



DOSSIER · SUBSTANCE

Citicolin (CDP-Choline)

Citicolin, also CDP-Choline, is a choline compound with an unusually broad study base. However, the focus of controlled research is not in everyday cognition, but in acute medicine and ophthalmology. The most cited works in the field examine acute ischaemic stroke.

180

STUDIES IN
TOTAL

144

IN HUMANS

85

OF WHICH
CONTROLLED

10

IN ANIMALS

1

IN THE LAB

Figures from the IHR study database · Last updated 2026-10-16

How to Read This Dossier

ESTABLISHED

measured in humans, with a comparison group

PLAUSIBLE

supported by mechanism, animal studies or observation

HYPOTHESIS

a likely connection that still needs to be tested

Citicoline (CDP-Choline) at a Glance

ORIGIN:
Citicoline, also CDP-Choline or Cytidine diphosphocholine, is Cytidine-5'-diphosphocholine, named after its components Cytidine, Diphosphate residue and Choline. Review articles classify the substance among the Choline supplements; [65] lists it alongside Choline alfoscerate (α-GPC), Choline bitartrate and Lecithin as a cholinergic precursor. It is administered orally, and in acute medicine also as an infusion; the database includes works from four decades.

EVIDENCE BASE:
180 evaluated works · 85 controlled human studies · 59 observational studies · 9 review articles · 10 animal studies · 1 cell culture study

- FINDINGS FROM INDIVIDUAL STUDIES:**
- Cognition and psyche: In 30 Alzheimer patients, ADAS scores improved under 1000 mg/day over 12 weeks in APOE-E4 carriers (group difference -3.2 ± 1.8; p < 0.05), more pronounced in mild dementia (p < 0.01) [49].
 - Cognition and psyche: In 60 adults with bipolar depression or major depression and methamphetamine dependence, IDS-C scores improved significantly more under 2000 mg/day than under placebo (n = 28 vs. n = 20) [54].
 - Cognition and psyche: In 44 outpatients with a history of mania or hypomania and cocaine dependence, a significant group effect appeared after 12 weeks on the alternative word list of the RAVLT (P = 0.006) [52].
 - Acute medicine: In a study of 899 patients with acute ischaemic stroke, the proportion with an NIHSS change ≥7 points after 90 days was 51 % under placebo and 52 % under citicoline [25].
 - Safety and tolerability: In [25] and [48] the frequency and type of adverse events were similar between groups; in [54] citicoline was well tolerated and completion rates were higher.

- LIMITATIONS:**
- Several abstracts of the key works ([46], [47], [4], [51], [10]) break off before presenting results; effect estimators and adjusted regression results are therefore not included.
 - In [48] the planned primary analysis failed due to the proportional-odds assumption; the secondary analyses at 90 days showed no group differences, including Barthel Index ≥95.
 - The endpoints are not interchangeable: a changed MRI or electroretinogram marker is not a changed disease course, and a better test score is not a benefit in daily life.

CLASSIFICATION:
Citicoline is a cholinergic precursor with an unusually broad base of controlled studies, whose acute-medicine results have so far shown no difference.

1. What Citicoline Is

Citicoline is Cytidine-5'-diphosphocholine, abbreviated CDP-Choline. The name denotes the components: Cytidine, a Diphosphate residue and Choline. In the literature the substance appears under both designations, sometimes as Citicoline, sometimes as CDP-Choline or Cytidine diphosphocholine; the review articles classify it among the Choline supplements. In the studies it is administered orally — one work already carries “Oral citicoline” in the title — and in acute medicine also as an infusion. The database includes works from four decades, the earliest from the late 1980s. Very different populations were examined: patients with acute ischaemic stroke, with traumatic brain injury, with glaucoma, with Alzheimer dementia, older people without dementia, and patients with bipolar disorder and cocaine dependence.

For understanding all works it is crucial that they measure very different things. Some studies record imaging or electrophysiological parameters: ischaemic lesions on diffusion-weighted MRI, retinal and cortical responses, brain-wave activity and cerebral perfusion. Another group records neuropsychological test results such as verbal memory or scales for functional and cognitive status. These levels are not interchangeable. A changed marker on MRI or electroretinogram is not proof of a changed disease course, and a better test score is not proof of a benefit in daily life. Anyone reviewing the literature must therefore first ask which endpoint was recorded, in which population and at what time after the event.

2. What the Studies Show in Detail

The key human studies and the most important reviews — by indication, with population, duration, preparation, measure and result as reported in the original works. Numbers appear only where the work states them.

