Studies show that individuals with the TT genotype have decreased habitual consumption of caffeine. These individuals most likely refrain from caffeine consumption to avoid the anxiety inducing effects they experience from caffeine.

Pharmacogenomic Testing

Does this mean we should start ordering pharmacogenomic tests for all of our patients who drink coffee? No, that would be extreme.

> For another patient, identifying a genetic variant may be the missing piece of the puzzle to optimize caffeine usage. Using science-based evidence to make small tweaks to supplements can have meaningful differences in performance.

At best, pharmacogenomic testing for the CYP1A2 enzyme would confirm a patient's suspicions about why caffeine keeps them up all night, gives them anxiety, or doesn't give them the boost they were looking for. Most patients will have already determined adjustments needed in their caffeine consumption to reach the effects they are seeking through trial and error. Although it is nice to know the "why" behind the unintended side effects or lack of efficacy for any drug.

While it may not be necessary to order these tests, some patients may already have access to their CYP1A2 status and this is where pharmacists have an opportunity to provide education. As direct-to-consumer (DTC) pharmacogenomic testing becomes more widely available to patients and more providers start incorporating pharmacogenomic panels into their practices, this information may be readily be available in their EHR. Pharmacists are primed to be the experts in providing evidence-based recommendations on pharmacogenomic test results.

An athlete who is wanting to use caffeine to enhance performance or endurance may benefit from knowing if their genetics may affect their outcomes. A study by Guest et al showed that individuals with the AA genotype of the CYP1A2 gene (rs762551) had improved 10-km cycling times compared to those with the CC genotype.[7] Another study by Wong et al showed that caffeine decreased handgrip strength in athletes with the CC genotype. [8] Other studies show insignificant differences in the performance enhancing effects of caffeine.[9]

Conclusion

The reality is that every patient has a unique genetic profile. There are many factors that can contribute to a patient's metabolism and sensitivity to caffeine. A patient's response to caffeine may be affected by their pharmacogenomic profile. Patients who have completed pharmacogenomic testing should consult their provider or pharmacist about their results, especially before making any changes to their medications. One patient's test results could have little impact on any clinical decisions around caffeine usage. For another patient, identifying a genetic variant may be the missing piece of the puzzle to optimize caffeine usage. Using science-based evidence to make small tweaks to supplements can have meaningful differences in performance.

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Lion's Mane as a Nootropic

By Dr. Hussam Hamoush, Pharm.D.

Owner at Stonebriar Pharmacy and Certified Sports Nutrition Coach

Recently a new show came out on HBO max that really caught my attention. The name of the show is "The Last of Us" and man what is intense. I heard about the story long before. It was one of the first video games I played on my new PlayStation 4. The video game was marvelous. Suspenseful nonstop action. HBO made it into a show starring the famous Pedro Pascal. My wife and I loved every episode. Why are we talking about a hit show? The show introduced the idea of Cordyceps to the public. My only critique is how they really didn't go into scientific detail as to how the infection started and how it spread. Pier Antonio Micheli was the first to publish descriptions of Fungi in 1729 and the first medicinal use was used by Heinrich Anton de Bary in 1858. But fungi have been around since the dawn of time. [2]

But Dr. H, how does this apply to Nootropics? Let's start with a little bit of information on Lion's mane (*Hericium Erinaceus*). It is an edible fungus with a long history of use in traditional Chinese Medicine [1]. It has shown great promise for the treatment of Alzheimer's and Parkinson's diseases. The fungus was well tolerated in two clinical studies with few adverse events reported. LM grows on old or dead broad leaf trees and is used both as food and medicine. The bioactive metabolites of *H. erinaceus* can be classified into high molecular weight compounds, such as polysaccharides, and low molecular weight compounds, such as polyketides and terpenoids. [1].

