NATURAL MEDICINE JOURNAL
RESEARCH GUIDE

SPONSORED BY KYOWA HAKKO USA, INC.

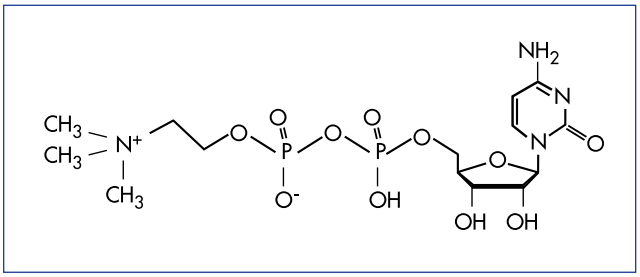
# The Unique Benefits of CITICOLINE

## An emerging nootropic and brain-health nutrient

**Author:** Sarah Cook, ND

## What is Citicoline?

Citicoline is an ingredient in dietary supplements that is sometimes referred to as the organic molecule called cytidine 5'-diphosphocholine, cytidine diphosphate choline, or CDP-choline. Present in every cell of the human body, CDP-choline is a nucleotide that is composed of choline, cytosine, ribose, and pyrophosphate.




CDP-choline is an essential precursor for the synthesis of membrane phospholipids and acetylcholine in the central nervous system. CDP-choline is endogenously produced from choline, but the rapid turnover of phospholipids in cell membranes creates a high demand for this molecule.

The demand for CDP-choline can partially be met by dietary consumption of choline, but data from the National Health and Nutrition Examination Survey (NHANES) show that only 8% of US adults consume the recommended amount of choline on a daily basis. Even if choline consumption were sufficient, there are additional benefits to consuming sources of CDP-choline itself. For example, CDP-choline is required for the rate-limiting step of phospholipid synthesis, making choline insufficient to support cell membrane integrity on its own. Unfortunately, CDP-choline is present in very small amounts in food, with only liver, brain, and organ meats providing appreciable amounts.

Supplementation with citicoline offers a way to boost endogenous levels of CDP-choline in a way that cannot be achieved by other means. The oral bioavailability of citicoline exceeds 90%, its metabolites cross the blood-brain barrier, and citicoline is resynthesized in the brain after oral consumption.

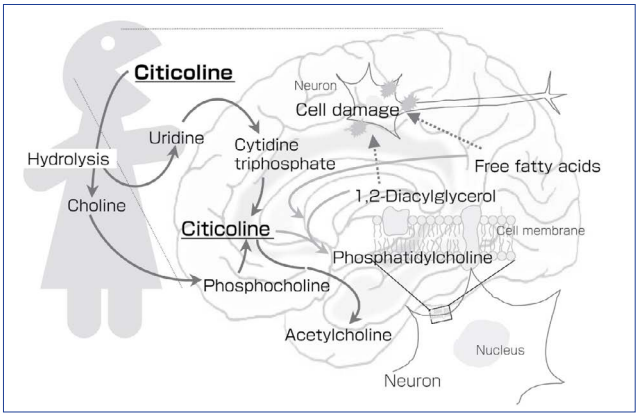
CDP-choline was discovered by Eugene Kennedy and Samuel Weiss at the University of Chicago in 1955. Kennedy synthesized citicoline for the first time in 1956. Citicoline was then manufactured and commercially distributed in Japan as a therapy for patients recovering from an ischemic stroke and later introduced as a prescription drug in Europe for the treatment of cognitive impairments. Citicoline has been available as a dietary supplement in the United States since the 1980s.

Citicoline and CDP-choline have the same molecular structure. CDP-choline refers to the endogenous form that is present in every cell of the human body. Citicoline refers to the form that is taken exogenously. Citicoline is available in 2 forms: citicoline sodium is a prescription medication used to treat neurological disorders in numerous countries, whereas citicoline free-base has been available as a dietary supplement in the United States for more than 3 decades.

## Citicoline Metabolism

Citicoline can be administered orally, intramuscularly, or intravenously. Oral administration is most common because its bioavailability is approximately 92%. After oral ingestion, citicoline is hydrolyzed in the small intestine and liver into 2 major metabolites: cytidine and choline.

