

Citicoline: A Novel Therapeutic Agent with Neuroprotective, Neuromodulatory, and Neuroregenerative Properties

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Abstract

Citicoline (cytidine diphosphocholine, CDP-choline) is a novel nutrient with a broad spectrum of benefits for conditions associated with symptoms of neurological dysfunction. An endogenous compound, citicoline is an essential intermediate in the synthesis of cell membrane phospholipids and its formation is the rate-limiting step in phosphatidylcholine synthesis. It plays several important roles in human physiology, including enhancement of structural integrity and signaling for cell membranes, support of acetylcholine synthesis, and synthesis of betaine, a methyl donor. Citicoline provides the brain with a source of choline and cytidine, which are efficiently used in the Kennedy cycle to generate phospholipids. It is able to attenuate the production of free radicals in ischemic conditions, while it also stimulates glutathione synthesis and the activity of glutathione reductase. Studies in animals and humans provide evidence of citicoline's ability to promote learning and memory and improve cognitive impairment in Alzheimer's and Parkinson's disease, as well as in victims of mild to moderate stroke and cerebral ischemia. Citicoline administration may also reduce the duration of coma and the severity of mental and motor deficits associated with traumatic head injuries. Other areas in which benefits of citicoline are supported by the literature include: eye health, mental health, satiety, and substance abuse. Pharmacokinetic studies suggest that citicoline is well absorbed and highly bioavailable with oral dosing. Effective dosing of citicoline based on data from clinical trials ranges from 500 mg to 2,000 mg per day. Based on evidence from several trials and toxicological studies, citicoline is safe for use in pediatric and adult populations.

Introduction

Citicoline (cytidine diphosphocholine, CDP-choline) is a mononucleotide composed of ribose, cytosine, pyrophosphate, and choline. As an endogenous compound, citicoline is an essential intermediate in the synthesis of cell membrane structural phospholipids and its formation is the rate-limiting step in phosphatidylcholine synthesis.

Citicoline is also an exogenous source for acetylcholine synthesis, a key neurotransmitter and a member of the group of molecules that play important roles in cellular metabolism known as nucleotides.¹

First identified in 1955 by Kennedy and colleagues and synthesized in 1956,² citicoline has been studied in Europe, Japan, and the United States for several decades. It is widely available as an approved drug for the treatment of neurological disorders in many countries and is sold as a dietary supplement in the United States.

Citicoline Versus Choline

Choline is a component of the diet and is produced in the brain, albeit in small amounts. Due to its low endogenous production, it is considered an essential nutrient and classified with the B-vitamin complex. It plays several essential roles in human physiology, including enhancement of structural integrity and signaling for cell membranes, supporting acetylcholine synthesis, and synthesis of betaine, a methyl donor.³

When administered, citicoline is hydrolyzed in the intestinal tract and in circulation to form choline and cytidine, which is the nucleoside of cytosine. Citicoline provides the brain with a source of choline and cytidine, which are efficiently used in the Kennedy cycle to generate phospholipids. While choline on its own is preferentially used for the synthesis of acetylcholine, cytidine is very efficiently used in the brain for the synthesis of various nucleotides. Studies in neuronally related cell lines have also shown that cytidine administration increased the incorpo-

ration of choline into membrane phosphatidylcholine.⁴

In terms of safety, choline is a substance with a low level of toxicological concern, and administering choline with cytidine, in the form of citicoline, lowers the toxicity index an additional 20fold.⁵ Furthermore, citicoline administration is significantly different than administration of choline in cases of cerebral ischemia caused by stroke and other conditions. Citicoline's therapeutic effects in such conditions stem from its ability to: 1) increase phosphatidylcholine synthesis, the primary component of neuronal membranes; 2) enhance acetylcholine synthesis, ameliorating the symptoms resulting from ischemic loss of cholinergic neurons; 3) promote the synthesis of several other membrane phospholipids, including phosphatidylethanolamine and phosphatidylserine, leading to repair and regeneration of axons and synapses; and 4) prevent the accumulation of free fatty acids and the generation of free radicals at the site of ischemia, thereby preventing the initiation of a proinflammatory cascade of events.⁵ Thus, citicoline's therapeutic impact extends well beyond that of choline alone for the treatment of neurological conditions.

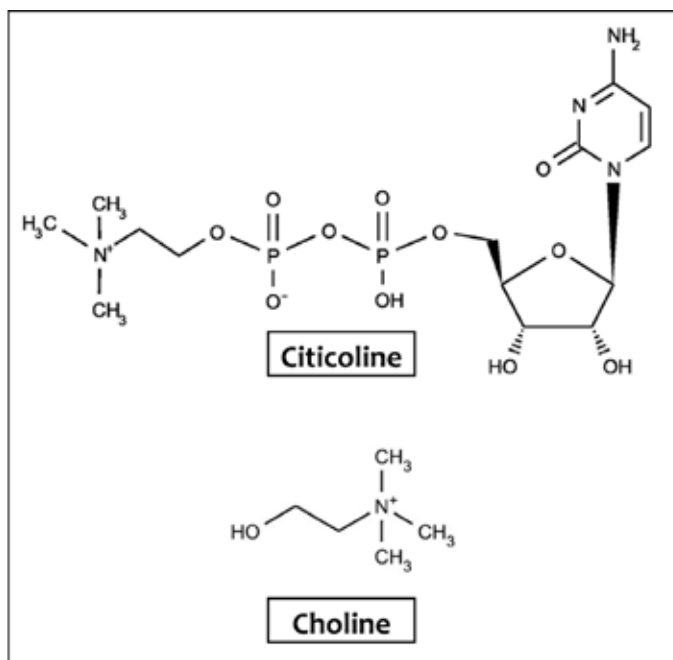


Figure 1. Chemical Structures of Citicoline and Choline

Bioavailability/Pharmacokinetics

The pharmacokinetics of an oral dose of ¹⁴C-labeled citicoline have been studied in humans. Administration of a single 300 mg dose to healthy adults was shown to have a nearly complete absorption, with less than 1% of the labeled compound found in feces following a 5-day collection period. Absorption of citicoline gave rise to 2 chromatographic peaks in concentrations of radioactivity in the plasma, the first at 1 hour, and the second larger peak at 24 hours post-dosing. The main route of excretion was found to be via respiratory CO₂, with significant excretion also occurring through the urine. After 5 days, 16% of the administered dose had been recovered, which suggests that the

remainder had been incorporated into tissues or was available for biosynthetic and biodegradative pathways.⁶

A pharmacokinetic study in rats using ¹⁴C-methyl-labeled citicoline confirmed almost complete absorption with oral administration, with calculated oral bioavailability being approximately 92% of that obtained from intravenous (IV) dosing. The researchers categorized its absorption as slow and complete, with sustained blood levels, the highest being at around 5.5 hours after administration. Radioactive labeling found citicoline and its metabolites to be widely distributed throughout tissues, including distribution of metabolites to the brain, confirming their ability to participate in the synthesis of phospholipids.⁷

A confirmatory study, again using radiolabeled citicoline in rats, found 62.8% of total radioactivity was distributed in brain tissue as phospholipids, including phosphatidylcholine and sphingomyelin. These results suggest that metabolites of orally administered citicoline are available in the brain for resynthesis of endogenous citicoline, which yields significant beneficial effects for the synthesis and incorporation of neuronal cell membrane phospholipids.⁸ While only a small percentage of the total citicoline dose crosses the blood-brain barrier as choline and cytidine, the utilization of these precursors in brain tissue for phospholipid biosynthesis is extremely efficient.⁴

Mechanism of Action

Citicoline has several important mechanisms of action leading to a broad range of beneficial effects on neurological function. In terms of its benefits in cerebral ischemia, citicoline primarily acts by increasing the synthesis of phosphatidylcholine, the primary neuronal membrane phospholipid, and enhancing the production of acetylcholine. Brain phospholipid synthesis is impaired following stroke and ischemic events. Oral citicoline administration increases the plasma levels of choline and cytidine, building blocks used to restore neuronal membrane integrity.⁵

