Citicoline: pharmacological and clinical review, 2022 update

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Summary. This review is based on the previous one published in 2016 (Secades JJ. *Citicoline: pharmacological and clinical review*, 2016 update. Rev Neurol 2016; 63 (Supl 3): S1-S73), incorporating 176 new references, having all the information available in the same document to facilitate the access to the information in one document. This review is focused on the main indications of the drug, as acute stroke and its sequelae, including the cognitive impairment, and traumatic brain injury and its sequelae. There are retrieved the most important experimental and clinical data in both indications.

Key words. Alcoholism. Alzheimer disease. Amblyopia. Apoptosis. CDP-choline. Cerebral edema. Cerebral ischemia. Citicoline. Cognitive disorder. Drug addiction. Glaucoma. Head injury. Memory. Neuronal membrane. Neuroplasticity. Neuroprotection. Neurorepair. Neurotransmission. Parkinson disease. Phosphatidylcholine. Phospholipase. Remyelination. Senile dementia. Stroke. Structural phospholipids. Traumatic brain injury.

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Introduction

Phospholipids are essential constituents of cells, specifically cell membranes, and have a very high turnover rate, which involves a continuous synthesis of these compounds to ensure adequate function of cell membranes, and thus cells [1-3].

The chemical structure of a phospholipid shows esterification of a polyalcohol (glycerol or sphingosine) with two long-chain fatty acids and a molecule of phosphoric acid that is in turn esterified with nitrogenated bases (choline, ethanolamine), amino acids (serine), or inositol [3,4]. The main phospholipids in humans are phosphatidylcholine, phosphatidylethanolamine, phosphatidylinositol, and sphingomyelin [4]. The major phospholipid present in most eukaryotic membranes is phosphatidylcholine (PC), comprising ~50% of phospholipid content [5]. The main function of the phospholipids is to be part of cell membrane structures, and these compounds are indispensable to fulfil membrane functions, particularly maintenance of homeostasis and cell compartmentalization, as well as enzymatic activities associated to membrane systems, and coupling between receptor and intracellular signal [1]. Thus, phospholipid plays a pivotal role in regulating physiological functions and maintaining cellular membrane structures [6], also serves as a source of several lipid mediators [7] and orchestrates humoral immunity, highlighting the metabolic control of context-dependent immune signaling and effector programs [8]. Additional specific functions of the neuronal membrane include nerve impulse conduction and neurotransmission [1,9].

There are various conditions in which a phospholipids loss or decreased synthesis occurs, leading to an impairment in cell functions that may have a pathophysiological impact [1,10]. At central nervous system levels, structural phospholipids of the neuronal membrane are essential for adequate brain maturation [11-14], including astroglial cells [15]. Phosphatidylcholine has been proposed as an important molecule for neurite growth and neuronal regeneration [16]. Impaired cell membrane and phospholipid metabolism have been implicated in the pathophysiology of cerebral edema and traumatic brain injury [17-26], as well as cerebral hypoxia [27,28] and cerebral ischemia [29-42]. Moreover, it has been shown that there are certain changes in neuronal membranes and metabolism of structural phospholipids associated to brain aging [43-45] and certain neurodegenerative diseases such as cognitive impairment, vascular dementia and senile dementia of the Alzheimer type [39,46-58], contributing to the neuroplasticity mechanisms [59], and in other conditions where changes in neurotransmission [60-63] and excitotoxic aggression [64,65] are also involved. Changes in phospholipid metabolism, particularly phosphati-

Figure 1. Chemical structure of CDP-choline (citicoline).

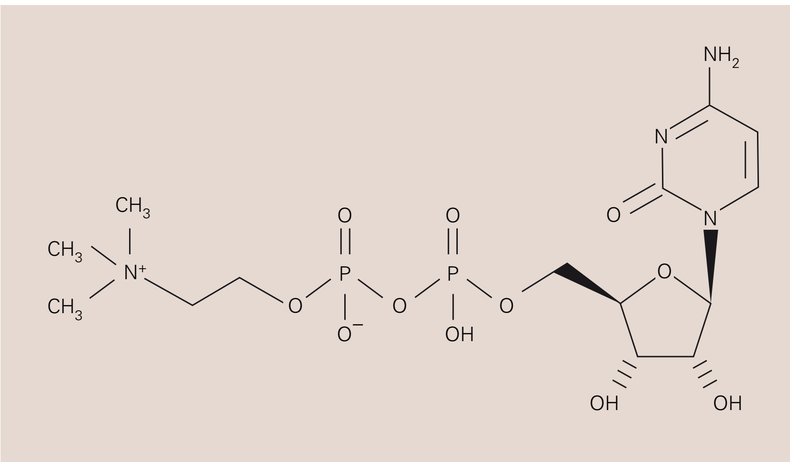
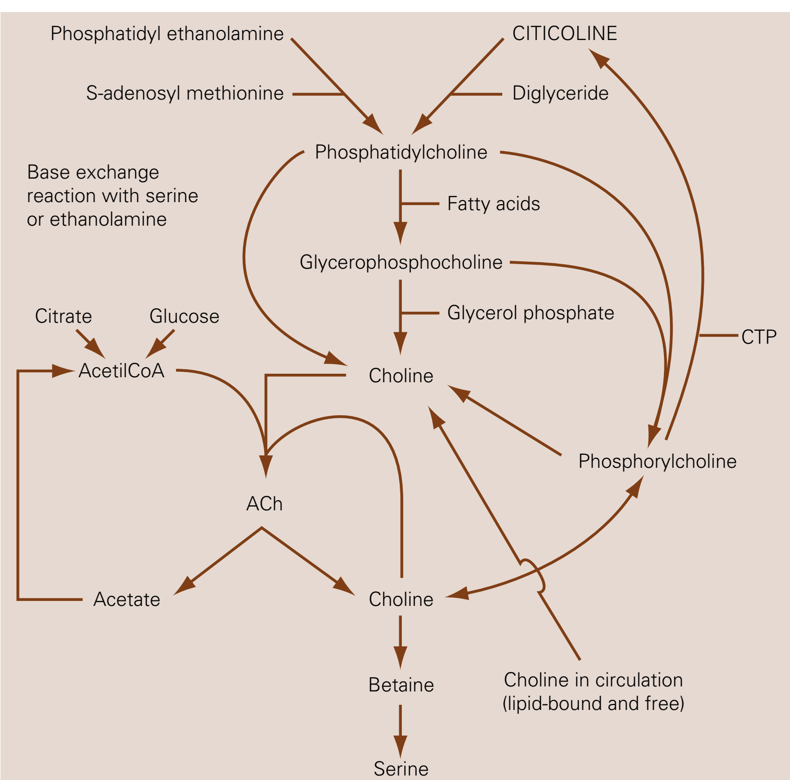


Figure 2. Relationship between citicoline and choline metabolism, cerebral phospholipids and acetylcholine.



dylcholine, have been implicated as mechanisms triggering the apoptotic cascade in several conditions [62-71]. Because of these pathophysiological conditions, there is an agreement on the need for having drugs that may accelerate and/or increase synthesis of membrane structural phospholipids in such situations, that is, having a protective and a restorative or reparative activity on the nervous system [72-77].

Citicoline is the generic name of the pharmaceutical substance that chemically is cytidine-5'-diphosphocholine (CDP-choline), which is identical to the natural intracellular precursor of phospholipid phosphatidylcholine [78]. CDP-choline is a mononucleotide consisting of ribose, cytosine, pyrophosphate, and choline whose chemical structure (Fig. 1) corresponds to 2-oxy-4-aminopyrimidine [79]. CDP-choline is involved as an essential intermediate in the synthesis of structural phospholipids of cell membranes [4,78-92], and formation of this compound from phosphorylcholine is the rate-limiting step of this biosynthetic pathway [82,93-104]. The CDP-choline cycle is integrated into a larger metabolic network and its interruption can affect the distribution of lipid-related metabolites in several other pathways [105]. As shown in figure 2, CDP-choline is also related to acetylcholine metabolism. Thus, administration of CDP-choline is an exogenous source of choline and cytidine. Choline participates in several relevant neurochemical processes. It is the precursor and metabolite of acetylcholine, plays a role in single-carbon metabolism and is an essential component of different membrane phospholipids [106]. The cytidine fraction, once transformed in uridine, is used for DNA and RNA synthesis as well as for the synthesis of membrane constituents and glycosylation, also having an important effect on purinergic receptors [107].

Pharmacological actions

Traumatic lesions and experimental cerebral edema

Javaid et al [108] described the pathophysiological changes in brain phospholipids induced by traumatic brain injury, specially of choline-containing phospholipids such as phosphatidylcholine, and they highlight the role of choline-specific therapeutic strategies, such as the administration of citicoline, for the amelioration of traumatic brain injury.

Horrocks and Dorman [109] have shown that citicoline and CDP-ethanolamine prevent degradation of choline and ethanolamine phospholipids during decapitation ischemia in rats and induce a partial reversion of free fatty acid release during reperfusion after experimental global ischemia in gerbils. Citicoline and CDP-ethanolamine, when administered together, have a synergistic effect and stimulate resynthesis of choline, ethanolamine, and inositol phospholipids, markedly decreasing free arachidonic acid levels.

In an experimental rat model of acute induced ischemia, LePoncin-Lafitte et al [110] assessed integrity of the blood-brain barrier with labelled iodinated albumin, and brain metabolism using histoenzymological studies. In this experimental model, administration of citicoline was able to reduce vasogenic cerebral edema and to restore blood-brain barrier integrity. Authors also found that the size of induced infarctions was smaller with citicoline, and this compound decreased the activity of lactate dehydrogenase, succinyl dehydrogenase, monoamine oxidase, and acid phosphatase, emphasizing its protective role through a direct action at cell membrane level.

Mykita et al [111] found in neuronal cultures that addition of citicoline after a hypocapnic lesion resulted in culture protection. Hypocapnia increases incorporation of labelled choline into phospholipids, while this process is slowed in the presence of citicoline. These authors concluded that citicoline is able to protect neurons under alkalosis conditions and may promote cell proliferation.

Yasuhara et al [112, 113], in an electrophysiological study in rabbits, showed that citicoline decreased in the threshold for the arousal reaction and the threshold for muscle discharge, and concluded that this is a valuable drug for treatment of brain lesions because of its effects on consciousness and on the motor activity of the pyramidal system and its afferent pathways.

Martí Viaño et al [114] compared the effects of pyriglutine, piracetam, centrophenoxine, and citicoline in a study on antagonism of barbiturate coma in mice. No differences were seen in animals treated with pyriglutine, piracetam, or centrophenoxine as compared to the control group, while with citicoline both coma duration and depth, as well as respiratory depression, were decreased as compared to all other groups. Arousal effects of citicoline were found to be due to increased cerebral blood flow, improved O_2 cerebral uptake and utilization of energy metabolism, and enhanced mitochondrial breathing.

Ogashiwa et al [115], in an experimental model of head injury in monkeys, established a significant dose-effect relationship between citicoline dose and coma duration, that started to be significant at doses of 60 mg/kg ($p < 0.05$).

Watanabe et al [116], studying the effects of several activators of brain metabolism, found that citicoline increased glucose incorporation and metabolism and decreased lactate accumulation in the brain, and also induced a slight increase of cerebral blood flow.

Alberghina and Giuffrida [17], in a study on nerve tissue response to a contusion lesion, showed that a moderate increase occurred in the activity of cholinephosphotransferase and was associated to a greater increase in the activity of phospholipase A_2 and several lysosomal hydrolases. They also found an increased number and size of lysosomes during neuronal regeneration. Arrigoni et al [117] have shown citicoline to be able to completely inhibit activation of phospholipase A_2 without altering cholinephosphotransferase activity. On the other hand, Freysz et al [118] showed that, in addition to decreasing phospholipase A_1 and A_2 activity, citicoline decreases free fatty acid release under hypoxic conditions, thus adding a protecting effect to its activating capacity of phospholipid reconstruction. Massarelli et al [119] also showed citicoline action upon phospholipase A_1 and agreed with all other authors in their conclusions. Kitazaki et al [120] also showed the inhibitory effect of citicoline upon membrane-associated phospholipase A_2 in rat brain cortex. Based on these characteristics, citicoline has been considered a non-specific inhibitor of phospholipase A_2 at intracellular level [121].

Algate et al [122] tested the effects of citicoline in an experimental model of epidural compression in anesthetized cats. They noted that animals treated with citicoline had a greater resistance to the effects of mechanic brain compression as compared to animals in the control group. They also found that respiratory and cardiovascular changes were less intense in treated animals and concluded that citicoline provides a significant protection against the lethality of epidural compression. These results agreed to those obtained by Hayaishi [123] and Kondo [124] who showed an improvement in the electroencephalogram tracing following administration of citicoline to cats undergoing experimental brain compression, and also in survival quality.

Tsuchida et al [125] administered ^{3}H-citicoline by the intraperitoneal route to rats subjected to cerebral cryogenic lesion by dry ice application on the scalp and confirmed the presence of the labelled drug in brain parenchyma, particularly in the white matter, and above all in damaged areas.

Boismare [18,126] conducted an experimental model of craniocervical trauma without direct blow ('whiplash') in order to assess the effects occurring upon central catecholamine levels and found increased dopamine levels and decreased norepinephrine levels in the brain following trauma. This type of lesion causes postural dysregulation of brain supply and behavioural and learning disorders, that are related to accelerated degradation of cerebral norepinephrine. In animals treated with citicoline, trauma did not change the levels of these amines. The author stressed the protective role of citicoline, due to this stabilizing effect of catecholamine brain levels.

Clendenon et al [127] showed that the decrease in Mg^{++}-dependent ATPase activity in the mitochondrial and synaptosomal membrane occurring in traumatic lesions is prevented by citicoline administration.

Cohadon et al [20,21,128], in a series of studies on a model of cryogenic cerebral edema in rabbits, showed that treatment with citicoline 20 mg/kg/day:

- Slowed the drop in enzymatic activity of mitochondrial ATPase.
- Restored Na^+/K^+ ATPase activity.
- Restored oligomycin-sensitive ATPase activity.
- Accelerated cerebral edema reabsorption, with normal values achieved in the fourth day, while such levels were not reached until the tenth day with spontaneous resorption.

These authors stated that the beneficial activity of citicoline in cerebral edema occurred by two mechanisms: by restoring insertion of membrane enzymes and enhancing their activity, and by acting upon edema by reducing water imbibition of brain parenchyma.

Lafuente and Cervós-Navarro [129,130] conducted a microgravimetric study in experimental cerebral edema induced by ultraviolet radiation in cats to assess the effect of citicoline in this situation. The results suggested an action of citicoline decreasing the amount of edema, enhancing fluid reabsorption and accelerating fluid drainage to ventricles, i.e., increasing cerebral compliance. Authors concluded that CDPamines are helpful to control tissue lesions related to increased free fatty acids and to restore cell energy metabolism by restarting the Na^+/K^+ pump.

Majem et al [131] assessed the electroencephalogram changes occurring in rats when cryogenic edema is induced, and how such electroencephalogram changes were modified by citicoline administration. These authors noted a significant increase in the theta frequency band during the awakening state, with decreased delta and slow alpha bands and a lesser interindividual scatter of the overall frequency bands, which resulted in a greater electrogenic cerebral stability. They concluded that citicoline protected from the effects of cryogenic cerebral edema.

Roda [132], in an experimental model of cryogenic cerebral edema, measured extravasation of Evans blue through the blood-brain barrier and fluorescein uptake by astrocytes and neurons, and found that citicoline administration significantly reduced both processes as compared to control animals, thus allowing to state that citicoline has a direct effect upon transmembrane transport of sodium, potassium, water, and proteins at both blood-brain barrier endothelial cell level and astrocyte and neuron level. Though the exact mechanism of this action is not completely understood, its effect appears to occur at two levels: on the interface separating capillaries from the neuroglia and on cell membranes. Citicoline reduces microvascular permeability during experimental endotoxemia [133] and in early burn edema in rats [134]. Farshad et al [135] propose citicoline as a potential protective agent in a model of hepatic encephalopathy, a known cause of cerebral edema. They found that citicoline supplementation enhanced the animal's locomotor activity and improved brain tissue markers of oxidative stress, concluding that the effects of citicoline on oxidative stress markers could play a fundamental role in its neuroprotective properties.

Dixon et al [136] analyzed the effects of exogenous administration of citicoline on motor deficits, spatial memory capacity, and acetylcholine levels in dorsal hippocampus and neocortex in a model of traumatic brain lesion in rats, induced by a controlled lateral impact. Citicoline was administered by the intraperitoneal route at a dose of 100 mg/kg for 18 days from the first day following induction of the traumatic lesion. Another group of animals was treated with saline solution. Motor assessment was performed using a balance test for which animals had previously been trained, and cognitive assessment was made with a variant of the Morris maze test, that is sensitive to cholinergic function. Microdialysis methods were also used to analyze the effects upon acetylcholine release. In the motor function study, citicoline-treated animals showed on day 1 after the lesion a significantly longer balance period as compared to animals receiving saline (39.66 ± 3.2 seconds versus 30.26 ± 2.9 seconds; $p < 0.01$). In addition, animals treated with citicoline had significantly less cognitive deficits. In microdialysis studies, after a single administration of citicoline by the intraperitoneal route, a rapid increase in acetylcholine production was seen as compared to baseline, that was maintained for up to three hours, in both dorsal hippocampus ($p < 0.014$) and neocortex ($p < 0.036$), while no changes were noted in animals receiving saline. Authors concluded that post-traumatic deficits in spatial memory function are due, at least partly, to deficiency changes in cholinergic transmission, that are attenuated with citicoline administration.

Plataras et al [137] analyzed the effects of different citicoline concentrations (0.1-1 mM) upon the activities of acetylcholinesterase, Na^+/K^+-ATPase, and Mg^{++}-ATPase in total brain homogenates from rats and extracts of non-membrane bound pure enzymes. Following 1-3 hours preincubation with citicoline, peak stimulations of 20-25% ($p < 0.001$) and 50-55% ($p < 0.001$) are seen for acetylcholinesterase and Na^+/K^+-ATPase respectively, while no significant effects are seen on Mg^{++}-ATPase. Authors concluded that citicoline may stimulate cerebral acetylcholinesterase and Na^+/K^+-ATPase independently from acetylcholine and norepinephrine, which could partly account for the clinical effects of the drug.

Baskaya et al [138] examined the effects of citicoline upon cerebral edema and rupture of the blood-brain barrier in a rat model of traumatic brain injury. Animals received citicoline (50, 100, 400 mg/kg) or saline by the intraperitoneal route twice following induction of the traumatic brain lesion. Induction of the traumatic lesion caused an increase in water content percentage and Evans blue extravasation (a marker of blood-brain barrier rupture) at the damaged cortex and ipsilateral hippocampus. The 50 mg/kg dose of citicoline was not effective, while at 100 mg/kg a reduction was seen in Evans blue extravasation in both regions, although this dose only decreased cerebral edema in the damaged cortex. The 400 mg/kg dose of citicoline significantly reduced cerebral edema and the blood-brain barrier rupture in both regions. Authors concluded that these results suggest citicoline to be an effective neuroprotective agent upon secondary lesions occurring in association to traumatic cerebral injury.

Dempsey and Rao [139], using an experimental model of controlled lateral impact in rats, have shown that intraperitoneal administration of citicoline 200-400 mg/kg following induction of the traumatic brain injury prevents neuronal damage in hippocampus associated to the traumatic lesion, decreases cortical contusion volume, and improves neurological recovery.

It has been demonstrated a synergistic effect in the association of propofol with citicoline in an experimental model of traumatic brain injury in rats [140], resulting in a higher reduction of the lipidic peroxidation when the drugs are administered together.