Distribution of **controlled human studies** by indication — the numbers are not additive, as one work may be assigned to several areas:

INDICATION	CONTROLLED STUDIES
Cognition and psyche	53
Safety and tolerability	27
Metabolism	13
Musculoskeletal system	5

INDICATION	CONTROLLED STUDIES
Oxidative stress	5
Heart and circulation	3
Fatigue and stress	2
Inflammatory processes	2

Safety and Tolerability

The ICTUS study [46] examined citicolin in moderate to severe acute ischaemic stroke in 2298 patients recruited between 26 November 2006 and 27 October 2011 in 37 centres in Spain, 11 in Portugal and 11 in Germany. Randomisation was 1:1 within 24 hours of symptom onset; the verum group received 1000 mg every 12 hours intravenously for the first 3 days and thereafter orally for a total of 6 weeks (2×500 mg tablets every 12 hours). All participants were blinded. The primary endpoint was recovery at 90 days, measured by a global test of three success criteria: National Institutes of Health Stroke Scale ≤ 1 , modified Rankin Score ≤ 1 and Barthel Index ≥ 95 .

As safety endpoints the study [46] recorded symptomatic intracranial haemorrhage in patients treated with recombinant tissue plasminogen activator, neurological deterioration and mortality. How these three safety endpoints were distributed across the 2298 randomised patients remains open.

Cognition and Psyche

The Citicolin-010 study [2] investigated in a double-blind, placebo-controlled manner whether citicolin limits the growth of ischaemic lesions in acute stroke. Patients with symptom onset ≤ 24 hours before treatment start, NIHSS ≥ 5 and lesions of 1 to 120 cc in the grey matter on diffusion-weighted MRI were included. Citicolin was given at 500 mg/day orally for 6 weeks; follow-up lasted 12 weeks. Of 100 enrolled patients, the primary MRI analysis comprised 40 placebo- and 41 citicolin-treated patients with data at baseline and week 12; it showed no significant difference in lesion-volume change. From baseline to week 12 the lesion volume expanded by 180 % (107) under placebo versus 34 % (19) under citicolin.

The pooled analysis of individual patient data from [47] summarised four randomised, placebo-controlled, double-blind studies of oral citicolin (doses 500, 1000 and 2000 mg). Of 1652 randomised patients, 1372 met the inclusion criteria, 583 on placebo and 789 on citicolin. The primary endpoint was combined recovery (NIHSS ≤ 1 , modified Rankin Score ≤ 1 , Barthel Index ≥ 95 after 3 months).

The COBRIT study [4] was a phase-3, double-blind, randomised trial in 1213 patients at 8 US level-1 trauma centres (20 July 2007 to 4 February 2011). Complicated mild, moderate and severe traumatic brain injuries were examined. The intervention consisted of 2000 mg citicolin or placebo daily for 90 days, enterally or orally. Primary outcomes were function and cognition after 90 days assessed with the TBI Clinical Trials Network Core Battery and evaluated with a global statistical test across 9 scales; secondary outcomes were functional and cognitive improvement at 30, 90 and 180 days as well as maintenance of effects. The published design [11] planned 1292 patients over 32 months at 8 centres with 1000 mg citicolin twice daily and the same endpoint structure.

In a double-blind, randomised, placebo-controlled study in Alzheimer patients [49], 30 individuals (age 73.0 ± 8.5 years; range 57–87) with mild to moderate senile dementia of the Alzheimer type (GDS stages 3–6) were treated after a 2-week wash-out phase with either placebo ($n = 17$; age 73 ± 5) or 1000 mg/day citicolin ($n = 13$; age 76 ± 9) for 12 weeks. In APOE-E4 carriers citicolin improved cognitive performance (ADAS: group difference -3.2 ± 1.8 , $p < 0.05$; ADAS-cog: -2.3 ± 1.5 , ns); in mild dementia (GDS < 5) the effect was more pronounced (ADAS $p < 0.01$; ADAS-cog: -2.8 ± 1.3 , $p < 0.06$).

In older volunteers [10] examined verbal memory. The initial study was randomised, double-blind, placebo-controlled and parallel-group; 47 women and 48 men aged 50 to 85 years were screened for dementia, memory disorders and other neurological problems and received placebo or 1000 mg/day citicolin for 3 months. For a second phase, 32 participants with relatively inefficient memory were recruited and received, in crossover design, 2 months of placebo and 2000 mg/day citicolin each. Delayed recall of a logical story and plasma choline concentrations were measured. Citicolin improved delayed recall only in a subset of subjects; the abstract breaks off before the full subgroup description.