Interestingly, citicoline seems to have differential effects on phosphatidylcholine synthesis in younger versus older adults. Phosphatidylcholine is an essential compound for cell membrane integrity and repair. It is normally reduced in brain cell membranes as a result of aging. A study using protein magnetic resonance spectroscopy to measure brain concentrations of cytosolic choline-containing compounds before and after a single oral dose of citicoline found that the choline resonance in the brain of younger individuals increased, whereas it decreased in older subjects. It is presumed that the cytidine component of citicoline enhanced the incorporation of brain choline into neural cell membrane phosphatidylcholine in older subjects resulting in the decrease.⁹ However, more recent clinical data suggest that uridine and choline, and not cytidine, are the circulating substrates through which orally administered citicoline facilitates an increase in brain membrane phospholipid synthesis. Uridine crosses the blood-brain barrier and is converted to uridine triphosphate. Research also suggests that

uridine may be directly converted to cytidine triphosphate intracellularly.¹⁰

The ability of citicoline to stimulate brain phospholipid synthesis in humans is further supported by studies showing that healthy subjects consuming 500 mg/day orally for 6 weeks (administered as Cognizin® citicoline) showed increased levels of phosphodiesterases in brain tissue, such as glycerophosphocholine and glycerophosphoethanolamine, as assessed by phosphorus magnetic resonance spectroscopy. These findings support citicoline's ability to increase phosphatidylcholine synthesis.¹¹ Findings from a study of healthy middle-aged adults confirm these results but suggest that the increase in phosphorus metabolites attributed to citicoline intake are regionally specific, with the frontal lobe being the preferred site of deposition, ultimately enhancing frontal lobe energetics and improving phospholipid membrane turnover. This area of the brain contributes to memory function by supporting vigilance, attention, and working memory capacity, and by reducing mental fatigue. Since citicoline's effect was most prominent in this brain region, this is a likely explanation for its clinical benefit of improved cognitive function.¹²

Citicoline may further benefit patients experiencing ischemia by decreasing the accumulation of free fatty acids at the site of the lesion, which occurs as a result of neuronal cell damage and death. Soon after the initiation of ischemia, there is a significant increase in proinflammatory arachidonic acid, glycerols, and free fatty acids caused by the breakdown of neuronal membranes. Toxic metabolites as well as prostaglandins, thromboxanes, and free radicals can accumulate, leading to further damage. Animal studies have shown that intracerebral administration of citico-

line prior to induction of ischemia reduces the rise in free fatty acids, arachidonic acid, and other toxic metabolites, attenuating free radical damage and restoring membrane function.⁵

Some evidence points to the ability of citicoline to normalize neurotransmitter release patterns. In conditions of cerebral hypoxia, as exist in ischemia, norepinephrine release may decrease, while the release of dopamine may increase. In several animal models, citicoline has been shown to inhibit the impairment of neurotransmitter release in hypoxic conditions. Furthermore, citicoline administration to rats kept in a chronic hypoxic state reduced behavioral deteriorations and increased survival time. Additional studies have found that citicoline is able to increase the dilation of blood vessels in animals with cerebral microcirculation injury, significantly increasing cerebral blood flow.⁴

Citicoline shows neural restorative effects, presumably via action on the dopaminergic system of the central nervous system (CNS). Rats with substantia nigra lesions have been shown to regenerate nerve cells after treatment with citicoline, indicating its protective effect in this region. Further studies have found that citicoline administration to rats increases striatal dopamine synthesis. Several other investigations in animal models have yielded evidence of citicoline's ability to enhance dopaminergic synthetic pathways—likely through increases in endogenous striatal acetylcholine levels.⁴ This is a result of the activation of tyrosine hydroxylase and inhibition of dopamine reuptake, which is related to citicoline's activity on phospholipid synthetic pathways. Citicoline is also known to have effects on serotonin and norepinephrine.¹³ Studies in rats have shown

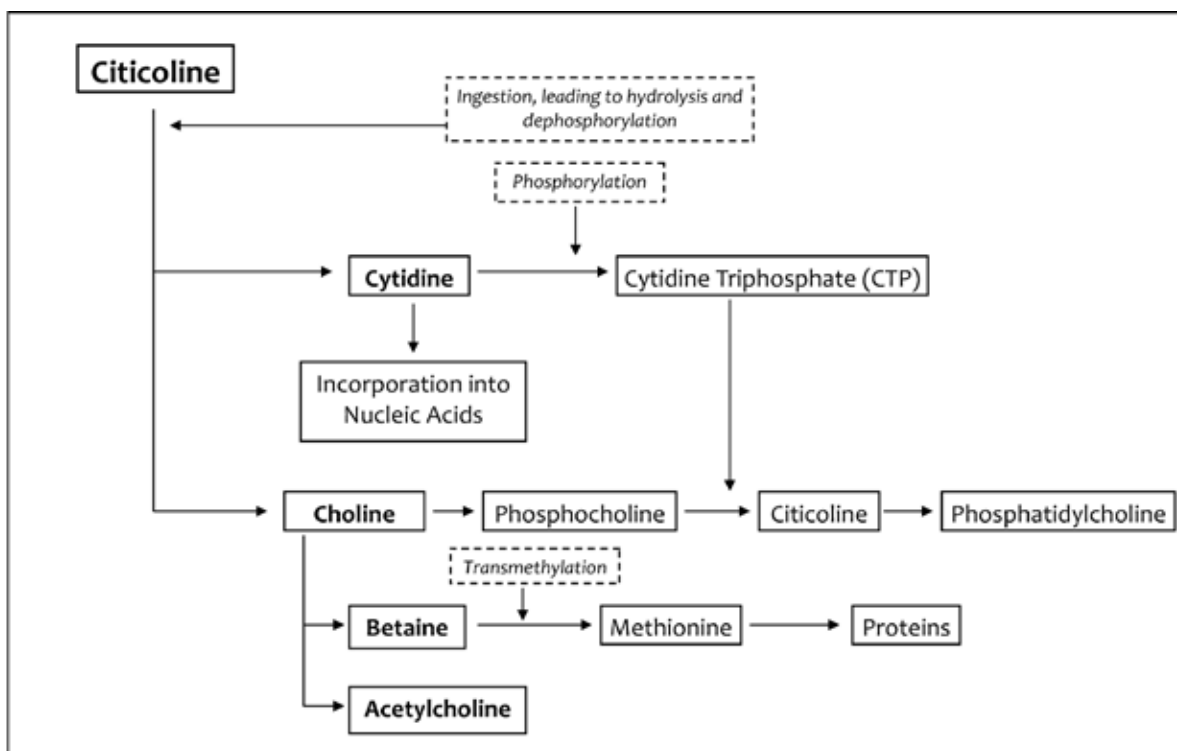


Figure 2. Major Metabolic Pathways for Citicoline
(Based on: Weiss GB, 1995)

citicoline to improve learning and memory capacity in these animals and enhance motor performance and coordination in aged rats. These findings provide further evidence for citicoline's cholinergic activity.¹⁴

Additional mechanisms through which citicoline may promote neuroprotective effects have been highlighted in recent research. Studies suggest that citicoline enhances the preservation of an inner mitochondrial membrane component known as cardiolipin, which is an important regulatory factor for preservation of mitochondrial function. Citicoline facilitates the preservation of sphingomyelin, which promotes signal transduction in nerve cells. Citicoline exhibits direct antioxidant effects, as research shows that it has an ability to stimulate glutathione synthesis and the activity of the enzyme glutathione reductase. Furthermore, citicoline attenuates lipid peroxidation. These downstream effects may be attributable to citicoline's larger function of attenuating the activation of phospholipase A₂, thus reducing inflammation in neural tissues and in general.¹⁵ Citicoline has been shown to have direct free-radical suppressive effects, as seen in animal models of transient cerebral ischemia, where citicoline had a suppressive effect on hydroxyl radical generation.¹⁶

Citicoline may significantly impact brain-remodeling activity. The effects of citicoline on neurological development were investigated in a study in which rats were fed citicoline from conception (maternally) to day 60 postnatally. Citicoline treatment significantly increased the length and branch points of dendrites, increasing the overall surface area occupied by neurons, which leads to an increased efficiency of sensory information processing.¹⁷ This mechanism of activity could potentially account for a significant portion of citicoline's neurorestorative functions.

Clinical Applications

Learning and Memory

Citicoline is an endogenous compound that serves as a precursor for neuronal membrane phospholipids and is an important nutritional substance for supporting learning ability and memory functions. Experiments in animals and humans provide evidence of its ability to promote these important cognitive processes.