Jacotte-Simancas et al [141] examined the effects of citicoline and of voluntary physical exercise in a running wheel (three weeks), alone or in combination, on traumatic brain injury-related short-term (three hours) and long-term (24 hours) object recognition memory deficits, and on neurogenesis and neuroprotection, using a rodent model of traumatic brain injury (controlled cortical impact injury). Citicoline improved memory deficits at the two times tested, while physical exercise only in the long-term test. Some degree of neuroprotection of citicoline was suggested by reduced interhemispheric differences in the volume of the hippocampal formation. But, contrary to what was expected, the effects of citicoline and physical exercise did not sum up.

Qian et al [142] demonstrate the protection of citicoline against white matter and grey matter damage due to closed head injury through suppressing oxidative stress and calpain overactivation, providing additional support to the application of citicoline for the treatment of traumatic brain injury. Gan et al [143] in a zebrafish traumatic brain injury model assessed the anti-inflammatory actions of citicoline. In this model the authors demonstrate that citicoline could activate microglia, reduces neuronal apoptosis and promotes neuronal proliferation around the lesioned site.

Abdolmaleki et al [144] evaluated the anticonvulsant effect of citicoline in the pentylenetetrazole seizure model. In this study it was showed that the acute administration of citicoline has anticonvulsant activity and sedative effect, suggesting a positive effect of citicoline on post-traumatic epileptogenesis. Rasooli et al [145] indicated that citicoline has anticonvulsant effects probably through the inhibition of nitric oxide.

Effect of citicoline upon traumatic spinal cord lesion was also studied, and it was shown that intraperitoneal administration of citicoline 300 mg/kg five minutes after lesion induction significantly reduced lipid peroxidation and improved motor function in treated animals [146], having the same efficacy than methylprednisolone in the behavioral and neuroanatomical recovery [147]. It has been demonstrated that the administration of repeated doses of citicoline prevents the tissue damage associated with the spinal cord shock in acute phase [148], and that the combination of ischemic post-conditioning with citicoline confers protection in a model of ischemic spinal cord lesion [149], through the inhibition of the caspases pathway and the increase of antiapoptotic proteins. In a model of spinal cord injury, Paulose et al [150] suggest that the neurotransmitters combination along with bone marrow or citicoline with bone marrow can reverse the muscarinic receptor alterations in the spinal cord of spinal cord injured rats, which is a promising step towards a better therapeutic intervention for spinal cord injury because of the positive role of cholinergic system in regulation of both locomotor activity and synaptic plasticity.

Also, it has been observed some beneficial effects of citicoline in experimental models of partial optic nerve crush in the rat [151]. Kitamura et al [152] investigated the effectiveness of a single or a combination of topical neurotrophic factors, including citicoline, in protecting retinal ganglion cells in the rat optic nerve crush model, and conclude that the combination of the three neurotrophic factors, including citicoline, was the most effective way to protect retinal ganglion cells after the optic nerve crush. Also, there are some data suggesting that citicoline promotes nerve regeneration and reduces postoperative scarring after peripheral nerve surgery [153]. Aslan et al [154] demonstrated that CDP-choline improves the functional recovery and promotes the regeneration of injured sciatic nerves treated with immediate or delayed surgical repair in rats. The same team [155] demonstrated that intraperitoneal administration of CDP-choline improves nerve regeneration and functional recovery in a rat model of sciatic nerve injury, also improving nerve adherence and separability. Kaplan et al [156] concluded that citicoline exhibits dose-dependent effects on axonal regeneration and recovery without scar formation in a rat model of peripheral nerve incision and primary anastomosis. In this context, CDP-choline modulates matrix metalloproteinase activity and promotes the expression of tissue inhfibitor of metalloproteinases to stimulate axonal regeneration [157]. These data help to explain one mechanism by which CDP-choline provides neuroprotection in peripheral nerve injury. Samadian et al [158] described a role of citicoline for peripheral nerve regeneration. Emril et al [159] demonstrated that in situ administration of 0.4 mL of 100 μmol/L CDP-choline prevents the occurrence of neuropathic pain and induces motoric recovery four weeks after sciatic nerve injury. Ahlawat and Sharma [160] concluded that simultaneous administration of S-methylisothiourea sulfate (a selective iNOS inhibitor) and citicoline may provide potential therapeutics for diabetic neuropathic pain. Savran et al [161] demonstrated that CDP-choline may be effective for preventing postoperative epidural fibrosis in an experimental model. After a systematic review of the literature on rodent models, Wang et al [162] consider that CDP-choline is one of the most effective adjuvant treatments after surgery in peripheral nerve laceration.

Because of its biochemical, pharmacological, and pharmacokinetic characteristics, citicoline is a potentially useful drug for the treatment of traumatic cerebral injuries [163].

Cerebral hypoxia and ischemia

In vitro studies using nerve tissues have shown anoxia to induce a decrease in the synthesis of structural phospholipids that is time-dependent, i.e., the longer the hypoxia the stronger the impact upon neuronal phospholipids metabolism [164]. Moreover, a decreased incorporation of marked precursors into phospholipids of neuronal subcellular fractions obtained from animals subjected to experimental hypoxia has also been shown [26]. It is also known that, when cerebral ischemia is experimentally induced, glycerophospholipids in cell membranes are broken down by the action of different phospholipases, producing free fatty acids and arachidonic acid derivatives. With prolonged ischemia, induced aggression upon membranes becomes more intense and membranes lose their functions. Na^{+} and Ca^{2+} accumulate inside the cell, triggering the ischemic cascade and invariably leading to cell death [7,33,37,41,121,165].

Under ischemia conditions, with the attendant neuronal distress, endogenous CDP-choline synthesis is compromised because the cell, under such conditions, lacks the high-energy phosphate compounds necessary for this biosynthetic route [37,166].

Because of the importance of restoring neuronal activity following cerebral ischemia [4] and based on the experimental data discussed, various authors have investigated the effects of citicoline administration in various experimental models of cerebral ischemia and/or hypoxia.

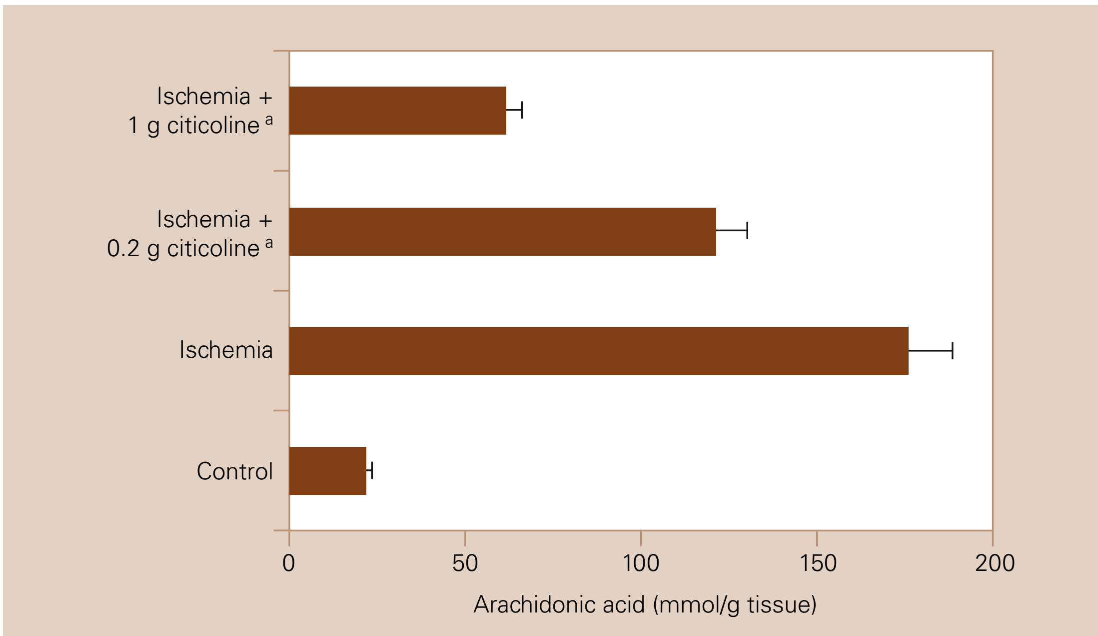
Boismare et al [167] reported that treatment with citicoline 20 mg/kg by the intraperitoneal route in rats induced, during acute hypoxia, a decrease in vegetative responses, protection from conditioned avoidance responses, and stabilization of dopamine and norepinephrine brain levels. This same group [168] found in dogs subjected to normobaric hypoxia increases in blood pressure, heart rate, cardiac output, and regional blood flows, while no changes occurred in total peripheral resistance. Administration of citicoline abolished these hemodynamic effects induced by acute hypoxia, suggesting that this action was correlated to a dopaminergic agonistic effect of the drug. In cats subjected to short periods of cerebral ischemia, these authors [169] noted that a depression occurred in cortical evoked potentials. Such depression was attenuated by prior administration of citicoline by the intracarotid route. These authors think that the protective effects of citicoline are metabolic/biochemical rather than hemodynamic in origin, and do not rule out a direct action of the drug upon central dopaminergic structures.

Alberghina et al [170] investigated the effect of citicoline upon incorporation of labelled precursors into cerebral phospholipids of guinea pigs subjected to hypoxia. A group of animals were given 100 mg/kg of citicoline by the intraperitoneal route. Ten minutes later, the labelled precursors [2-^{3}H] glycerol and [1-^{14}C]palmitate were administered by the intraventricular route. Another group of animals only received the precursors, and acted as control group. Investigators noted that, as compared to the control group, citicoline-treated animals showed an increase in specific radioactivity of total lipids and phospholipids in purified mitochondria obtained from brain hemispheres, cerebellum, and brain stem. In a subsequent study, this same investigating team [171] showed citicoline to be able to counteract the effects of hypoxia upon incorporation of labelled precursors into RNA and proteins, particularly at nuclear and mitochondrial level.

Various experimental studies have shown citicoline to prevent fatty acid release during cerebral ischemia and hypoxia, and to increase synthesis of structural phospholipids [172-191]. Horrocks et al [172,175,177], using an experimental model of global cerebral ischemia by decapitation, showed that administration of a mixture of citicoline and CDP-ethanolamine decreased free fatty acid release and increased synthesis of the corresponding glycerophospholipids, suggesting an involvement of choline and ethanolamine phosphotransferases.

Trovarelli et al [173,174], using an experimental global ischemia model consisting of bilateral carotid ligation in gerbils, found that intraperitoneal citicoline administration partially prevents changes in lipid metabolism induced by cerebral ischemia, correcting the increase in free fatty acids, changes in neutral lipids such as diacylglycerol, and the decrease in phosphatidylcholine. Suno and Nagaoka [176] experimentally studied in rats the effects of citicoline administration upon free fatty acid release caused by total cerebral ischemia lasting five minutes. It was shown that the tested drug reduced the increase in free fatty acids, and that the intensity of this effect depended on the dose used. Arachidonic acid contents in brains from control group animals subjected to ischemia was 174 ± 22 mmol/g, as compared to 119 ± 8 mmol/g and 61 ± 8 mmol/g in animals receiving 200 and 1,000 mg/kg intraperitoneal of citicoline respectively (Fig. 3). Authors concluded that these results suggest that administration of citicoline may prevent ischemic cerebral damage [179-181]. Agut and Ortiz [178] treated male rats weighing 190-200 g with 4 mg/kg of ^{14}C-methyl-citicoline (50 μmCi) by the oral route. At 24 hours, brain radioactivity levels and the presence of labelled phospholipids were assessed under conditions of normoxia, hypoxia, and hypoxia following additional administration of 100 mg/kg of unlabelled citicoline. Investigators found a marked incorporation of radioactivity into the brains of normoxic and hypoxic animals, mostly associated to phosphatidylcholine. In addition, administration of unlabelled citicoline reduced the elevation in cerebral lysophosphatidylcholine caused by hypoxia. Rao et al [182] showed that citicoline significantly decreased blood-brain barrier dysfunction after ischemia with a six-hour reperfusion in gerbils and, in the same model of transient cerebral ischemia, considerably reduced the increase in arachidonic acid and leukotriene C_4 synthesis 24 hours after ischemia induction. They also showed that the cerebral edema volume was substantially lower at three days in animals treated with citicoline. Following six days of reperfusion, ischemia was seen to cause 80 ± 8% neuronal death at the hippocampal CA_1 layer level, and citicoline provided a neuroprotection of 65 ± 6%. In a subsequent study, these authors [183] showed citicoline to be able to significantly restore phosphatidylcholine, sphingomyelin, and cardiolipin levels after induction of transient cerebral ischemia in gerbils. For these authors, the main action mechanism of citicoline would be inhibition of stimulation of phospholipase A_2 activity in ischemia conditions, though they also stress its effects upon glutathione synthesis and glutathi-

Figure 3. Effect of citicoline on arachidonic acid release in ischaemic rat brains. Citicoline (200 and 1,000 mg i.p.) was administered 10 min before decapitation. Five minutes later, free fatty acids were extracted. Arachidonic acid levels were determined by gas chromatography. [a] $p < 0.05$; [b] $p < 0.001$ versus untreated ischaemia.



one reductase activity. Thus, the drug would prevent membrane destruction, decrease free radical generation, and preserve the natural defenses of the nervous system against oxidative damage [184-188]. More recently, this investigating team has also shown that citicoline enhances phosphatidylcholine synthesis, which is impaired under ischemia conditions, attenuating the loss of CTP-phosphocholine cytidyltransferase activity [189,190]. Thus, the drug has effects preventing phospholipid degradation and its implications and promoting regeneration of cerebral phosphatidylcholine, effects that are seen to result in a decreased volume of the cerebral ischemic lesion [191].

Tornos et al [192] conducted a pharmacological study on the protective effect of citicoline against toxicity in an experimental model of hypoxia induced by potassium cyanide. They found that treatment with oral citicoline for four days before hypoxia induction had a protective effect, demonstrated by a longer survival time in treated animals. These benefits of citicoline may also be ascribed to the activation of the cerebral energy metabolism [193] and the increased activity of mitochondrial cytochrome oxidase [194] induced by this drug.

Narumi and Nagaoka [195] investigated the effects of citicoline administration upon metabolism of cerebral monoamines in two rat models of global cerebral ischemia. In the first model they performed cerebral ischemia, using bilateral carotid occlusion, for 30 minutes in spontaneously hypertensive rats and noted that a significant decrease occurred in norepinephrine levels in the brain cortex. In this model, administration of 1,000 mg/kg of citicoline decreased dopamine contents in striatum and diencephalon, normalizing the decrease in the dopamine metabolites/dopamine ratio induced by ischemia. In the second model, bilateral carotid occlusion was also performed 24 hours after electrocauterization of both vertebral arteries in Wistar rats. In this model, norepinephrine, dopamine, and serotonin levels decreased 70%-80% in the brain cortex. Similar decreases were also seen in norepinephrine and serotonin levels in hippocampus, in dopamine levels in the nucleus accumbens, in dopamine and serotonin levels in striatum, and in norepinephrine levels in diencephalon and brain stem. Administration of citicoline at a dose of 500 mg/kg significantly enhanced the ischemia-induced decrease in striatal dopamine levels. These authors therefore suggest that citicoline appears to restore dopamine turnover in the striatum of rats subjected to experimental cerebral ischemia.

Nagai and Nagaoka [196] reported the results of a study investigating the effect of citicoline upon glucose uptake in different brain areas from rats with global cerebral ischemia induced by the occlusion of both carotid arteries for 30 minutes after electrocauterization of both vertebral arteries. Glucose uptake by the brain was measured four days after recirculation. Without citicoline administration, global cerebral uptake was found to be reduced to 81% of the normal value. With administration of citicoline at a dose of 250 mg/kg intraperitoneal twice daily for three days after the start of recirculation, postischemic reduction of glucose uptake was significantly lower in the brain cortex. This suggests that citicoline improves energy metabolism in the brain under ischemic conditions.

Kim et al [197] investigate the effect of citicoline in the context of hypoglycemia-induced neuronal death in a rat model with insulin-induced hypoglycemia. Acute hypoglycemia was induced by intraperitoneal injection of regular insulin (10 U/kg) after overnight fasting, after which isoelectricity was maintained for 30 minutes. Citicoline injections (500 mg/kg, intraperitoneal) were started immediately after glucose reperfusion. Treatment with citicoline resulted in significantly reduced neuronal death, oxidative injury, and microglial activation in the hippocampus when compared to vehicle-treated control groups at seven days after induced hypoglycemia. Citicoline administration after hypoglycemia decreased immunoglobulin leakage through blood brain barrier disruption in the hippocampus when compared to the vehicle group. Citicoline increased choline acetyltransferase expression for phosphatidylcholine synthesis after hypoglycemia. These findings suggest that neuronal membrane stabilization by citicoline administration can save neurons from the degeneration process after hypoglycemia, as seen in several ischemia studies. Therefore, these results suggest that citicoline may have therapeutic potential to reduce hypoglycemia-induced neuronal death.

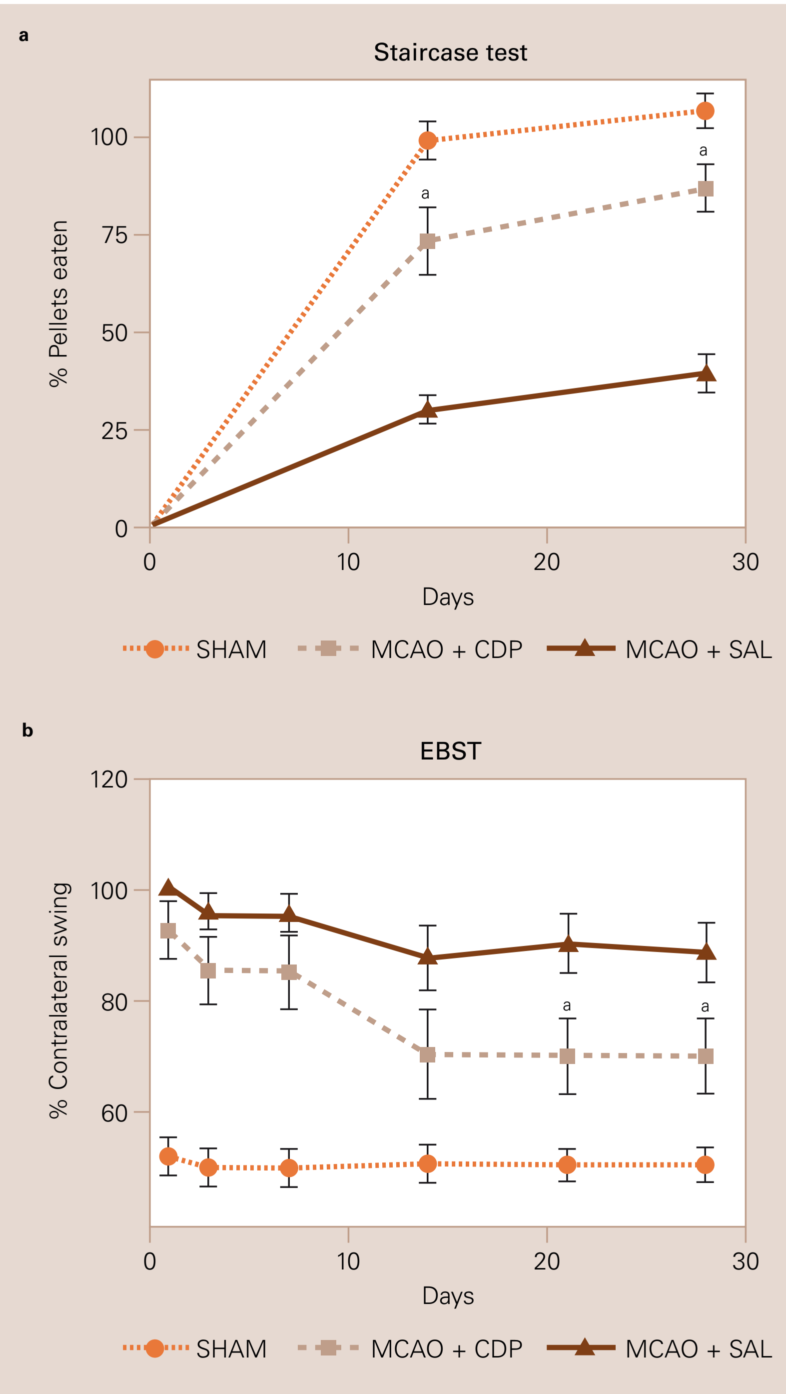
Hurtado et al [198] have shown that administration of citicoline significantly increased adenosine triphosphate (ATP) brain levels in both healthy and ischemic animals, and that this increase in ATP was correlated to a positive effect on glutamate transporters, restoring their normal activity and therefore decreasing both brain parenchymal and circulating glutamate levels. This was correlated to a decreased cerebral infarction volume. The same authors demonstrated that citicoline redistributes the glutamate transporter EAAT2 to lipid raft microdomains and improves glutamate uptake and this effect is also found after experimental stroke, when citicoline is administered four hours after the ischemic occlusion [199]. In another study [200], they found that a chronic treatment with citicoline, initiated 24 hours after the insult, is able to increase the neuronal plasticity as well as to promote functional recovery (Fig. 4). Zhao et al [201] also showed a positive effect of citicoline on spatial learning and memory of rats after focal cerebral ischemia.