Cytidine and choline enter the systemic circulation, where cytidine is further metabolized into uridine. Both uridine and free choline cross the blood-brain barrier. In the central nervous system, uridine is converted to cytidine triphosphate, choline is converted to phosphocholine, and the 2 combine to resynthesize CDP-choline.



## How Does Citicoline Work?

Citicoline is a brain nutrient that supports mental energy, focus, attention, and overall cognitive health. Experimental studies have revealed several mechanisms by which citicoline works. It acts by supporting phospholipid metabolism, neurotransmitter synthesis, mitochondrial function, and neuroplasticity.

### Phospholipid Metabolism

Phospholipids create the structural integrity of all cell membranes and are therefore essential to cellular growth and repair. In the brain, phospholipids are also essential for synaptic function, the foundation of communication among all brain cells. The primary phospholipid in the brain—phosphatidylcholine—makes up 30% of the gray matter. CDP-choline is a precursor for phosphatidylcholine as well as other phospholipids, including phosphatidylserine and phosphatidylethanolamine.

Despite the importance of CDP-choline in phospholipid synthesis, however, the brain preferentially uses CDP-choline for production of the neurotransmitter acetylcholine. If availability of CDP-choline is low, phospholipids are stolen from neuronal membranes for acetylcholine production, phospholipid synthesis slows down, and membrane integrity becomes compromised.

Supplementing the diet with citicoline ensures a steady and adequate supply of CDP-choline to support growth, repair, and function of neuronal membranes and synapses in the brain.

Animal studies have shown that 90 days of oral supplementation with citicoline significantly increases brain concentrations of phosphatidylcholine by up to 25% and increases phosphatidylserine and phosphatidylethanolamine levels.

A human study conducted by Babb and colleagues at Harvard Medical School evaluated brain changes after citicoline supplementation in healthy older adults. The researchers detected changes in magnetic resonance spectroscopy that indicated increased phosphatidylcholine synthesis after 6 weeks of supplementation with 500 mg of citicoline per day.

### Neurotransmitter Synthesis

Neurotransmitters are indispensable communication molecules in the nervous system. Acetylcholine acts as a neurotransmitter in areas of the brain that promote alertness, attention, learning, and memory. Disruptions in acetylcholine function are associated with memory problems, such as Alzheimer's disease. A direct precursor for acetylcholine production is choline. Animal studies show that citicoline provides a source of choline to increase acetylcholine production in the hippocampus and the neocortex of the brain.

The brain consumes approximately 20% of the entire body's energy while at rest, placing a high demand on cellular mitochondria. Citicoline has been shown to improve mitochondrial health via numerous mechanisms.

In addition to serving as a choline donor for acetylcholine synthesis, citicoline has been shown to increase norepinephrine in the cerebral cortex and hypothalamus and increase serotonin in the cerebral cortex, striatum, and hypothalamus. Citicoline also increases dopamine levels in the corpus striatum by enhancing tyrosine hydroxylase activity and inhibiting dopamine reuptake.

### Mitochondrial Function and Brain Energy

The brain consumes approximately 20% of the entire body's energy while at rest, placing a high demand on cellular mitochondria. Citicoline has been shown to improve mitochondrial health via numerous mechanisms. First, citicoline maintains healthy levels of cardiolipin in mitochondrial membranes. Cardiolipin is a phospholipid that is essential for mitochondrial electron transport and may decline with age. Second, citicoline helps to restore mitochondrial ATPase activity. Third, citicoline decreases oxidative stress by inhibiting the release of arachidonic acid and other free fatty acids from cell membranes.

The ability of citicoline to improve mitochondrial function and brain energetics was demonstrated in a human study published by Silveri and colleagues of Harvard Medical School in 2008. The study involved 16 healthy, middle-aged men and women. It demonstrated that 6 weeks of supplementation with 500 mg citicoline per day produced a 14% increase in ATP in the frontal lobe of the brain. The study also showed that the area of the brain most activated by citicoline was the anterior cingulate cortex (ACC), which is involved in cognitive functions like focus and attention.

## Neuroprotection

The ability of citicoline to improve phospholipid metabolism and reduce oxidative stress would suggest that it has a neuroprotective effect. Additional mechanisms also contribute to the neuroprotective effects of citicoline. Citicoline may control excitotoxicity by reducing glutamate activity and increasing expression of excitatory amino acid transporter-2 (EAAT2); it has demonstrated an ability to increase glutathione synthesis; and citicoline enhances neuroplasticity after a stroke, suggesting that it helps brain cells reorganize and form new connections to compensate for injury or disease.

