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)

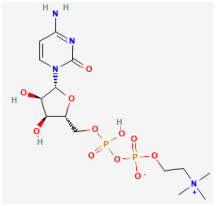
Evidence Summary

Citicoline is safe and very well-tolerated form of choline with good brain bioavailability, and may help protect against cognitive dysfunction related to inadequate choline, and may offer modest benefit in neurodegenerative disease.

Neuroprotective Benefit: Citicoline may promote cognitive function by ensuring adequate brain choline levels. It may be beneficial as an adjunct to other therapies in neurodegenerative diseases, but does not show clear evidence of neuroprotection on its own.

Aging and related health concerns: Citicoline may very modestly slow neurodegeneration in ocular diseases, such as glaucoma and diabetic retinopathy, but impacts to vision loss appear minor. Preclinical studies suggest benefits for peripheral nerve injury.

Safety: Citicoline is widely used and well-tolerated with few-to-no adverse effects, even in multi-year trials. Citicoline shows several fold lower toxicity in animals relative to other supplemental forms of choline.

Availability: OTC (oral supplement) Medical device with CE marking (ophthalmic solution)	**Dose**: Clinical trials have typically used oral doses of 500 mg/day in healthy adults and 1000 mg/day in patients with neurodegenerative disease.	**Chemical formula:** $C_{14}H_{26}N_4O_{11}P_2$ **MW**: 488.32 g/mol  Source: PubChem
Half-life: ~50 (via respiration) to 70 (via urinary excretion) hours	**BBB**: Penetrant	
Clinical trials: Citicoline has been tested in RCTs for stroke, traumatic brain injury, dementia, Parkinson's disease, glaucoma, diabetic retinopathy, and substance abuse disorders. Many of these studies were underpowered and/or supplement company sponsored.	**Observational studies**: Citicoline intake has been associated with better cognition in case-control studies of Alzheimer's disease patients when used in combination with other symptomatic agents.	

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, and its production is a rate-limiting step in the biosynthesis of cellular phospholipids [1]. Additionally, the CDP-choline pathway is integrated into a larger metabolic network, such that its disruption can interfere with the production of other lipid-related metabolites. 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 [1]. Choline is an essential dietary nutrient found in high abundance in eggs, meat, fish, and dairy, with a recommended daily intake of 425 to 550 mg/day (NIH). These metabolites may cross the blood brain barrier (BBB) where they can be used as precursors in the synthesis of various cellular metabolites, including lipids, proteins, and nucleic acids. Choline can be used for the production of the neurotransmitter acetylcholine, or in the oxidation of betaine providing for the conversion of homocysteine to methionine [2]. Choline and cytidine are used in the synthesis of the phospholipid phosphatidylcholine via the "Kennedy pathway". In the blood, cytidine is converted to uridine, which acts as a precursor for components of synaptic membranes. where they can be used as precursors in the synthesis of acetylcholine or phosphatidylcholine. Additionally, there is some evidence to suggest that the intact CDP-choline molecule itself may have some neuroprotective properties [3].

Citicoline is considered to be the most brain bioavailable form of choline, an essential nutrient for brain function, and thus has been clinically tested primarily for neurodegenerative conditions including stroke, dementia, traumatic brain injury, and glaucoma. To date, the effects of citicoline appear to be minor compared to standard of care treatment for these conditions, as it may be most effective as an adjunct treatment. It is also used as a nootropic and has been tested in clinical trials for its impacts on cognition in healthy populations.

Neuroprotective Benefit*:* Citicoline may promote cognitive function by ensuring adequate brain choline levels. It may be beneficial as an adjunct to other therapies in neurodegenerative diseases, but does not show clear evidence of neuroprotection on its own.