Kakihana et al [202] investigated distribution of labelled citicoline and its effects on acetylcholine synthesis from glucose in the brain cortex of rats subjected to 30 minutes of ischemia followed by reperfusion. Treatment with citicoline improved glucose metabolism and significantly restored acetylcholine synthesis from glucose. For these authors, the results obtained suggest that citicoline improves brain energy metabolism in ischemia conditions. These authors [203] subsequently evaluated the effects of citicoline on neurological sequelae and glucose metabolism in the brain in an experimental rat model of transient cerebral ischemia, showing that high-dose citicoline improved the neurological state of animals subjected to ischemia, which was correlated to an improved brain energy metabolism and to drug incorporation in the fraction of membrane phospholipids. These results agree with those obtained by Fukuda et al [204] in a preliminary study.

Nagaoka [205] studied the effects of citicoline on stroke onset and mortality in spontaneously hypertensive rats subjected to cerebral ischemia. Ischemia was induced by occluding both common carotid arteries. Citicoline (200-1,000 mg/kg intraperitoneal), administered before ischemia induction, caused a dose-dependent delay in the onset of stroke and respiratory arrest. These effects were also seen in animals treated after ischemia induction. In addition, citicoline 500 mg/kg intraperitoneal improved the neurological status in rats undergoing brain ischemia for 40 minutes and reperfusion. These results suggest that citicoline has a neuroprotective role against cerebral ischemia and reperfusion.

Saligaut and Boismare [206] studied the effects of citicoline, administered at a dose of 1,000 mg/kg

Figure 4. Effect of chronic treatment with CDP-choline on functional recovery, as determined as sensorimotor integration (a) and asymmetrical motor behaviour (b). CDP-choline (MCAO+CDP) or saline (MCAO+SAL) were administered 24 h after pMCAO and for 28 days following pMCAO. Sensorimotor integration and asymmetrical motor behaviour were studied by the staircase skilled reaching test and the elevated body swing test (EBST), respectively. Data are means ± SEM, *n* = 16. [a] $p < 0.05$ versus MCAO+SAL.



p.o., in Wistar rats undergoing acute hypobaric hypoxia (15 minutes at a simulated altitude of 7,180 meters), assessing a behavior-conditioning test, striatal dopamine uptake, and levels of this neurotransmitter and its metabolites in the striatum. In the behavior-conditioning test, citicoline was seen to protect against hypobaric hypoxia in a different way and to a greater extent than apomorphine. Biochemical studies showed a presynaptic effect, probably because of activation of tyrosine hydroxylase, inducing changes in dopamine uptake, as well as an improved dopamine release. Similar results on the effect of citicoline on tyrosine hydroxylase activity have been obtained by other teams [207].

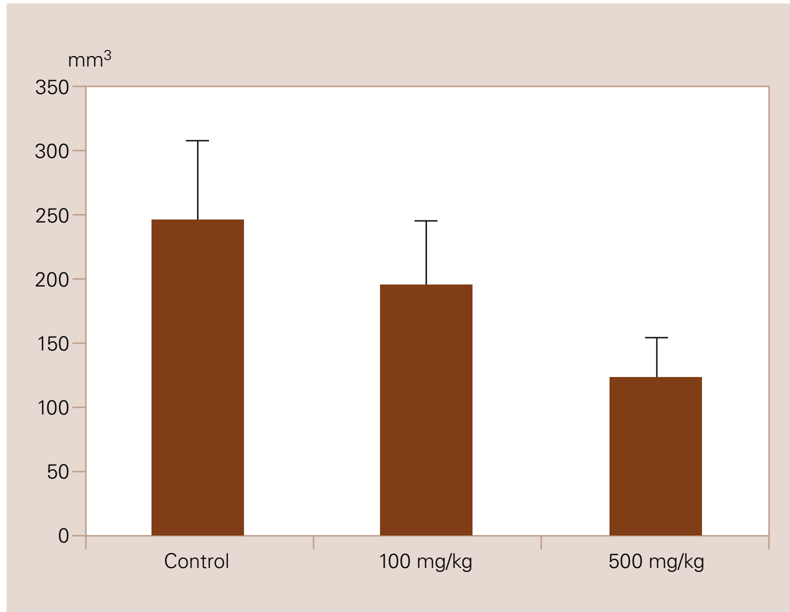
LePoncin-Lafitte et al [110] studied the effects of citicoline on various histological brain changes in an experimental model of multifocal cerebral ischemia in cats, in which ischemic lesion was caused by introducing in the internal carotid artery calibrated microspheres, that will produce cerebral microinfarctions, characterized by having a central necrosis area surrounded by a penumbra area, together with edema due to rupture of the blood-brain barrier. Citicoline administration considerably decreased the number of lesions, and also the amount of extravasated albumin, which confirms, for these authors, that citicoline exerts its neuroprotective role against ischemia by acting upon cell membranes. Araki et al [208] also found some neuroprotective effect of citicoline in complete cerebral ischemia induced by decapitation and potassium cyanide poisoning in mice.

Aronowski et al [209] evaluated the effects of chronic citicoline administration (500 mg/kg) upon recovery in spontaneously hypertensive rats undergoing occlusion of the middle cerebral artery for 30 to 120 minutes. Drug or saline were administered by the intraperitoneal route from 15 minutes after ischemia induction and were continued for 14 days. Morphological lesion and neurological disorders (motor and sensorimotor capacities) were analyzed by measuring the maximum morphological lesion volume, maximum neurological change, and ischemia duration causing half the maximum morphological lesion or maximum neurological change. Maximum morphological lesion volume was not affected by citicoline (101.6 ± 11.4 mm^3 for citicoline, 103.3 ± 13.6 mm^3 for saline); however, citicoline significantly increased ischemia duration required to cause half the morphological lesion, that changed from 38.3 ± 5.9 to 60.5 ± 4.3 minutes ($p < 0.05$). Similarly, citicoline did not change the value of maximum neurological change

(8.5 ± 0.7 for citicoline, 10.1 ± 4.0 for control), but did significantly increased ischemia duration required to cause half the maximum neurological change from 41.9 ± 4.6 to 72.9 ± 24.5 minutes ($p < 0.05$). According to these authors, citicoline shows a greater efficacy in animals that experience a submaximal lesion, occurring in this model with 30-75 minutes of ischemia.

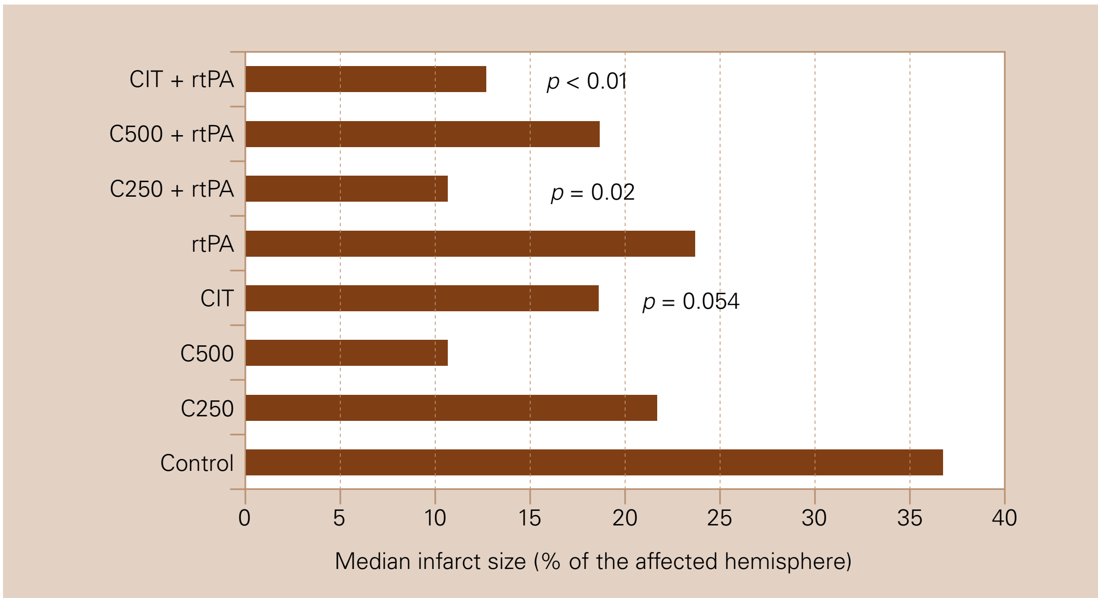
Schäbitz et al [210] evaluated the effects of long-term treatment with citicoline in a model of transient focal ischemia (two hours) in rats. Ten animals were randomly assigned to each of the groups: placebo (saline 0.3 mL/day/7 days), low dose (citicoline 100 mg/kg/day/7 days intraperitoneal) and high dose (500 mg/kg/day/7 days intraperitoneal). Treatment was started at the time of reperfusion, once the two-hour ischemia period had ended. Daily neurological assessments were made (modified Zea Longa scale), and surviving animals were killed on day 7, after which cerebral edema and infarction volume were calculated. No differences were seen in neurological assessment of animals at study end, but a more favorable trend was noted in the citicoline high-dose group. Mean infarction volume (Fig. 5) was 243.5 ± 88.6 mm^3 in the placebo group, 200.2 ± 19.9 mm^3 in the low-dose group, and 125.5 ± 45.2 mm^3 in the high-dose group. These differences were statistically significant ($p < 0.01$). A dose-dependent decrease in cerebral edema volume was also seen, but did not reach statistical significance.

Figure 5. Effect of citicoline at a low dose (100 mg/kg) or high dose (500 mg/kg) on infarct volume. The values represent the mean ± SD. The infarct volume was significantly smaller ($p < 0.01$) in the high-dose citicoline group than in the control group.



In a series of conducted studies, citicoline was shown to have a synergistic effect with other drugs in the treatment of cerebral ischemia, such as thrombolytic [211-215] and neuroprotective drugs [216-224]. Andersen et al [211] conducted an experimental study in a rat model of carotid embolism to evaluate the effect of different doses of citicoline, administered alone or combined with recombinant tissue plasminogen activator (rTPA), on infarction size. Ninety Sprague-Dawley rats subjected to embolism in the carotid territory were randomized into six groups: a) saline-treated animals; b) citicoline 250 mg/kg; c) citicoline 500 mg/kg; d) rTPA 5 mg/kg; e) rTPA 5 mg/kg + citicoline 250 mg/kg; and f) rTPA5 mg/kg + citicoline 500 mg/kg. Treatment with rTPA was given at a suboptimal dosage (5 mg/kg infused over 45 minutes, starting treatment 45 minutes after embolization). Citicoline was administered daily by the intraperitoneal route for four days. Brains from surviving animals were fixed at four days and infarction volume, calculated as percentage of the total volume of the hemisphere affected, was measured using a microscope. Mean infarction volume values suggested that high-dose citicoline and the combination of citicoline with rTPA decreased the size of ischemic lesion (Fig. 6). In the control group, mean infarction volume was 41.2% (5.9-87%). In groups treated with citicoline alone, values were 30.4% (1-70%, n.s.) in group 2, and 22.2% (0.7-76.6%; $p < 0.05$) in group 3. With rTPA alone (group 4), mean volume was 24.5% (1.4-71.1%, n.s.), while with combined treatment, mean volumes were 13.5% (0.2-47.8%; $p = 0.002$) in group 5 and 29.2% (0.11-72.1%, n.s.) in group 6. This study showed that high-dose citicoline and a combination of citicoline at lower doses with rTPA significantly reduced the size of brain infarctions. Díez-Tejedor et al [212,213] reported similar results, stating that results of this association are improved when citicoline is administered immediately after rTPA administration. The same team [214] compared the effects of high doses of CDP-choline (1,000 mg/kg) with rTPA (5 mg/kg) in an experimental animal model of embolic stroke. CDP-choline and rTPA produced a significant reduction in brain damage considering infarct volume, cell death, and inflam-

Figure 6. Effect of the association of citicoline (CIT) and rtPA on infarct size in a model of embolic stroke in rats. C250: citicoline 250 mg/kg; C500: citicoline 500 mg/kg; rtPA: rtPA, 5 mg/kg.



matory cytokines (tumour necrosis factor-alpha and interleukin 6) compared with the infarct group. Additionally, CDP-choline significantly decreased infarct volume, cell death, and interleukin 6 levels with respect to the rTPA group. From these results, they concluded that high-dose CDP-choline may be an effective treatment for acute ischaemic stroke even in absence of thrombolysis. Shuaib et al [215] investigated the neuroprotective effects of citicoline alone or combined with urokinase in a rat model of focal cerebral ischemia induced by embolization at the origin of the middle cerebral artery. Both drugs were administered two hours after ischemia induction. Animals were killed at 72 hours. In saline-treated animals, infarction volume was 33.1 ± 9.7%. Citicoline-treated animals were divided into two groups, one of which was given a single dose of citicoline 300 mg/kg, while the other group received a daily dose of 300 mg/kg for three days, both by the intraperitoneal route. A significant reduction in infarction volume was seen in both groups (20.9 ± 9.7% with single doses; $p = 0.01$; 18.9 ± 11.4% with multiple doses; $p = 0.008$). Animals treated with urokinase alone, at doses of 5,000 u/kg, also had a smaller infarction volume (19.5 ± 12.5%; $p = 0.01$). However, the greatest volume reduction was achieved in the group of animals treated with the combination of citicoline and urokinase (13.6 ± 9.1%; $p = 0.0002$). These authors concluded that citicoline provides a significant neuroprotective effect that may be enhanced by association with a thrombolytic. Synergistic effects have also been shown with the association of citicoline with MK-801 or dizocilpine [216], basic fibroblast growth factor [217], lamotrigine [218], nimodipine [219,220], N-nitro L-arginine methyl ester [221], homotaurine [222], docosahexaenoic acid [223], and azelnidipine [224], but no with piracetam [225] in models of cerebral ischemia. It has been demonstrated that citicoline with hypothermia is more effective than used alone in ameliorating cerebral damage after transient focal ischemia [226]. Also, it has been demonstrated that pre-conditioning with CDP-choline attenuates oxidative stress-induced cardiac myocyte death in a hypoxia/reperfusion model [227]. Zazueta et al [228] demonstrate that citicoline protects liver from ischemia/reperfusion injury preserving mitochondrial function and reducing oxidative stress. Also, it is known that citicoline and mesenchymal stem cells administration show equal efficacy in the neurological recovery, the decrease of neuronal death and the increase of neuronal repair in a model of cerebral infarction in rats, but the combination does not increase the benefit [229], despite that citicoline treatment induces brain plasticity markers expression in experimental animal stroke [230]. Diederich et al [231] designed a study to check whether citicoline also enhances neuroregeneration after experimental stroke. Animals were subjected to photothrombotic stroke and treated either with daily injections of CDP-choline (100 mg/kg) or vehicle for 10 consecutive days starting 24 hours after ischemia induction. Sensorimotor tests were performed after an adequate training period at days 1, 10, 21, and 28 after stroke. Then brains were removed and analyzed for infarct size, glial scar formation, neurogenesis, and ligand binding densities of excitatory and inhibitory neurotransmitter receptors. Animals treated with citicoline showed a significantly better neurological outcome at days 10, 21, and 28 after ischemia, which could not be attributed to differences in infarct volumes or glial scar formation. However, neurogenesis in the dentate gyrus, subventricular zone, and peri-infarct area was significantly increased by CDP-choline. Furthermore, enhanced neurological outcome after citicoline treatment was associated with a shift toward excitation in the perilesional cortex. The present data demonstrate that, apart from the well-known neuroprotective effects in acute ischemic stroke, CDP-choline also possesses a substantial neuroregenerative potential. Also, citicoline potentiates angiogenesis [232] and astroglial cell proliferation and differentiation [233], both mechanisms involved in neuroplasticity.

Fresta et al conducted a series of experiments in models of transient cerebral ischemia in rats using liposomal citicoline, in which they showed a significantly increased survival in animals treated with this citicoline formulation [234-236], and more recently, that this same drug formulation significantly reduces the maturation phenomenon, that is, delayed cerebral neurodegenerative lesion, that occurs after an ischemic event, resulting in a significant improvement in brain functions [237]. These results agree with previously discussed results [192] showing that administration of liposomal citicoline is more effective as compared to non-liposomal citicoline [238-240]. Other ways to improve neuroprotective efficiency of citicoline are the stereotactic delivery [241], nanocarriers [242] or simple diffusion delivery via brain interstitial route [243].

Citicoline has also been shown to have a neuroprotective effect against neurotoxic damage induce by kainic acid in retinal cells [244-247] and in in vitro models of retinal neurodegeneration [248]. Komnatska et al [249] demonstrate that citicoline restores the microcirculation in the vessels of the ciliary body in rabbits, measured with laser Doppler flowmetry. Bogdanov et al [250] suggest that topical administration of citicoline in liposomal formulation could be considered as a new strategy for treating the early stages of diabetic retinopathy.

Hamdorf and Cervós-Navarro [251] exposed 48 rats for 103 days to a decreasing amount of oxygen, i.e., they were exposed to chronic hypoxia. Citicoline showed a protective effect by increasing vigilance under moderate hypoxic conditions (15% O_2). In a subsequent study, these same authors [252] analyzed the effects of citicoline in Wistar rats subjected to hypoxia for five months. Behavioral changes induced by hypoxia were attenuated in the group or animals treated with citicoline. Interestingly, therapeutic administration of citicoline was found to be more effective than prophylactic administration. In addition, under extreme hypoxia conditions, citicoline showed a protective effect by lengthening survival. Lee et al [253] demonstrated that citicoline protects against cognitive impairment in a rat model of chronic cerebral hypoperfusion.