Clinical Trials

From the Association for the Advancement of Restorative Medicine they described a clinical trial involving mice. In a behavior test on wild-type mice, oral supplementation with *H. erinaceus* induced a statistically significant improvement in spatial short-term and visual recognition memory. In a double-blind placebo-controlled clinical trial of 50–80-year-old Japanese adults (n=30) diagnosed with mild cognitive impairment, oral intake of *H. erinaceus* 250 mg tablets (96% dry powder) three times a day for 16 weeks was associated with marked improvement in the revised Hasegawa Dementia Scale (HDS-R) as compared to controls. Scores on the HDS-R decreased, however, by 4 weeks after cessation of the intervention. In these trials they suggest that lion's mane may reduce inflammation and biological markers of Alzheimer's, improve cognition, and increase the release of nerve growth factor (a protein that can increase the length of nerve cell processes). [3]

Clinical Uses

We can talk all day about different studies and how they can work in a controlled setting, but how does this apply to our general population and pharmacy patients? For the past 6 months we have been under an unprecedented time when it comes to ADHD treatments. Patient's are having an even harder time finding the correct medications for them. While the use of ADHD treatments has been increasing through the years, the supply of medications

has been decreasing. The rise of being able to see a clinician online and get narcotic medications delivered directly to your home has been been causing these shortages. As you read more in this issue, the theme is common. We are clinicians that are trying to find new ways to help patients in a more natural way. Lion's mane is very commonly used in pharmacies to aid patients in focus, energy, and can be used as a natural replacement for ADHD medications when in a pinch. Now, you should always discuss this with your doctor/pharmacist before changing any therapies, but it could be a viable option for you. It's very important to source your product and vet each company that you order from. Reach out to a wellness pharmacist and they can guide you as their process into how to choose a good source of Lion's mane. One of my favorites comes from a company called Green Roads and is available only in select pharmacies. As a user myself, I take 1 capsule daily every morning and can tell a difference in my ability to focus and has no effect on my heart rate of blood pressure. Again, reach out to your doctor or pharmacist to make sure that its safe for you.

Conclusion

Lion's mane as a nootropic has demonstrated an enhance in cognitive function and reduce brain fog. Studies have shown that it can help treat neurological dysfunction such as Alzheimer's and Parkinson's. It can also help with ADHD because it contains chemicals that promote new neuron growth. The applications can be applied for over-the-counter supplementations in a safe and effective way to help with focus, energy, and enhanced cognitive capabilities. Reach out to your clinician for more information and to make sure it's safe for you.

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3. "The Lion's Mane Mushroom: A Review" by Rop et al. This article, published in the Journal of Restorative Medicine, provides an overview of the history, traditional uses, and therapeutic potential of Lion's Mane.

Lion's mane as a nootropic has demonstrated an enhance in cognitive function and reduce brain fog. Studies have shown that it can help treat neurological dysfunction such as Alzheimer's and Parkinson's.

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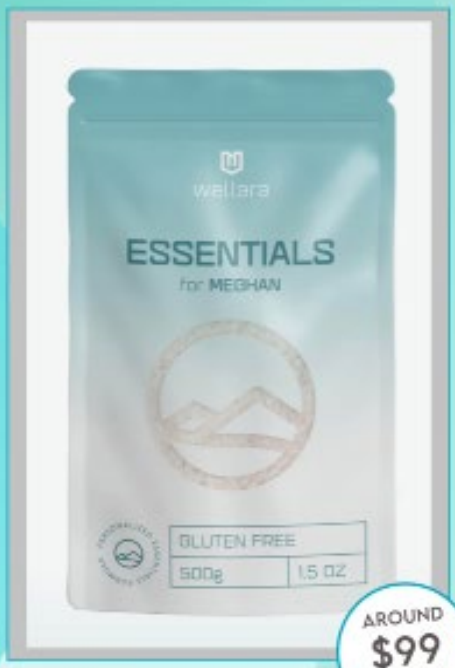

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Getting Groovy Smart with Cholinergics!

By Dr. Jessica Beal-Stahl, Pharm.D.

Co-Author: Sean Casey, RD CSCS

AUTHOR BIO:

Jessica Beal-Stahl, PharmD, is the founder of The Athlete's Pharmacist company, tying her passions of athletics and pharmacy together where she works privately with clients to improve their performance in sport and life. She received her Doctorate of Pharmacy from Mercer University in 2009 and has been practicing as a Director of Clinical Services at Hobbs Pharmacy in Merritt Island, Florida, since graduation. Jessica also knows what it's like to be a high-level athlete, having played D1 volleyball, medaled internationally in Olympic weightlifting, and set at 41 years old a world record in Olympic Weighting for snatch in her age/weight class. She holds additional certifications in Integrative Medicine, Nutrigenomics, and Sports Nutrition.