Types of evidence:

- 1 meta-analysis of RCTs in patients with vascular cognitive impairment, vascular dementia, and senile dementia
- 3 meta-analyses of RCTs in patients with acute ischemic stroke
- 1 meta-analysis of clinical trials in traumatic brain injury
- 1 systematic review of clinical studies in Parkinson's disease
- 5 case-control observational studies in Alzheimer's patients
- 1 prospective observational study in vascular cognitive impairment
- 1 RCT in patients with Alzheimer's disease
- 1 RCT in patients with mild vascular cognitive impairment
- 7 RCTs in healthy individuals (young, middle age, and elderly)
- 1 RCT in traumatic brain injury
- 4 small open label, non-controlled studies in Alzheimer's patients
- Numerous mechanistic preclinical studies

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

Choline is an essential nutrient, particularly in the nervous system, where it serves as a precursor for the neurotransmitter acetylcholine, and the membrane lipids phosphatidylcholine and sphingomyelin [2]. Adequate levels are necessary to ensure that the demand to create sufficient levels of all of these downstream products is met, to prevent a situation of biosynthetic trade-offs. High dietary intake of choline has been associated with better cognition and lower levels of cerebrovascular pathology [4]. As

a highly brain bioavailable form of choline, citicoline is considered to be the best choline supplement for brain health [5]. Clinical trials suggest that supplementation may boost some aspects of cognitive function, at least temporarily, though to date, there is no evidence to suggest that citicoline supplementation offers a significant benefit over adequate intake of choline from dietary sources in terms of long-term brain health and dementia prevention.

No studies to date have tested whether citicoline supplementation can prevent or delay dementia onset.

Many of the studies testing citicoline were partially funded by groups that provide citicoline supplements. This, in addition to the lack of negative studies, suggests that there is some bias. In most of these studies, citicoline was taken at 250-1,000 mg/day up to 12 weeks.
Citicoline (250 or 500 mg) for four weeks improved tasks of speed and attention in teenage males [6], 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 [7]. However, in another study, citicoline (500 or 1,000 mg) only provided cognitive benefits to healthy young adults that were low-performers at baseline while impairing cognition in high-performers [8], 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 [9; 10; 11].

A study in 40 healthy volunteers comparing 500 mg/day citicoline for two weeks with placebo on measures of vigilance found that citicoline treatment was associated with better performance on measures of vigilance and working memory [12]. Citicoline treatment was associated with improved performance relative to baseline on Total Reaction Time (mean ± SD from 666.18±24.62 to 493.53±12.58 ms), Recognition Reaction Time (from 453.37±22.59 to 400.31± 401.47±19.56 ms), Movement Reaction Time (from 229.87±17.49 to 193.22±11.97 ms), and working memory accuracy based on the Working Memory-2 back (from 55.32±8.55 to 77.63±7.65%) and Working Memory-3 back (40.29±8.93 to 49.84±7.56%) tests. In contrast, no significant effects were seen on any of these parameters in the placebo group. Citicoline was also associated with a reduction in serum levels of the oxidative stress marker malondialdehyde (MDA)from 19.11±2.66 to 15.63±1.33 nmol/mL, while levels of MDA increased in the placebo group from 19.44±2.11 to 29.66±3.28 nmol/mL.

A company sponsored study tested citicoline at a dose of 500 mg/day for 12 weeks in healthy older adults (ages 50-85) with age-associated memory impairment, based on Mini-Mental State Examination (MMSE) score (≥24) (n=100) (NCT03369925) [13]. Cognitive performance was assessed using Cambridge Brain Sciences computerized tests. There was improvement in performance on the primary outcome, the Spatial Span test (mean ± SEM from 4.65 ± 0.09 to 4.90 ± 0.12), a measure of short-term spatial memory, in the citicoline group at 12 weeks relative to baseline, though the effect was not significantly different from placebo. Improvements relative to baseline, but not to placebo, were also seen in the citicoline group on the Feature Match test (from 86.7 ± 2.8 to 96.8 ± 3.5), a measure of selective attention, and the Composite Memory score (from 75.6 ± 1.4 to 79.1 ± 1.7). Only the Paired Associate test, a measure of episodic memory, showed a significant effect with citicoline relative to placebo (mean: 0.15 vs. 0.06). No significant improvements were seen on other tests assessing working memory (Monkey Ladder), short-term verbal memory (Digit Span), selective attention (Interlocking Polygons Task), or sustained attention (Sustained Attention to Response Task).