[51] investigated in an open, randomised parallel study whether citicolin prevents cognitive decline after first ischaemic stroke. 347 patients (mean age 67.2 years; 186 men, 56.6 %; mean schooling 5.7 years) were randomised 6 weeks after stroke according to age, sex, education and stroke type and received 1 g/day citicolin or usual treatment without citicolin for 12 months. Neuropsychological tests at 1, 6 and 12 months were summarised into 6 domains (attention and executive function, memory, language, spatial perception, motor speed, temporal orientation). The abstract ends before the adjusted regression results.

[52] tested citicolin as an adjunct in 44 outpatients with a history of mania or hypomania and cocaine dependence in a 12-week, randomised, placebo-controlled, parallel proof-of-concept design. The primary aim was memory; mood and cocaine use were additionally recorded (Inventory of Depressive Symptomatology-Self-Report, Young Mania Rating Scale, Rey Auditory Verbal Learning Test, urine drug screens). On the alternate word list of the Rey Auditory Verbal Learning Test a significant group effect ($P = 0.006$) favouring citicolin was observed; the abstract breaks off at the remaining endpoints.

[54] randomised 60 adults with bipolar depression or major depression and methamphetamine dependence to 2000 mg/day citicolin or placebo for 12 weeks. Mood was assessed with the Inventory of Depressive Symptomatology-Clinician Version, cognition with the Hopkins Auditory Verbal Learning Test, consumption via urine drug screens. In the intent-to-treat analysis the patients treated with citicolin ($n = 28$) showed a statistically significantly greater improvement in IDS-C scores than the placebo group ($n = 20$); time in study was also significantly longer and completion rates higher. No significant differences were found for memory or methamphetamine use; citicolin was well tolerated; the work cites heterogeneity of the sample and small case number as limitations.

Review articles frame these findings. [61] notes that neuroprotective activity has been repeatedly shown in preclinical models of cerebral ischaemia and trauma, yet two large pivotal clinical studies found no benefit in ischaemic stroke and traumatic brain injury; in slowly progressive neurodegenerative diseases such as glaucoma and mild vascular cognitive impairment the substance appears to act. The work concludes that an adequate description of the mechanism of action is currently lacking and suggests examining whether, in addition to the rapid degradation products, the intact molecule or

phosphorylated intermediates (cytidine monophosphate, phosphocholine) are effective. [65] classifies citicoline as a cholinergic precursor. [66] summarises experimental and clinical work on citicoline in retinal ganglion cells and reports anti-apoptotic effects, increased retinal dopamine levels and attenuation of nerve-fibre-layer thinning in the animal model as well as reduced ganglion-cell damage in glaucoma and non-arteritic ischaemic neuropathy. [67] lists citicoline among phase-III candidates with multiple mechanisms of action, [68] places it among potentially neuroprotective substances for glaucoma treatment, and [64] names it among substances that could promote brain repair after stroke. A clinical study that directly addresses the mechanism of action described in [61] as not adequate remains open.

Oxidative Stress

In a 118-centre study [25], 899 patients with acute ischaemic stroke (≤ 24 hours, clinically in the territory of the middle cerebral artery, NIHSS ≥ 8) were randomised double-blind to placebo ($n = 446$) or 1000 mg citicoline twice daily orally ($n = 453$) for 6 weeks, with 6-week follow-up. Mean time to treatment was 13 hours in both groups, mean age 67 years under placebo and 68 years under citicoline. Mean baseline NIHSS scores were 14.5 (placebo) and 13.9 (citicoline; $p = 0.06$), medians 14 and 13 ($p = 0.04$). Frequency and type of adverse events were similar between groups. In the primary analysis no group differences emerged: the proportion with an NIHSS change ≥ 7 points after 90 days was 51 % under placebo and 52 % under citicoline.

A 33-centre study [48] compared placebo ($n = 127$) with citicoline ($n = 267$) at a dose of 500 mg daily orally for 6 weeks in 394 patients, again with 6-week follow-up. Patients with acute (24 hours) ischaemic stroke in the territory of the middle cerebral artery and NIHSS ≥ 5 were included. Mean time to treatment was 12 hours, mean age 71 years (placebo) and 70 years (citicoline). With similar mean baseline NIHSS values the placebo group had a higher proportion with NIHSS < 8 (34 % vs. 22 %; $P < 0.01$). Frequency and type of adverse events were similar. The planned primary analysis (logistic regression, 5 categories of the Barthel Index) failed because the proportional-odds assumption was not met and was rated unreliable; in the planned secondary analyses at 90 days no group differences were found, including Barthel Index ≥ 95 .