Hurtado and colleagues demonstrated in 2013 a novel mechanism by which citicoline may offer further neuroprotection. These Spanish researchers showed that citicoline increases protein expression of sirtuin 1 (SIRT1) in rat brain, in cultured neurons, and in circulating blood mononuclear cells. SIRT1 is an enzyme that has repeatedly demonstrated neuroprotective effects in models of neurodegenerative diseases, such as Alzheimer's disease and Parkinson's.

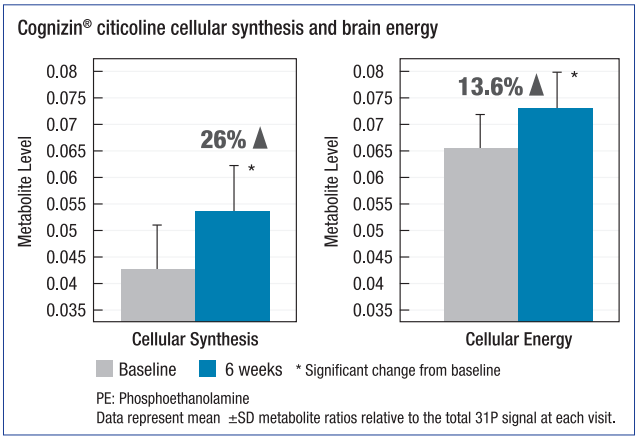
## Summary of How Citicoline Works

Numerous animal and human studies have revealed mechanisms by which citicoline provides brain health benefits. Citicoline enhances endogenous pathways that protect cell membrane integrity and function; it promotes healthy neurotransmitter production and neuronal signaling; it enhances neuroplasticity; it reduces oxidative stress; and it boosts energy production in the brain. In the next section, we examine how citicoline can be used in a clinical setting.

### Citicoline vs. Choline

Citicoline is a source of choline and, therefore, provides all of the benefits of choline. Both choline and citicoline support phospholipid metabolism, acetylcholine production, and cell signaling. But citicoline is also a source of cytidine. It is the cytidine component that gives citicoline an advantage over choline.

The cytidine component of citicoline converts to uridine before crossing the blood-brain barrier. Researchers at Massachusetts Institute of Technology demonstrated that the uridine component is required for the rate-limiting step of phosphatidylcholine production and that uridine also promotes neuronal growth. Uridine is the molecule responsible for increasing brain levels of norepinephrine and dopamine, improving mitochondrial function, and boosting energy production in the brain.




## Clinical Uses of Citicoline

The most important use for citicoline in clinical practice is to support brain health.

Citicoline can be taken by healthy young adults and teenagers to support attention and focus or by healthy older adults to support cognitive function. Citicoline is widely prescribed as a medication in Europe to treat cognitive impairments and has been studied as an intervention for cognitive recovery after ischemic stroke. Emerging research suggests that citicoline may also support eye health and promote recovery from addictions and eating disorders.

### Focus and Attention in Healthy Adults and Teens

Citicoline is considered to be a nootropic agent, meaning that it enhances focus, attention, and cognitive function in healthy individuals. Two recent placebo-controlled trials have demonstrated benefits of citicoline in healthy adults and teens.

A double-blind, placebo-controlled trial, published by McGlade and colleagues at the University of Utah in 2012, evaluated the effects of citicoline on attention in healthy women (aged 40 to 60 years). A total of 60 women were randomized to take 500 mg of citicoline, 250 mg of citicoline, or placebo for 28 days. They were evaluated with the computerized performance test second edition (CPT-II). At the completion of the study, participants taking 500 mg of citicoline demonstrated