Animal Studies

Rats and mice were subjected to a number of standardized methods to assess learning and memory retention following the administration of citicoline orally and by intraperitoneal injection. Administered doses ranged between 10 and 500 mg/kg body weight given once or twice daily for 5 to 7 days. In the step-through maze task, citicoline administered to rats at an oral dose of 20 mg/kg for 5 days prior to training increased step-through latency, indicating an improvement in learning and memory retention. Furthermore, a single oral dose of citicoline (ranging from 10 to 500 mg/kg) given to mice 1 hour prior to training for the step-through task revealed significant effects on memory, increasing step-through latency. Particularly

significant effects were seen at dose ranges between 25 and 500 mg/kg, while the 10 mg/kg dose only showed a trend toward increased memory ability. The drug piracetam was also used as a comparison treatment with citicoline. Piracetam at a dose of 200 mg/kg was shown to be ineffective at improving memory retention; however, a combination of piracetam (200 mg/kg) with citicoline (10 mg/kg) proved to be effective for improving memory. The authors conducted additional experiments in rats using citicoline to assess performance on the step-down platform test. Rats were observed before treatment and grouped as good learners, poor learners, or intermediate learners based on their memory abilities. Citicoline administered at doses of 10 and 50 mg/kg twice daily for 7 days doubled the percentage of rats in the poor-learners group that had managed to master the task of staying on the platform for 60 seconds, while no effect was seen in the good-learners group. In intermediate learners, there was actually a trend toward regression.¹⁸ These experiments show that citicoline enhances cognitive activity; however, certain subgroups of animals were found to benefit from the use of citicoline more than others.

Further evidence of citicoline's memory-enhancing effects comes from a report of studies conducted in healthy young (5 months) and old (22 months) rats and those with scopolamine-induced memory deficits. Similar standardized assessments of learning and memory were used in these studies as in the research highlighted above. Repeated evaluation using these assessment tools following oral administration highlighted citicoline's memory-enhancing effect—particularly in rats with impaired memory function (aged rats and those with scopolamine-induced memory deficits).¹⁹

Teather and Wurtman (2003) conducted additional rat studies to assess the impact of citicoline on memory in young and older rats. Sixteen female Sprague-Dawley rats aged 3 months (young) and 16 female rats aged 15 months (early-aged) consumed a diet containing citicoline (500 mg/kg/day), or a control diet for 8 weeks, and were then trained to perform several versions of the Morris water maze test. Results showed that untreated early-aged rats had significantly higher escape latencies on the water maze test than all other groups, coupled with a considerably lower ability to learn the task than young rats. All but 1 of the early-aged rats supplemented with citicoline performed as well as the young rats on the water maze task, indicating citicoline's ability to improve hippocampal-based memory function. No effect of citicoline on memory was found in young rats. The authors concluded the positive effects likely resulted from citicoline's ability to enhance the production of neuronal membrane phospholipids, conferring a neuroprotective effect. Furthermore, this indicates that chronic supplementation with citicoline may prove to be valuable for delaying the development of cognitive deficits associated with aging.²⁰

The same group performed another experiment in which young rats were raised in distinct environmental conditions: enriched conditions versus impoverished conditions. The enriched conditions included stimulating the rats mentally by

allowing them to play with toys, and rotating new toys among this group to enhance their mental development. These rats were housed in conditions in which they had interactions with their peers. The group of rats raised in impoverished conditions, on the other hand, were kept in isolation for the most part, not given toys to play with, and not stimulated mentally to the extent of the enriched group. These rats were found to develop similar hippocampal-dependent memory deficits to the aging rats in the prior experiment. When the rats in the current experiment were exposed to a citicoline-supplemented diet, the young rats in the impoverished group had improved performance from baseline on the Morris water maze task, indicating a memory-enhancing effect. However, young rats in the enriched-conditions group showed no memory-enhancement effect associated with citicoline supplementation. Again, these findings provide further evidence of one of the major mechanisms of action of citicoline: enhancement of membrane phospholipid synthesis and a subsequent neuroprotective effect.²¹

Human Clinical Trials

Clinical studies evaluating citicoline administration for cognitive enhancement have been conducted dating back several decades. A review of trials utilizing citicoline as a treatment for senile alterations of memory was conducted by de la Morena and published in 1991.²² The results of a trial published in 1979 by Garay and colleagues, which was conducted as an open study regarding the effects of supplementation with citicoline for 30–60 days in 40 senile patients, most with chronic cerebrovascular disease, found that memory deficits either significantly improved or completely disappeared in nearly 50% of participants. A study published in 1986 by Lozano and colleagues evaluated citicoline supplementation in 2,067 patients with neuropsychiatric issues and found that memory deficits diminished in 71% of subjects after 2 months of treatment. A double-blinded placebo-controlled, crossover study performed by Eberhardt and Schurmann in 89 patients with cerebral insufficiency found significant memory improvements following the use of citicoline when assessed clinically and using a labyrinth test and numerical memory assessments. Several other smaller trials in patients presenting with cerebrovascular disease and dementia have shown benefits on cognitive parameters associated with the use of citicoline.²²

A randomized, double-blinded placebo-controlled study was undertaken to assess the effects of citicoline supplementation on verbal memory function in an elderly population. The study consisted of 95 healthy subjects aged 50–85 (47 women and 48 men) who were administered citicoline (500 mg orally twice daily) or placebo for 3 months. The study subjects were well educated, with a mean of 14.3 years of education. Baseline testing included a logical memory assessment test, which was used to classify those with relatively inefficient memories. At the end of the initial study, 32 individuals (16 from the citicoline group and 16 from the placebo group) from this pool were recruited to participate in a follow-up crossover study. The

initial study found citicoline improved delayed recall for only those with relatively inefficient memory at the beginning of the trial. In the follow-up crossover study, the dose of citicoline was increased to 2,000 mg per day. In the subjects with relatively inefficient memory function, the higher dose of citicoline improved immediate and delayed logical memory.²³

The effects of citicoline administration on memory performance were investigated in an open-label crossover trial consisting of 24 elderly individuals without dementia. Subjects were randomly divided into 3 groups of treatment; individuals were assigned to oral citicoline (500 mg or 1000 mg/day), or citicoline (300 mg/day) in conjunction with nimodipine (90 mg/day). Half of the individuals in each group received active treatment for the first 4 weeks and no treatment during the next 4 weeks, while the other half received no treatment the first 4 weeks and active treatment during the next 4 weeks. This design was chosen to control for the potential effects of retest on memory performance. The Mini-Mental State Exam (MMSE), the cognitive component of the Alzheimer's Disease Assessment Scale, and the Syndrome-Kurz test were used to evaluate neuropsychological function at baseline and 4 and 8 weeks later. To demonstrate memory impairment in these elderly subjects, assessments were conducted in 24 young controls with a mean age of 29.20 ± 5.74 years, and the memory scores of each of these 2 age groups were compared. The results showed that citicoline significantly improved memory performance compared to the no-treatment periods, as evidenced by reduced error scores on word recall tasks, immediate object recall, and delayed object recall from day 1–28. Word recognition and object recognition task scores did not register a statistically significant improvement with citicoline treatment. Overall, a beneficial effect for citicoline supplementation on memory function was found in all 3 treatment groups.²⁴

Alzheimer's Disease and Dementia

Citicoline supplementation has been well studied for benefits in Alzheimer's disease and vascular dementia. In one such study, oral citicoline was administered at a dosage of 1,000 mg/day for 30 days to 19 patients with Alzheimer's disease (mean age 66.21 ± 1.48 years). Brain electrical activity mapping was used to determine the effects of supplementation in these individuals. Patients were further subcategorized into early-onset Alzheimer's disease and late-onset Alzheimer's disease. Citicoline was found to significantly improve cognitive function in the early-onset group and trended toward increasing cognitive function in the overall group of 19 individuals. Brain spectral data readings provided an indication that the brains of early-onset Alzheimer's patients show greater damage than those of late-onset Alzheimer's patients, while both groups had the same degree of cognitive impairment. According to the researchers, the therapeutic effects of citicoline may be mediated by an enhancement of cholinergic neural transmission, activation of repair mechanisms to rejuvenate neuronal membranes, a regulatory effect on parameters associated with blood flow and circulation, as well as regulation of several immunological responses

that, if left unchecked, lead to potential neuronal dysfunction and cell death. Interestingly, previous studies by the same group with citicoline found a moderate antidepressant effect in patients with Alzheimer's disease and multi-infarct dementia, stabilization of cardiovascular measures, and a significant reduction of serum IL-1 β levels in individuals with early-onset Alzheimer's. Furthermore, citicoline administration has been found to attenuate hypoperfusion patterns in blood flow to the brain in individuals with senile dementia.²⁵