The Cochrane review [27] classifies CDP-choline as a precursor of phosphatidylcholine synthesis, a membrane component that is degraded to free fatty acids and free radicals during cerebral ischaemia. Animal experiments suggest that CDP-choline protects cell membranes through accelerated phospholipid resynthesis and suppresses the release of free fatty acids. The authors emphasise that decades of clinical use have led to developments in dose, route of administration and patient selection and that study modalities (observation period, severity of disorder, assessment methodology) were heterogeneous; CDP-choline is a frequently prescribed medication in several European countries for cognitive impairment, especially in predominantly cerebrovascular disease. Which patient selection and route of administration would reverse the absent group differences in [25] and [48] remains open.

Further Investigations

In a randomised clinical study [7], 40 patients with open-angle glaucoma were divided into two age-matched groups: a citicoline group ($n = 25$) and a placebo group ($n = 15$). The citicoline group received 1000 mg/day citicoline intramuscularly (as Neuroton) for 60 days; the placebo group received physiological saline with additives. After a 120-day wash-out phase (day 180) the citicoline group was divided again: in 10 patients (GC1) the wash-out phase was extended by a further 120 days, in 15 (GC2) a second 60-day citicoline treatment followed with a subsequent 120-day wash-out phase; in the placebo group the wash-out phase was extended by 180 days. Retinal and cortical responses were recorded by visual evoked potentials (VEP) and pattern electroretinograms (PERG) at baseline, after 60 and after 180 days; additionally at day 300 in GC1 and at days 240 and 360 in GC2 and the placebo group.

A systematic review with formal meta-analysis [14] identified 10 randomised, double-blind, placebo-controlled studies of citicoline in acute ischaemic stroke. Citicoline administration was associated with a significantly higher rate of independence, independent of the assessment method (odds ratio 1.56, 95 % CI 1.12–2.16 under random-effects; OR 1.20, 95 % CI 1.06–1.36 under fixed-effects). In the subgroup of patients not treated with recombinant tissue plasminogen activator the results were OR 1.63 (95 % CI 1.18–2.24, random-effects) and OR 1.42 (95 % CI 1.22–1.66, fixed-effects); the authors interpret this as confirmation of their hypothesis of dilution of the citicoline effect.

Regarding amblyopia [53] reports preliminary results of an open and a double-blind study. The open study began in 1991; 50 patients with amblyopia beyond the plastic phase of the visual system received 1000 mg/day citicoline intramuscularly for 15 days. Occlusion or other anti-amblyopic treatments were not used concurrently. A statistically significant improvement in visual acuity was found in both the amblyopic and the healthy eye in 46 of the 50 patients (92 %); the improvement remained stable for at least 4 months. A double-blind study in 10 further patients randomised to treatment or placebo over 6 months supported this result. No adverse effects were observed.

In a randomised, double-masked, placebo-controlled, multicentre 3-year study [17] it was examined whether citicoline eye drops in addition to intraocular-pressure-lowering therapy slow glaucoma progression. Mean 3-year progressions were -1.03 (2.14) dB under citicoline and -1.92 (2.23) dB under placebo ($P = 0.07$) for 24-2-MD and -0.41 (3.45) dB under citicoline versus -2.22 (3.63) dB under placebo for 10-2-MD.

A randomised controlled study [18] examined the addition of citicoline to occlusion patching in amblyopia at ages 4 to 13 years. In phase 1 both groups received patching therapy until plateau. In phase 2 group I received citicoline plus patching, group II continued with patching only. Visual acuity was measured monthly in logMAR, in phase 1 until plateau and thereafter for 12 months. In phase 1 no significant difference in mean visual acuities appeared until plateau. In phase 2 no significant difference existed in the first four months, but from the fifth to the twelfth month a significant difference did. The result was the same in younger (< 7 years) and older (> 7 years) patients. Mean proportional improvement was significantly greater in group I than in group II from two months onward.

47 eyes completed the study: 24 eyes received topical citicoline (OMK1®, Omikron Italia, 3 drops/day) for 4 months followed by a 2-month wash-out phase; 23 eyes were treated with beta-blocker monotherapy only. Pattern electroretinogram and VEP were recorded at baseline and at month 4 and month 6. After treatment a significant increase in PERG-P50-N95 and VEP-N75-P100 amplitudes as well as a significant shortening of VEP-P100 latencies (each $p < 0.01$) were observed; the shortening of VEP-P100 latency correlated significantly with the increase in PERG-P50-N95 amplitude ($p < 0.01$). After the 2-month wash-out phase the values were again similar to baseline. Whether the visual-acuity and electrophysiology effects observed in [7, 17, 18, 53, 63] reach clinical endpoints and whether topical administration reaches the ocular fundus sufficiently remains open.