Other mechanisms proposed to explain the neuroprotective effects of citicoline are the restoration of the barrier function of endothelial cells [254], the inhibition of mitochondrial permeability transition [255,256], and providing neuronal membrane integrity and protection of membrane stability in cortical spreading depression [257]. Another mechanism investigated has been the participation of sirtuin 1 in the neuroprotective actions of CDP-choline [258]. Treatment with CDP-choline increased sirtuin 1 protein levels in brain concomitantly to neuroprotection. Treatment with sirtinol blocked the reduction in infarct volume caused by CDP-choline, whereas resveratrol elicited a strong synergistic neuroprotective effect with CDP-choline. These results demonstrate a robust effect of CDP-choline like sirtuin 1 activator by up-regulating its expression.

On the other hand, Masi et al [259] have shown citicoline to have a certain antiplatelet aggregant effect, that may provide an additional benefit for the treatment of cerebral vascular disease. Pinardi et al [260] investigated in Sprague-Dawley rats the effects of citicoline infusion on relaxation induced by exogenous acetylcholine in the isolated external carotid vascular bed, having no cholinergic nerve supply, and the isolated internal carotid vascular bed that, by contrast, has an abundant cholinergic nerve supply. Changes in perfusion pressure were measured during a dose-response curve to acetylcholine and following infusion of 1 mg/minute/30 minutes of citicoline. Authors noted that citicoline caused relaxation in both vascular beds, which would suggest the presence of muscarinic receptors. In the internal carotid vascular bed, citicoline infusion for 30 minutes significantly shifted to the left the dose-response curve to acetylcholine, enhancing relaxation. However, this did not occur in the external carotid bed. The effect of citicoline was masked when it was jointly infused with hemicholinium. According to these authors, results suggest that citicoline would act by increasing choline levels at cholinergic endings, increasing acetylcholine synthesis and/or release.

Clark et al [261] examined whether citicoline was able to reduce ischemic damage and improve the functional neurological result in an intracerebral hemorrhage model in mice. They caused hemorrhage in 68 Swiss albino mice by injecting them collagenase at the caudate nucleus. Animals randomly received saline or citicoline 500 mg/kg intraperitoneal before administration of collagenase and at 24 and 48 hours. Mice were assessed using a 28-item neurological scale and were killed at 54 weeks to assess hematoma volume, total damage, and surrounding ischemic damage. As regards neurological course, citicoline-treated animals had a better score than placebo-treated animals (10.4 ± 2 versus 12.1 ± 2.4; $p < 0.01$). No differences were seen in hematoma volumes, but a significant reduction in the volume of the surrounding ischemic damage was noted in animals treated with citicoline, with values being 13.8 ± 5.8 mm^3 (10.8 ± 4.3% of hemisphere) and 17 ± 7.1 mm^3 (13.3 ± 5.1%) for placebo, with $p < 0.05$. According to authors, these results support a potential role of citicoline for treatment of intracerebral hemorrhage.

Apoptotic mechanisms have been shown to play a primary role in the pathophysiology of cerebral ischemic damage both at experimental level [262-266] and in humans [267,268]. We therefore investigated [269] whether citicoline could influence apoptotic mechanisms following focal cerebral ischemia. A model of permanent distal occlusion of the middle cerebral artery was used in Sprague-Dawley rats. Animals were randomized into four groups: B + A, citicoline 500 mg/kg intraperitoneal 24 hours and one hour before occlusion and 23 hours after occlusion; A, citicoline 500 mg/kg intraperitoneal within 30 minutes and 23 hours following occlusion; C, saline solution intraperitoneal; D, Sham-operated. Animals were killed at 12 (seven animals per group) and 24 hours (seven animals per group) following occlusion. Immunohistochemistry for procaspases 1, 2, 3, 6, and 8 was performed using goat polyclonal antibodies and, using gel electrophoresis and Western blotting, specific substrates for caspase action were tested using poly-ADP-ribose polymerase (PARP) antibodies. Ischemia induced expression of all procaspases and PARP in both the infarction and the penumbra areas 12 and 24-hours following ischemia. Citicoline reduced expression of all procaspases at 12 and 24-hours following ischemia, except for procaspase 3 at 24 hours in group A and PARP expression (Fig. 7), and results were clearer in group B + A, suggesting a certain prophylactic role of citicoline, results that have been confirmed recently [270]. Citicoline has been shown to be able to inhibit certain intracellular signals involved in apoptotic processes [271] and to maintain these inhibitory effects in different experimental models to study apoptotic mechanisms [142,226,272-276].

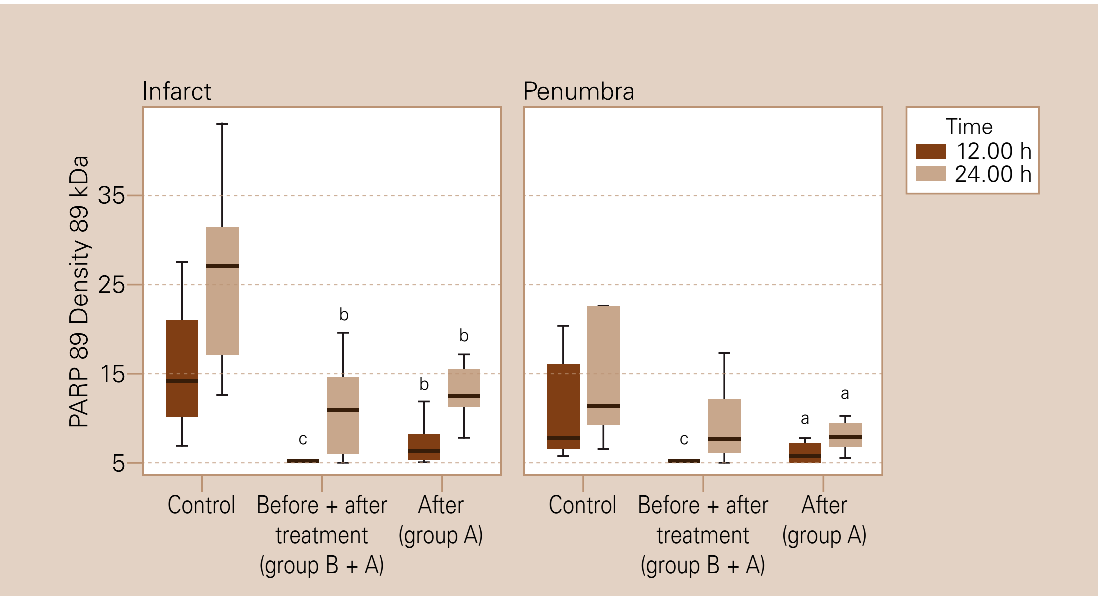
Fiedorowicz et al [277] found that citicoline can attenuate brain damage in a rat model of birth asphyxia. It has been demonstrated that meta-analysis provides an effective technique for the aggregation of data from experimental stroke studies. With this technique, Bustamante et al confirm that citicoline reduces the infarct volume and improves outcome [278], pointing doses of 300-500 mg/kg as the optimal dose to be translated into a candidate neuroprotective drug for human stroke [279].

According to Drago et al [280], citicoline is a drug of choice for treatment of cerebrovascular diseases, particularly in its chronic form, because its clinical use is justified by the pharmacological actions it exerts on the central nervous system. To sum up, citicoline (Fig. 8):

- Interferes positively with the brain energy metabolism.
- Stimulates central neurotransmission.
- Activates cell repair mechanisms.
- Decreases ischemic lesion size.
- Inhibits apoptosis associated to ischemia.
- Has synergistic effects with thrombolytic and neuroprotective drugs.

These characteristics confer citicoline a suitable pharmacological profile for the treatment of cerebral ischemia [39,40,281-283]. Also, it has been postulated a role of citicoline in the treatment of complications of infectious diseases, such as cerebral malaria [284,285]. Abdel-Aziz et al [286] conclude that citicoline avoid both short and long-

Figure 7. Band densitometry analysis for PARP by western blotting in different groups of rats in the infarct zone and penumbra zone 12 and 24 h after ischaemia. [a] $p < 0.05$; [b] $p < 0.025$; [c] $p < 0.0001$.



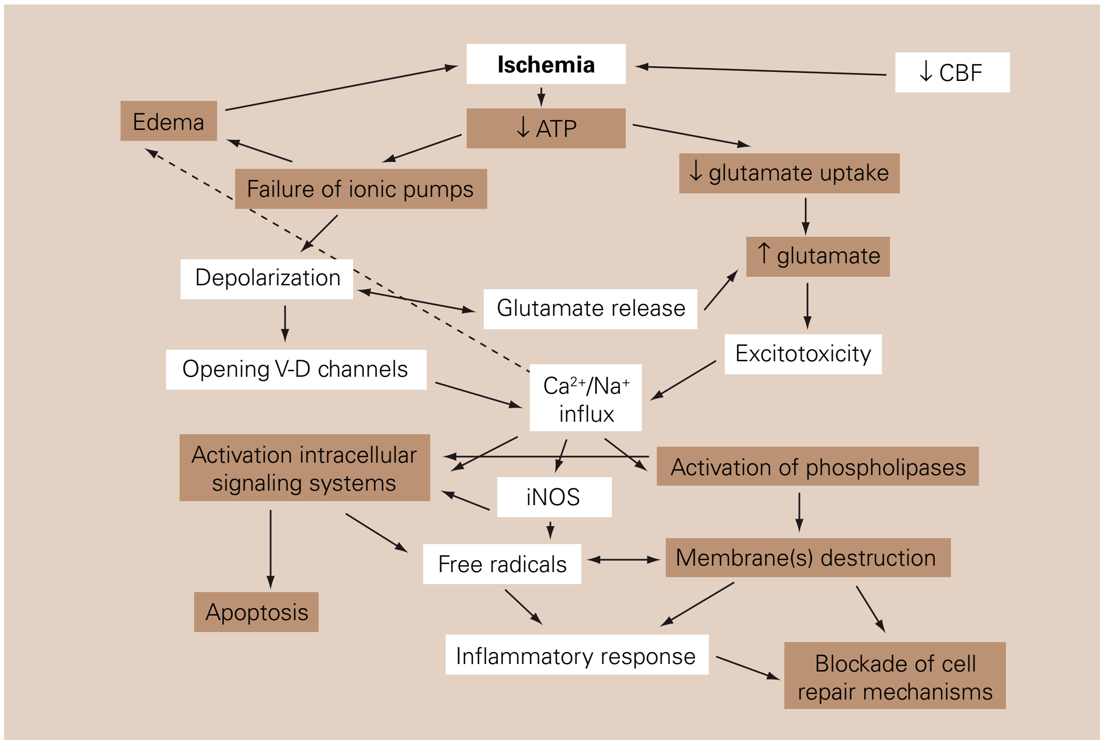
term damages to the neuroendocrine disturbances, oxidative stress, inflammation, and apoptosis induced by head irradiation in a rat model.

Synaptic transmission, intracellular signalling systems and neurotransmitter levels

As previously discussed, citicoline exerts some of its effects through its action on the levels of certain neurotransmitters and on some intracellular signaling processes. This section will discuss these specific effects upon neurotransmission and on intracellular signaling processes. As will be seen below, most studies have focused on analyzing the effect of citicoline on central dopaminergic transmission and on nicotinic cholinergic neurotransmission.

Martinet et al [287] conducted a study in which the effects of citicoline administration on norepinephrine, dopamine, and serotonin levels were assessed in different rat brain regions. For this, conversion of ^{3}H-tyrosine and ^{3}H-tryptophan, administered by the intravenous route, into ^{3}H-norepinephrine, ^{3}H-dopamine, and ^{3}H-serotonin was measured, comparing the results obtained with administration of saline to those obtained after administration of citicoline at different doses. Metabolism of each neurotransmitter was studied in the brain regions where it has functional activity. Thus, for catecholamines citicoline action was studied in the striate body, brain cortex, and midbrain, while for serotonin the hypothalamus was also studied. The synthesis rate of dopamine, norepinephrine, and serotonin was expressed as a conversion index equal to the ratio between the amount of labelled neurotransmitter per gram of brain (cpm/g) and the tyrosine or tryptophan-specific radioactivity (cpm/mmol) in brain. As shown in figure 9, citicoline significantly increased dopamine levels and synthesis rate in the striate body, and the effect exerted on tyrosine levels was very similar. Norepinephrine levels were increased in cortex, but showed no changes from control in the brain stem. As regards effects on serotonin, the drug was seen to cause decreases in the levels and synthesis rate of this neurotransmitter in the brain stem and hypothalamus, and no changes were seen in the cortex or striate. According to these authors, increased dopamine synthesis could be attributed to an enhancing effect of citicoline upon tyrosine hydroxylase activity, the rate-limiting step in dopamine synthesis. This activation of tyrosine hydrox-

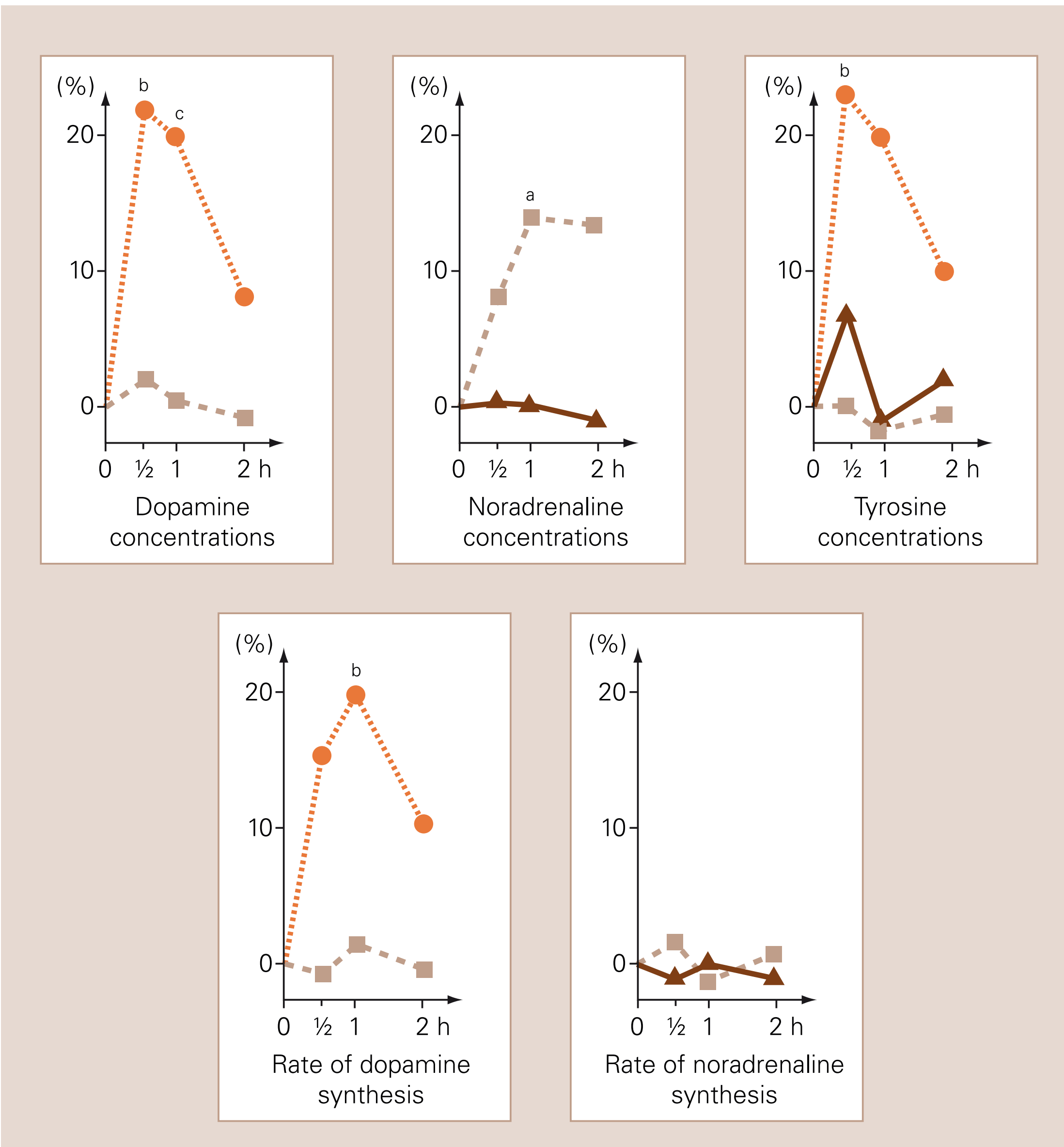
Figure 8. Ischaemic cascade. Darkest boxes show the processes where citicoline has demonstrated pharmacological effects.



ylase would lead to an inhibition of dopamine reuptake at the synapse, an action that has been shown in *ex vivo* studies [288,289]. By contrast, the increase seen in dopamine synthesis does not appear to be related to increased levels of tyrosine, since this completely saturates tyrosine hydroxylase under physiological conditions. The effects of citicoline upon striatal dopamine synthesis are particularly interesting because changes in dopamine synthesis by extrapyramidal dopaminergic neurons are in the origin of Parkinson's disease.

Saligaut et al [290] obtained results in agreement with the previous ones when studying dopamine reuptake in synaptosomes taken from the striate body of rats previously treated with citicoline. Following long-term treatment with this drug, a decreased dopamine reuptake by synaptosomes was seen, and authors related this fact to the increase in tyrosine hydroxylase activity, that would involve an increased dopamine synthesis. They think that a structural change in neuronal membranes, mainly of phospholipid levels, could be one of the factors responsible for the change in synaptosomal reuptake of the neurotransmitter induced by citicoline. Hypobaric hypoxia was also seen to antagonize the inhibitory effect of citicoline on dopamine reuptake by synaptosomes. This antagonism may be explained by the fact that hypoxia decreases activity of tyrosine hydroxylase, an enzyme that requires oxygen, thus counteracting enzyme activation exerted by citicoline. This leads to a decreased dopamine synthesis and a subsequent increase in dopamine reuptake. These same authors studied citicoline action in the experimental oxotremorine-induced cholinergic syndrome in mice [291] and showed that citicoline pretreatment does not potentiate this syndrome, but inhibits salivation induced by oxotremorine. Levodopa antagonized brain symptoms such as tremor-akinesia induced by oxotremorine. However, this antagonism disappeared in animals under long-term oral treatment with citicoline, thus

Figure 9. Influence of citicoline (30 mg/kg i.v.) on catecholamine synthesis at different time points after administration. The graphs show variations in catecholamine concentrations and rates of synthesis, in percentages with respect to the control, at different locations. ● Corpus striatum; ■ Cortex; ▲ Brainstem-mesencephalon; [a] $p < 0.1$, [b] $p < 0.05$; [c] $p < 0.01$.



confirming the action of citicoline on dopaminergic pathways. Citicoline effects appear to be mediated by hypersensitivity of some dopaminergic receptors, rather than by a direct stimulating effect on striatal dopaminergic receptors. In another series of experiments, these authors examined the effects of citicoline on catecholamine metabolism in the striate and hypothalamus from rats subjected to acute hypobaric hypoxia [292]. The results show that citicoline partially counteracts the effects of hypoxia upon the release and metabolism of certain neurotransmitters. In another study, Saligaut et al analyzed the effects of citicoline in rats with unilateral nigrostriatal lesion induced by 6-hydroxydopamine [293]. In damaged animals, amphetamine administration induced an ipsiversive circling behavior, while such circling behavior was contraversive with administration of levodopa and apomorphine. This appears to be mediated by the development in the damaged side of a supersensitivity of postsynaptic dopaminergic receptors. Subchronic treatment with citicoline did not induce behavioral effects. Citicoline did not change the stimulating effect of apomorphine, but potentiated the effects of levodopa and amphetamine. These data show that citicoline effects are mediated by a presynaptic mechanism. Although potentiation of levodopa may not be explained by an activation of tyrosine hydroxylase, this effect appears to be related to an improved release of dopamine synthetized from exogenous levodopa. Kashkin et al [294] evaluate the effect on the combination of citicoline with levodopa/carbidopa in the rotenone model of Parkinson's disease in rats, confirming that the combination therapy had more pronounced therapeutic effect on extrapyramidal disorders than monotherapy.