Further research corroborates several of the potential mechanisms of action attributed to citicoline's cognitive effects. Oral administration of citicoline (1,000 mg/day) to 20 patients (age range 57–78 years) with early or late-onset Alzheimer's disease resulted in improvements in mental function, particularly in early-onset Alzheimer's patients. Furthermore, this 1-month treatment with citicoline resulted in an increased blood flow velocity from baseline measures (assessed by transcranial Doppler ultrasound) in the middle cerebral artery of Alzheimer's disease patients, which has been found to decrease with age, possibly resulting in neuropathological changes. Citicoline's cholinergic effects and influence on cytokine production may also partially account for its benefits in these individuals.²⁶

An interesting line of research has investigated the regulatory effects of citicoline on blood histamine levels. Studies indicate that alterations in the histamine system are present in Alzheimer's disease, as high levels have been found in several CNS regions, cerebrospinal fluid, and serum. Histamine may also participate in the aging process, with histamine-related changes being reported in several different tissues, including the central nervous system. In this study, 14 individuals with Alzheimer's disease (7 early-onset, 7 late-onset) were administered citicoline (1,000 mg/day for 30 days). Blood histamine measurements were taken at baseline, at 2 hours after administration of the first dose of citicoline, and after 30 days of treatment with citicoline. Two hours after taking the first dose, all participants experienced an acute reduction in blood histamine levels compared to baseline. After 30 days of treatment, blood histamine levels decreased from baseline in both groups; early-onset Alzheimer's patients saw a decrease in blood levels of histamine of about 55% at the end of the study compared to baseline, whereas late-onset individuals saw a 45% decrease. It is important to note that early-onset Alzheimer's patients clearly had higher baseline levels of histamine than late-onset patients. The significance of this effect of citicoline for Alzheimer's disease is that it shows citicoline's ability to regulate immune function through mechanisms associated with neuronal membrane repair and phospholipid synthesis. Reducing endogenous histamine excesses may support cognitive function, as excessive histamine levels have been implicated in etiopathogenic events in Alzheimer's disease.²⁷

The effects of citicoline administration (1,000 mg/day orally for 3 months) were assessed in a trial in patients with senile dementia (Alzheimer's disease and multi-infarct dementia) to determine whether the nutrient is able to restore immune func-

tion and improve mental parameters. The study consisted of 4 groups: control subjects (n=8), early-onset Alzheimer's subjects (n=11), late-onset Alzheimer's subjects (n=7), and multi-infarct dementia subjects (n=10). After 3 months of treatment, citicoline supplementation improved mental performance in all groups (including controls), as assessed by several standard assessment tools (including the MMSE and the Hamilton Rating Scale for Depression). Early-onset Alzheimer's patients showed increased levels of IL-1 β at baseline. IL-1 β levels may be correlated with brain damage in Alzheimer's disease. Citicoline administration normalized these levels in the early-onset Alzheimer's group. The researchers concluded that citicoline shows benefit in senile dementia patients as a restorative and palliative treatment, improving vascular risk factors, stabilizing immune function, and improving mental performance.²⁸

A study published in the *Annals of the New York Academy of Sciences* consisted of 19 patients, 13 of whom were categorized as having early-onset Alzheimer's and 6 with late-onset Alzheimer's disease. The researchers investigated citicoline's effects on cognition, brain mapping, cerebrovascular circulation, and cytokine levels. After 30 days of treatment with an oral dose of 1,000 mg/day, the researchers found a trend toward improvement in MMSE scores in the overall study, with statistically significant benefits seen in the early-onset subgroup. There was a slight decline in MMSE scores in the late-onset Alzheimer's disease subtype. Transcranial Doppler ultrasound measurements showed significant improvements in most parameters of cerebrovascular blood flow as a result of citicoline treatment after 1 month. Citicoline also tended to reduce serum IL-1 β levels, while diminishing serum histamine levels in early-onset, but not in late-onset, Alzheimer's disease patients. Brain mapping showed clear-cut changes induced as a result of citicoline administration. As histamine and IL-1 β both may be involved in senile plaque formation, decreasing the levels of both of these immune factors may result in a down-regulation of neurodegenerative activity and tissue destruction.²⁹

Citicoline was further studied in a double-blinded, placebo-controlled randomized trial in 30 patients with apolipoprotein E (APOE) genotyped Alzheimer's disease. All 30 participants were categorized as having mild to moderate dementia. Citicoline (1,000 mg/day orally) or placebo was administered daily for 12 weeks after baseline assessment on the MMSE and the global deterioration scale (GDS), a measure of dementia. The efficacy of citicoline was further evaluated on the basis of each of the individuals' APOE genotype. The significance of APOE genotyping is that some researchers have found greater correlations between the development of certain symptoms and signs of Alzheimer's with differing APOE genotypes. The primary outcome measures of the study included the cognitive function subscale of the Alzheimer's disease assessment scale (ADAS) and the clinical interview-based impression of change (CIBIC). Other measures included brain bioelectrical activity pattern, cerebrovascular blood flow, and circulating levels of histamine and IL-1 β . The results of the study showed that CIBIC

scores worsened significantly in the placebo group, whereas a clear trend toward improvement in the citicoline group was observed. In those individuals bearing the $\epsilon 4$ allele of the APOE (APOE4), citicoline was found to induce significant improvements on the ADAS scale. Furthermore, statistically significant improvements in ADAS scores were found with citicoline administration in the subset of APOE4 patients with mild cognitive deterioration (as assessed by GDS scores <5). Citicoline was found to improve scores on the cognitive subscale of the ADAS compared with placebo; however, this improvement did not reach statistical significance. An overall increase in cerebral blood flow velocity was also seen with citicoline compared to placebo, while beneficial changes were further noted in brain bioelectrical activity. Histamine levels were unchanged in the placebo group or with citicoline treatment; however, IL-1 levels decreased after 4 weeks of treatment with citicoline. Given a greater improvement noted in individuals with milder cognitive impairments, the researchers propose that citicoline may work via non-cholinergic mechanisms, possibly in addition to its cholinergic effects.³⁰

Parkinson's Disease

Given its neuroprotective and neuronal membrane-stabilizing effects, it is expected that citicoline may benefit individuals with Parkinson's disease. Citicoline was administered by intramuscular (IM) injection to 20 patients aged 52–76 years at a dosage of 1,000 mg/day for 15 days, followed by 500 mg/day for an additional 15-day period. All of the patients were receiving levodopa alone or in combination with other drugs before and during the trial. The efficacy of citicoline administration was assessed using several measures, including the Columbia rating scale (one of several validated and reliable rating tools for disability in Parkinson's³¹) time to walk 10 meters, time to turn over in decubitus position, a hand-writing test, a subjective assessment scale, and a scale for dyskinesia. After 30 days of citicoline administration, mean scores on the Columbia rating scale improved by 7.3%, rigidity improved 18.8%, time to walk 10 meters was reduced 17.5%, time to turn over was reduced 37.4%, and handwriting test scores improved 19.7%. Results from the self-assessment revealed that symptomatology was improved in 15 of the 20 patients, which included improvements in speech, gait, posture, tremor, agility, and slowness of movements. Five patients showed minor improvements in dyskinesia; however, this was otherwise unaffected by citicoline treatment.³²