Inflammatory Processes

A review [30] describes how inflammatory cytokines such as tumour-necrosis-factor-alpha and interleukin-1 activate phospholipase A2 and phosphatidylcholine-specific phospholipase C and thereby hydrolyse phosphatidylcholine. Hydrolysis releases free fatty acids including arachidonic acid as well as lyso-PC, an inhibitor of CTP-phosphocholine cytidylyltransferase; arachidonic-acid metabolism via cyclo-oxygenases and lipoxygenases is a major source of reactive oxygen species. TNF-alpha also stimulates proteolysis of CCT. The authors formulate the hypothesis that the favourable effects of CDP-choline may rest on counteraction against TNF-alpha- or interleukin-1-mediated processes — **Hypothesis:** supported by the mechanism description, not by direct cytokine measurement in this work. The substance is classified as non-xenobiotic, safe and well tolerated; a re-evaluation of the phase-III data is described as encouraging.

A review article [69] classifies citicoline alongside coenzyme Q10 as neuroprotective, antioxidant and anti-inflammatory and summarises studies of the past 10 years on eye diseases such as glaucoma, diabetic retinopathy and age-related macular degeneration. A measurement of the cited cytokines and oxidation markers under citicoline in humans that directly tests the mechanism from [30] remains open.

Heart and Circulation

In a study with a randomised crossover design [60], 12 mildly hypertensive, otherwise healthy fasting subjects received orally 500, 2000 or 4000 mg CDP-choline or a placebo at 8:00 a.m. on four different treatment days in random order. Eleven plasma samples per subject were examined for choline, cytidine and uridine immediately before treatment and 1 to 12 hours thereafter; the fasting interval ended at midday with a light lunch containing approximately 100 mg choline. Plasma choline rose in a dose-dependent manner in peak values and areas under the curve and remained significantly elevated after the three doses for 5, 8 and 10 hours respectively. Plasma uridine was significantly elevated after all three doses for 5 to 6 hours, by up to 70–90 % after the 500-mg dose and by 100–120 % after the 2000-mg dose; increasing from 2000 to 4000 mg produced no further rise. Plasma cytidine was not reliably detectable, as it was below twice the blank value or below 100 nM at all doses. In neuron-specific PC-12 cells, uridine was directly converted to CTP; whether this cell finding applies to humans has not been investigated.

It remains open whether the choline and uridine levels measured in [60] explain the central effects described in the clinical studies and whether the kinetics also apply to older or pre-diseased persons; 12 mildly hypertensive, otherwise healthy subjects were investigated.

Oncology

An overview article [62] on the cholinergic nervous system in glaucoma describes citicoline as a naturally occurring compound and as a nootropic and lists putative mechanisms of action: preservation of cardiolipin, sphingomyelin and arachidonic acid contents of phosphatidylcholine and phosphatidylethanolamine, restoration of phosphatidylcholine, stimulation of glutathione synthesis, lowering of glutamate concentrations and prevention of glutamate excitotoxicity, rescue of mitochondrial function and prevention of oxidative damage and neuronal apoptosis, myelin synthesis and improvement of neuronal membrane integrity, improvement of acetylcholine synthesis and reduction of mental stress as well as prevention of endothelial dysfunction.

The work [62] does not examine oncological endpoints but classifies citicoline as neuroprotective. It therefore remains open whether and with what design citicoline should ever be tested on tumour-related questions; this is not provided for in the present literature.

Viral Infections

An overview article [70] discusses possible anti-inflammatory and antioxidant effects of citicoline in the context of COVID-19. According to the authors, SARS-CoV-2 infections are accompanied by neurological manifestations that arise through cytokine-mediated disruption of the blood-brain barrier, neuroinflammation and peripheral nerve damage or through direct neurotropism. The work places citicoline in the search for new active substances against SARS-CoV-2.

The overview [70] contains no own clinical trial in COVID-19 patients; the authors describe the efficacy of implemented active substances against SARS-CoV-2 as not sufficiently proven. A controlled study on citicoline in COVID-19 with measurable inflammation and course endpoints remains open.

Overall Picture

Across all areas, the large randomised acute-stroke studies mainly support the statements on tolerability: in [25] the frequency and type of adverse effects were similar between citicoline and placebo, in [54] citicoline was described as well tolerated, in [53] no adverse effects occurred, and [30] classifies the substance as non-xenobiotic, safe and well tolerated. At the same time, efficacy in acute stroke and traumatic brain injury is at the beginning: in [2] no significant difference in lesion-volume change was shown, in [25] no difference in the primary endpoint (51 % vs. 52 %), and [61] refers to two large pivotal studies without benefit. In contrast, the meta-analysis [14] shows a higher rate of independence (OR 1.56 under random-effects) as well as the eye studies [7, 17, 18, 53, 63] with improvements in visual acuity and VEP or PERG parameters.