***Human research to suggest benefits to patients with dementia*:**

While there are no formal medical guidelines indicating a higher intake of choline for dementia patients, dementia patients may be more sensitive to inadequate levels of dietary choline, and due to ongoing neurodegenerative processes, choline requirements in the brain may be higher than average [2]. As such, choline supplementation, such as with citicoline, could potentially be useful to ensure adequate brain levels are reached. Citicoline would not be expected to act as a disease modifying agent, but rather to ensure that the brain is able to function to the best of its capacity. As such, it may be most useful in combination with other symptomatic agents, particularly those also enhancing cholinergic neurotransmission. Preclinical studies suggest that it may also help promote neural repair, but clear clinical evidence to support that is currently lacking.

Three open-label, non-controlled pilot studies (full text unavailable) reported some benefits in cognition (e.g. MMSE improved 1 point) in dementia patients with 1-3 months of 1,000mg/day of citicoline [14; 15; 16]. Another pilot RCT of 30 patients (full text unavailable) reported cognitive benefits (compared to placebo) in ApoE4 individuals after 12 weeks of citicoline treatment (1,000 mg/day), increased cerebral blood flow velocity and reduced serum IL-1B [17]. These studies were all done by the same group in Spain, and although they reported positive results, it is not clear the results are clinically meaningful. A meta-analysis of seven studies including 1,489 dementia patients examining the effect of citicoline on cognitive function found an association between citicoline and improved cognition with pooled

standardized mean differences (SMD) ranging from 0.56 (95% Confidence Interval [CI] 0.37 to 0.75) to 1.57 (95% CI 0.77 to 2.37), however the quality of the included studies was low [18]. The effects became more apparent over time, and required long-term administration.

Alzheimer's disease: POTENTIAL MINOR BENEFIT ON COGNITION IN COMBINATION WITH OTHER SYMPTOMATIC AGENTS WITH LONG-TERM USE

Five retrospective case-control studies conducted in Italy looked at whether oral citicoline (1,000 mg/day) is beneficial in Alzheimer's disease (AD) patients already taking an acetylcholinesterase inhibitor and/or an NMDAR antagonist. In the CITIRIVAD study in 174 patients over 9 months, adding oral citicoline to rivastigmine (acetylcholinesterase inhibitor) improved MMSE scores compared to controls [19]. The follow-up CITIMERIVA study including 104 AD patients found that adding citicoline to memantine (NMDAR antagonist) and rivastigmine was associated with a 0.69 point improvement in MMSE score at 12 months, while those without citicoline showed decline of 0.25 [20]. In the CITICHOLINAGE study of 448 patients over 9 months, adding citicoline to any acetylcholinesterase inhibitor improved MMSE scores by one point while those on acetylcholinesterase inhibitors alone had a one point worse score [21]. In the follow-up CITIMEA study, in which citicoline was combined with memantine and an acetylcholinesterase inhibitor (n=170), there was a small increase in MMSE between baseline and 12 months in those with citicoline (14.88±2.95 to 15.09±3.00), but a slight decline in those not taking citicoline over this period (14.37±2.63 to 14.03±2.92) [22]. The retrospective CITIMEM study examined the combination of citicoline with memantine (10-20 mg/day) in 126 patients with AD or mixed dementia [23]. In this study, MMSE score significantly declined over 12 months in those taking memantine alone (16.2±2.6 to 14.6±3), but increased in those taking the combination treatment (16.6 ± 2.9 to 17.7±2.8). These studies generally did not find differences in measures of activities of daily living, or neuropsychiatric symptoms between groups.

These studies suggest that the addition of citicoline may have symptomatic benefit on cognition in AD patients when used in conjunction with other symptomatic agents, though it is unclear whether the results are clinically meaningful. The modest effects generally required long-term administration of at least one year.