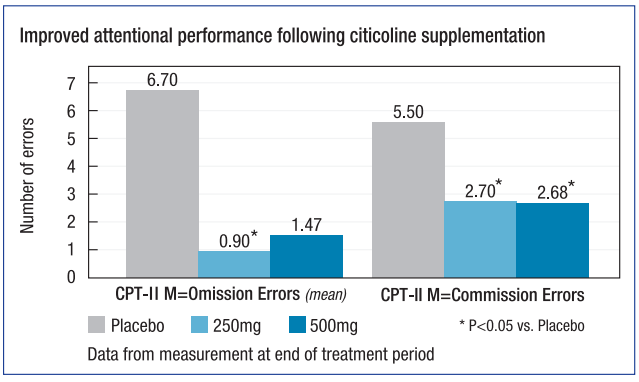
significantly fewer commission errors (doing something wrong) than those taking placebo. Participants taking 250 mg of citicoline demonstrated significantly fewer commission errors and omission errors (failing to do something) than those taking placebo. The authors concluded that both dosages of citicoline were equally effective to improve cognitive inhibition and attentional performance in healthy adult women.

A second randomized, placebo-controlled trial, published by McGlade and colleagues in 2015, evaluated the effects of citicoline on attention, psychomotor function, and impulsivity in 75 healthy teenaged boys. The teens were randomized to take 500 mg of citicoline, 250 mg of citicoline, or placebo for 28 days. Both groups of teens taking citicoline demonstrated significant improvements in motor speed, attention, and impulsivity. However, the higher dosage (500 mg) produced significantly greater improvements, particularly in accuracy and impulsivity.

## Cognitive Function in Healthy Older Adults

Normal brain aging is accompanied by diminishing concentrations of phosphatidylcholine in cell membranes as well as gradual changes in acetylcholine metabolism and function. There are fewer studies of citicoline in healthy individuals than in those with existing pathology, but the studies that do exist have produced promising results.

Alvarez and colleagues demonstrated in 1997 that citicoline improved immediate and delayed memory recall in older adults with memory deficits but not dementia. In the study, 24 participants (mean age = 66 years) were randomized to take 1,000 mg, 500 mg, or 300 mg of citicoline per day with nimodipine. After 4 weeks, the results were similar in all 3 groups, demonstrating cognitive benefits of citicoline in this group of healthy older adults.




A double-blind, placebo-controlled trial, published by Spiers and colleagues in the *Journal of the American Medical Association*, demonstrated that citicoline supplementation improved verbal memory in healthy older adults who had "relatively inefficient memories." The study initially compared 1,000 mg of citicoline per day with placebo in 95 healthy adults (aged 50 to 85 years) without memory problems, dementia, or other neurological disorders. The initial study found that citicoline improved delayed recall memory only in the subset of adults who had relatively inefficient memories. That subgroup (32 participants) was then enrolled in a crossover trial to compare the effect of 2,000 mg of citicoline per day with placebo. In the subset of adults with relatively inefficient memories, citicoline improved immediate and delayed logical memory.

## Head Injury, Stroke, and Cognitive Disorders

Numerous human clinical trials have been conducted on the effects of citicoline in patients with cognitive impairments resulting from head injury, stroke, or other causes. Most of these studies suggest that citicoline supports cognitive health and neurological recovery.

Citicoline has been used as a supportive therapy after traumatic brain injury (TBI) for more than 3 decades. A 2017 meta-analysis, published by Meshkini and colleagues, concluded from 4 randomized controlled trials that citicoline does not significantly affect global outcomes after acute TBI but may offer some benefit in improving the neurocognitive state of chronic TBI patients. A second 2017 meta-analysis, published by Agarwal and colleagues, concluded from 12 clinical trials that citicoline significantly improves functional outcomes after stroke or TBI.

One well-publicized clinical trial (the ICTUS trial), published in the *Lancet* in 2012, showed that citicoline did not affect global outcomes following stroke. The trial involved 2,298 patients from multiple centers in Europe. Patients received citicoline or placebo for a total of 6 weeks post-stroke. Some authors have argued that the duration of the trial was too short to detect positive results.

In contrast to the ICTUS trial, yet published in the same year, the VITA study showed a beneficial effect of citicoline in post-stroke patients. The VITA study evaluated 197 patients with moderate-to-severe neurological deficits resulting from stroke. An intravenous dose of citicoline (2 grams in 500 mL of saline for 5-10

days) was effective at improving functional independence, reducing the burden of care, and improving temporal orientation, attention, and executive functions for up to 2 months.