The cognitive and psychiatric effect is inconsistent: in [49] citicoline improved ADAS scores in APOE-E4 carriers, in [54] IDS-C scores, while the memory effect in [52] was significant only on the alternative word list and in [10] occurred only in a subset of subjects. Open questions concern the mechanism of action, which [61] describes as not adequately characterised, the transition from the choline and uridine levels measured in [60] to the clinical effects, and the question whether trophic or neuroprotective effects predominate in the eye diseases. **Plausible:** that the recurring findings on the retina and visual pathway represent a testable, independent area of action.

Methodology of the Study Situation

The controlled human studies comprise randomised, double-blind, placebo-controlled designs with treatment durations of 6 weeks to 12 months. Frequent endpoints are functional and cognitive scales (NIHSS, modified Rankin Score, Barthel Index, TBI Core Battery), electrophysiological parameters (VEP, PERG) and imaging (DWI, lesion volume), rarely biochemical markers such as choline, uridine and cytidine [60]. Direct tests of the mechanism of action and independent replications in the small populations of the cognition and eye studies as well as controlled data on COVID-19 [70] remain open.

Citation Strength and Application Proximity Diverge

In everyday life citicoline is mainly marketed as an agent for concentration and memory. The citation lists tell a different story. The most frequently cited works in the field deal with acute ischaemic stroke and traumatic brain injury, i.e. emergency situations with a narrow time window. Ophthalmology constitutes a second, independent strand. Although cognitive research is numerically the largest application area, its works rank behind the acute studies in the citation order. Anyone who infers from the stroke literature an effect in healthy or mildly impaired adults is transferring findings between populations for which they were not obtained.

The second point concerns the endpoints. A considerable proportion of the works measure quantities that lie between metabolism and clinic: lesion volume on MRI, retinal and cortical responses, brain electrical activity, perfusion. Such values can change without the course of the disease changing. Conversely, a functional endpoint can improve without a marker moving. The 2016 meta-analysis and the overview article on choline supplements do not eliminate this separation.

HYPOTHESIS:

Part of the heterogeneous findings is explained by the fact that different studies answer the same question with different measurement instruments.

3. How Reliable the Research Is

The controlled human studies are distributed unevenly. Cognition is by far the most frequent application area, followed by safety and metabolism. Thereafter come small groups: musculoskeletal system, antioxidant questions, cardiovascular system, fatigue, inflammation as well as individual works on intestine and bone. The most strongly cited works, however, almost all belong to stroke research: the international multicentre ICTUS study, the phase-III trial, the pooled evaluation of individual data from several studies and the COBRIT study on traumatic brain injury. A second strand lies in ophthalmology, where works on glaucoma and retinal ganglion cells are available. The observational studies supplement this picture with overviews on stroke and other diseases of the central nervous system.

Methodologically the field is in a better position than the heterogeneity might suggest. There are randomised, double-blind and placebo-controlled studies, several multicentre trials, a formal meta-analysis of randomised placebo-controlled works on acute ischaemic stroke and systematic overviews. At the same time it is noticeable that among the most frequently cited works of the entire field there is an animal-experimental study, namely a study on intracerebral haemorrhage in mice. Preclinical works therefore stand here on an equal footing with clinical ones. It is further striking that the authors of several stroke studies have pooled the individual data — an indication that individual trials could not decide the question on their own. **Plausible:** The dispersion of endpoints makes summarisation more difficult than the number of studies. What remains to be clarified is which endpoints permit a joint evaluation at all.

4. What Is Frequently Claimed — and What the Data Provide

STATEMENT	STUDY SITUATION
Citicoline as a nootropic for healthy adults	Controlled studies on cognition do exist, though predominantly in clinical populations: older adults, chronic cognitive impairments and post-stroke states. A 1996
Acute ischaemic stroke	Here lies the densest evidence: several randomised, placebo-controlled studies, a multicentre examination and a formal meta-analysis. The studies measure lesi
Glaucoma and retinal diseases	A placebo-controlled study from 1999 reports improved retinal and cortical responses in glaucoma patients. These are electrophysiological markers, not visual fi
Traumatic brain injury	The COBRIT study examined functional and cognitive status after traumatic brain injury; a separate paper describes design and methodology. Thus the field has

5. Profile: Molecule and Charge

Citicolin (CDP-Choline) is not a single molecule, but a **mixture** — there is no molecular formula and no fixed molecular mass. What can be described are functional groups, charge behaviour and redox properties; that is exactly what the next section is about.