There are currently two active placebo-controlled RCTs examining the effect of oral citicoline (1,000 mg/day) for three months on measures of sleep and cognition (RAVLT, MoCA, and Trail Making Test) in patients with mild cognitive impairment (MCI) (~n=100) (NCT06029894) and AD (~n=20) (NCT05200208). AD biomarkers, namely CSF Aβ and tau, will also be assessed in the MCI study. These studies are expected to be completed in 2024.

Vascular dementia: POTENTIAL MINOR BENEFIT
A Cochrane meta-analysis of 14 RCTs in patients with vascular cognitive impairment, vascular dementia, and senile dementia reported no benefit of 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 [24].

In an RCT of 349 patients with vascular cognitive impairment (excluding probable Alzheimer's), with nine months of citicoline (500 mg bid) there was a significant difference in MMSE between groups (favoring citicoline) but no differences in activities of daily living [25].

A prospective observational study included 81 participants with vascular risk factors and subjective cognitive complaints or MCI treated with citicoline (1 g/day) for 12 months [26]. Over the follow-up period, 81.25% (26/32) of patients with subjective cognitive complaints remained cognitively stable, and showed improvements on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) in language, attention, and visuospatial domains. In the MCI cohort, 70.7% (29/41) remained stable, 29.9% (12/41) reverted back to a status of subjective cognitive complaints. The latter group had a mean improvement of 8.32 points on the Trail Making Test, part B, and 2.69 in total RBANS score.

Ischemic stroke: NO CLEAR BENEFIT OVER CURRENT STANDARD OF CARE
A 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 three months. Citicoline was associated with a significant increase in a measure of independence (OR: 1.56, 95%CI 1.12 to2.16). 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 [27].
A Cochrane meta-analysis of 10 RCTs including 4,281 patients with acute ischemic stroke testing citicoline administered either intravenously and/or orally, at doses ranging from 500 mg to 2,000 mg per day found little to no effect on all-cause mortality in pooled analysis of eight trials (399/2,313 vs. 379/2049; RR: 0.94, 95% CI 0.83 to 1.07) [28]. There was also no significant effect on proportion of patients with a moderate or lower degree of disability or dependence using the Rankin Scale (RR: 1.11, 95% CI 0.97 to 1.26), or on functional recovery according to the Barthel Index (RR: 1.03, 95% CI 0.94 to 1.13) based on four trials. Quality of life measures were not reported. All included studies were deemed

to have a high risk of bias, thus the quality of evidence in this analysis is low. A separate meta-analysis including 8,357 patients with either acute ischemic stroke (15 studies) or hemorrhagic stroke (2 studies) treated with various forms of choline similarly found that citicoline was not associated with improved neurological function based on the NIHSS (n=3,901) (OR: 1.05; 95% CI 0.87 to 1.27) or functional recovery based on the modified Rankin Scale (n=4,487) (OR: 1.36, 95% CI 0.99 to 1.87) in acute ischemic stroke [29]. There was also no significant effect on activities of daily living (n= 3,819) (OR: 1.12, 95% CI 0.81 to 1.53). Similarly, there was no clear effect on functional recovery in hemorrhagic stroke (n= 1,055) (OR:1.75, 95% CI 0.00 to 964.00).

Parkinson's disease: POTENTIAL BENEFIT AS ADJUNCT TO LEVADOPA
A systematic review of seven studies (two crossover, three randomized controlled, and two open prospective studies) including 355 participants tested citicoline (intravenous, intramuscular, or oral) as adjuvant therapy for Parkinson's disease (PD) found that citicoline treatment was associated with significant improvements in measures of rigidity, akinesia, tremor, handwriting, and speech [30]. Though, the included studies were small and only one study characterized baseline disease severity using the standard Unified Parkinson Disease Rating Scale (UPDRS), thus more rigorous studies are needed [1]. Improvements were associated with reductions in levodopa dosing. This may be related to the reported ability of citicoline to increase dopamine synthesis and inhibit reuptake.