Levodopa is often used in the long-term management of Parkinson's disease; however, prolonged use of levodopa is marked by a progressive decrease in efficacy and the development of dyskinesia and other side effects, which often occur after about 3 years of treatment. Citicoline has been found to have a levodopa-sparing effect and an ability to increase dopamine synthesis. This nutrient was studied in a trial in which 85 Parkinson's disease patients were randomly assigned to 2 groups: patients were to receive either their usual dose of levodopa (mean 381 mg/day) or half their usual dose (mean 196 mg/

day); both groups were simultaneously administered 1,200 mg citicoline (as 400 mg by mouth, 3 times/day). The Webster Rating Scale, a measure of neurologic and clinical symptoms, showed no significant changes in either group. A drawing test was used to evaluate degree of tremor. In the group taking the full levodopa dose plus citicoline, there were no significant changes on this test. However, in the group consuming half of their usual levodopa dose plus citicoline, significant improvements were noted at week 6 (which was the end of the 4th week of citicoline administration). Slight improvements (not statistically significant) were also noted in this group on a writing test designed to detect degree of tremor and on a visual analog scale measuring emotional state. As a result of this trial, researchers concluded citicoline has the ability to compensate for the reduction of levodopa dosage, which could be of significance in reducing side effects associated with long-term usage of levodopa in Parkinson's disease.³³

A similar trial was performed in 30 individuals with Parkinson's disease in which the participants were being treated with levodopa and concomitantly received 500 mg of citicoline by IM injection daily for 30 days. Significant improvements in neurological signs were noted (including moderate improvements in facial expression and digital skill and marked improvements in posture, gait, and ability to rise from a seated position) as well as in certain electrophysiological parameters. A side effect that was seen in this group was an increase in dyskinesia. In the second phase of the trial, the levodopa dosage was reduced by one-third. This restored the incidence of dyskinesia to pretreatment levels, while the therapeutic response remained stable.³⁴ These results confirm that citicoline may increase the efficacy and reduce the dosage requirements for levodopa, improving clinical outcome in patients with Parkinson's disease.

A double-blinded, placebo-controlled trial with a crossover design was performed in which citicoline was administered to patients with Parkinson's disease who were already being treated with levodopa and a dopa decarboxylase inhibitor. A total of 30 participants with a mean age of 62.9 years were administered IM citicoline (500 mg/day) or placebo for 10 days, after which the treatments were crossed over for an additional 10-day period. The Webster Rating Scale and the Northwestern University Disability Scale were used to assess improvement; clinical assessment included ratings for tremor, bradykinesia, and rigidity. Citicoline treatment resulted in improvements in bradykinesia and a 26.97% improvement from baseline on the Webster Rating Scale. This improvement was highly statistically significant compared to baseline and compared to placebo. Significant improvements were also noted in rigidity with citicoline treatment, while no improvement in rigidity occurred with placebo. The improvements noted with citicoline administration in Parkinson's disease seem to be due to the action of citicoline on the dopaminergic system.³⁵ The authors mention 2 previously published studies from the 1970s in Parkinson's patients using citicoline alone. Both of these studies also found the main therapeutic effects of citicoline to be an improvement in rigidity and bradykinesia.

Stroke and Cerebral Ischemia

Citicoline is an essential precursor for the synthesis of phosphatidylcholine. Animal models have shown that citicoline can support brain health in cerebral ischemia by accelerating the resynthesis of phospholipids, thus protecting the integrity of neurons, and by suppressing the degradation of cell membranes to toxic free radicals and free fatty acids. Taking these beneficial effects of citicoline into account, researchers conducted a multicenter double-blinded, placebo-controlled trial to evaluate the efficacy of citicoline administration in patients with acute cerebral infarction. The study consisted of 272 Japanese patients with a confirmed diagnosis of cerebral infarction and a mild to moderate impaired level of consciousness. Patients were randomly assigned to receive citicoline (1,000 mg/day IV) or placebo for 14 days. When assessed at days 7 and 14, citicoline treatment resulted in significant improvements in level of consciousness and neurologic status in acute stroke patients.³⁶

A second trial also yielded positive results with citicoline administration in acute stroke patients. This was a multicenter, randomized trial conducted in the United States (the US Citicoline Stroke Treatment Study) in which initial treatment was to be initiated within 24 hours of stroke onset and continued orally for 6 weeks. Three oral dose groups of citicoline were established, in addition to the placebo group: 500 mg/day, 1,000 mg/day, or 2,000 mg/day. The Barthel Index was used as the primary outcome measure to assess functional improvement. The odds ratio for improvements were calculated by statistical analysis at the end of the study; in the 500 mg/day citicoline group, the odds ratio was 2.0 and in the 2,000 mg/day group the ratio was 2.1, signifying that individuals in these groups were twice as likely to achieve higher Barthel scores than those in the placebo group. Overall, the results showed that citicoline (500 mg/day or 2,000 mg/day groups) significantly improved functional recovery after 6 weeks of treatment compared with placebo, as assessed at the 12-week follow-up visit. Interestingly, the group taking 1,000 mg/day of citicoline did not produce a comparable benefit in this study since this dosage has been found to be effective in prior studies. As the authors stated, this was a puzzling result since all baseline characteristics of each group were essentially identical, except for weight, which was higher in this group than in the other treatment groups. They postulate this may have played a role in the outcome.³⁷

A multicenter, randomized placebo-controlled trial (RCT) was conducted in acute stroke patients given an oral dose of citicoline (500 mg/day) for 6 weeks. The 500 mg dose was chosen because it was proven to be effective in earlier studies. Patients with acute stroke clinically assessed to be in the distribution of the middle cerebral artery, and with NIH Stroke Scale scores of 5 or greater, were enrolled in this study. The primary outcome measure of this trial was also the Barthel Index as assessed at 12 weeks following initiation of treatment. The results of this trial found no benefits for stroke recovery associated with citicoline intake at 500 mg/day, unlike earlier studies. A significant confounding factor may have impacted the analysis. The

authors revealed that there was a baseline imbalance in the stroke severity between treatment and placebo groups despite proper randomization. More participants with milder strokes as assessed by the NIH criteria ended up populating the placebo arm of the study, which likely adversely affected the ability to see a treatment effect of citicoline.³⁸

A larger phase-III multicenter RCT was conducted to assess the effectiveness of high dose citicoline (2,000 mg/day for 6 weeks) for stroke recovery. This study featured recruitment from 118 stroke centers from which 899 patients were randomized to receive citicoline or placebo. Unlike earlier trials that assessed the efficacy of citicoline in moderate stroke patients, this study recruited participants with NIH Stroke Scale scores of 8 or higher, designating more severe strokes. The major endpoint of this trial was a comparison of the proportion of individuals having an improvement of 7 or more points on the NIH Stroke Scale as assessed at week 12. While no significant differences were noted between groups using the NIH Stroke Scale, a benefit was seen for citicoline on the Barthel Index at 6 weeks, as a significantly higher proportion of those in the citicoline group had returned to their baseline function. The authors speculate that given the safety of citicoline, it is possible that an extended treatment period may have yielded additional benefits.³⁹

Hazama and colleagues conducted a double-blinded, placebo-controlled trial in 1980 to assess the impact of citicoline administration in post-stroke recovery from hemiplegia. Citicoline was administered by IV injection to patients who were assigned to one of 3 groups: citicoline high-dose group (1,000 mg/day IV), citicoline low-dose group (250 mg/day IV), or placebo (isotonic saline). Each group received its assigned treatment once per day for 8 weeks while continuing rehabilitative therapy. Upper and lower limb joint range of motion was assessed at intervals throughout the study, as were subjective symptoms, neurological signs, and mental symptoms. The high-dose citicoline group had a 44.4% improvement in functional recovery graded in the upper limb at week 4 and 53.3% at week 8. Recovery in the low-dose group was initially slower but achieved a similar rate by 8 weeks, with improvements of 29.3% at week 4 and 54.8% by week 8. The placebo group did not improve to the same extent, with a rate of 29.3% by week 4 and 31.8% by week 8. No significant differences were noted between groups in the lower limb, although both citicoline groups showed a slightly higher rate of improvement compared to placebo. The higher-dose citicoline group tended to show the greatest improvement at the 8th week. Based on the results of this study, citicoline therapy was deemed to be an effective adjunct to a regular rehabilitation program for promoting recovery of motor activity from hemiplegia. It also seems clear that the higher dose was more advantageous in that recovery was quicker in the high dose group.⁴⁰

Citicoline was evaluated in a study consisting of 92 patients with chronic cerebrovascular conditions. In this placebo-controlled study, 46 patients were randomized to each group.