Cansev et al [295] found that peripheral administration of citicoline increases plasma adrenaline and noradrenaline concentrations. Also, CDP-choline modulates monoaminergic [296] and cholinergic [297] transporters in rat brain.

Agut et al [298] indirectly studied the effect of citicoline upon dopamine synthesis in the striate body by measuring local levels of dopamine metabolites in animals in which blockade of dopaminergic receptors had been induced by administration of haloperidol. Pretreatment with citicoline 100 mg/kg/day/5 days significantly increased levels of homovanillic acid and 3,4-dihydroxyphenylacetic acid in the striate of treated animals as compared to the control group. Increase in levels of these metabolites was even stronger in a group of animals also receiving apomorphine. Results obtained in this study suggest that citicoline increases dopamine synthesis in the striate of rats in which activation of such synthesis has been experimentally induced by haloperidol administration. This same investigating team subsequently conducted a study to examine whether citicoline alone, without provoking an increased dopamine demand by dopaminergic receptors, caused an increased synthesis of this neurotransmitter, resulting in increased striatal levels of its main metabolites, homovanillic acid and 3,4-dihydroxyphenylacetic acid [299].

Action of citicoline upon the dopaminergic system has also been studied by investigating its pharmacological actions in experimental models used for that purpose, such as hypothermia induced by apomorphine, tardive dyskinesia induced by haloperidol, or acrylamide-induced lesion. Agut et al [300] studied the effect of citicoline administration on hypothermia induced by apomorphine, considered to be the result of the agonist action of apomorphine on D_2 receptors. Experimental animals received, in addition to apomorphine, haloperidol at a sufficient dose to partially block apomorphine-induced hypothermia in order to obtain a pharmacological system sensitive to citicoline action upon the dopaminergic system. A group of animals received a dose of citicoline 100 mg/kg p.o., and haloperidol 0.15 mg/kg was administered at 30 minutes by the intraperitoneal route. Thirty minutes later, rectal temperature was measured and apomorphine 1 mg/kg was administered by the subcutaneous route. Rectal temperature was again measured at 30, 60, and 90 minutes. Another group of animals received water instead of citicoline using the same scheme. Effects of chronic administration of citicoline at a dose of 100 mg/kg/day p.o. for five days were also analyzed. The same protocol as for acute administration was followed on the last day. Table I shows the mean temperature decrease seen in each animal batch and at the different evaluation time points. Acute administration of citicoline causes hypothermia, that is significant for all control time points. Chronic administration only achieves a significant result at 90 minutes. Authors concluded that a 100 mg/kg dose of citicoline administered acutely by the oral route has a hypothermizing effect similar to the one reported for various dopaminergic agonists. On the other hand, they considered that the fact that chronic citicoline administration only caused a significant hypothermia in the last time point analyzed probably reflects that, with this form of administration, the tested product predominately acts upon phospholipids rather than acetylcholine synthesis. This second action pathway of citicoline would predominate with acute administration, as this would involve a relatively rapid utilization of the choline provided, that would be used for acetylcholine synthesis, thereby increasing tyrosine hydroxylase activity through cholinergic interneurons. By contrast, chronic administration of citicoline would result in a progressively greater availability of cytidine, and would therefore divert cerebral choline

Table I. Decrease in temperature for each batch studied relative to time zero, expressed as the mean for $n = 20$.

Batch	Drugs	Time		
		+ 30 min	+ 60 min	+ 90 min
A	Water (10 mL/kg v.o.) Apomorphine (1 mg/kg s.c.) Haloperidol (0.5 mg/kg i.p.)	1.19 ± 0.23	0.61 ± 0.17	0.19 ± 0.15
B	Citicoline (0.1 g/kg v.o.) Apomorphine (1 mg/kg s.c.) Haloperidol (0.5 mg/kg i.p.)	1.39 ± 0.18 [b]	0.74 ± 0.17 [a]	0.38 ± 0.14 [b]
C	Water (10 mL/kg/5 d v.o.) Apomorphine (1 mg/kg s.c.) Haloperidol (0.5 mg/kg i.p.)	1.13 ± 0.22	0.63 ± 0.25	0.26 ± 0.12
D	Citicoline (0.1 g/kg/5 d v.o.) Apomorphine (1 mg/kg s.c.) Haloperidol (0.15 mg/kg i.p.)	1.11 ± 0.25	0.70 ± 0.19	0.41 ± 0.12 [b]

[a] $p < 0.05$; [b] $p < 0.01$ versus controls.

toward the synthetic pathway of CDP-choline and phospholipids, which would indirectly result in a dopaminergic agonistic effect. These authors developed an experimental model of tardive dyskinesia induced by haloperidol (2 mg/kg/day/7 days) in rats in a study including chronic administration of haloperidol or water to a total of 120 animals [301], finding that the administration of citicoline plus apomorphine in rats treated with haloperidol induced a motor activity similar to the activity seen in the group receiving citicoline only. Data provided in this study show that, in a model of haloperidol-induced dopaminergic hypersensitivity, administration of oral citicoline induces hypermotility; this may induce a phenomenon of competition against other agonists, leading to a partial reduction of the effect of apomorphine in animals pretreated with citicoline. In the model of acrylamide-induced lesion, these same authors [302] show that administration of low oral doses of citicoline, 50 mg/kg, is effective for correcting the neurological syndrome induced by acrylamide. Simultaneous administration of both substances, inducing an obvious weight loss in mice, has also been shown to cause an activation of the dopaminergic system, as seen in the results obtained with the apomorphine stereotype test.

Shibuya et al [303] measured, using fluorometry, striatal dopamine levels after administration of citicoline in a single dose of 500 mg/kg intraperitoneal, and found that a significant ($p < 0.05$) increase occurred in striatal dopamine levels one hour after injection. On the other hand, Stanzani [304] showed citicoline to have a neuroprotective effect in substantia nigra, noting how citicoline protects this area against lesion induced by peroxydases (horse radish), achieving an increased number of surviving cells. Porceddu and Concas [305] also reported a trophic and/or stimulating effect of citicoline upon nigrostriatal dopaminergic neurons in a model of lesion induced by kainic acid. Also, there are experimental studies showing the protective effect of citicoline in cultures of dopaminergic neurons exposed to 6-hydroxydopamine [306], 1-methyl-4-phenylpyridinium [307,308], and glutamate [307]. Miwa et al [309] suggested that citicoline may act as a dopamine reuptake inhibitor after administration of a single dose, and that this drug may change the activity of dopaminergic neurons through changes in compositions of the neuronal membrane following repeated administration. In addition, these authors found citicoline to have certain muscarinic effects. In this regard, Giménez et al [310] show that chronic administration of citicoline to aged mice promotes partial recovery of the function of dopaminergic and muscarinic receptors, that normally decreases with aging, and think that this action may be explained based on mechanisms involving fluidity of neuronal membrane, in agreement with the results obtained by Petkov et al

[311]. This latter investigating team, when comparing the effects of citicoline to those of the nootropic drugs adafenoxate and meclofenoxate upon the levels of the cerebral biogenic monoamines norepinephrine, dopamine, and serotonin in the frontal cortex, striate, hippocampus, and hypothalamus of rats [312], found that adafenoxate increased norepinephrine levels in striate and decreased norepinephrine levels in hypothalamus, increased dopamine levels in the cortex and hypothalamus and decreased them in the striate, and increased serotonin levels in the cortex but decreased them in the hippocampus. Meclofenoxate induced decreases in norepinephrine levels in the cortex and hypothalamus, while it increased dopamine levels in hippocampus and hypothalamus, and serotonin levels in the cortex, striate, hippocampus, and hypothalamus. Administration of citicoline has also recently been shown to increase dopamine levels in the retina [313]. Mao et al [314] showed that an intraperitoneal injection of citicoline could retard the myopic shift induced by form deprivation in guinea pigs, which was mediated by an increase in the retinal dopamine level. Citicoline increases norepinephrine levels in cortex and hypothalamus, dopamine levels in striate, and serotonin levels in cortex, striate, and hippocampus, having a slightly different profile as compared to nootropic drugs. As regards action of citicoline upon norepinephrine, a study by López-Coviella et al [315] shows that administration of citicoline increased total urinary excretion of 3-methoxy-4-hydroxyphenylglycol, reflecting noradrenergic activity, in rats and humans, suggesting that citicoline increases norepinephrine release. Recently, citicoline has also been experimentally shown to be able to influence the relationship between excitatory (glutamate) and inhibitory (gamma-aminobutyric acid) amino acids at the brain cortex of rats [316]. A series of experiments assessed the potential of citicoline to produce a central cholinergic activation. Intracerebroventricular administration of citicoline was shown to cause an increase in levels of vasopressin [317] and other pituitary hormones [318], due mainly to central cholinergic activation. Same effect has been demonstrated after intravenous administration [319]. Citicoline has also been shown to have a pressor effect in cases of hypotensive animals [320], or even in cases of hypotension due to hemorrhagic shock [321,322]. Amín et al [323] study the effects of citicoline on cardiovascular function in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) -treated albino rats. MPTP is a chemical that changes into the neurotoxin 1-methyl-4-phenylpyridinium, which causes catecholamine depletion. In this model, citicoline increased cardiac norepinephrine and tyrosine hydroxylase and improved markers related to Reactive oxygen species scavenger, mitochondrial permeability, calcium homeostasis on the cellular level, metabolic homeostasis, and mitochondrial biogenesis. Authors conclude that citicoline improved cardiovascular dysautonomia and that was reflected on cardiac contractility, electrical activity, blood pressure, and vascular reactivity. Also, a contribution of the central histaminergic system is involved in this effect of citicoline [324]. The central cholinergic activating effect exerted by citicoline was again emphasized, involving this effect to explain the cardiovascular [325-328] and metabolic effects [329-332] of the drug. Citicoline also modulates cerebral metabolism through glutamate-linked enzyme activities [333]. Sbardella et al [334] shown that citicoline greatly affects the proteolytic activity of the 20S proteasome, functioning as a bimodal allosteric modulator, likely binding at multiple sites, suggesting its potential role as a regulator of proteostasis in nervous cells. Ilcol et al [335] observed that citicoline treatment alters serum lipid responses to endotoxin and prevents hepatorenal injury during endotoxemia through a nicotinic acetylcholine receptor mediated mechanism. CDP-choline attenuates scopolamine induced disruption of prepulse inhibition in rats thanks to the involvement of central nicotinic mechanisms [336]. Yilmaz et al [337] show that citicoline administration restores the abnormalities in the primary, secondary, and tertiary hemostasis and prevents the development of disseminated intravascular coagulation during experimental endotoxemia in dogs probably by increasing both neuronal and nonneuronal cholinergic activity. Kocaturk et al [338] show that treatment with citicoline improves functions of cardiovascular and respiratory systems in experimental endotoxemia in dogs and suggest that they may be useful in treatment of endotoxin shock in clinical setting. Doolittle et al [339] demonstrated that citicoline corrects alveolar type II cell mitochondrial dysfunction in influenza-infected mice through preventing the declines in oxidative phosphorylation, mitochondrial membrane potential, and cardiolipin synthesis.

Roohi-Azizi et al [340] concluded that administration of citicoline, as an adjuvant drug, in combination with citalopram, enhanced the effectiveness of selective serotonin reuptake inhibitors drugs for depression treatment in a mice model of depression. Khakpai et al [341] concluded that the administration of citicoline, as an adjuvant drug, in combination with imipramine increased the efficacy of tricyclic antidepressant drugs for modulation of pain and depression behaviors in mice.

Also, citicoline has antinociceptive effects involving the cholinergic system [342-344], opioid and gamma-aminobutyric acid receptors [345,346], the arginine-vasopressin system [347], and the Na^+/K^+ ATPase activity [348].

Citicoline, administered prior to thiopental sodium anesthesia, can improve brain function by decreasing the duration of lack of response to corneal reflex and also increasing the effect on analgesia duration [349], and a significant increase in heart and respiration rate, an insignificant increase in oxygen saturation and an insignificant decrease of rectal temperature in animals [350]. Citicoline also has a protective effect in models of epilepsy induced by xylocaine [351] and pentylenetetrazol [352,353], but not when the epilepsy is induced by pilocarpine [354]. Bekhet et al [355] aimed to formulate citicoline-loaded niosomes for efficient brain delivery via the intranasal route to improve management of epilepsy. The protection against pentylenetetrazol-induced generalized seizures and mortality were determined in rats and compared with the oral drug solution at the exact dosage. The in vivo results revealed that a low dose of citicoline-loaded niosomes in situ gel had a powerful protective effect with delayed the latency for the start of convulsions and this can be considered as a method to boost the efficacy of citicoline in epilepsy management.

Nashine and Kenney [356] characterized the cytoprotective effects of purified citicoline in transmitochondrial age-related macular degeneration retinal pigment epithelium cybrid cells which carry diseased mitochondria from clinically characterized age-related macular degeneration patients and demonstrated that citicoline downregulates apoptosis-associated genes and reduces caspase-3 and caspase-7-mediated apoptosis in this model, together with a reduction of the oxidative stress.

In reference to the intracellular signaling systems, it has been demonstrated an effect of citicoline on the following systems:

- Platelet- activating factor [357, 358].
- MAP kinase [271].
- ERK1/2 [232,246].
- Rho/Rho-kinase [359].
- Calpain [142].
- Phospholipase-thromboxane [360].
- Phospholipase-prostaglandin [361].
- Proinflammatory cytokines [143,362-366].

To sum up, the effects of citicoline in the experimental models used to reveal pharmacological actions upon the dopaminergic system have been studied. Citicoline has been shown to act as a dopaminergic agonist and has a particularly significant effect upon levels of dopamine and its metabolites in the corpus striatum. The results obtained suggest that, with citicoline administration, striatal dopamine synthesis is increased, probably through tyrosine hydroxylase activation. Increase in dopamine levels would partly result from inhibition of dopamine reuptake, possibly related to citicoline action upon phospholipids synthesis. In addition, citicoline also has some effects upon the other monoamines, serotonin and norepinephrine, muscarinic and nicotinic receptors, and glutamate, opioids and gamma-aminobutyric acid, together to important modulating effects on several intracellular signaling processes.

Learning performance, memory, and brain aging

It has been shown that hypobaric hypoxia decreases learning performance in rats undergoing sound avoidance conditioning, and that this effect may be antagonized by pretreatment with apomorphine or other dopaminergic agonists. These effects of hypoxia appear in relation to an inhibition of metabolism of cerebral catecholamines that would be ultimately responsible for an understimulation of central postsynaptic dopaminergic receptors. Based on these assumptions, Saligaut and Boismare [206] conducted a study on the effects of citicoline administration upon learning performance in rats subjected to hypobaric hypoxia. Under hypoxic conditions, citicoline was administered at 300 mg/kg/day for 12 days to a group of rats that underwent learning tests of a sound avoidance conditioning in the last five days of treatment. Effects seen in this group were compared to those seen in another group receiving apomorphine 0.5 mg/kg 30 minutes before each daily conditioning session and to those recorded in animals receiving both treatments. A group of animals acted as control and received an ascorbic acid solution under the same experimental conditions. Citicoline partially restored learning performance. The same effect, but to a lesser extent, was seen with administration of apomorphine and with combined administration of both drugs. These results suggest that administration of citicoline counteracts, as with dopaminergic agonists, the effects of hypoxia. Previously we commented the protective effect of citicoline against the cognitive impairment induced by chronic cerebral hypoperfusion [253].

Drago et al [367] administered citicoline 10-20 mg/kg/day intraperitoneal for 20 days to 24-month-old Sprague-Dawley male rats from a strain showing cognitive and motor deficits. The drug was also given to rats with behavioral changes induced by a single injection of scopolamine, a cholinergic antagonist, by prenatal exposure to methylazoxymethanol, or by bilateral injections of kainic acid into the magnocellular basal nuclei. In all cases, citicoline improved learning and memory performance, evaluated using active and passive avoidance tests. In the old rat group, improved motor capacity and coordination was also seen. For these authors, these results suggest that citicoline affects the central mechanisms involved in cognitive behavior, probably through a cholinergic action.

In a model of scopolamine-induced memory impairment, Petkov et al [368] showed citicoline to be able to prevent amnesia induced by scopolamine. Subsequently, Mosharrof and Petkov [369] showed that citicoline 100 mg/kg completely prevented amnesia induced by scopolamine, as did the association of citicoline 50 mg/kg and piracetam 500 mg/kg, also causing a significant increase in retention. Authors suggested that this effect is mediated by drug actions on neurotransmission. Takasaki et al [370] suggest that citicoline has ameliorative effect on the impairment of spatial memory induced by scopolamine, reducing the neuronal death and improving the impaired cholinergic signal. Citicoline acts as a memory-enhancing drug, and this effect is particularly marked in animals with memory deficits [371]. On the other hand, Álvarez et al [372] showed that citicoline antagonized amnesia induced by bromazepam in rats. Bruhwyler et al [373] found that chronic administration of citicoline has facilitating effects on learning and memory processes in dogs, but does not affect the established capacities and does not show, in this model, any effect on the motor, neurovegetative, or motivational systems. According to these authors, this represents an argument in favor of the selectivity of drug action in memory processes. Citicoline has even been shown to have a protective effect against mnesic disorders in aged animals [374] and in animals in isolation conditions [375] when administered as a dietary supplement, as well as in spontaneously hypertensive rats [376]. Ahmad et al [377] compare the relative efficacy of nootropics like piracetam, modafinil and citicoline on learning and memory in rats using the Morris water maze test. A total of 30 Wistar rats were used for the study. The animals were divided into five groups ($n = 6$). The groups I to V received gum acacia orally, scopolamine 2 mg/kg intraperitoneally, piracetam (52.5 mg/kg), modafinil (2.5 mg/kg), citicoline (25 mg/kg) respectively orally for 20 days. Learning and memory was evaluated using the Morris water maze test. The animals were trained in the Morris water maze on the last five days of dosing. Scopolamine 2 mg/kg was administered intraperitoneally to the above groups of animals (except groups I and II) for induction of amnesia, 45 minutes before the behavioural test. Scopolamine induced marked impairment of memory evidenced by significant reduction ($p < 0.01$) in the number of entries and time spent in the target quadrant when compared to the control group. There was significant ($p < 0.05$) increase in the number of entries and time spent in target quadrant of the Morris water maze in the animals who were pre-treated with piracetam, modafinil and citicoline, in comparison to the scopolamine treated group. Amongst the three nootropics, modafinil and citicoline showed significant ($p < 0.05$) memory enhancement in comparison to piracetam. Abdel-Zaher et al [378] investigated the potential protective effect of citicoline on aluminum chloride-induced cognitive deficits in rats, and demonstrated, for the first time, that citicoline can protect against the development of these cognitive deficits through inhibition of aluminum-induced elevation of glutamate level, oxidative stress, and nitric oxide overproduction in the hippocampus. Hosseini-Sharifabad et al [379] showed that magnesium increases the protective effect of citicoline on aluminum chloride-induced cognitive impairment in mice.

