

Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Citicoline (CDP-choline)

Evidence Summary

Some evidence exists for cognitive benefits in stroke patients, Alzheimer's patients, and in healthy individuals. However, it may not be more beneficial than standard of care (e.g. tPA in stroke or donepezil in Alzheimer's).

Neuroprotective Benefit: There is some evidence for the efficacy of citicoline in Alzheimer's disease; however, the data is weak and well-designed clinical trials are lacking.

Aging and related health concerns: Some preclinical studies suggest benefits for peripheral nerve injury and stroke (see above), but no studies in other age-related indications.

Safety: Citicoline is well-tolerated with few-to-no adverse effects, and it is widely used; however, there are few long-term controlled trials.

What is it?

CDP-choline is a naturally occurring compound produced by the body. It is a precursor in the synthesis of phosphatidylcholine, a major component of biological membrane. The pharmaceutical version (i.e. exogenous CDP-choline) is called citicoline.

Citicoline is reported to be metabolized in the gut and liver to cytidine and choline. These metabolites may cross the blood brain barrier where they can be used as precursors in the synthesis of acetylcholine or phosphatidylcholine. Acetylcholine and phosphatidylcholine compete for free choline, and it is hypothesized that when choline levels decrease neurons may break down phosphatidylcholine in the cell membrane to produce acetylcholine – a process called ‘autocannibalism’ – which may accelerate neuronal degeneration. Citicoline may mitigate this effect by acting as an exogenous source of choline and phosphatidylcholine (although this is somewhat controversial ([Grieb 2014](#))).

Citicoline is used for stroke, dementia, and as a nootropic. It may have other neuroprotective properties including acting as an intermediate in the synthesis of sphingomyelin, restoring levels of cardiolipin, preventing apoptosis, and increasing the levels of SIRT1 ([Gareri et al, 2015](#); [Conant and Schauss, 2004](#)). The effects of citicoline appear to be minor compared to standard of care treatment for Alzheimer’s disease and stroke.

Neuroprotective Benefit: There is some evidence for the efficacy of citicoline Alzheimer’s disease; however, the data is weak and well-designed clinical trials are lacking.

Types of evidence:

- 1 RCT in patients with Alzheimer’s disease
- 2 observational studies in Alzheimer’s patients
- 3 small open label, non-controlled studies in Alzheimer’s patients
- 1 meta-analysis of RCTs in patients with vascular cognitive impairment, vascular dementia, and senile dementia
- 1 meta-analysis of RCTs in patients with acute ischemic stroke
- 1 RCT in patients with mild vascular cognitive impairment
- 5 RCTs in healthy individuals (young, middle age, and elderly)

Human research to suggest prevention of dementia, prevention of cognitive decline, or improved cognitive function?

Citicoline (250 or 500mg) for four weeks improved tasks of speed and attention in teenage males ([McGlade et al, 2015](#)), and a citicoline-caffeine drink improved a number of measures of cognition, including reaction time and go/no-go tasks, in healthy adults in their 20s ([Bruce et al, 2014](#)). However, in another study, citicoline (500 or 1000mg) only provided cognitive benefits to healthy young adults that were low-performers at baseline while impairing cognition in high-performers ([Knott et al, 2015](#)), suggesting a possible inverted U-shaped curve for citicoline's effects on cognition (i.e. too much citicoline impairs cognition).

In healthy adult or elderly individuals, citicoline improved attention and memory in individuals with lower memory at baseline and increased phosphodiester levels in the brain, which correlated with better verbal learning ([Babb et al, 2002](#); [McGlade et al, 2012](#); [Spiers et al, 1996](#)).

In most of these studies, citicoline was taken at 250-1000mg/day up to 12 weeks.

Human research to suggest benefits to patients with dementia:

Three open-label, non-controlled pilot studies reported some benefits in cognition (e.g. MMSE improved 1 point) in dementia patients with 1-3 months of 1000mg/day of citicoline ([Cacabelos et al, 1993](#); [Caramano et al, 1994](#); [Cacabelos et al, 1996](#)). Another pilot RCT of 30 patients reported cognitive benefits (compared to placebo) in ApoE4 individuals after 12 weeks of citicoline treatment (1000mg/day), increased cerebral blood flow velocity and reduced serum IL-1 β ([Alvarez et al, 1999](#)). These studies were all done by the same group in Spain, and although they reported positive results, the results may not be clinically meaningful.

Two retrospective case-control studies looked at whether citicoline is beneficial in Alzheimer's patients already taking an acetylcholinesterase inhibitor. In a study in 174 patients over 9 months, adding citicoline to rivastigmine improved MMSE scores compared to controls ([Castagna et al, 2016](#)). Additionally, in another retrospective study of 448 patients over 9 months, adding citicoline to any acetylcholinesterase inhibitor improved MMSE scores by 1 point while those on acetylcholinesterase inhibitors alone had a 1 point worse score ([Gareri et al, 2017](#)).