Traumatic brain injury: POTENTIAL MINOR BENEFIT WITH I.V. ADMINISTRATION; NO CLEAR BENEFIT ON MORTALITY
Citicoline has been tested in a variety of clinical trials as a potential neuroprotective agent in patients with traumatic brain injury (TBI), however, enthusiasm has waned largely due to the lack of clinical benefit in the 2012 COBRIT trial, a Phase 3 placebo controlled RCT including 1,213 patients [31]. The patients received 2,000 mg/d citicoline via enteral route within the first 24 hours, then orally for 90 days. This unconventional route of administration is now thought to have contributed to the study outcome, due to reduced citicoline absorption and brain bioavailability, as well as reduced compliance, resulting in inadequate levels of citicoline. In that study, at least 40% of patients were not adherent to the medication.
A meta-analysis of 11 clinical studies including 2,771 patients with TBI testing citicoline (intravenously, intramuscularly, and orally) found that citicoline was associated with a higher rate of independence (RR: 1.18, 95% CI 1.05 to 1.33), though there was a considerable degree of heterogeneity across studies (I^2: 42.6%) [32]. The effect did not show a clear relationship with dose, with doses ranging from 300 mg to 6 g, and treatment duration ranging from 10 to 90 days. The majority of studies included patients with

moderate to severe TBI, and no significant effect on mortality was seen with citicoline treatment across studies. The one study that showed an effect on mortality was a retrospective matched pair analysis in which 67 severe TBI patients (Glasgow Coma Scale score <13) who received citicoline from a prospectively collected cohort of 778 were retrospectively compared with 67 matched patients [33]. Treated patients received citicoline (125 mg/ml) via continuous intravenous drip infusion at a rate of 120 mg/h starting immediately after ICU admission, for a maximum of 21 days. After adjustment for age, Glasgow Coma Scale score, and Injury Severity Score, citicoline treatment was associated with better odds of ICU survival (OR: 6.7, 95% CI 1.6 to 28.8, p=0.014) and six-months favorable outcome (OR: 2.6, 95% CI 1.1 to 6.0).

A recent RCT (n=69) found that oral citicoline treatment (2,000 mg 2x/day) for two weeks did not have any significant impacts on changes in Glasgow Coma Scale score, quadriceps muscle force score, Barthel Index score, achieving the status without intubation, or spontaneous breathing over the course of six months in patients with moderate to severe TBI [34].

Together these studies suggest that intravenous citicoline administered shortly after injury may offer very modest protection in some patients, but rigorous studies would be needed to provide sufficient evidence. Other routes of administration do not appear to be sufficiently bioavailable to offer neuroprotection in this context.

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 [35; 36]. Its mechanism of action, however, is somewhat unclear, as there are numerous proposed mechanisms of neuroprotection.

One hypothesis for citicoline's neuroprotective benefits is that it can increase levels of brain membrane phospholipids. 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 exogenouse source of choline and phosphatidylcholine [35]. A single dose of citicoline increased brain choline levels in younger subjects, but slightly decreased levels in older subjects [37]. However, a later study by the same group reported that daily oral citicoline over six weeks increased phospholipid levels in the elderly [9]. Animal ischemia studies also suggest that citicoline can restore phospholipid levels in response to injury [38]. This may also protect mitochondrial membranes. The stabilization of mitochondrial membranes, via the inhibition

of phospholipase A2, which hydrolyzes the major mitochondrial membrane phospholipid, cardiolipin, may help protect against metabolic dysfunction, oxidative stress and inflammation [38]. In addition to phospholipids, citicoline has also been shown to stimulate the synthesis of sphingomyelin, a major component of neuronal cell membranes and myelin, which may help promote axon repair [3].
Some authors speculate that citicoline may also 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 [39]. Other pre-clinical studies provide conflicting results whether choline supplementation increases brain acetylcholine levels [36].

Citicoline has also been reported to restore redox homeostasis and mitigate oxidative stress [3]. Various clinical trials have found that citicoline treatment was associated with a reduction in levels of oxidative stress markers, most commonly malondialdehyde (MDA).