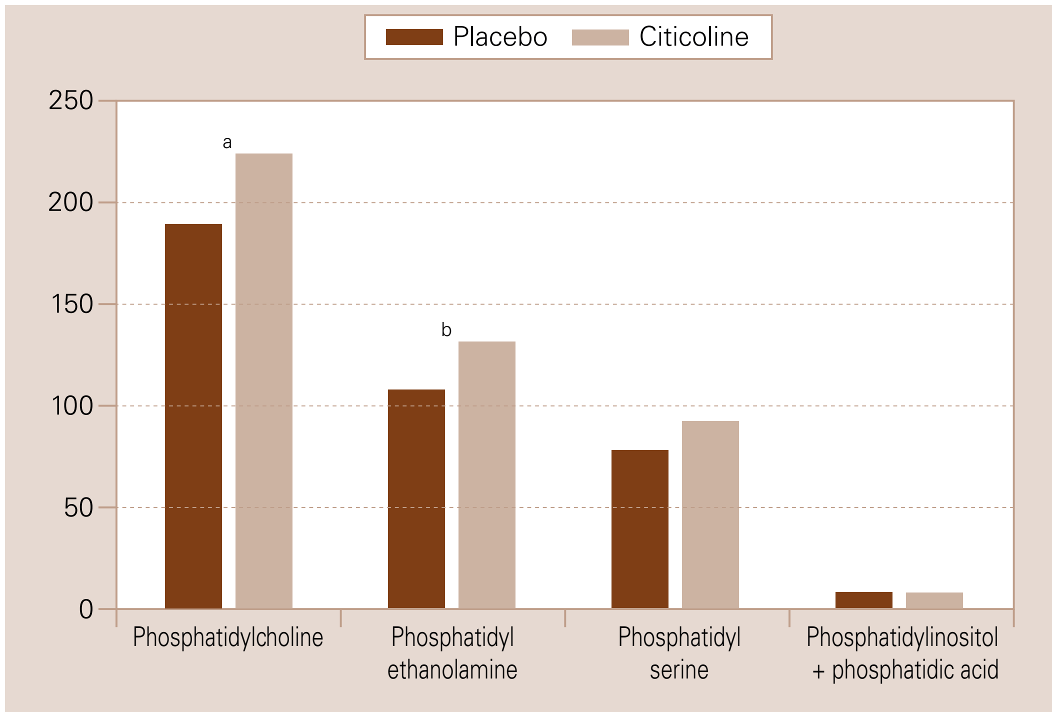
Cakir et al [380] investigated the effects of citicoline on the well-known negative effects of rapid eye movements sleep deprivation on learning and memory in adult male Wistar albino rats, and the results obtained suggest that citicoline reduces rapid eye movements sleep deprivation-induced impairment in memory, at least in part, by counteracting the disturbances in biochemical and molecular biological parameters.

Safavi et al [381] compare the individual effects of benfotiamine and citicoline and their co-administration on memory impairments in diabetic mice. Diabetes was induced by a single dose of streptozotocin (140 mg/kg, intraperitoneal) and benfotiamine and/or citicoline were administered for three weeks. Memory was evaluated using the object recognition task and passive avoidance test. In passive avoidance test, co-administration of benfotiamine and citicoline was more effective than either alone in improving memory. Regarding object recognition task, although benfotiamine added to citicoline improved memory notably, the difference between combination therapy and single-drug therapy was not considerable.

There are multiple morphological, neurochemical, and physiological changes characterizing brain aging in mammals. General agreement exists between investigators on the existence of aged-related changes in certain neurochemical parameters, such as enzyme activity, receptor binding, and neurotransmission. Biochemical evidence is available of the existence of a component of cholinergic dysfunction and impaired cerebral phospholipids metabolism in the pathophysiology of brain aging [1,4,5]. De Medio et al [382] investigated the effects of citicoline upon changes in lipid metabolism in the brain during aging. Thus, they measured in vivo lipid synthesis in different brain areas from 12-month-old male rats. For this, they administered, by injection in the lateral cerebral ventricle, a mixture of (2-^{3}H)glycerol and (Me-^{14}C)choline, as lipid precursors, and measured, one hour after isotope administration, incorporation of these precursors into the fractions of total lipids, water-soluble intermediates, and choline phospholipids. In another series of experiments, citicoline was injected intraventricularly to aged rats 10 minutes before killing, and the same radioactivity tests as described above were performed. Distribution of the radioactivity contained in citicoline in the brain 10 minutes following administration showed enrichment, in the studied areas, of nucleotides and related water-soluble compounds. Incorporation of labelled glycerol, that is greatly decreased in aged rats, increased in all areas. Incorporation of labelled choline also decreases with aging, and citicoline was able to increase such incorporation in the cortex. As a result, the ^{3}H/^{14}C ratio was increased in total lipids and in phosphatidylcholine and choline plasmalogens following citicoline treatment. Following this line of research, López-Coviella et al [383] studied the effects of oral citicoline on phospholipids content in mouse brain. These authors supplemented animal diet with citicoline 500 mg/kg/day for 27 months in 3-month-old mice, and for 90, 42, and 3 days in 12-month-old mice, after which phosphatidylcholine, phosphatidylethanolamine and phosphatidylserine levels, and contents of phosphatidylinositol plus phosphatidic acid were measured in brain cortex. After 27 months of treatment, phosphatidylcholine and phosphatidylethanolamine levels significantly increased by 19 and 20% respectively, while phosphatidylserine levels increased by 18%, but statistical significance was not reached (Fig. 10). Similar increases were noted when 12-month-old animals were treated for three months, but not with shorter treatment periods. These results suggest that chronic administration of citicoline may have significant effects on phospholipid composition of the brain that may partly be responsible for the reported therapeutic efficacy of this drug. Wang and Lee [384] obtained similar results in their study. Plataras et al [385] showed citicoline to be able to restore activity of hippocampal acetylcholinesterase and Na^+/K^+ pumps, involving these mechanisms in the improvement of memory performance exerted by citicoline. Zhang et al [386] suggest the citicoline could play a role in improving memory performance and exert protective effects against Alzheimer's disease by increasing expression or activity of Na^+/K^+-ATPase. Giménez et al [387] showed that citicoline, administered for two months to aged rats, caused a significant activation of cytidine triphosphate:phosphocholine cytidyltransferase, which according to authors would explain the reparative effects of the drug on damaged membranes of aged animals. This same investigating team made a more extensive study of the effects of citicoline on the activity of this enzymatic system and showed that, in addition to its effect on phospholipid metabolism, citicoline also has a regulatory effect upon platelet activating factor levels in the brain [357,358]. All such effects occur with no changes in plasma levels of homocysteine, a known risk factor [388]. However, citicoline also offers beneficial actions on brain metabolism of nucleic acids and proteins [385,389-391], on dopaminergic, nicotinic and muscarinic receptors [324], and on neuroendocrine and neurosecretory changes [392-394] in experimental aging models, as well as a neuroprotective effect against neurotoxic aggressions [394-402], an immunomodulatory effect [403], and an antiapoptotic effect [404,405] in various models of neurodegeneration and cerebrovascular dementia. Sahraiian and Khazali [406] showed that citicoline, as ghrelin, improves passive avoidance learning by altering the N-methyl-D-aspartate receptor (NMDAR1) and the serotonin receptor 1A (HTR1a) expression in the hippocampus in adult male rats.

Because of such actions, various studies have shown the positive effects of citicoline on learning and memory in aged animals [373,407,408]. Based on these effects and the effects on neuroplasticity [409] and on proliferation and differentiation of astroglial cells [15,410] it has been postulated the use of citicoline in neurodegenerative diseases, but

Figure 10. Effect of chronic administration of citicoline on the brain titres of phospholipids in 30-month-old mice fed a dietary supplement with citicoline (500 mg/kg/day) or placebo for 27 months. [a] $p < 0.05$; [b] $p < 0.01$.



there are some exceptions, such the no protective effect of the drug in a model of Huntington's disease [411] and in a model of amyotrophic lateral sclerosis [412]. Gromova et al [413] considered that the pharmacological effects of CDP-choline are realized via multiple molecular mechanisms contributing to the nootropic actions of this molecule in different experimental models.

Experimental withdrawal syndrome and intoxications

If citicoline 300 mg is injected by the intracarotid route to cats, effects similar to those seen with administration of 2 mg of morphine by the same route are obtained. The animal shows symptoms of anger and alertness, and the tail is placed in a rigid and upright position. This finding led to think that both substances could have some parallel effects at neuroreceptors of endogenous opiates, and that administration of citicoline could be of value in the opiate withdrawal syndrome by slowing the effects of sudden drug discontinuation [414]. Tornos et al [415] studied the effects of citicoline administration upon experimental withdrawal syndrome by analyzing various methods, such as the jumping test in mice and studies of the behavior and body temperature changes in rats. The withdrawal syndrome caused by administration of naloxone to morphine-dependent mice was assessed based on the number of jumps by the animals. A decrease in severity was seen in the group of animals treated with citicoline 2 g/kg p.o. as compared to the untreated animal group. This decreased severity of the withdrawal syndrome was demonstrated by a 39% decrease in the mean number of jumps by the animals within 10 minutes of administration of the opiate antagonist. Similarly, the behavioral study in morphine-dependent rats showed that administration of an oral dose of citicoline 2 g/kg at the same time as naloxone was able to significantly decrease the severity of manifestations that characterize the withdrawal picture provoked. As regards hypothermia caused by naloxone administration in morphine-dependent rats, administration of a single oral dose of citicoline neutralizes such effect almost completely. Nejati et al [416] studied the effects of intraperitoneal injections of citalopram and citicoline on morphine-induced anxiolytic effects in non-sensitized and morphine-sensitized mice and demonstrated a synergistic effect of citalopram and citicoline upon induction of anti-anxiety behavior in non-sensitized and morphine-sensitized mice.

Characteristic findings of fetal alcohol syndrome include delayed maturation and late development of dendrites in neocortex, hippocampus, and cerebellum. Based on these data, Patt et al [417] conducted a study to investigate the effects of citicoline on Purkinje cells from rats newborn from alcoholic dams, showing that this stabilizing agent of neuronal membranes decreases the harmful effect of alcohol on the central nervous system. Wang and Bieberich [418] demonstrated that prenatal alcohol exposure triggers ceramide-induced apoptosis in neural crest-derived tissues concurrent with defective cranial development and that treatment with CDP-choline may alleviate the tissue damage caused by alcohol. Petkov et al [419] have also shown that citicoline decreases mnesic deficits in rats pre- and post-natally exposed to alcohol, which may be related with the beneficial effects upon acetylcholine synthesis and release shown using cerebral microdialysis in rats chronically exposed to alcohol [420,421]. Citicoline has also shown a protective effect in nicotine intoxication [422] and in mercury intoxication [423]. Buelna-Chontal et al [424] demonstrated that citicoline circumvents mercury-induced mitochondrial damage and renal dysfunction in a model of renal failure in rats. Laksmita et al [425] demonstrated the potential benefits of citicoline for management of ocular methanol intoxication in an experimental rat model.

Aminzadeh and Salarinejad [426] analyzed the effect of citicoline on lead-induced apoptosis in PC12 cells and their findings revealed that citicoline exerts a neuroprotective effect against lead-induced injury in PC12 cells through mitigation of oxidative stress and at least in part, through suppression of mitochondrial-mediated apoptotic pathway. Gudi et al [427] tried to confirm previous results showing that citicoline improves remyelination and to determine the potential regenerative effects of lower doses of citicoline (100 and 50 mg/kg). The effects of citicoline were investigated in the toxic cuprizone-induced mouse model of de- and remyelination. The authors found that even low doses of citicoline effectively enhanced early remyelination. The beneficial effects on myelin regeneration were accompanied by higher numbers of oligodendrocytes. They concluded that citicoline could become a promising regenerative substance for patients with multiple sclerosis and should be tested in a clinical trial. Shaffie and Shabana [428] indicated that citicoline treatment can protect against toluene-induced toxicity in rats.

Masoud et al [429], in an experimental study in mice, showed that dexamethasone and citicoline attenuate the cisplatin-induced peripheral neuropathy through an anti-inflammatory effect, improving antioxidant capacity, and inhibiting lipid peroxidation.

Zhong et al [430] concluded that citicoline can protect against neomycin-induced hair cell loss by inhibiting reactive oxygen species aggregation and thus preventing apoptosis in hair cells, and this suggests that citicoline might serve as a potential therapeutic drug in the clinic to protect hair cells and thus preventing hearing loss associated to aminoglycoside use.

Toxicity

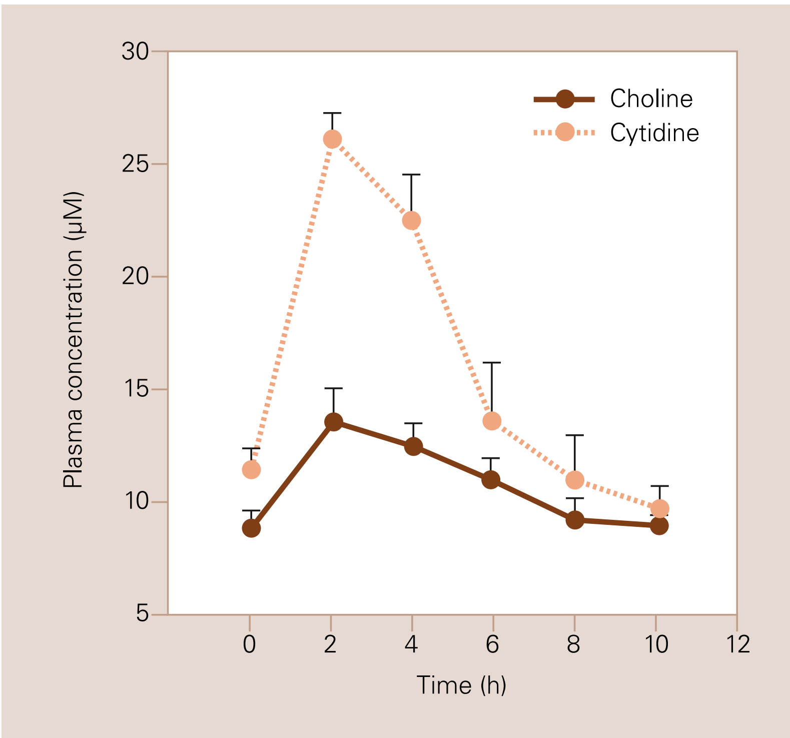
Acute toxicity

Acute toxicity from single citicoline administration has been studied in various animal species and using different administration routes. The intravenous LD_{50} in mice, rats, and rabbits is 4.6, 4.15, and 1.95 g/kg, respectively [431,432]. Oral LD_{50} is 27.14 g/kg in mice and 18.5 g/kg in rats [433]. The intravenous LD_{50} of citicoline is approximately 44 times higher than the LD_{50} of choline hydrochloride at equivalent doses, and it has been shown that choline doses inducing cholinergic crises do not cause any toxicity sign when equivalent doses of citicoline are administered [434,435]. This suggests that administration of choline has metabolic implications clearly different from those of exogenous choline administration. The administration of 2,000 mg/kg of citicoline p.o. during 14 days was well tolerated [436].

Subacute toxicity

Intraperitoneal administration to rats of doses up to 2 g/kg/day of citicoline for 4.5 weeks did not results in clinical toxicity signs or significant changes in the hematological, biochemical, or histological parameters analyzed. A slight decrease in intake and weight gain was only seen from two weeks of the study [433]. Similar results were seen following

Figure 11. Plasma concentrations of choline and cytidine immediately after administration of a single oral dose of 2 g citicoline in humans.



subcutaneous administration to male rats of up 1 g/kg for four weeks [432]. Oral administration of 1.5 g/kg/day to rats for 30 days did not cause weight, hematological, biochemical, or histological changes [437].

Chronic toxicity

Chronic oral (1.5 g/kg/day for 6 months in dogs) and intraperitoneal (1 g/kg/day for 12 weeks in rats) toxicity studies did not reveal either significant abnormalities related to drug administration [432,438]. Intravenous administration of citicoline 300-500 mg/kg/day for three months in dogs only caused toxic signs immediately after injection, including vomiting and occasional diarrhea and sialorrhea [435]. In a 90-day study in rats, 100, 350, and 1,000 mg/kg/day oral doses resulted in no mortality. In males, slight significant increases in serum creatinine (350 and 1,000 mg/kg/day) and decreases in urine volume (all treated groups) were observed. In females, slight significant increases in total white blood cell and absolute lymphocyte counts (1,000 mg/kg/day), and blood urea nitrogen (100 and 350 mg/kg/day) were noted. A dose-related increase in renal tubular mineralization, without degenerative or inflammatory reaction, was found in females (all treated groups) and two males (1,000 mg/kg/day). Renal mineralization in rats (especially females) is influenced by calcium:phosphorus ratios in the diet. A high level of citicoline consumption resulted in increased phosphorus intake in the rats, and likely explains this result [436].

Teratogenicity

Citicoline was administered to albino rabbits at a dose of 800 mg/kg during the organogenesis phase, i.e., from days 7th to 18th of pregnancy. Animals were killed on day 29th, and a detailed examination was made of fetuses and their mothers. No signs of maternal or embryofetal toxicity were seen. Effects on organogenesis were imperceptible, and only a slight delay in cranial osteogenesis was seen in 10% of treated fetuses (unpublished data).

Pharmacokinetics

Plasma level curves. Bioavailability

Labelled citicoline (methyl ^{14}C) was administered to rats at a dose of 4 mg/kg by jugular vein injection and by the oral route using a nasogastric tube [439]. The results obtained, expressed as percent radioactivity in 10 mL of blood for each administration route, are shown in table II. From these data, the ratio between bioavailability of the oral and the intravenous administration route was estimated and found to be virtually one, which agrees with the fact, demonstrated in the same study, that no residual radioactivity is found in feces excreted in the 72 hours following oral administration.

López-Coviella et al [440] studied the effects of citicoline on plasma levels of cytidine, choline, and CDP-choline in healthy volunteers receiving the substance by the oral or intravenous route and in rats treated by the intravenous route. Two hours following administration of a single oral dose of citicoline 2 g, choline plasma levels increased 48%, and cytidine plasma levels 136% (Fig. 11). In individuals receiving three 2 g doses at two-hour intervals, choline plasma levels reached a peak, representing approximately 30% of baseline value, four hours after administration of the initial citicoline dose, while cytidine plasma levels increased up to six hours (Fig. 12) and were five-fold higher than the baseline value ($p < 0.001$). Citicoline administered by the intravenous route was rapidly hydrolyzed in both humans and rats [441]. In healthy individuals receiving a citicoline infusion of 3 g in 500 mL of physiological saline over 30 minutes, CDP-choline levels were virtually undetectable just after the end of the infusion period, when plasma levels of cytidine and choline reached a peak, though their concentrations remained significantly increased up to six hours after the start of infusion (Fig. 13). These observations show that citicoline, administered by both the oral and intravenous routes, is converted into two major circulating metabolites, cytidine and choline. However, plasma cytidine is converted in humans to uridine, its circulating form, that is transformed in the brain to uridine phosphate, that will in turn be converted to cytidine triphosphate at neuronal level [442].

Tissue diffusion and distribution. Transport and metabolism

Tissue diffusion of citicoline and its components has been studied in rats intravenously administered (methyl ^{14}C, 5-^{3}H) citicoline, labelled in the choline and the cytidine fraction [443,444]. In the same battery test, plasma radioactivity levels were measured for 30 minutes following administration. Renal and fecal excretion of labelled metabolites was also measured for 48 hours. As early as two minutes following injection, less than 10% of administered radioactivity was found in plasma. In addition, radioactivity excreted by the kidney during the first 48 hours only accounted for 2.5% of ^{14}C and 6.5 % of ^{3}H administered. In the same time interval, fecal excretion did not exceed 2% of the administered dose. These results suggest that citicoline rapidly diffuses to tissue following administration and is actively used by tissues. Figure 14 shows the radioactivity levels found in liver, brain, and kidney at different time points following intravenous administration of dually labelled citicoline. There is a special interest in changes in brain levels. Radioactivity uptake by the brain gradually increases for the first 10 hours after drug administration, and the levels achieved remain unchanged at 48 hours.