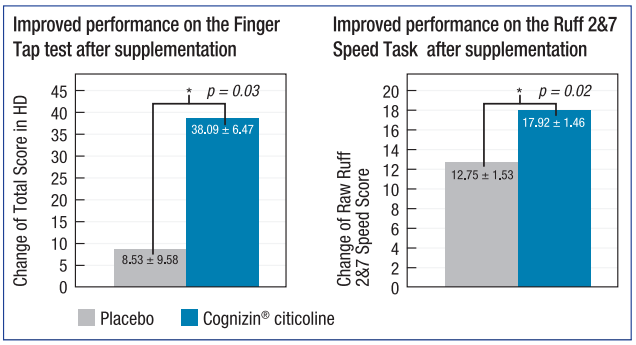
For cognitive impairment resulting from causes other than stroke or brain injury, citicoline has also demonstrated some benefit. The IDEALE study, an open-label Italian study published by Cotroneo and colleagues in 2013, compared the effects of 1,000 mg of citicoline per day to no treatment in 349 patients with mild vascular cognitive impairment. A unique feature of this study was that it followed patients for 9 months rather than only a matter of weeks. Whereas the control group experienced worsening scores on the mini mental state exam (MMSE), those taking citicoline demonstrated mild (albeit nonsignificant) improvement in MMSE scores over the course of the 9-month study.

A Cochrane Review evaluated 14 studies of citicoline in patients with a wide variety of cognitive impairments: subjective memory disorders, mild-to-moderate vascular cognitive impairment, vascular dementia, and mild-to-moderate senile dementia. Only 1 of the studies extended longer than 3 months, but the reviewers concluded that citicoline had a positive effect on memory and behavior, at least for the short-term.

## Emerging Research

Citicoline is gaining attention as a compound to support eye health. Amblyopia, also called lazy eye, is a common condition in children and is routinely treated by patching the stronger eye for a period of time each day. A study of 61 children with amblyopia found that citicoline acted to maintain the visual acuity achieved by patching for a longer duration of time than patching alone. Citicoline has also been researched as a neuroprotective agent for the optic nerve in glaucoma. A 2-year study of patients with progressive visual field loss from glaucoma found that 500 mg of oral citicoline per day significantly reduced the rate of disease progression.

Because of its ability to influence synaptic communication and neurotransmitter levels in the brain, citicoline has also been explored as a supportive therapy for patients battling addictions. The majority of studies have evaluated its use in cocaine dependence and have demonstrated positive effects. Two studies have suggested benefit in methamphetamine dependence, and one in patients with alcohol dependence. Not all studies resulted in reduced use of the addictive substance, but




all at least showed improvements in other parameters, such as attention, concentration, memory, or mood.

Finally, a team of researchers at Harvard University Hospital reported in 2010 that citicoline may influence appetite in healthy adults. The study, published by Killgore and colleagues, used functional magnetic resonance imaging to detect increased activation of certain areas of the brain in response to food stimuli. They showed that 2,000 mg per day of citicoline altered brain activity and decreased appetite in healthy adults. Further research may show that citicoline could play a role in appetite control or eating disorders.

One area that requires more study is the use of citicoline to enhance memory, focus and attention in healthy individuals. As consumers become more interested in enhancing brain health with nootropics, it is likely that this will become a new focus of research interest.

## Dosing Considerations

The majority of citicoline clinical trials—particularly those involving healthy adults and teens—have utilized dosages of 250 mg or 500 mg per day. Both of these dosages have produced beneficial effects.

Dosages as high as 2,000 mg per day have shown benefit in patients with addictive disorders, and dosages of 2,000-4,000 mg per day for 6-12 weeks produced more significant improvements than lower dosages in patients recovering from a stroke.

No serious adverse events have been reported in clinical trials of citicoline at dosages ranging from 250 mg to 4,000 mg per day. Mild adverse effects, including gastrointestinal discomfort, uneasiness, or irritability have been reported.

Therapeutic nutrients often work in synergy with other nutrients. Because citicoline offers neuroprotection via

numerous mechanisms, it is reasonable to consider that it might complement other nutrients that also support neurotransmission, combat oxidative stress, or support mitochondrial function. Most studies have evaluated citicoline as an isolated therapy, but researchers in Spain showed in 2013 that citicoline works synergistically with resveratrol to activate SIRT1 in an animal model of cerebral ischemia.