Citicoline is also reported to increase levels of the NAD-dependent deacetylase sirtuin-1 (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 [40].

APOE4 interactions: UNCLEAR
A pilot RCT of 30 patients (full text unavailable) reported cognitive benefits (compared to placebo) in ApoE4 individuals after 12 weeks of citicoline treatment (1,000 mg/day), increased cerebral blood flow velocity, and reduced serum IL-1B [17]. In a prospective observational study of 81 individuals with vascular risk factors and cognitive dysfunction treated with citicoline (1,000 mg/day) for 12 months, ApoE4 genotype did not influence cognitive outcomes [26]. In an open-label study conducted in Russia including 82 relatives of individuals with AD experiencing cognitive dysfunction, cognitive benefits were preferentially seen in non-ApoE4 carriers [41].

Aging and related health concerns*:* Citicoline may very modestly slow neurodegeneration in ocular diseases, such as glaucoma and diabetic retinopathy, but impacts to vision loss appear minor. Preclinical studies suggest benefits for peripheral nerve injury.

Types of evidence:

- 1 systematic review of clinical trials in glaucoma

- 3 RCTs in glaucoma (2 described in systematic review)
- 1 RCT in diabetic retinopathy
- Preclinical studies for neuropathy

Glaucoma: POTENTIAL MINOR BENEFIT WITH LONG-TERM ADMINISTRATION

Citicoline has been reported to show numerous neuroprotective effects and to promote an environment conducive to nerve repair in preclinical studies [3]. Clinical testing of citicoline as a neuroprotective agent in glaucoma as an adjunct to intraocular pressor (IOP) lowering medications began in the 1980s. Most studies have reported benefits on measures related to neurodegeneration, but there is less evidence regarding whether citicoline can meaningfully impact glaucoma-related visual impairment. A systematic review of 10 studies testing citicoline in glaucoma patients (n=424) found that the evidence from these studies was not sufficient to support a role for citicoline in protecting against disease progression and vision loss [42]. However, many of these studies may have been too short to see an effect, as more recent studies suggest that longer term treatment (>12 months) may be needed to see evidence of neuroprotection with citicoline.

A company-sponsored placebo-controlled crossover trial tested an oral citicoline solution containing 500 mg/day of citicoline for three months in 155 patients with chronic open-angle glaucoma [42]. In the study, both citicoline and placebo arms showed improvement on the primary outcome of "intra-patient" composite score of the Visual Function Questionnaire-25 (VFQ-25) relative to baseline, however, the majority of patients were close to the ceiling of the measurement, so potential improvements could only be measured for a small subset.

A two-year placebo-controlled clinical trial including 60 patients with primary open-angle glaucoma and well-controlled IOP tested the effect of an oral daily citicoline solution containing 500 mg citicoline with a periodic dosing schedule of four months on, two months off, and then a schedule of six months on and two months off for the remainder of the two-year study [43]. Standard automated white-on-white perimetry mean deviation, a visual field test measure, declined in both groups, but the decline was significantly more pronounced in the placebo group (from −6.39 to −8.64 db) relative to the citicoline group (from −6.51 to −7.25 db) by 18 months. The citicoline group also showed a slowing in the thinning of the retinal nerve fiber layer (RNFL) which became more pronounced over time, suggestive of an attenuation in the progression of neurodegeneration.

A three-year placebo-controlled trial testing citicoline eye drops in patients with open-angle glaucoma and well-controlled IOP (n=80) (NCT04020705) found that citicoline treatment was associated with a non-significant trend toward a reduction in disease progression based on differences in the visual field mean deviation on the 24-2 (-10±3.9 dB vs -10.6±3.9 dB) and 10-2 tests (-8.6±2.7 vs -9.8±2.8) at 36