Individuals received citicoline (1,000 mg/day IM) or placebo for 2 treatment cycles of 4 weeks each with a 1-week interval between cycles. Patient response was evaluated on several psychometric tests measuring memory, behavior, attention, and emotional control. The results of the study showed that citicoline significantly improved attention ability by decreasing the number of wrong responses on the Toulouse-Piéron Test for nonverbal stimuli. Furthermore, a constant and progressive improvement was noted with citicoline treatment on memory tests and on emotional and behavioral assessments.⁴¹

Citicoline's effect on the growth of cerebral ischemic lesions in acute stroke sufferers was measured in a study using diffusion-weighted MRI, which is a useful tool for detecting ischemic injury within minutes after onset. The current study was conducted as a prospective multicenter RCT to investigate citicoline's effects on lesion volume when citicoline therapy was instituted within 24 hours of stroke occurrence. Patients with NIH Stroke Scale scores of 5 or more and who showed an ischemic lesion on diffusion-weighted MRI exam of 1–66 cm³ within the area of the middle cerebral artery were selected. Most patients included in the trial met these criteria; however, the criteria were altered based on the availability of results from a previously conducted citicoline trial. The criteria for enrollment were then changed to include those with an NIH Stroke Scale score of 8 or more, and maximum lesion volume of 120 cm³. Individuals were asked to consume 500 mg of citicoline orally or placebo daily for 6 weeks. Of the 2,300 patients screened for the trial, 100 met the inclusion criteria. Of these, the data from 74 patients who completed the baseline and 12-week scans was included in the analysis. Ultimately, no statistically significant differences were found between the study groups. The citicoline group did however show a larger reduction in lesion volume compared to placebo. The placebo group had a mean percentage increase of 180% in lesion volume over the 12-week period, while the citicoline group showed a mean increase of 34% over the same period. The lack of statistical significance from these results may have been due to a number of factors related to study design, including insufficient power to detect a treatment effect due to the atypically high placebo response.⁴²

Citicoline treatment of patients with hemorrhagic, nontraumatic cerebral infarction has been found to enhance the recovery of muscular strength associated with recuperation. A double-blinded randomized trial conducted with 32 study subjects divided between those receiving 250 mg of IV citicoline twice daily or a placebo for 14 days showed that, compared to baseline, muscular strength in the citicoline group increased significantly more than in the group receiving placebo.⁴³

An editorial published in the *Journal of Neurological Sciences* describes the conclusions from a meta-analysis (published in the journal *Stroke* in 2002), which declared citicoline to be the first clinically effective neuroprotective agent in ischemic stroke. This significant editorial recommends that citicoline be the agent of choice in trials of combination therapy for stroke with thrombolytic agents because of its high level of safety and

efficacy in promoting recovery from ischemic conditions.⁴⁴ Furthermore, a review conducted by The Cochrane Collaboration analyzed the outcomes from several trials utilizing citicoline in the treatment of cognitive and behavioral symptoms resulting from chronic cerebral conditions in the elderly. Researchers ultimately included 14 studies in their review. Their analysis of the overall results from trials that met the specified inclusion criteria revealed that citicoline showed positive benefits for improved memory function and behavior but no benefit on attention in elderly individuals with chronic cerebral disorders. The authors also advocate that longer-term studies be conducted to further elucidate citicoline's benefits.⁴⁵

As is evident from the research summarized above, citicoline has a number of beneficial effects, which can be helpful in significantly aiding recovery from acute ischemic events. More recently, a consensus seems to have emerged that effective approaches for stroke recovery should involve combinations of therapeutics that can act on multiple pathways. Given its efficacy and safety and its broad-spectrum activity as a neuroprotectant, citicoline should be included as an integral part of stroke recovery protocols.

Traumatic Head Injuries

Research into the beneficial effects of citicoline for traumatic head injuries and concussions has been ongoing for several years. Injuries to the brain decrease the production of cell membrane phospholipids, resulting in an accumulation of intracellular water, which leads to cytotoxic edema and possible deterioration of the hematoencephalic barrier. Citicoline can have therapeutic benefits in these conditions, as it is a precursor for the synthesis of neuronal membrane phospholipids. A single-blinded randomized study included 216 patients with severe or moderate head injuries treated either with conventional treatments or IV citicoline (1 g every 6 hours for 2 days, followed by 1 g every 8 hours on the 3rd and 4th days) in addition to conventional therapy. Citicoline resulted in an improvement of symptoms that was superior to conventional therapy alone, with a higher percentage of patients classified with “good recovery” as assessed by the Glasgow Outcome Scale 3 months after injury. Citicoline also showed a trend toward shortening the hospital stay for severe head injury patients while improving motor, cognitive, and mental symptoms.⁴⁶ The authors further cite earlier research on citicoline in treating moderate to severe head injuries, which showed that citicoline increased chances of recovery to a nondependent condition (including the ability to walk and perform activities of daily living), improving their quality of life. Additional research indicates that citicoline improved levels of consciousness assessed at 60 days after injury in traumatic coma patients and reduced the percentage of patients showing focal neurological signs at 60 and 90 days from the time of injury.⁴⁶

Citicoline therapy may also help alleviate postconcussional symptoms. In one such preliminary randomized trial with 14 young adults (median age 25 in the citicoline group and 20 in the placebo group) with mild to moderate head inju-

ries, participants were administered 1 g of citicoline orally or a placebo. After a baseline assessment, patients were given an appointment for a 1-month follow-up. Assessments included tests of memory function, fluency, and attention. While results did not reach statistical significance, the group given citicoline trended toward higher improvement in several categories at the follow-up visit, including improvements in recognition memory, and decreased incidence of headaches, dizziness, and tinnitus.⁴⁷

Several published review articles further examine trials conducted to assess the efficacy of citicoline for the treatment of traumatic head injuries. A review published in the *Journal of the Neurological Sciences* in 1991 reports on trials dating back to 1967 of citicoline in patients with cranial trauma. This particular 1967 study found the benefits of citicoline administration to include the recuperation of neurological signs and symptoms and improvement with the level of consciousness in 70% of participants. Other trials detailed in the review assessing the impact of citicoline on the level of consciousness in patients with traumatic head injuries have shown that citicoline treatment reactivates and accelerates the normalization of consciousness. A double-blind study conducted by Carcassonne and LeTourneau published in 1979 assessed citicoline treatment in 43 children mostly between the ages of 5 and 15 (although 4 children were under 5 years of age) with altered levels of consciousness caused by traumatic injury. They concluded that citicoline significantly accelerated recuperation to normal levels of consciousness, enhanced the disappearance of neuropsychiatric disorders, and facilitated normalization of cerebral electrogenesis, while promoting a better quality of life compared to placebo. Furthermore, citicoline was well tolerated and free of adverse effects, even in this young age group. Several additional trials summarized in this review article point to significant benefits of citicoline treatment for improving recuperation from traumatic head injuries and promoting an earlier recovery of consciousness, enhancing clinical indicators, and leading to electroencephalographic (EEG) improvements. The review paper also highlights several trials related to traumatic coma sufferers treated with citicoline, which led to better recovery of motor function and walking ability compared with placebo. The overall results of these trials indicate that citicoline treatment reduces the duration of coma and the incidence and severity of mental and motor deficits associated with traumatic head injuries. Citicoline was also shown to be safe and well tolerated in patient populations of several age ranges and with many types of traumatic head injuries.⁴⁸

Eye Health and Visual Function

Several trials with citicoline show beneficial effects on eye health, specifically in cases of amblyopia and glaucoma. Amblyopia, or lazy eye, is the leading cause of decreased visual acuity in children, where one eye tends to wander inward or outward, decreasing the efficiency of cooperation between eyes and resulting in poor depth perception. Glaucoma, a group of conditions resulting in damage to the optic nerve, usually as

a result of elevated intraocular pressure, is a leading cause of blindness in US adults.