Finally, the duration of use may influence citicoline's efficacy. Researchers Gareri and colleagues, who conducted the Italian VITA and IDEALE studies, propose that citicoline administration of at least 6 months is required to observe its greatest neuroprotective effects.

## Safety and Regulatory Information

There are two forms of citicoline: citicoline sodium and citicoline free-base. Citicoline sodium is the form that is approved as a prescription medication in some European countries and throughout Asia. Citicoline free-base is the form that is available as a dietary supplement and food/beverage ingredient in the United States. In Europe, citicoline is approved as a Novel Food ingredient and is authorized to be used in food supplements up to 500 mg per day. It is also authorized to be used for Food for Special Medical Purposes (FSMPs) in amounts of 250 mg/serving and up to 1,000 mg per day.

Citicoline free-base is produced in Japan by Kyowa Hakko Bio Co. Ltd. under the brand name of Cognizin. Cognizin is considered to be safe and received self-designated Generally Recognized As Safe (GRAS) status in 2009. In Europe, citicoline was approved as a Novel Food ingredient in 2014. Whereas most companies produce citicoline synthetically, Cognizin is produced using a patented, natural fermentation process. It is vegetarian and allergen-free. Kyowa Hakko manufactures and supplies Cognizin as a raw ingredient to many manufacturers around the world.

## Selected References


Agarwal S, Patel BM. Is aura around citicoline fading? A systemic review. *Indian J Pharmacol.* 2017;49 (1):4-9.

Alvarez XA, Laredo M, Corzo D et al. Citicoline improves memory performance in elderly subjects. *Methods Find Exp Clin Pharmacol.* 1997;19 (3):201-210.

Babb SM, Appelmans KE, Renshaw PF, Wurtman RJ, Cohen BM. Differential effect of CDP-choline on brain cytosolic choline levels in younger and older subjects as measured by proton magnetic resonance spectroscopy. *Psychopharmacology* (Berl). 1996;127 (2):88-94.

Babb SM, Wald LL, Cohen BM et al. Chronic citicoline increases phosphodiesters in the brains of healthy older subjects: an in vivo phosphorus magnetic resonance spectroscopy study. *Psychopharmacology* (Berl). 2002;161 (3):248-254.

Cho HJ, Kim YJ. Efficacy and safety of oral citicoline in acute ischemic stroke: drug surveillance study in 4,191 cases. *Methods Find Exp Clin Pharmacol.* 2009;31 (3):171-176

Cohen BM, Renshaw PF, Stoll AL, Wurtman RJ, Yurgelun-Todd D, Babb SM. Decreased brain choline uptake in older adults. An in vivo proton magnetic resonance spectroscopy study. *JAMA.* 1995;274 (11):902-907.

Cotroneo AM, Castagna A, Putignano S et al. Effectiveness and safety of citicoline in mild vascular cognitive impairment: the IDEALE study. *Clin Interv Aging.* 2013;8 131-137.

Dávalos A, Alvarez-Sabín J, Castillo J et al. Citicoline in the treatment of acute ischaemic stroke: an international, randomised, multicentre, placebo-controlled study (ICTUS trial). *Lancet.* 2012;380 (9839):349-357.

D'Orlando KJ, Sandage BW. Citicoline (CDP-choline): mechanisms of action and effects in ischemic brain injury. *Neurol Res.* 1995;17 (4):281-284.

Fioravanti M, Yanagi M. Cytidinediphosphocholine (CDP-choline) for cognitive and behavioural disturbances associated with chronic cerebral disorders in the elderly. *Cochrane Database Syst Rev.* 2005(2):CD000269.

Gareri P, Castagna A, Cotroneo AM, Putignano S, De Sarro G, Bruni AC. The role of citicoline in cognitive impairment: pharmacological characteristics, possible advantages, and doubts for an old drug with new perspectives. *Clin Interv Aging.* 2015;10 1421-1429.

Hurtado O, Lizasoain I, Moro MÁ. Neuroprotection and recovery: recent data at the bench on citicoline. *Stroke.* 2011;42 (1 Suppl):S33-5.

Hurtado O, Hernández-Jiménez M, Zarruk JG et al. Citicoline (CDP-choline) increases Sirtuin1 expression concomitant to neuroprotection in experimental stroke. *J Neurochem.* 2013;126 (6):819-826.