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Quick Hit Summary

Many neurotransmitters within the brain influence cognitive processes. One critical pathway is the cholinergic system, which influences attention and higher-order cognitive processing. Specific nootropic nutraceuticals have been studied for their ability to enhance the cholinergic system, including choline-containing compounds, Alpha GPC, Citicoline (CDP-Choline), and the acetylcholine esterase inhibitor Huperzine A. Depending on desired results, the effective doses for these compounds appear to be 1) Alpha-GPC: 400-1200 mg/day (d) 2) Citicoline: 250 – 1000 mg/day 3) Huperzine A: 50-200 mcg/day (general); 200-800 mcg/day (Alzheimer's). No known drug-nutraceutical interactions exist for Alpha-GPC and Citicoline, yet Huperzine A should be avoided if taking an acetylcholinesterase inhibitor.

Ladies and Gents – Start Your Nootropic Neurotransmitter Engines!

Optimizing neurotransmitter flow within the brain is a hot topic in the nootropic/cognitive support field. It makes sense – if we can optimize the 'traffic' flowing between the nerves in our brain, cognition will improve!

One of the most popular neurotransmitters being targeted to ratchet up brain function is Acetylcholine (ACh). ACh is commonly called the "learning neurotransmitter" since it involves (you guessed it) learning, memory, and focus. ACh also plays a critical role in muscle contractions, supporting muscle movement, performance, and the mind-muscle connection, as you can see – pretty dang important!

At the heart of ACh are two substances. One, choline, an essential nutrient responsible for cell membrane structural integrity and cell-to-cell communication. S acetyl coenzyme A, which comes from glucose.

Unlike many other neurotransmitters synthesized inside the neuron, ACh is synthesized within the connections between neurons. ACh is also not re-absorbed or re-released repeatedly; instead broken down by acetylcholinesterase enzyme and excreted. Result – ACh must constantly be replenished, which means there must be building blocks readily available (i.e., choline) to maintain optimal levels.

In the central nervous system, ACh plays a vital role in your pre-frontal cortex, which is responsible for higher thought and personality. ACh helps us to grasp abstract concepts and new ideas and develop an understanding and integration of new material into existing knowledge frameworks.

Although the precise mechanism(s) of ACh's effects on memory are complex and not yet fully understood, some researchers believe it plays a central role in synaptic plasticity.[1] This mechanism allows neurons to store new information and memories by modifying their connection.

Due to ACh's role in stimulating learning and

memory, it's being investigated whether dietary supplements that increase ACh levels might influence cognitive functioning.

While choline bitartrate or citrate forms are the most common forms of supplemental choline on the market, often due to their low expense, neither crosses the blood-brain barrier. As a result, these have little direct nootropic effect.

This article will review three specific cholinergic-supporting nutraceuticals shown to support brain function: Alpha-GPC, Citicoline, and Huperzine A.

Alpha GPC

Our body naturally produces Alpha-GPC as a byproduct of phosphatidylcholine. When your brain needs more choline, it breaks down phosphatidylcholine from cell membranes. And is turned into Alpha-GCP in the process.

Natural sources contain only trace amounts of Alpha-GCP. Choline-rich foods, such as beef liver, eggs, chicken, whole grains, and soybeans, can provide a choline source for your body to make Alpha-GCP. Your body loves Alpha-GCP supplementation; it crosses the blood-brain barrier and doesn't have to cannibalize its cells to get more choline.[2]

In 400-1200mg/day doses, oral supplementation of Alpha-GPC is primarily of interest for nootropic or cognitive-enhancement purposes. However, most research supporting Alpha-GPC use for cognitive enhancement has been completed in rodents and patients with mild to moderate dementia. Little research has shown it to be supportive in healthy younger adults.

In older adults with mild to moderate dementia — which involves disrupted cholinergic neurotransmission — Alpha-GPC improves cognitive symptoms (memory and attention impairment).[3,4] Alpha-GPC may also improve the effectiveness of the Alzheimer medication class acetylcholinesterase inhibitors (medications that slow the breakdown of ACh, thus increasing its availability).[3]

Comprehensive reviews looked at the effects of Alpha-GPC in over 20 clinical trials and 4,000 older people with dementia. Each confirmed Alpha-GPC's potential to shield the brain and prevent cognitive decline, independent of the cause. The patient's attention and memory were better than the choline or lecithin groups, without any significant side effects.[5,6,7,8] In some European countries, Alpha-GCP is a prescription drug for Alzheimer's (Gliatilin, Delecit).