Vascular Cognitive Impairment, Vascular Dementia, Stroke

A Cochrane meta-analysis of 14 RCTs in patients with vascular cognitive impairment, vascular dementia, and senile dementia reported no benefit on attention with citicoline. However, citicoline

provided small benefits in memory, behavior, and on the clinical global impression scale. The authors reported that although there are a number of small positive studies on the use of citicoline, there was little data available for negative studies, suggesting the possibility of publication bias ([Fioravanti and Yanagi, 2004](#)).

In an RCT of 349 patients with vascular cognitive impairment (excluding probable Alzheimer's), with 9 months of citicoline (500mg bid) there was a significant difference in MMSE between groups (favoring citicoline) but no differences in activities of daily living ([Cotroneo et al, 2013](#)).

An interesting systematic review and meta-analysis looked at RCTs over 30 years in 4,420 ischemic stroke patients on citicoline (or placebo) plus standard of care and were followed up to 3 months. Citicoline was associated with a significant increase in a measure of independence (OR 1.56; 95%CI 1.12-2.16). However, in a sensitivity analysis, it was discovered that this benefit was largely due to older trials before better drugs (such as tPA) became the standard of care. Although citicoline may be beneficial in stroke patients when no other treatment is available, it probably does not add much benefit over the current standard of care ([Secades et al, 2016](#)).

Mechanism of action from preclinical studies

Citicoline is beneficial in a number of animal models including hypoxia, neurodegeneration, memory in aged rats, stroke, spinal cord trauma, and amyloid toxicity ([Grieb, 2014](#); [Tayebati and Amenta, 2013](#)). It's mechanism of action, however, is somewhat unclear.

One hypothesis for citicoline's neuroprotective benefits is that it can increase levels of brain membrane phospholipids. A single dose of citicoline increased brain choline levels in younger subjects, but slightly decreased levels in older subjects ([Babb et al, 1996](#)). However, a later study by the same group reported that daily oral citicoline over six weeks increased phospholipid levels in the elderly ([Babb et al, 2002](#)). Animal ischemia studies also suggest that citicoline can restore phospholipid levels in response to injury ([Amenta et al, 2002](#)).

Some authors speculate that citicoline may increase acetylcholine levels in the brain, but a study in rats suggested that citicoline increased acetylcholine levels in the cerebellum, but not in the frontal cortex or striatum ([Tayebati et al, 2011](#)). Other pre-clinical studies provide conflicting results whether choline supplementation increases brain acetylcholine levels ([Tayebati and Amenta, 2013](#)).

Citicoline is also reported to increase levels of SIRT1. In an animal model of focal ischemia, citicoline was reported to increase SIRT1 expression, and neuroprotection with citicoline was reported to partially depend on SIRT1. Citicoline and resveratrol acted synergistically to offer further neuroprotection ([Hurtado et al, 2013](#)).

APOE4 interactions:

A pilot RCT of 30 patients reported cognitive benefits (compared to placebo) in ApoE4 individuals after 12 weeks of citicoline treatment (1000mg/day), increased cerebral blood flow velocity, and reduced serum IL-1 β ([Alvarez et al, 1999](#)).

Aging and related health concerns: Some preclinical studies suggest benefits for peripheral nerve injury and stroke (see above), but no studies in other age-related indications.

Types of evidence:

- Multiple preclinical studies in peripheral nerve injury

Peripheral nerve injury

In rat models of sciatic nerve injury, citicoline was reported to increase axon regeneration, improve peripheral nerve conduction, and increase myelination ([Gundogdu et al, 2015](#); [Caner et al, 2012](#); [Aslan et al, 2011](#)).

Safety: Citicoline is well-tolerated with few-to-no adverse effects and it is widely used; however, there are few long-term controlled trials.

Types of evidence:

- Multiple small clinical studies

There are no serious adverse events reported with citicoline ([Grieb, 2014](#)). In fact, in a meta-analysis for cerebral dysfunction in elderly individuals, citicoline treatment had a trend to be more tolerable than placebo ([Fioravanti and Yanagi, 2005](#)), and a recent European Food Safety Authority panel suggested that available human data do not suggest safety concerns, and it should be considered a novel food ingredient ([reference](#)).

Drug Interactions:

[Drugs.com](https://www.drugs.com) lists three minor drug interactions with dopamine drugs.

Sources and dosing:

Citicoline is widely available at most supplement stores. Typical doses are 250-1000mg/day.

Research underway:

Some evidence suggests that citicoline is beneficial in addiction disorders, and it is currently in addiction clinical trials for alcohol, cocaine and methamphetamine abuse (clinicaltrials.gov).

Search terms:

Pubmed:

- Citicoline + Alzheimer, dementia, atherosclerosis, longevity, cardiovascular, orthostatic hypotension, osteoarthritis, peripheral neuropathy

Google search: citicoline + safety

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If you have suggestions for drugs, drugs-in-development, supplements, nutraceuticals, or food/drink with neuroprotective properties that warrant in-depth reviews by ADDF's Aging and Alzheimer's Prevention Program, please contact INFO@alzdiscovery.org. To view our official ratings, visit [Cognitive Vitality's Rating page](#).