months [44]. However, the study may not have been adequately powered to detect a change because it was powered according to the baseline rates of 24-2 MD change, and underestimated the variability of the progression rates in this cohort. The rate of decline in RFNL thickness was significantly less for citicoline-treated eyes (-1.86 µm) relative to placebo-treated eyes (-2.99 µm) over the course of the three-year study, suggesting it may have modestly attenuated the rate of retinal neurodegeneration. In these studies, benefits could only be detected at time points longer than one year, suggesting long-term treatment may be necessary for neuroprotective effects to manifest, and may help modestly slow rates of disease progression in individuals whose IOP is otherwise well-controlled with other medications. While citicoline may help preserve retinal axons, its potential benefits with respect to vision loss appear very modest, and may take several years to become detectable.
Preclinical studies suggest that similar to other neurodegenerative diseases, the neuroprotective benefits of citicoline in glaucoma may be related to its ability to modulate phospholipid homeostasis, and thus membrane composition and function, redox homeostasis, mitochondrial dynamics, and neurotransmission [3].

Diabetic retinopathy: POTENTIAL MINOR BENEFIT WITH LONG-TERM ADMINISTRATION
A pilot randomized, double-masked trial tested the effect of eye drops containing 2% citicoline, 0.2% hyaluronic acid, and 0.05% cyanocobalamin (vitamin B12) in patients with Type 1 diabetes and mild signs of non-proliferative diabetic retinopathy (NCT04009980). The study was conducted in 20 participants receiving one drop of the citicoline or placebo solution in one eye three times per day for 36 months. Humphrey Matrix frequency doubling technology (FDT) measures visual contrast sensitivity and functional loss. The 10-2 FDT measures functional loss in the macular area. Placebo-treated eyes declined on the 10-2 FDT test, while citicoline treated eyes did not decline on this measure with long-term follow-up. However, it is unclear how meaningful this effect is, since there were no significant differences between groups on the 24-2 FDT, mean deviation, pattern standard deviation, or mean sensitivity visual field measures. Morphologically, retinal outer plexiform layer thickness, a layer of neuronal synapses, was maintained in the citicoline group, while it declined over time in the placebo group based on optical coherence tomography (OCT) measures. Additionally, citicoline treated eyes did not show the decline in foveal vascular density seen in placebo-treated eyes. Multifocal electroretinogram testing was performed to assess retinal function. Increases in response amplitude densities were observed in 72% of citicoline-treated eyes, while 90% of placebo-treated eyes showed reductions from baseline. This small study adds support to the notion that long-term citicoline administration may modestly slow retinal degeneration in conjunction with other therapies, though due to the combinatorial nature of the eye drops, these effects cannot not be clearly attributed to citicoline.

Peripheral nerve injury and neuropathy: POTENTIAL BENEFIT (Preclinical)
In rat models of sciatic nerve injury, citicoline was reported to increase axon regeneration, improve peripheral nerve conduction, and increase myelination [45; 46; 47]. These studies were conducted by a single lab.
In a male mouse model of cisplatin-induced peripheral neuropathy, citicoline (40 mg/kg i.p.) starting one day prior to cisplatin, mitigated pain based on the latency to withdrawal from a thermal stimulus, attenuated markers of oxidative stress (i.e, reduced MDA and increased total antioxidant capacity), and reduced levels of the pro-inflammatory cytokines TNFα and IL-1β [48]. In a male rat model of oxaliplatin-induced neuropathic pain, intracerebroventricular injection of citicoline (2.0 µmol) starting the second day after oxaliplatin exposure reduced mechanical hyperalgesia [49]. The effect appears to be related to the modulation of cholinergic neurotransmission, since it was blocked by nicotinic receptor antagonists. These studies suggest that citicoline may help protect against the induction of neuropathic pain, but its potential benefit in the chronic phase is unclear.

Safety: Citicoline is widely used and well-tolerated with few-to-no adverse effects, even in multi-year trials. Citicoline shows several fold lower toxicity in animals relative to other supplemental forms of choline.