Kennedy E. The synthesis of cytidine diphosphate choline, cytidine diphosphate ethanolamine, and related compounds. *J Biol Chem.* 1956;222 (1):185-191.

Killgore WD, Ross AJ, Kamiya T, Kawada Y, Renshaw PF, Yurgelun-Todd DA. Citicoline affects appetite and cortico-limbic responses to images of high-calorie foods. *Int J Eat Disord.* 2010;43 (1):6-13.

López-Coviella I, Agut J, Savci V, Ortiz JA, Wurtman RJ. Evidence that 5'-cytidinediphosphocholine can affect brain phospholipid composition by increasing choline and cytidine plasma levels. *J Neurochem.* 1995;65 (2):889-894.

Martinet M, Fonlupt P, Pacheco H. Effects of cytidine-5' diphosphocholine on norepinephrine, dopamine and serotonin synthesis in various regions of the rat brain. *Arch Int Pharmacodyn Ther.* 1979;239 (1):52-61.

McGlade E, Agoston AM, DiMuzio J et al. The Effect of Citicoline Supplementation on Motor Speed and Attention in Adolescent Males. *J Atten Disord.* 2015.

McGlade E, Locatelli A, Hardy J et al. Improved Attentional Performance Following Citicoline Administration in Healthy Adult Women. *Food and Nutr Sci.* 2012;3:769-733.

Meshkini A, Meshkini M, Sadeghi-Bazargani H. Citicoline for traumatic brain injury: a systematic review & meta-analysis. *J Inj Violence Res.* 2017;9 (1).

Ottobelli L, Manni GL, Centofanti M, Iester M, Allevena F, Rossetti L. Citicoline oral solution in glaucoma: is there a role in slowing disease progression. *Ophthalmologica.* 2013;229 (4):219-226.

Putignano S, Gareri P, Castagna A et al. Retrospective and observational study to assess the efficacy of citicoline in elderly patients suffering from stupor related to complex geriatric syndrome. *Clin Interv Aging.* 2012;7 113-118.

Roberti G, Tanga L, Michelessi M et al. Cytidine 5'-Diphosphocholine (Citicoline) in Glaucoma: Rationale of Its Use, Current Evidence and Future Perspectives. *Int J Mol Sci.* 2015;16 (12):28401-28417.

Ruggiero FM, Cafagna F, Petruzzella V, Gadaleta MN, Quagliariello E. Lipid composition in synaptic and nonsynaptic mitochondria from rat brains and effect of aging. *J Neurochem.* 1992;59 (2):487-491.

Silveri MM, Dikan J, Ross AJ et al. Citicoline enhances frontal lobe bioenergetics as measured by phosphorus magnetic resonance spectroscopy. *NMR Biomed.* 2008;21 (10):1066-1075.

Spiers PA, Myers D, Hochanadel GS, Lieberman HR, Wurtman RJ. Citicoline improves verbal memory in aging. *Arch Neurol.* 1996;53 (5):441-448.

Wallace TC, Fulgoni VL. Usual Choline Intakes Are Associated with Egg and Protein Food Consumption in the United States. *Nutrients.* 2017;9(8).

Wang L, Pooler AM, Albrecht MA, Wurtman RJ. Dietary uridine-5'-monophosphate supplementation increases potassium-evoked dopamine release and promotes neurite outgrowth in aged rats. *J Mol Neurosci.* 2005;27 (1):137-145.

Wignall ND, Brown ES. Citicoline in addictive disorders: a review of the literature. *Am J Drug Alcohol Abuse.* 2014;40 (4):262-268.

## About the Author

Sarah Cook, ND, is a freelance medical writer and content marketing strategist for the integrative medical market. She holds a naturopathic doctorate from the Southwest College of Naturopathic Medicine, a marketing certificate in biomedical writing from the University of the Sciences in Philadelphia, and a professional diploma in digital marketing from the Digital Marketing Institute. You can connect with Sarah at www.ndpen.com.

## Editor's Note

This Research Guide was made available thanks to a grant from Kyowa Hakko USA, Inc. For more information visit http://www.cognizin.com.

The author of this guide does not have any conflict of interest and has not received any financial gain from sales of Kyowa Hakko USA, Inc. products.