

The use of citicoline for the treatment of cognitive decline and cognitive impairment: A meta-analysis of pharmacological literature

Author Name¹

¹ Paul Tardner, Head of Nootropics Research, IJEST, New York City

E-mail: paul.tardner@ijest.org

Received 29/08/2020

Accepted for publication 30/08/2020

Published 01/09/2020

Abstract

Citicoline, often called CDP-Choline, Cognizin® (in its branded form), cytidine diphosphate-choline or cytidine 5'-diphosphocholine is a widely-consumed nootropic supplement. It is primarily used to enhance executive cognitive functions such as focus, information processing, and learning. Lately, it has been suggested that citicoline is effective for the treatment of mild cognitive impairment, and that it may have neuroprotective effects. In this article we will examine the most robust and relevant literature relating to citicoline as a potential treatment for cognitive decline, particularly as it relates to older people.

Keywords: Citicoline, CDP-Choline, nootropics, cognition, cognitive decline, memory, focus

1. About Citicoline

Citicoline is a naturally-occurring compound found in the cells of all animals, particularly in the organs. It is more properly known as cytidine diphosphate-choline or cytidine 5'-diphosphocholin.

Citicoline is an intermediary in the synthesis of phosphatidylcholine (an important structural component of brain cell membranes) from choline. As such, it is found in relatively large quantities in the brain (albeit as a transient intermediary).

As well as acting as an intermediary in the synthesis of phosphatidylcholine, citicoline has other interesting properties. Consumed citicoline acts as a choline donor to the brain. In simple terms, orally consumed citicoline is readily absorbed by the human digestive system, and it can quickly cross the blood-brain barrier (which cannot be said about simple choline). Once in the brain, citicoline is broken down into its constituent parts, and the choline is used to synthesize both phosphatidylcholine and acetylcholine. As the brain's primary executive neurotransmitter, acetylcholine levels are

directly linked to cognitive performance. It is generally accepted that higher citicoline levels will produce enhanced cognitive capacities across a broad range of measures, including verbal acuity, concentration span, recall speed, and decision-making speed.

Obviously, citicoline is a compound of choline and cytidine, with a phosphate group attached. By weight, citicoline is just 18% choline. This makes it significantly less choline-dense than other cholinergics such as Alpha-GPC (which is 40% choline by weight). However, the structure of citicoline gives it some unique properties. Most notable is the presence of cytidine, which is a base material needed for the formation of RNA. The exact structure of citicoline also allows it to be easily absorbed by the digestive system, and it can easily cross the blood-brain barrier; here it compares favorably to regular choline.

These properties make citicoline an extremely popular choice among nootropics users. At the time of writing, it is one of the most popular ingredients used in pre-made nootropic stacks, in which it is frequently the central ingredient.

2. What does Citicoline do?

Supplementing with citicoline is said to have several different effects relating to cognitive performance and brain health. The validity and strength of the clinical evidence varies from claim to claim. We will not go through the main benefits said to result from citicoline supplementation, outlining the mechanism of action. We will also discuss the reliability of the clinical data supporting said claim.

2.1 Citicoline and focus

The most frequent claim made by supplement manufacturers regarding citicoline is that it can drastically increase focus and concentration, and by extension promote more efficient learning. There is some strong clinical data to support this claim.

One interesting study, published in the June 2012 issue of *Food and Nutrition Sciences*, took 60 healthy middle-aged women and gave them either 250mg of Citicoline, 500mg of Citicoline, or a placebo for 28 days and monitored their performance in the Continuous Performance Test II (CPT-II), which is an excellent measure of focus and attentional performance. The researchers found that both citicoline treatment groups made significantly fewer commission and omission errors than the placebo group. In simple terms, citicoline seemed to help the participants remember facts better and to remember them more accurately (with fewer false positives). The implication is that it improved the participants' ability to focus and process information while committing things to memory.

2.2 Citicoline and brain injury

As well as enhancing cognitive function in healthy people, citicoline likely supports brain healing following injury. Interestingly, the clinical data supports the idea that citicoline helps the brain recover from both traumatic brain injury and events such as strokes.