A few clinical studies have tested the pro-cognitive effects of Alpha-GPC in young, healthy adults. In one study examining Alpha-GPC's effects on exercise and cognitive performance, little-to-no significant impact on physical exercise performance or mental aspects of performance, including reaction time, logical reasoning, vigilance, spatial memory, or working memory.[9] This may be because choline or acetylcholine doesn't appear to be the key limiting factor in performance. That said, one study used a dose of 600 mg/day to increase isometric mid-thigh pulling strength.[10]

Alpha-GPC is generally well tolerated; mild side effects include fatigue, headaches, nervousness, nausea, and heartburn.[11, 12, 13] Because Alpha-GPC causes an energy boost, avoid dosing in the evening. Serious side effects have not been reported at the dosage of 1,200 mg/day for six months.[14]

Citicoline

Citicoline is another popular cholinergic compound with extensive research supporting its use as a nootropic agent. Citicoline is a naturally occurring mononucleotide within the body, consisting of cytosine, ribose, pyrophosphate, and choline.[15]

As previously discussed, choline can be directly incorporated into acetylcholine. The cytosine component also holds brain-supporting benefits. Once ingested, cytosine is converted into uridine, which can be converted into phosphatidylcholine and phosphatidylethanolamine within the brain. The body then can use it for ACh synthesis and supporting overall phospholipid metabolism in brain tissue.[16]

In addition to its more direct effect on ACh, Citicoline has been shown to improve brain energetics. A 2008 study found that administering 500 mg of citicoline increased ATP levels by ~ 14% within the brain's frontal lobe![17]

Citicoline has been studied in various populations with effective doses ranging from 250 -1000 mg/day.

With respect to attention, daily consumption of 250 mg of Citicoline increased focus and attention in healthy middle-aged females.[18] Similar positive effects on attention and psychomotor speed have been found in adolescent boys consuming doses between 250-500 mg of citicoline.[19]

Beneficial effects of Citicoline, doses of 500 mg/day for 12 weeks, have been found in healthy older adults with age-associated memory impairment. Citicoline was also found to improve episodic

memory.[15] This data aligns with a 2023 meta-analysis that concluded "citicoline has positive effects on cognitive function," although more stringently designed studies are needed. [20]

Collectively, data indicates that Citicoline may provide brain-supporting benefits to healthy individuals and those experiencing memory impairment with minimal reported side effects.

Huperzine A

Two key things influence ACh levels. First, choline-containing food and supplements can affect the foundational building blocks required to build ACh. Second, how fast ACh is removed from the system via the enzyme acetylcholinesterase.

In attempts to improve brain function, researchers have studied Huperzine A, an extract from the Huperzia Serrata moss plant. They found Huperzine A acts as an acetylcholinesterase inhibitor, reducing the breakdown of ACh so it can 'hang out' longer within the nervous system.

Various clinical trials have examined the effects of Huperzine A on cognitive function in those with memory impairment diseases such as Alzheimer's. In a 2013 meta-analysis of 20 randomized control trials and 1823 participants, doses between 200-800 mcg/day of Huperzine A appeared to lead to an "improvement of cognitive function, daily living activity, and global clinical assessment."[21]

While little research has been published on enhancing cognition in already healthy individuals, those looking to support general cognitive function have noted doses between 50-200 mcg/day to be effective. For those with memory-related issues, studied doses have ranged between 200-800 mcg/day.

Side effects have been pointed out, such as loss of appetite loss, nausea, and other GI-related side effects, especially when consuming larger doses. [21] Additionally, Huperzine A should be avoided if taking acetylcholinesterase inhibitor medications.

Wrapping Things Up

The cholinergic system is one of great intrigue for healthy individuals looking to enhance cognitive function and those looking to slow down age-related memory decline.

Alpha-GPC, Citicoline, and Huperzine A are exciting nootropic candidates, but more research must be conducted to determine effectiveness and dosing strategies across different demographic populations.

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Rhodiola Rosea

The Energizing Adaptogen, A Nootropic too?

By Dr. Jessica Beal-Stahl, Pharm.D.