Types of evidence:

- 1 systematic review of clinical trials in glaucoma
- 2 meta-analyses of RCTs in ischemic stroke
- 1 meta-analysis of clinical trials in traumatic brain injury
- 1 review of clinical studies in dementia patients and healthy adults for cognition
- 1 review on citicoline clinical studies
- Numerous preclinical studies

CDP-Choline is considered one of the safest forms of supplemental choline, as citicoline has been shown to be several fold less toxic relative to choline in animal toxicology studies [3]. In preclinical studies, the intravenous LD_{50} of citicoline is approximately 44 times higher than that of LD_{50} of choline hydrochloride at equivalent doses [1].

There are no serious adverse events reported with citicoline [35]. In fact, in a meta-analysis for cerebral dysfunction in elderly, citicoline treatment had a trend to be more tolerable than placebo [24], and a recent European Food Safety Authority (EFSA) panel suggested that available human data do not suggest safety concerns and it should be considered a novel food ingredient [50].

Citicoline has been tested in clinical trials in a variety of formulations and routes of administration, including intravenous, intramuscular, enteral, oral, and topical. No serious adverse events have been associated with citicoline in any of these forms. Longer-term treatment (up to three years) appears to show a similar safety profile relative to short-term treatment.
In clinical trials testing citicoline for acute ischemic stroke, adverse events were rarely reported, and no differences on measures of cardiovascular events, CNS events, respiratory events, gastrointestinal events, musculoskeletal events, renal events, or hematological events were reported [28]. Safety concerns were not noted in trials of citicoline in TBI [32].
In dementia patients, minor adverse events included gastric intolerance, restlessness, and headache [51]. In healthy older adults, there were mild, transient cases of gastrointestinal events and headache [13].
In glaucoma patients, no citicoline-related side effects were reported with oral, or eye drop formulations over the course of multi-year studies [3].

Drug Interactions:
According to Drugs.com, citicoline has a minor interaction with the dopamine drug, levodopa.

Sources and dosing:

In clinical trials, citicoline has been tested in a wide variety of formulations including intravenous, intramuscular, enteral, oral, and topical. Intravenous administration may be required in the context of brain trauma, such as TBI or stroke, in order to get sufficiently high brain levels. Oral dosing appears to be able to raise choline levels in healthy adults. In clinical trials, long-term administration (>1 year) was generally required to see signs of potential benefit on measures related to neuroprotection.
Citicoline (CDP-choline) is widely available as an oral supplement from many providers. Doses range from 250-1,000 mg/day. Trials in healthy adults typically used doses of 500 mg/day, while trials in patients with neurodegenerative disease typically used doses of 1,000 mg/day. According to the EFSA, the recommended maximum daily dose of citicoline is 500 mg/day for supplements and 1,000 mg/day for medical foods in middle-aged to elderly adults [50].

For ocular conditions, citicoline is also available in the form of eye drops . These products have been registered in Italy and due to licensing agreements, are available in a wide range of countries in the European region.

Research underway:

According to Clinicaltrials.gov, there are active clinical trials testing citicoline in primary open angle glaucoma (oral; NCT05315206), in open angle glaucoma (2% eye drops; NCT05710198), in combination with magnesium and Gingko biloba for chronic open angle glaucoma (oral; NCT04499157), in ischemic stroke (i.v.;NCT05154903), for neuroprotection in neonates exposed to hypoxia (NCT03949049) and preterm (NCT03966170), on sleep and cognition in MCI (oral; NCT06029894) and in Alzheimer's disease (oral; NCT05200208), and Covid-19 with respiratory failure (i.v.;NCT05881135).

Some evidence suggests that citicoline is beneficial in addiction disorders, and it is currently also in clinical trials for youth alcohol disorder (oral; NCT05870111), and amphetamine type stimulant-using adolescents (oral; NCT02630069).

Search terms:
Pubmed:
Citicoline + Alzheimer, dementia, atherosclerosis, longevity, cardiovascular, orthostatic hypotension, osteoarthritis, peripheral neuropathy

Google search: citicoline + safety

Websites visited for Citicoline:

- Clinicaltrials.gov
- Examine.com
- Drugs.com
- WebMD.com
- PubChem
- DrugBank.ca
- ConsumerLab.com

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