In a group of animals, radioactivity levels of the labelled compounds were measured in the brain at 0.5, 1, 4, and 48 hours of administration of dually labelled citicoline. Radioactivity corresponding to

Figure 12. Plasma concentrations of choline and cytidine immediately after administration of three consecutive oral doses (2 g) in humans.

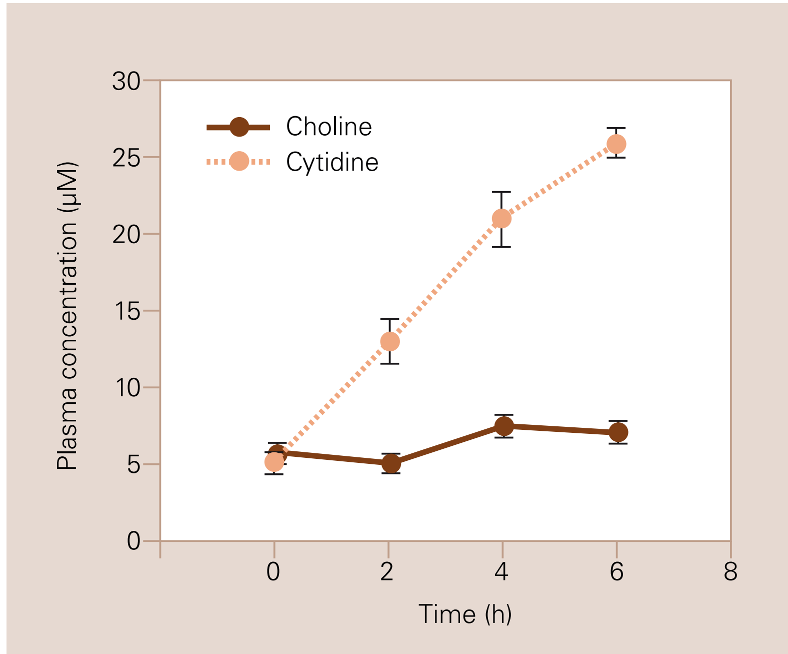
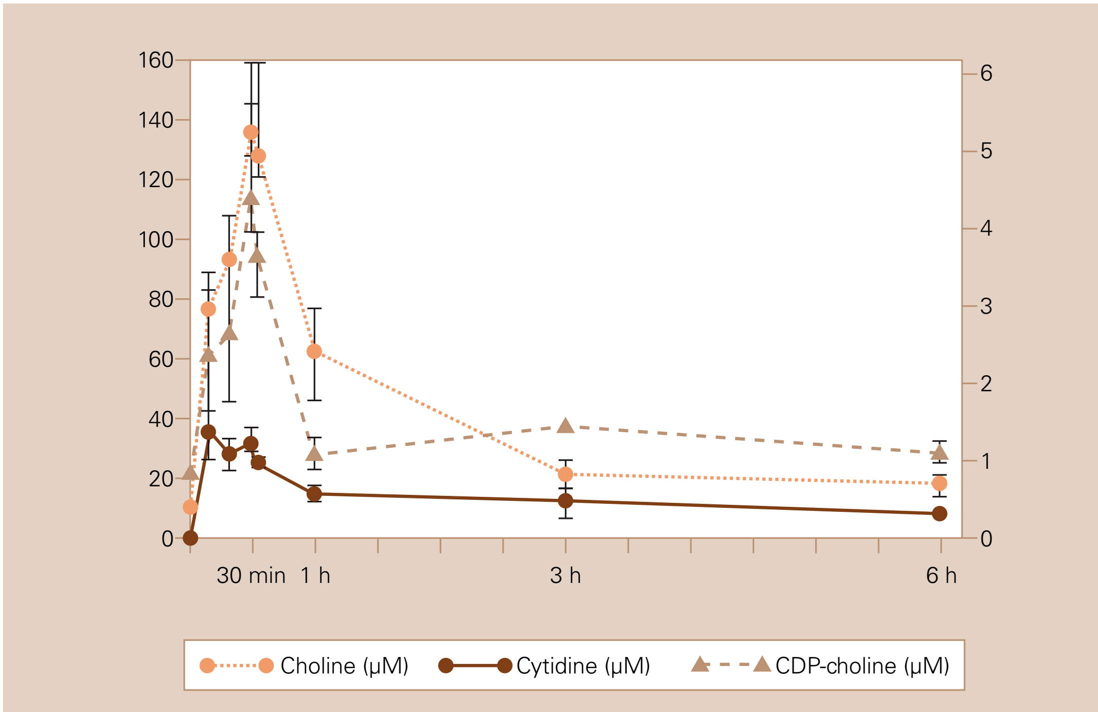


Table II. Blood kinetics of the total radioactivity of 4 mg/g methyl ^{14}C-citicoline after oral or intravenous administration to male rats. The percentages of radioactivity (mean ± SD) with respect to the total administered are shown.

Time	Oral route	Intravenous route
10 min	0.26 ± 0.12	3.05 ± 0.24
20 min	0.40 ± 0.02	2.59 ± 0.31
30 min	0.74 ± 0.01	1.47 ± 0.22
1 h	1.32 ± 0.40	1.40 ± 0.02
2 h	2.33 ± 0.63	2.84 ± 0.02
3 h	3.31 ± 0.86	2.50 ± 0.05
4 h	3.57 ± 0.88	2.77 ± 1.00
5 h	4.17 ± 0.83	3.37 ± 0.31
6 h	4.18 ± 0.03	3.68 ± 0.02
7 h	3.81 ± 0.73	–
24 h	2.48 ± 0.40	3.12 ± 0.19

Figure 13. Concentrations of choline, cytidine and CDP-choline in human plasma after intravenous infusion of a solution of citicoline (3 g/500 mL physiological saline solution).



^3H in the brain was mainly concentrated in cytidine nucleotides at the beginning, but subsequently concentrated in nucleic acids. As regards compounds labelled with ^{14}C, the highest levels initially corresponded to betaine, choline, and phosphorylcholine, while at four hours ^{14}C-methionine and ^{14}C -phospholipids accounted for 26.4 and 24.2% respectively of total cerebral radioactivity corresponding to ^{14}C. At 48 hours, this radioactivity mainly concentrated in phospholipids and proteins. Thus, labelled phospholipids were seen to continuously increase in the 48 hours following administration of dually labelled citicoline. As shown in figure 15, such increase is fast in the first five hours, but then becomes slower.

In another test battery, the presence of the drug in various brain areas and its distribution in cerebral ultrastructures was measured following administration of (methyl ^{14}C) citicoline [445-449]. In a study performed with high-performance autoradiography in mouse brain 24 hours following administration of labelled citicoline [445], the radioactive marker was seen to be widely incorporated into the different cerebral areas studied, brain cortex, white matter, and central grey nuclei. It was found in both intra and extracellular spaces, with a particular presence in cell membranes. In the same experimental model, but 10 days following administration of the labelled drug [446], concentration of radioactivity in the more myelinated areas was seen, as well as a marked uptake by the cerebellar Purkinje cells. Using low-performance autoradiography, distribution of radioactivity of labelled citicoline in rat brain was analyzed five and 24 hours after drug administration [447]. At 24 hours, most radioactivity was detected at intracellular level. In another study, incorporation of radioactivity from (methyl ^{14}C) citicoline after oral administration to male Sprague-Dawley rats was analyzed in the different cerebral phospholipid fractions [448]. Of total radioactivity measured in brain, 62.8% was found to be part of brain phospholipids, particularly phosphatidylcholine and sphingomyelin, showing that citicoline administered by the oral route influences the synthesis of structural phospholipids of cell membranes. These results agree with those obtained by Aguilar et al [449], who showed radioactivity from labelled citicoline to be associated to cytoplasmic and mitochondrial membranes in brain homogenate.

In conclusion, these studies show that the citicoline administered is widely distributed in brain structures, with a rapid incorporation of the choline fraction into structural phospholipids, and of the cytosine fraction into cytidine nucleotides and nucleic acids. Citicoline reaches the brain and incorporates actively into the cytoplasmic and mitochondrial cell membranes, being part of the structural phospholipid fraction [441,450,451].

Elimination route and kinetics

When labelled citicoline is administered by either the oral or intravenous route, radioactivity is eliminated very slowly by the urinary or fecal route and in expired CO_2 [452].

Figure 16 shows total radioactivity excretion for the five days following oral administration of ^{14}C citicoline to healthy volunteers. Table III gives the main data on the elimination kinetics of the product.

Two phases are differentiated in urinary elimination of the drug: a first phase, lasting approximately 36 hours, in which excretion rate decreases rapidly, and a second phase in which excretion rate decreases much more slowly. The same occurs with expired CO_2, whose elimination rate decreases rapidly for the first 15 hours, approximately, after which a slower decrease is seen.

Clinical experience

Head injury and sequelae

The above reported experimental studies showed that administration of citicoline led to a significant regression of brain edema and improvements in the electroencephalographic tracing and impairment of consciousness, as well as in survival quality. The effect on consciousness level is attributable to the facilitating action of the electroencephalographic arousal reaction, induced by stimulation of the ascending reticular activating system at brain stem level.

Based on these experimental assumptions, many clinical trials have been conducted to verify if these effects have some implications for treatment of patients with traumatic brain injury.

Figure 14. Concentrations of radioactivity in the liver (a), brain (b) and kidneys (c) of rats at different time points after injecting double-labelled citicoline at a dose of 2 mg/kg. All values represent the means obtained from 10 animals.

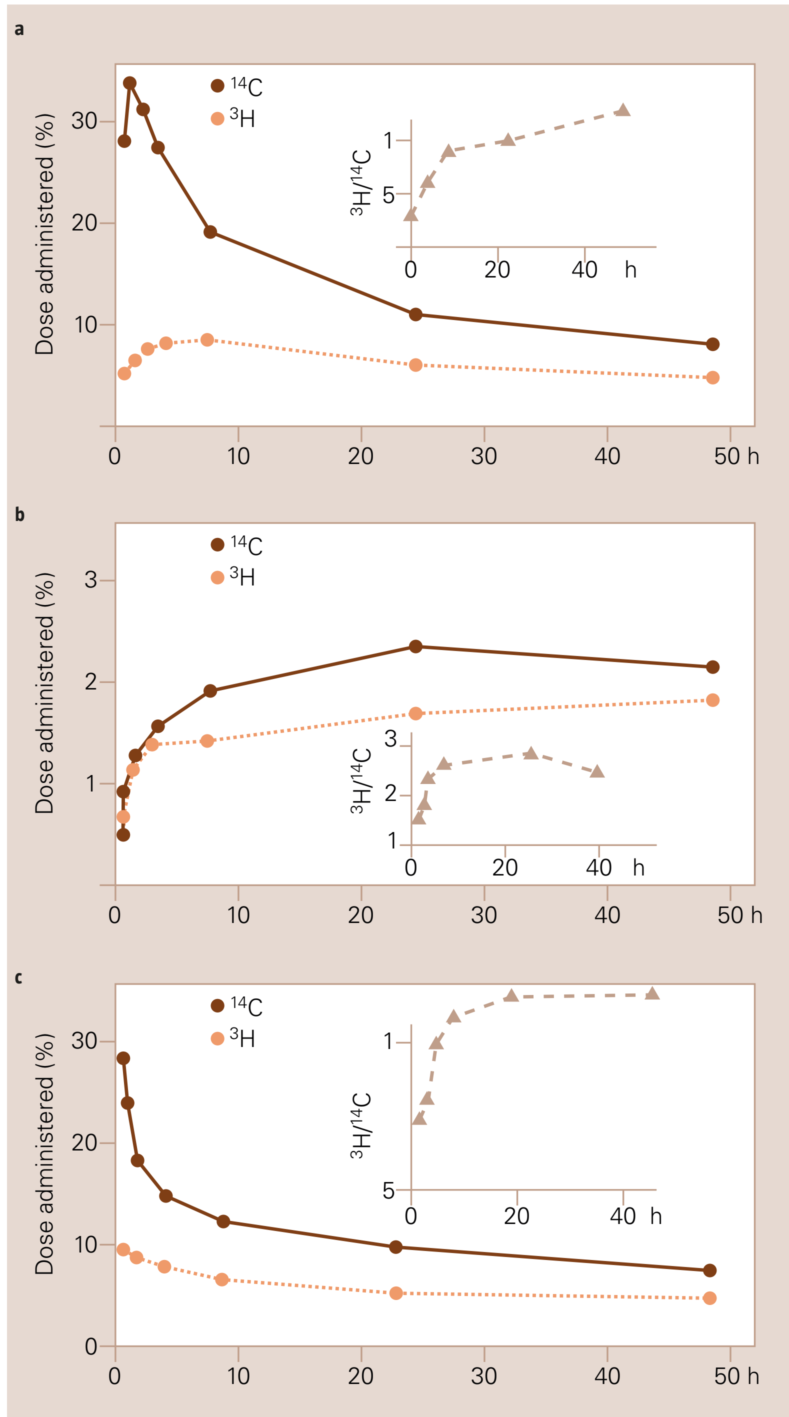


Table III. Most significant parameters in the elimination kinetics of ^{14}C-citicoline after oral administration. Data show the means of six individuals.

	CO_2	Urine	Faeces
Maximum rate of excretion (% dose/h)	1.22 ± 0.59	0.159 ± 0.084	0.021 ± 0.008
Time of maximum excretion (h)	1.60 ± 0.73	1.3 ± 0.8	56 ± 18
First phase of elimination			
Apparent half-life	2.58 ± 0.60	6.62 ± 1.28	–
Apparent rate of elimination (% dose/h)	0.279 ± 0.055	0.107 ± 0.017	–
Second phase of elimination			
Apparent half-life (h)	56.22 ± 33.39	71.08 ± 58.16	19.39 ± 6.63
Apparent rate of elimination (% dose/h)	0.030 ± 0.049	0.013 ± 0.006	0.039 ± 0.014

In 1967, Moriyama et al [453] published their study on the effects of citicoline in 25 patients with head injury and depressed consciousness. The drug was shown to be effective, leading to recovery from neurological clinical symptoms and return to a conscious state, in 70% of cases, and was very well tolerated, causing no side effects.

Ayuso and Saiz [454] conducted a double-blind study on the value of citicoline in mnesic dysfunction induced by bilateral electroshock in a series of 22 patients admitted to hospital for an endogenous depression. The group receiving active drug had a lower reduction in memory performance after four electroshock sessions as compared to the control group, thus showing the value of citicoline for treatment of patients with memory disorders of an organic base.

De la Herrán et al [455] compared the effects of citicoline administration in a series of 50 patients with an impaired level of consciousness, of a traumatic origin in 32 cases, to another series of patients with similar characteristics who were receiving standard treatment. 34% of patients recovered consciousness within 48 hours. After a few days, 66% of patients had recovered consciousness. These results were better than those achieved in the control group. With these results, authors showed that citicoline reactivates and accelerates normalization of the consciousness stated in patients with head injury.

Carcassonne and LeTourneau [456] conducted a double-blind study in a series of 43 children with a true consciousness disorder of a traumatic origin, after excluding severe cases and those requiring surgical treatment. After analyzing the results obtained, these authors arrived to the following conclusions:

- Citicoline is very well tolerated, both locally and systemically.
- Citicoline significantly accelerates recovery of a normal consciousness state.
- Citicoline accelerates disappearance of neuropsychological disorders and cerebral electrogenesis disorders.
- Citicoline confers a better quality to the course of patients.

Espagno et al [457] compared the effects of citicoline versus placebo in a series of 46 patients who had sustained a head injury. For this, authors conducted a double-blind study in which 22 patients received citicoline 250 mg/day by the parenteral route for 20 days, while 24 patients were given placebo. The results obtained showed that, in mild coma, citicoline significantly accelerated ($p < 0.05$) recovery of consciousness, while in more severe coma and at the administered dose, that is currently considered to be highly inadequate, citicoline improved prognosis, so that 75.2% of patients in the placebo group showed a late recovery (>15 days) of consciousness and/or progressed to death. By contrast, in the group treated with the active product, recovery from coma beyond the 15th day occurred in 31% of cases, and incidence of prolonged coma and/or death was 12.5%. In conclusion, citicoline resulted in an earlier recovery of consciousness and an increased number of clinical and electroencephalographic improvements and was also very well tolerated.

Richer and Cohadon [458] conducted a double-blind study in a group of 60 patients with coma of a traumatic origin who were distributed into two homogeneous groups, one of which was given the active drug, and the other placebo. As regards coma duration, the number of patients who had recovered consciousness at 60 days was significantly greater ($p < 0.01$) in the group treated with citicoline. After 90 days, a greater recovery ($p < 0.04$) from the motor deficit was found in the citicoline-treated group. Gait recovery was also shown to be significantly accelerated in the active drug group. As a result, a greater social and occupational reinsertion was found at 60 days in the group treated with citicoline ($p < 0.06$). This demonstrated the limiting effect of duration of posttraumatic coma of citicoline, as well as its participation in restoration of deficits related to the brain lesions associated to such coma. However, there were no changes in mortality associated to the treatments.

Lecuire and Duplay [459], in a double-blind trial, compared the effects of citicoline, at an intravenous dose of 750 mg/day, to those of meclofenoxate at 3 g/day intravenous in a group of 25 patients. An analysis of the results showed a significant improvement in the patient group treated with citicoline, particularly as regarded recovery of consciousness, electroencephalographic changes, and functional recovery. Mean coma duration was 10 days in the citicoline group, as compared to 20 days in the meclofenoxate group. At 10 days, electroencephalographic tracings had improved in 50% of citicoline-treated patients and in 18% of patients given meclofenoxate. Citicoline was therefore shown to be superior to meclofenoxate, and its main characteristic was accelerated recovery of the consciousness level, that is related to improvement in the electroencephalographic tracing. These same authors carried out an open label study in a series of 154 patients with head injury [460]. This study assessed the effects of citicoline treatment and found the drug to accelerate patient arousal and recovery from deficit syndromes, and to improve the quality of survival. Lecuire [461] subsequently performed a double-blind study comparing piracetam (6 g/day) versus citicoline (750 mg/day) in a group of 40 patients sustaining head injury and found a favorable course in 75% of patients in the citicoline group, as compared to 33% in the piracetam group.

Cohadon et al [21,462] showed the clinical efficacy of citicoline in a double-blind study conducted on a series of 60 patients with severe head injury. A standard treatment was used in both groups, and surgery was performed when required. A group of patients was given citicoline 750 mg/day by the intravenous route for the first six days, and subsequently by the intramuscular route for an additional 20 days. The other group was administered placebo. Clinical evaluation was continued up to six months. At 15 days, response to painful stimuli was already superior in the group of citicoline-treated

Figure 15. Evolution of ^{14}C-phospholipid concentrations in rat brains after intravenous administration of double-labelled citicoline. The concentrations represent the means of three animals and are expressed as a percentage of the total radioactivity corresponding to ^{14}C in the brain.