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Jessica Beal-Stahl, PharmD, is the founder of The Athlete's Pharmacist company, tying her passions of athletics and pharmacy together where she works privately with clients to improve their performance in sport and life. She received her Doctorate of Pharmacy from Mercer University in 2009 and has been practicing as a Director of Clinical Services at Hobbs Pharmacy in Merritt Island, Florida, since graduation. Jessica also knows what it's like to be a high-level athlete, having played D1 volleyball, medaled internationally in Olympic weightlifting, and set at 41 years old a world record in Olympic Weighting for snatch in her age/weight class. She holds additional certifications in Integrative Medicine, Nutrigenomics, and Sports Nutrition.

Rhodiola rosea has been used safely for centuries by traditional healers from various cultures, including the Chinese and the Vikings. R. rosea has been found to have brain-boosting benefits that can improve mood and focus, prevent stress, and reduce fatigue, making it a candidate for those looking to increase their cognitive performance and productivity. As an adaptogenic herb, R. rosea improves our physical and mental tolerance to stress by helping balance cortisol levels.

While some results appear promising, many studies have been small and considered biased. Meanwhile, R. rosea is considered safe when taken within suggested dosages, 200-600mg per day and has a low risk of side effects. Therefore, it may be a natural option worth trying for its supposed uses.

If you're taking supplements, then you should know what's in them. Not only that, but you should know what ingredients you should look for and if they effectively support why you are taking them.

Rhodiola Rosea (R.rosea) is an herbal compound used for generations in Arctic cultures for energy and cognitive benefits. Now commonly included as an ingredient in nootropic supplements on the market. This article will discuss this ingredient, how it works, its effectiveness, and other essential details allowing you to make an informed decision.

The genus Rhodiola consists of more than 200 species. Approximately 20 species, including R. rosea, have been used as medicinal herbs in Northern Europe, Asia, and Russia for thousands of years. The Vikings have used this herbaceous perennial to get psyched up for raids, and cosmonauts have used it to stay on task while in orbit.

Rhodiola grows primarily in the dry sandy ground at high altitudes in the arctic areas of Europe and Asia but is also cultivated in Europe and North America. The most common supplement species is R. rosea, known as 'golden root' or 'arctic root.'

The Journal of the American Botanical Council reported on 180 studies done on R. rosea since 1960. Most research shows how this herb treats physical endurance, fatigue, depression, impotence, infections, fertility, cold and flu, tuberculosis, cancer, and anxiety.[1]

Mechanism of Action: The power of a plant

R. rosea's specific mechanism of action is still not known precisely. One reason is that the *root* of the R. rosea contains over 140 different compounds, such as rosavins, salidrosides, tyrosol, cinnamyl alcohol, phenols, and flavonoids.[2] It is believed that the active ingredients which exert beneficial effects are '*rosavins'* and '*salidrosides.*[3]' Yet, depending on where Rhodiola is grown, it can markedly change the plant's chemical composition.

> What is neat is how many of the supplements in this issue will build on and enhance each other; this is why you will see many combined in most nootropic supplements on the market today.

Within the Rhodiola family, rosavin is unique to R. rosea, although salidroside is commonly found in many other Rhodiola species. R. rosea has higher concentrations of rosavin than salidrosides, in approximately 3:1 ratio.

R. rosea is an adaptogen and ergogenic; it also has a reputation in the nootropic community for its energizing and anti-fatigue qualities. Researchers have categorized R. rosea as an adaptogen because of its observed ability to increase resistance to various chemical, biological, and physical stressors.[4, 5]

A small study was done on cadets using two different doses to measure the effects of R. rosea on the capacity for mental work, again a background of fatigue and stress. R. rosea showed a "*pronounced anti-fatigue effect*" in the cadets.[6] Another small phase III clinical trial looked at stress-related fatigue and found repeated administration of R. rosea at doses of 576mg of extract/day exerts an anti-fatigue effect that increases mental performance, particularly the ability to concentrate, and decreases cortisol response to awakening stress in burnout patients with fatigue syndrome.[7]