In one study which looked at a large group of patients who recently suffered their first stroke, researchers found that citicoline administration was able to significantly improve post-stroke cognitive performance [2]. This is a significant finding; while it is lamentably understudied, the link between stroke and subsequent cognitive decline is well established, with stroke doubling the risk of dementia and vascular-related cognitive decline. Being able to attenuate the onset of cognitive decline following a stroke would represent a major boon for patients.

Some clinical trials have similarly found citicoline to be effective for promoting cognitive function and recovery following traumatic brain injury. For example, in a 2017 German trial [3], researchers found that citicoline administration was correlated with reduced mortality rates

among traumatic brain injury (TBI) patients admitted to ICU. It is worth quoting the researchers in full here:

“Our analysis revealed significantly reduced rates of intensive care unit (ICU) mortality (5% vs. 24%, $p < 0.01$), in-hospital mortality (9% vs. 24%, $p = 0.035$) and 6-month mortality (13% vs. 28%, $p = 0.031$), as well as of unfavorable outcome (34% vs. 57%, $p = 0.015$) and observed vs. expected ratio for mortality (0.42 vs. 0.84) in the WNH (citicoline receivers) group.”

However, other studies looking at citicoline and its effects on TBI have found the opposite; that citicoline administration does no better than placebo when it comes to improving patient outcomes following TBI [4]. Clearly, more work is needed to establish citicoline's efficacy as a treatment for TBI.

2.3 Citicoline and cognitive decline

Perhaps the most interesting claim about citicoline is that it may potentially help with the treatment or prevention of Alzheimer's Disease, dementia, and age-related cognitive decline more generally. This is certainly the area that has received the most attention from researchers, and it is this claim which has the most robust backing from clinical data. Dozens of clinical trials have examined citicoline's effects on cognitive decline, both with regards to pathological brain degeneration and age-related cognitive decline, and these trials have largely found that citicoline is indeed a highly effective nootropic for attenuating cognitive decline.

Perhaps the most important study in this area was a 1994 trial published in *Methods and Findings in Experimental and Clinical Pharmacology* [5]. Here researchers looked at the effects of chronic CDP-Choline (citicoline) administration in early-onset Alzheimer's Disease patients. These researchers found a significant improvement in mental performance after 1 month of citicoline treatment, as measured by brain electrical activity.

With regards to cognitive decline more generally, citicoline seems to be even more effective than it does when being used to treat Alzheimer's Disease. A 2006 meta-study published in *Clinical Interventions in Aging* looked at citicoline as an all-purpose cognitive enhancer in the context of age-related or pathological cognitive decline [6]. Here, researchers looked at a wide range of clinical trials published on citicoline and found that it was reliable and effective for attenuating cognitive decline, especially cognitive decline related to chronic cerebrovascular disorders.

All of this is compounded by the findings of a 2002 paper published in *Revista de Neurologia*, in which researchers determined citicoline to be likely effective for the treatment of mild cognitive impairment [7]. That paper is particularly interesting as it outlines 12 separate clinical trials in which citicoline supplementation was found to promote memory

and cognitive performance more generally in older people with chronic cognitive issues.

3. Conclusion

Supplementing with citicoline appears to be highly effective for the treatment of cognitive decline. Various studies show that citicoline enhances attentional performance in otherwise healthy people. It has also been shown that citicoline may improve cognitive performance following stroke and TBI. Most relevantly to our focus here, there are dozens of clinical trials showing that citicoline is effective at improve cognitive performance in people experiencing cognitive decline; this include mild cognitive decline, Alzheimer's Disease, dementia, and age-related cerebrovascular cognitive impairment.

We believe it is likely that the same core mechanisms are driving all of these effects. Specifically, the effects of citicoline on neurotransmitter synthesis and brain cell membrane formation are the most likely explanations for the effects we see on cognitive performance in the context of cognitive decline. However, more research needs to be done to identify the exact mechanism of action behind citicoline's demonstrated effects.

Acknowledgements

None of the work presented here would exist without the tireless work of the nootropics community. Together, bio-hackers are paving the way toward better cognitive function. It is through their research and their experimentation that we yield improvements in focus, memory, and productivity.

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