Amblyopia

An open trial and a pilot double-blinded follow-up study were conducted to assess possible benefits of citicoline therapy in patients with amblyopia. The open trial consisted of 50 patients aged 9–37 years, with a mean age of 16.6 years. A daily dose of 1,000 mg of citicoline was administered for 15 days by IM injection. Visual acuity of both eyes was tested 1 week after the initiation of treatment and continuing at weekly intervals for the first month, and then on a monthly basis for an additional 6–18 months. For the double-blinded portion of the study, 10 patients were divided into 2 groups; one group received citicoline (1,000 mg/day IM) while the other group received placebo. Initial visual acuity measurements occurred 1 week after initiation of treatment and continued weekly for 1 month; monthly follow-up for the double-blinded study was limited to 6 months. Citicoline improved visual acuity in 92% of the patients in the open study. Improvements were noted in both the sound and amblyopic eyes and were highly statistically significant. In the double-blinded study, significant improvements were noted between groups, with the citicoline group showing enhanced visual acuity.⁴⁹

A trial of citicoline was conducted in children with amblyopia aged 5 to 9 years old. Forty-five participants were divided into 3 treatment groups: Group A received 500 mg of citicoline daily via IM injection for 10 days every 6 months; group B received the same routine of citicoline as group A in combination with 1 hour of occlusion (of the sound eye) per day; group C only received daily occlusion therapy. While visual acuity improved in all groups at the end of the treatment period, treatment with citicoline was found to enhance the effect of occlusion therapy. Visual acuity improved in 73% of participants in group A, 86.6% of group B, and 66.6% of group C.⁵⁰

An open-label trial was performed in which oral intake of citicoline plus partial occlusion therapy was compared to occlusion therapy alone. Sixty-one children aged 5–10 years old were randomized into 2 groups: Group A received 800–1,200 mg/day of citicoline according to bodyweight along with 2 hours of daily occlusion therapy; group B received 2 hours of daily occlusion therapy alone. Both groups were treated for 30 days. Follow-up occurred at the end of the treatment period, and again 60 days after treatment was discontinued. While citicoline therapy did not result in greater efficacy than occlusion therapy alone, citicoline contributed to stabilizing the gains obtained during the treatment period when assessed at the 60-day post-treatment follow-up visit. Those receiving occlusion therapy alone showed a decrease in visual acuity gains at the 60-day follow-up, whereas those in the citicoline group maintained the gains achieved with occlusion therapy.⁵²

It seems that citicoline influences improvements in visual acuity in amblyopic individuals due to its ability to stimulate the availability of several neurotransmitters and neuromodulators. It also enhances the activity of endogenous dopamine, while improving vascular aspects of neurological function.⁵¹

Glaucoma

A randomized clinical study evaluating the effects of citicoline in 40 patients with open-angle glaucoma was published in 1999. Patients were divided into a group receiving daily IM injections containing 1,000 mg of citicoline or placebo for 60 days. The citicoline treatment was shown to significantly improve visual evoked potential (a measure of bioelectrical activity of the visual cortex in response to visual stimuli) and pattern-electroretinogram (which is used to evaluate the functional integrity of the innermost retinal layers) parameters compared with placebo. Patients in the citicoline group were then divided into 2 age-matched groups following a 120-day washout period. In one of these groups, the washout period was extended for an additional 120 days whereas the other group received a further 60-day treatment with citicoline. This 2nd group showed additional improvements in visual evoked potential and pattern-electroretinogram parameters, indicating citicoline's ability to enhance the retinal function and visual cortical response in glaucoma patients. The researchers theorize that these improvements may be ascribed in part to the dopaminergic activity of citicoline.⁵³

An additional double-blinded RCT assessing the benefits of citicoline in glaucoma patients confirms that administration of citicoline for 60 day-periods (1,000 mg/day IM) is superior to placebo and significantly improves retinal function and cortical bioelectrical responses. This particular trial included an analysis of 8 years of follow-up data. The investigator of this study supports the use of citicoline in glaucoma patients as a complement to hypotensive therapy.⁵⁴

A review examining the potential mechanisms through which citicoline exerts its beneficial influence in glaucoma patients theorizes that citicoline's ability to enhance the synthesis of phosphatidylcholine and other cell-membrane phospholipids is a major factor. Glaucoma is considered a neurodegenerative disease in which the pathology extends to retinal ganglion cells. Death of these cells is likely a result of apoptotic mechanisms. The enhancement of phosphatidylcholine synthesis as a result of citicoline intake counters the neuronal apoptotic mechanisms associated with glaucoma and confers neuroprotection.⁵⁵

Ischemic Optic Neuropathy

Non-arteritic ischemic neuropathy is an irreversible ischemic event associated with the intraocular optic nerve. The condition occurs acutely and painlessly, yet induces a loss of visual acuity and visual field. In a pilot-study designed to assess citicoline's effect on this condition, 26 patients with at least a 6-month history of non-arteritic ischemic optic neuropathy were divided into 2 groups: one received treatment consisting of oral citicoline (1,600 mg/day) for 60 days, while the 2nd group received no treatment. Following the 60-day treatment cycle, there was a washout period of 120 days. Following this, a 2nd period of treatment with citicoline for 60 days was instituted in the original citicoline group. A 3rd group of 14 age-matched healthy subjects provided control data. At the end of treatment, statistically significant improvements were noted in visual evoked potential, visual acuity, and pattern-electroretinogram param-

eters in the citicoline group compared to pretreatment values, whereas no such changes were observed in the untreated group of non-arteritic ischemic neuropathy subjects. Citicoline thus proved to play a beneficial role in this initial study of individuals with ischemic optic neuropathy.⁵⁶

Substance Abuse

Citicoline has been considered as an adjunct treatment for cocaine dependence by researchers in the field in recent years. The justification for its use stems from citicoline's ability to repair neuronal membranes, which are damaged by cocaine use, and its ability to increase central nervous system dopamine levels, attenuating cravings for cocaine and other substances with abusive potential.⁵⁷

A small double-blinded, placebo-controlled trial was conducted with 14 subjects having a history of cocaine dependence. Individuals with a diagnosis of psychotic, anxiety, or bipolar disorders were excluded from the study. Subjects were assigned to receive oral citicoline (500 mg twice per day for 14 days) or placebo. Assessments at baseline and after treatment included reaction-time performance, mood state, electrophysiological measures, and subjective questionnaires. Citicoline attenuated some measures of cocaine craving and drug use and caused no adverse events in this patient population.⁵⁸

An additional experiment was undertaken to investigate the influence of citicoline pretreatment on cocaine-induced cardiovascular and behavioral effects, and plasma levels of cocaine. Eight healthy adults who used cocaine on an occasional basis participated in this RCT. The study consisted of 3 visits during which participants received an acute intranasal dose of cocaine and were continuously monitored in the laboratory for 3.5 hours. The 2nd and 3rd visits were preceded by a 4-day pretreatment with 1,000 mg of citicoline or placebo. The primary outcome measure was to determine the safety of coadministration of citicoline with cocaine. As citicoline did not adversely impact cardiovascular endpoints associated with acute cocaine intake, the use of citicoline in this patient population is presumed to be safe. Although citicoline did not block the acute subjective effects of cocaine use, cocaine users experience a high incidence of major cerebrovascular events. Thus, the authors speculate that citicoline could play a role in attenuating these undesirable consequences of cocaine use, although further studies are needed to investigate these potential benefits.⁵⁹

Individuals suffering from bipolar disorder are at an increased risk for substance abuse, with cocaine use being particularly common in this condition. Both the disorder and cocaine use are associated with mood symptoms and cognitive deficits. Given these commonalities, a 12-week double-blinded RCT was conducted to assess the impact of citicoline supplementation on individuals with bipolar disorder and cocaine dependence. A total of 44 patients were enrolled in the study. Citicoline or placebo was administered as 1 tablet (500 mg/day) for 1 week, followed by an increase to 2 tablets at week 2, 3 tablets at week 4, and 4 tablets (2,000 mg/day) at week 6. Measures of mood, cocaine use (urine drug screens), and side effects were assessed

every 2 weeks; cognitive function was measured every 4 weeks. The study found that citicoline resulted in an improvement in some aspects of declarative memory. No evidence for antidepressant properties was seen with the use of citicoline. There was a significantly lower probability of a positive urine test for cocaine at the end of the study in the citicoline group. Further studies in this group of patients are indicated based on these initial results.⁶⁰