6. Charge, Electrons, Radicals

The available evidence provides no information on charge, cation exchange or electron transfer of citicolin (cytidine-5'-diphosphocholine, CDP-choline) ⁵⁶²⁴. A different process is described: citicolin is said to be a precursor for the synthesis of phosphatidylcholine, a membrane component that is broken down into free fatty acids and free radicals during cerebral ischaemia ⁸²⁸. Citicolin may reduce ischaemic damage in the CNS by stabilising cell membranes and decreasing the formation of free radicals ⁵⁶²⁴. Hypothesis: these sentences appear as background assumptions in the introductions of the studies and not as efficacy statements tested there.

Radical processes observed in humans appear only indirectly: the metabolism of arachidonic acid by cyclooxygenases and lipoxygenases is considered a significant source of reactive oxygen species ²⁶, and during ischaemia phosphatidylcholine is broken down into free fatty acids from which free radicals arise that exacerbate ischaemic damage ²⁷. Animal studies suggest that citicolin protects membranes by accelerating the resynthesis of phospholipids, suppressing the release of free fatty acids and lowering radical formation ²⁸. Radical-scavenger strategies have been tested in animals and humans with contradictory results ²⁵. It remains to be examined whether redox markers can be measured directly under citicolin in humans.

7. Interactions with Other Substances

With which other substances on the platform this substance has been jointly investigated or discussed in human studies and reviews — combination, comparison or shared mechanism of action. The number indicates studies in which both appear.

SUBSTANCE	SHARED STUDIES	OF WHICH CONTROLLED IN HUMANS
Cognitive Behavioural Therapy for Insomnia (CBT-I)	44	26
Art Therapy	21	12
Chronic Inflammation	12	2
Stress, Cortisol and Inflammation	9	1
High-Intensity Interval Training (HIIT)	8	5
Palmitoylethanolamide (PEA)	6	4
Acupuncture	4	4
Adaptogens	3	0
Coenzyme Q10	3	1
Ginkgo biloba	3	2

Combinations with other substances are described in particular. In a controlled human study, glaucoma patients received vitamin C, DHA, citicolin or DHA plus citicolin for 3 months; only the DHA+citicolin group showed a statistically significant improvement in MD (p = 0.006, from -0.1041 ± 0.2471 to 0.1383 ± 0.2544 dB/month) and VFI slope ^{29 29}. Another human observation examined a fixed combination of citicolin 500 mg, homotaurine 50 mg and vitamin E 12 mg in mild primary open-angle glaucoma ³¹. In a controlled 2020 study, citicolin was administered orally, intravenously or in combination and compared with placebo or standard therapy ²³.

Human observations also list citicolin alongside NMDA- and AMPA-receptor antagonists, clomethiazole, antioxidants, nitric oxide and immunoregulators as part of historical research ³⁰. The evidence sentences provide no information on absorption, CYP enzymes or binding. Citicolin is described as a combination of cytidine and choline and is marketed as a food supplement ³². It remains to be examined whether the combination findings in humans are attributable to citicolin alone and how simultaneous administration with other substances affects absorption and metabolism.

8. Overdose, Tolerability, Limits

Citicolin has repeatedly been described as well tolerated in controlled human studies. Safety variables did not differ from placebo in the ICTUS study ¹; tolerability after oral administration within 24 hours of stroke onset was likewise comparable to placebo ³. Safety was also explicitly recorded during long-term use for the prevention of cognitive decline after stroke ¹².

The evidence provides no information on overdose, toxicity or upper limits; a dose-finding study is still outstanding. Reported adverse effects remained low: 10.5 % under citicolin and 10.9 % in the control group discontinued treatment, 4 persons (2.3 %) experienced adverse effects without discontinuation ¹². Serious adverse events occurred in 4 patients per group ²¹. Other studies found no differences in adverse effects ³³ and no discontinuations due to adverse effects ¹³; citicolin was well tolerated and adherence was high ³⁴. None of the evidence sentences mention contraindications. Which persons should be excluded from treatment remains to be clarified.

9. The Most Robust Studies

Ordered by strength of evidence, not by familiarity. The complete evaluation comprises considerably more studies; the most robust ones are listed here.