Scientists are still trying to define how effective R. rosea can be and the *mechanisms* that allow it to work. R. rosea appears to act by modulating various signaling pathways in the brain; one effect is acting as a monoamine oxidase inhibitor (MAOI) or agent that slows the breakdown of monoamine neurotransmitters; serotonin, dopamine, and noradrenaline.[8] Increases in the levels of these crucial neurotransmitters are associated with mood stabilization, pleasure response, motivation, and drive/energy. This, in turn, improves neuronal communication and positively impacts mood, reduces fatigue perception, and enhances cognitive abilities.[9]

A study reported that repeated administration of *R. rosea* exerts an antifatigue effect that increases mental performance, particularly the ability to concentrate, and reduces cortisol response to awakening stress in patients with burnout and fatigue syndrome.[7] The adaptogenic and central nervous system activities of R. rosea may be attributable to its influence on the levels and activity of monoamines and opioid peptides such as beta-endorphins.[10]

While little research specifically investigates R. rosea's specific nootropic capabilities, animal and human studies indicate that R. rosea's proven ability to reduce fatigue positively influences cognitive skills, including memory, motivation, and capacity for mental work.

Studies revealed that other species of the genus Rhodiola were being substituted for R. rosea. While some of these mixed batches were highly variable in quality, others had *no pharmacological or nootropic effect.*[11]

The herb's complexity makes R. rosea so valuable in various ways. Thus, users of this supplement may encounter a broad spectrum of

results. But make sure you have high-quality and reputable products is critical for effectiveness.

Dosing and Safety Considerations

R. rosea has been used successfully for thousands of years and is considered non-toxic and safe. And very few side effects have been reported. Considerably higher than recommended doses could result in dry mouth, nausea, upset stomach, headache, insomnia, and weight loss.

Most studies utilized dosages between 200-600mg daily, taken on an empty stomach before breakfast or lunch. Avoid taking it before dinner or bedtime, as the mild stimulant effects may affect sleep. While some research has found *R. rosea* could take effect within a matter of days, you will experience more benefits from consistent use. Most studies showed it takes about 4 weeks to see improvement.[12]

Since R. rosea acts as an MAOI, you should not use it if you take MAOI meds. MAOIs are a type of anti-depressant drug used to treat bipolar disorder, panic disorder, social anxiety disorder, and PTSD.

The active ingredients in R. rosea are rosavins and salidrosides. Ideally, you want a standardized supplement containing about 3% rosavins and 1% salidrosides; this is the ratio found in the natural root. [11]

Lastly, R. rosea is not a banned substance; finding NSF or Informed Sport-certified R. rosea products can be challenging, so careful consideration must be taken if you choose to use a product. A 2016 study analyzed 40 *R. rosea* products found their quality and authenticity varied significantly.[13]

Nootropic Synergy

What is neat is how many of the supplements in this issue will build on and enhance each other; this is why you will see many combined in most nootropic supplements on the market today.

For example, R.rosea is often paired with bacopa monnieri because they complement each other well. R.rosea stimulates the sympathetic nervous system, while bacopa activates the parasympathetic nervous system. Following this thought a little further, taking alpha-GPC, CDP-choline, or Huperzine A, also creates a great synergy, as they provide the building blocks needed to produce acetylcholine which is necessary for working memory, learning, and mental focus.

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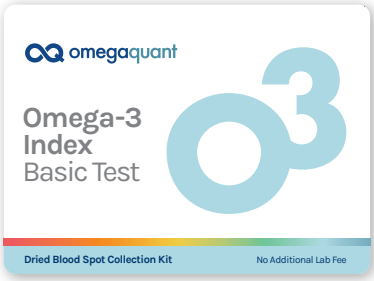

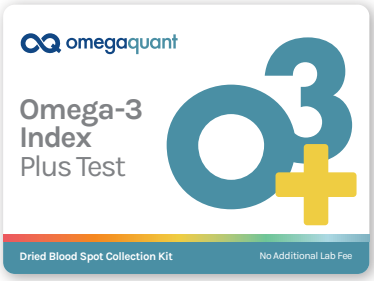

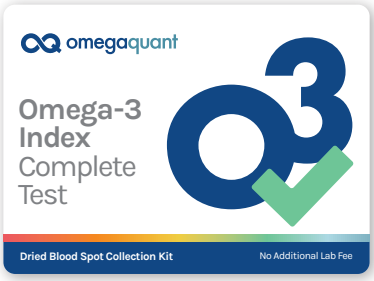

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