Infectious Disease

A recently published article highlighted the role citicoline may play as an adjunctive therapeutic agent for the treatment of disease arising from an infectious etiology. The authors describe an overwhelming dysregulation of the host immune response as a major factor in the pathology associated with infectious diseases, including bacterial infections leading to sepsis and parasitic infections such as cerebral malaria, conditions with serious neurological sequelae. While currently available treatments target the infectious agent, they do little to address the concurrent neurological abnormalities. These consequences, if unaddressed, lead to eventual mortality in a high percentage of cases. In the case of cerebral malaria, studies have highlighted cytokine-induced endothelial inflammation and the compromised blood-brain barrier as major pathological factors leading to the associated neurological signs and symptoms. Thus, treating this underlying pathology, rather than just eradicating the infection, becomes important. Ischemia is a large underlying mechanism for damage in sepsis as well as cerebral malaria. Since these underlying issues are similar to conditions such as stroke and myocardial infarction, it is likely that citicoline would yield benefit as an adjunct treatment for sequelae of sepsis and cerebral malaria. As citicoline provides precursors for neuronal membrane repair and has shown efficacy for neurological conditions with manifestations similar to those seen in neurological disorders of infectious origin, its efficacy in such conditions needs to be the subject of future studies.²

Appetite Control and Satiety

Given citicoline's ability to enhance cognitive function, confer neuroprotection and support neuroregenerative effects, and its action to support dopaminergic activity in the brain, researchers investigated the potential of citicoline administration for controlling appetite and promoting satiety. In this particular study, the effect of oral citicoline supplementation (as Cognizin® citicoline, 2,000 mg/day) for 6 weeks were assessed by functional MRI to elucidate cortico-limbic responses to images of various foods, along with subjective ratings of appetite and measures of weight. Sixteen healthy adults with an age range of 40–57 years and a body mass index (BMI) range of 20.1–38.6 were included in the study. Participants were assessed by interview and functional MRI scans at baseline and again 6 weeks later. Participants used a Likert scale to assess their typical appetite. Eight participants were assigned to a low-dose citicoline group (500 mg/day), and the other 8 were assigned to the high dose group (2,000 mg/day). The results of the study indicated

that self-assessment ratings for appetite declined significantly between visits in both groups, with the magnitude of decline in the high-dose group reaching statistical significance. No significant between-group differences were noted for the magnitude of weight change. The high-dose citicoline group also showed higher activation within the right lateral orbitofrontal cortex during visual perception of high-calorie foods than the low-dose group when assessed by functional MRI. This may indicate that high-dose citicoline leads to appetite suppression by increasing the responsiveness of this region to images of calorie-rich foods. There were also greater increases in left amygdala activation with the high-dose of citicoline than with the low dose. Both of these regions are likely involved in promoting feelings of satiation. As these findings are preliminary, the authors recommend further research to more fully investigate the potential effects of citicoline in promoting satiety and reducing appetite.⁶¹

Mental Health

Citicoline's influence on cognitive capacity and neurological health, including modulatory activity on neurotransmitter production and function, make it a logical choice for supporting mental health. A small trial evaluated the effect of citicoline administration in depressed patients. Eight patients with varying types of depressive psychoses were administered citicoline (500 mg/day IM, as 300 mg at 8 AM and 200 mg at 5 PM) for 21 days or longer. On the day preceding the beginning of treatment, plasma growth hormone was measured, levels of which indicated reduced growth hormone secretion in these patients. Treatment was discontinued for 1 study subject after 3 days because of a noted suicidal tendency. Significant improvements were noted for all other participants when assessed using the Hamilton Rating Scale for depression. Mean scores at baseline were 33.87 ± 2.78 , which gradually declined to 4.57 ± 1.913 at the end of the 3rd week of treatment. Although the study was small, the results indicate the potential for significant benefit from citicoline therapy in depressed individuals. Further trials are needed to confirm these findings.⁶²

A preliminary study considered combination treatment of citicoline with galantamine for schizophrenic patients. Evidence suggests that $\alpha 7$ nicotinic choline receptors have decreased functionality in schizophrenia. Citicoline provides choline, which is a known $\alpha 7$ nicotinic choline receptor agonist. Galantamine is a modulator of $\alpha 7$ nicotinic choline receptor function and was used to enhance the efficiency of choline binding to these receptors. Six schizophrenic patients participated in this 12-week open label pilot study. Each participant consumed 2 g of citicoline in combination with 24 mg of galantamine daily, which was titrated upwards during the initial 2 to 4 weeks to reach this dose level. The combination was well tolerated by all of the participants, with transient side effects occurring (all of which resolved within a few days), including gastrointestinal symptoms, restlessness, and syncope. No cardiovascular events or symptoms occurred, with 5 of the 6 participants having lower than baseline diastolic blood pressure readings at the end of the study. Improvements were noted in 5 out of 6 patients when assessed

by scores on the Clinical Global Impressions (CGI) inventory and the Positive and Negative Syndrome Scale (PANSS). Total PANSS scores and CGI-Severity scale scores decreased over the study period, providing encouraging results and suggesting that the combination therapy is potentially effective. Additional studies are needed to corroborate this information.⁶³

Safety and Dosing

Clinical investigations using citicoline have revealed a favorable safety profile with few reports of any major adverse events. The most common adverse reports were related to digestive disturbances. Citicoline has also been found to lack significant adverse events in children, as evidenced by its use in clinical trials with pediatric subjects in the areas of amblyopia⁵⁰ and children with traumatic head injuries.⁴⁸

Citicoline has undergone several toxicological evaluations in multiple animal species and has proven to have a high level of safety. Single-dose acute oral toxicity studies have been performed in mice and rats, with an LD₅₀ of 27.14 g/kg in mice and 18.5 g/kg in rats. Chronic oral toxicity tests in dogs (1.5 g/kg/day for 6 months) and subchronic intraperitoneal dosing studies in rats (1 g/kg/day for 12 weeks) showed no abnormal signs or symptoms.¹³

An acute 14-day study and a 90-day subchronic toxicity evaluation of Cognizin® citicoline in rats revealed that the supplement was well tolerated. In the 14-day study, a single dose of 2,000 mg/kg showed no abnormalities, and in the 90-day repeated oral dosing study, 100, 350, and 1,000 mg/kg/day doses resulted in no mortality in the animals. In male rats, slight increases in serum creatinine were noted in the 2 highest dose groups, while in females, a dose-related increase in renal tubular mineralization was noted and attributed to an increase in phosphorus intake as a result of high citicoline consumption. Mineralization in female laboratory rats of all universally used strains is a common incidental finding as a result of a decreased calcium:phosphorus ratio in the diet. Since citicoline yields a significant amount of phosphorus—thus influencing the calcium:phosphorus ratio—this finding was not unexpected.⁶⁴

A drug surveillance study was recently published examining the efficacy and safety of oral citicoline intake in acute ischemic stroke. The study of 4,191 Korean patients confirmed a high level of safety for citicoline (500–4,000 mg/day for 6 weeks or longer) with an incidence of 37 adverse events in 31 patients (only 0.73% of patients experienced adverse events). Adverse events in all but 1 of these 31 patients showed no relationship to citicoline administration. Thirty-two of the 37 reported events (nearly 84%) resolved over an average period of 9 days after onset. Furthermore, no dose-related effects of citicoline on the occurrence of adverse events were noted. The most frequent side effects included minor nervous system-related complaints (n=8) (numbness, headache, tingling sensations) followed by gastrointestinal symptoms (n=5) (abdominal discomfort, diarrhea).⁶⁵

Effective dosing of citicoline based on data from clinical trials ranges from 500 mg to 2,000 mg per day. Based on evidence from trials in children as young as 5 years of age, citi-

coline is safe for use in pediatric and adult populations.^{48,50} Oral doses of up to 1,200 mg per day have been used in children.⁵² Studies using oral, IM, and IV dosing of citicoline in children and adults, with minimal occurrence of adverse events, affirm its high level of safety.

Conclusions

Citicoline is a novel compound with a very broad spectrum of benefits in conditions associated with symptoms of neurological dysfunction. Citicoline acts at multiple levels to support and maintain neural health and optimal cognitive function. Citicoline promotes cholinergic and dopaminergic functions and supports phospholipid synthesis and incorporation into cell membranes. Citicoline also enhances antioxidant mechanisms in the body, while suppressing the damaging effects of free radicals on neural tissue. It also promotes anti-inflammatory activities and optimizes patterns associated with the release of neurotransmitters. Given its widespread activity on neural tissue, citicoline should be considered as a comprehensive therapeutic agent for supporting brain health.

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