Controlled Studies in Humans

- ¹ Citicoline in the treatment of acute ischaemic stroke: an international, randomised, multicentre, placebo-controlled study (ICTUS trial) (2012)
- ² Effect of citicoline on ischemic lesions as measured by diffusion-weighted magnetic resonance imaging. Citicoline 010 Investigators (2000)
- ³ Oral citicoline in acute ischemic stroke: an individual patient data pooling analysis of clinical trials (2002)
- ⁴ Effect of citicoline on functional and cognitive status among patients with traumatic brain injury: Citicoline Brain Injury Treatment Trial (COBRIT) (2012)
- ⁵ A phase III randomized efficacy trial of 2000 mg citicoline in acute ischemic stroke patients (2001)
- ⁶ A randomized efficacy trial of citicoline in patients with acute ischemic stroke (1999)
- ⁷ Cytidine-5'-diphosphocholine (citicoline) improves retinal and cortical responses in patients with glaucoma (1999)
- ⁸ Cytidinediphosphocholine (CDP-choline) for cognitive and behavioural disturbances associated with chronic cerebral disorders in the elderly (2005)
- ⁹ Double-blind placebo-controlled study with citicoline in APOE genotyped Alzheimer's disease patients. Effects on cognitive performance, brain ... (1999)
- ¹⁰ Citicoline improves verbal memory in aging (1996)
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- ¹² Long-term treatment with citicoline may improve poststroke vascular cognitive impairment (2013)
- ¹³ A randomized, placebo-controlled trial of citicoline add-on therapy in outpatients with bipolar disorder and cocaine dependence (2007)
- ¹⁴ Citicoline for Acute Ischemic Stroke: A Systematic Review and Formal Meta-analysis of Randomized, Double-Blind, and Placebo-Controlled Trials (2016)
- ¹⁵ Effect of citicoline on visual acuity in amblyopia: preliminary results (1995)
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10. Summary

In humans there is a broad controlled basis: randomised, double-blind, placebo-controlled studies, several multicentre trials as well as a formal meta-analysis of randomised placebo-controlled studies on acute ischaemic stroke. The results of acute medicine have so far shown no difference: In [25] 51 % under placebo and 52 % under citicoline showed an NIHSS change of ≥ 7 points after 90 days, in [48] the secondary analyses revealed no group differences. Two large pivotal clinical studies found according to [61] no benefit in ischaemic stroke and traumatic brain injury, while the neuroprotective activity in preclinical models of cerebral ischaemia and trauma has been repeatedly demonstrated.

PLAUSIBLE The dispersion of endpoints complicates the summary more than the number of studies; imaging, electrophysiological and neuropsychological measures are not interchangeable. Positive findings in humans have so far come from small populations: [54] with 60 adults, [52] with 44 outpatients, [49] with 30 Alzheimer patients, in whom citicoline improved ADAS scores in APOE-E4 carriers. **Hypothesis:** If the benefit is sought not in acute medicine but in defined subgroups such as APOE-E4 carriers, mild dementia or patients with substance use disorders, the choice of endpoint could determine the outcome of future trials.

What remains open after [61] is a clinical trial that directly addresses the mechanism of action described as inadequate: whether, in addition to the rapid degradation products, the intact molecule or phosphorylated intermediates such as cytidine monophosphate and phosphocholine are effective. After decades of clinical use, the question of dose, route of administration and patient selection is also not closed [27]. Finally, it remains to be clarified which endpoints allow a joint evaluation at all and which population could support a trial with a uniform endpoint.

11. What Remains Open

- **Endpoints:** Which functional endpoints would have to be chosen so that marker findings and disease course can be distinguished at all?
- **Transferability:** Can anything be inferred from the acute stroke studies about cognitive performance in non-acutely ill adults?
- **Long-term course:** The 2013 study on vascular cognitive impairment after stroke is cautiously worded in the title. Which controlled study examines a longer treatment duration?

12. Further Paths

Topics, pathways and chains in which this substance occurs — for all those who wish to look beyond the substance.

- Interaction network

Frequently Asked Questions

What do the studies on citicoline actually measure?

Very different things. One part records imaging and electrophysiological parameters such as lesion volume in diffusion-weighted MRI, retinal and cortical responses or brain wave activity. Another part records neuropsychological tests and scales for functional status. Both levels are to be read separately: A marker is not a course measure, a test value is not everyday benefit.

For which application areas is the data situation the broadest?

For acute ischaemic stroke, measured by citation strength and study form, and for cognition, measured by the number of controlled works. Safety is the second most common application area of the controlled studies. In addition, there are smaller fields such as metabolism, musculoskeletal system, cardiovascular and exhaustion, partly with only individual works.

How is safety investigated?

Safety is a separate, frequently addressed application area of controlled research. The tests were predominantly carried out within the framework of clinical studies on patients, that is on sick and not on healthy persons. Statements on tolerability with long-term intake by healthy people can only be derived to a limited extent from this.

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International Health Research

Research, put in context. Every statement leads to the original paper; the decision in the individual case rests with the treating professional.
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