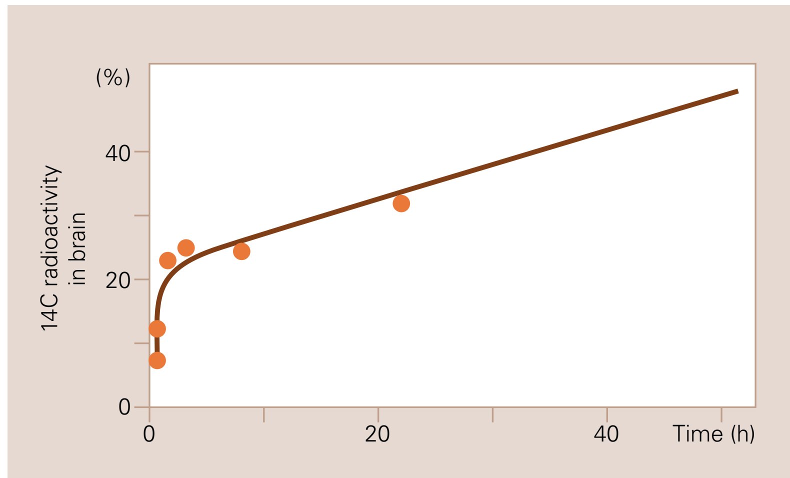


Figure 16. Total excretion of radioactivity (percentage of total administered) for 5 days after oral administration of ^{14}C -Citicoline. The mean values of six individuals are shown.

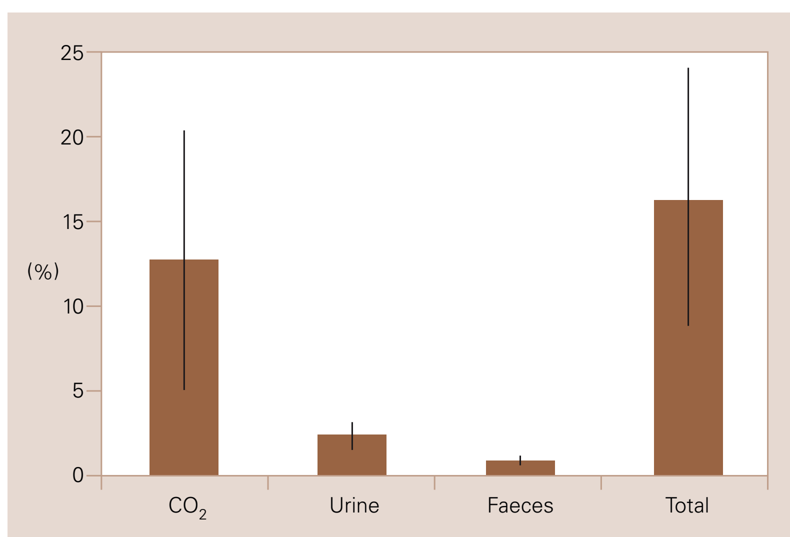
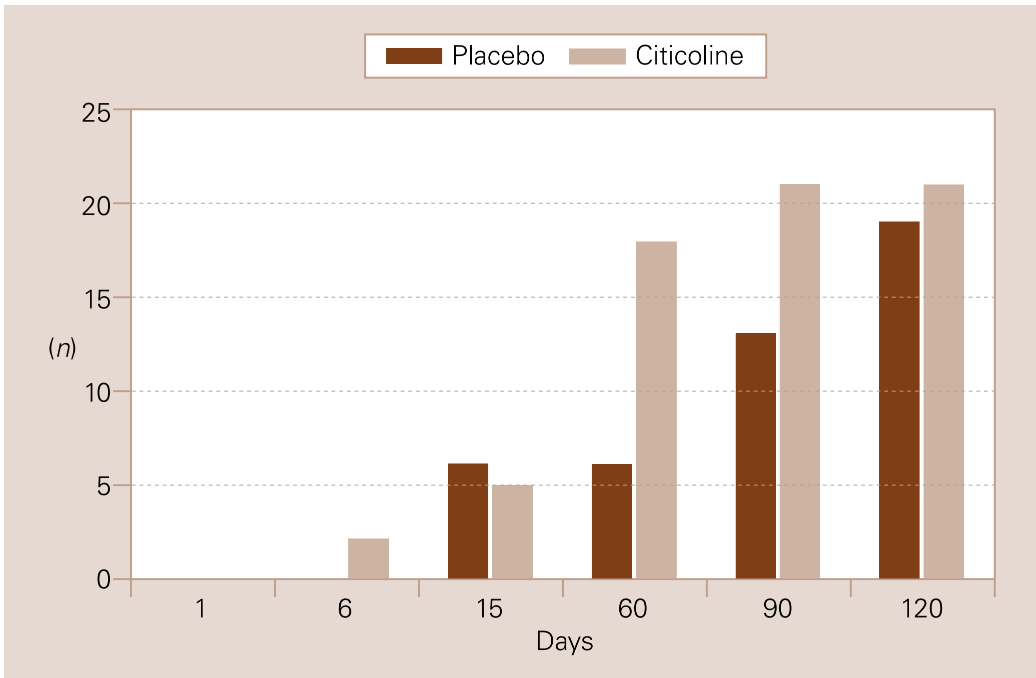


Figure 17. Normalisation of the state of consciousness in relation to time and treatment; $p < 0.01$ at day 60.



patients ($p < 0.01$), in which an earlier recovery of consciousness was also seen (Fig. 17). Authors also noted a greater recovery from neurological deficits in the active group. After 120 days, autonomous ambulation was seen in 84% of patients in the citicoline group, as compared to 62.5% of patients in the placebo group. This difference was statistically significant from day 60th ($p < 0.01$). Table IV shows the final outcome obtained in both groups, as assessed using the Glasgow Outcome Scale. The mortality rate was similar in both groups. Data reported in this study show that citicoline shortens the time elapsed to recovery of consciousness and accelerates recovery from neurological deficits in patients with severe head injury.

Deleuze et al [463] reported that citicoline is able to decrease serum creatine phosphokinase levels and lactate levels in cerebrospinal fluid, with a decrease in the lactate/pyruvate ratio, in patients with severe brain distress and coma. They also emphasized that the product was very well tolerated.

Ogashiwa et al [115] conducted a clinical trial in 101 patients with disorders of consciousness from different causes (20% of traumatic origin), showing the effectiveness of citicoline for improving the General Recovery Rate, closely related to the Principal Component Analysis Score. Authors found citicoline to be more effective in items related to the executive factor than in those related to the verbal factor, and that the greatest effect was achieved in patients less than 60 years of age and with a stabilized period of impaired consciousness not longer than three weeks. They also emphasized the excellent tolerability of the product, and even administered it by the intrathecal route in some cases [464,465].

At the Department of Neurosurgery of Centro Especial Ramón y Cajal in Madrid, a series of 100 patients with head injury treated with citicoline until discharge were studied, and their results were compared to those of another series of 100 patients with similar characteristics, but who did not receive citicoline [466]. Treatment with citicoline was started at doses of 600-1,200 mg/day by the parenteral route, switched to 300-900 mg/day by the oral route in the rehabilitation phase. The course was monitored by assessing mean coma duration, persistence of neurological and psychic symptoms, the Wechsler Adult Intelligence Scale test, and electrophysiological studies of muscle tension. Results achieved suggested that citicoline addition to the treatment regimen caused a decrease in duration of posttraumatic coma and rate of both neurological and psychic sequelae and achieved a better response in recovery from intellectual disorders and motor deficits.

Raggueneau and Jarrige [467], in a national survey conducted in France, recorded 921 cases of severe head injury, i.e., with an initial score in the Glasgow Coma Scale of 8 or less. Of these, 219 patients had been treated with citicoline, which allowed for distribution into two groups to compare the results obtained. No significant differences were found in mortality, but differences were seen in the number of dependent states, and the greatest effect was found in patients with an initial Glasgow Coma Scale score of 6-7 (Fig. 18). Citicoline improved quality of survival, allowing for more frequent social and familiar reinsertion, as well as return to work or school. Mortality in head injuries essentially depends on initial lesions which, except for epidural hematoma, are beyond any real therapeutic resolution.

Calatayud et al [468] reported the results of the influence of citicoline addition to the treatment of head injury. Two hundred and sixteen patients with an initial Glasgow Coma Scale score ranging from 5 and 10 were reported. Of these, 115 patients received treatment with citicoline. Mean citicoline dose administered was 4 g/day. Analysis of the results showed that citicoline:

– Decreased hospital stay ($p < 0.05$) and duration of outpatient follow-up ($p < 0.001$), with differences being more marked in the group of patients with an initial Glasgow Coma Scale score ranging from 5 and 7.
– Promoted the recovery of memory, motor disorders, higher neurological functions, and mood changes.
– Improved global functional outcome (Table V).

Lozano [469] reported the impact of citicoline therapy on the course of posttraumatic cerebral edema in a study conducted in 78 cases of head injury with an initial Glasgow Coma Scale score ranging from 5 and 7. In all cases, a computerized tomography of the head was performed at the start and end of the study to assess changes in the tomographic image of cerebral edema. Other parameters investigated included duration of hospital stay

Figure 18. Effect of treatment with citicoline on final results. Results are expressed as percentages. [a] $p < 0.001$ versus patients not treated with citicoline.

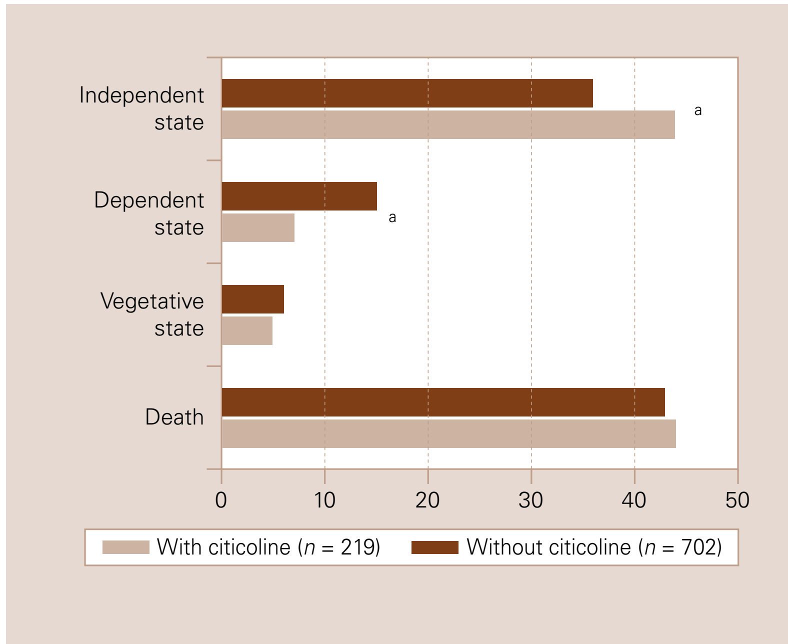


Table IV. Final results according to treatment.

	Glasgow Outcome Scale				
	I	II	III	IV	V
Placebo group	12	5	4	3	6
Citicoline group	11	9	3	2	5

Table V. Final result, evaluated with the Glasgow Outcome Scale (GOS), in relation to treatment ($p < 0.05$).

	Citicoline	Control
GOS I	77	51
GOS II	19	31
GOS III	1	7
GOS IV	0	2
GOS V	18	10

Figure 19. Evolution of the tomographic image of cerebral oedema after 14 days of treatment ($p < 0.005$).

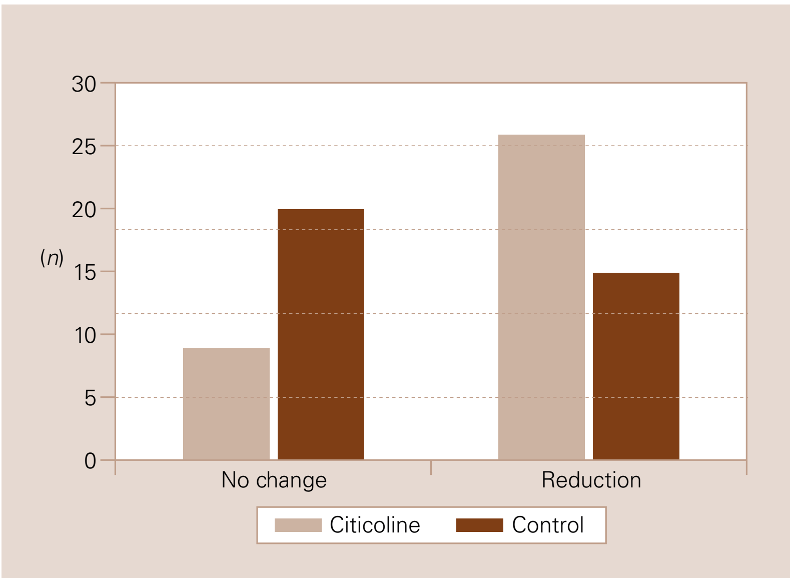


Table VI. Final result, evaluated with the Glasgow Outcome Scale (GOS), in relation to treatment (n.s.).

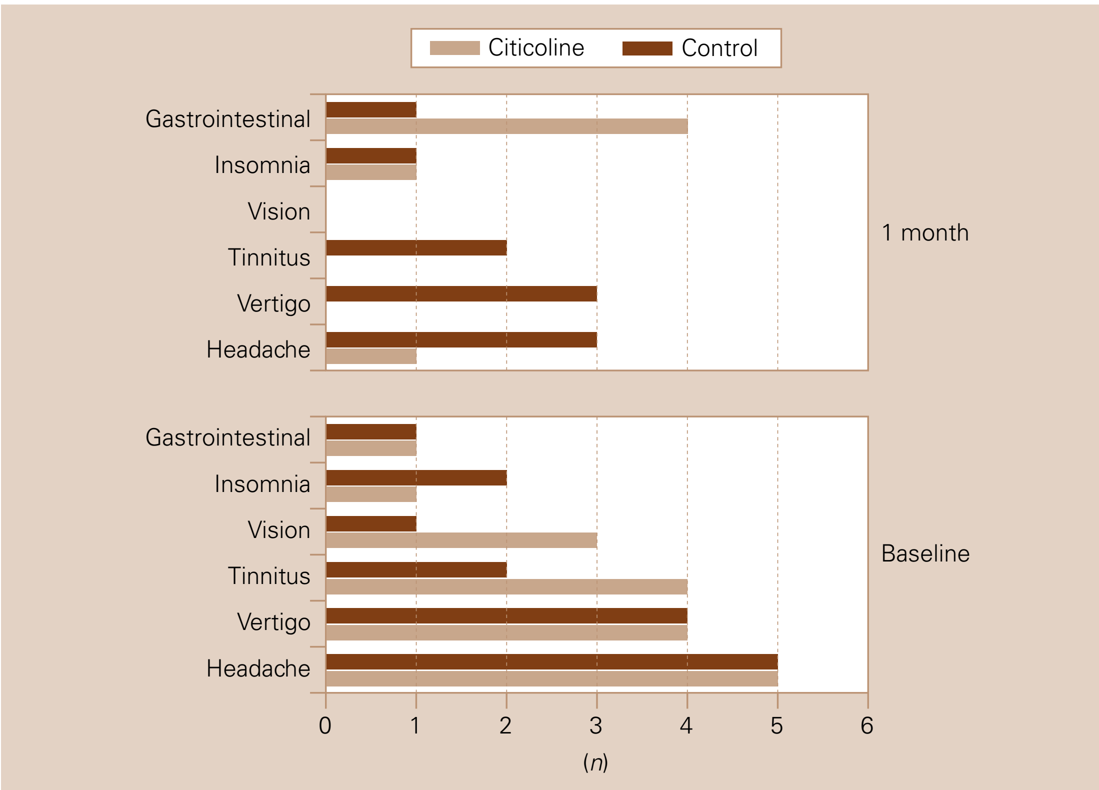
	Citicoline	Control
GOS I	15	11
GOS II	8	8
GOS III	6	7
GOS IV	4	6
GOS V	6	7

and the extent of autonomy at hospital discharge. Citicoline was administered to 39 patients for the first two weeks at a dose ranging from 3 and 6 g/day by intravenous infusion. After 14 days of treatment with citicoline, image of cerebral edema evolved as shown in figure 19. Cerebral edema had been reduced or normalized in a higher number of patients treated with citicoline as compared to control patients, with differences being highly significant ($p < 0.005$). No significant differences were seen between both groups in therapeutic requirements or treatments received. Mean hospital stay was 28.718 ± 21.6 days for the group receiving active treatment and 37.323 ± 35.22 days for the control group, with statistically significant differences ($p < 0.001$). Differences in final outcomes assessed according to the Glasgow Outcome Scale did not reach statistical significance due to the low number of cases and the special characteristics of this type of patients. However, a trend was seen to a more favorable resolution in the group of patients treated with citicoline (Table VI).

Levin [470] conducted a study in 14 patients with postconcussional syndrome following a mild to moderate head injury. This syndrome is characterized by the occurrence of symptoms such as headache, dizziness, mnesic disorders, and sleep disturbances mainly. In this study, patients treated with citicoline for one month experienced an improvement in memory tests, particularly recognition tests, that was statistically significant as compared to placebo. Figure 20 shows changes in symptoms after one month of treatment. Greater improvements were achieved in patients treated with citicoline as compared to placebo patients, except for gastrointestinal discomfort. Dizziness was significantly more common in patients from the placebo group after one month of study. However, in a simple-blind study in patients with mild head injury [471], the authors were unable to evidence differences between citicoline and control with regards to the evolution of the postconcussional symptoms. Despite that, CDP-choline is considered a therapeutic option for postconcussional syndrome [472].

León-Carrión et al [473-475] investigated in a series of studies the effects of citicoline on post-traumatic memory disorders. In a group of seven patients with severe memory deficits, these authors investigated the effects of administration of citicoline 1 g on cerebral blood flow, as measured by the ^{133}Xe inhalation technique. Two measurements were made, one at baseline and the other at 48 hours, under the same conditions, except those patients had taken the drug one hour before the test. All patients showed a significant hypoperfusion at the inferoposterior area of the left femoral lobe in the first measurement, that disappeared following citicoline administration. In a second study, 10 patients with severe memory deficits were randomized into two groups. Both patient groups were subjected to a short memory rehabilitation program. A group received citicoline 1 g/day p.o. for the three months the neuropsychological treatment program lasted, while the other group

Figure 20. Evolution of post-concussional symptoms after one month of treatment with citicoline or placebo. The number of patients reporting each symptom is shown.



was given placebo. The results obtained are shown in table VII. Neuropsychological rehabilitation associated to citicoline achieved improvements in all evaluated areas, reaching statistical significance in verbal fluency and the word recall Luria test. Citicoline is considered as a valid therapeutic option for the treatment of post-traumatic cognitive impairments [476], improving also the quality of survival [477].

A Cochrane protocol review of citicoline for the treatment of head injury is published at the Cochrane Database [478].

Krishna et al [479] conducted a randomized, single-blind, placebo-controlled, single center, prospective trial in a sample of 100 patients. Patients were randomized to receive citicoline (2 g/day/60 days p.o.) or placebo and the evaluations of outcomes were made at discharge and after 30 and 90 days. The authors concluded that the rate of recovery was earlier in the citicoline group in terms of a shorter duration of stay, early gaining of full consciousness and relief from cognitive symptoms.

In 2012, the Citicoline Brain Injury Treatment trial was published [480,481], registered as NCT00545662. The COBRIT trial, a phase 3, double-blind randomized clinical trial conducted between July 20, 2007, and February 4, 2011, among 1,213 patients with the objective to determine the ability of citicoline to positively affect functional and cognitive status in persons with complicated mild, moderate, and severe traumatic brain injury. Patients were randomized to a 90-day regimen of daily enteral or oral citicoline (2,000 mg) or placebo. The main outcome was the functional and cognitive status, assessed at 90 days using the TBI-Clinical Trials Network Core Battery. A global statistical test was used to analyze the nine scales of the core battery. Secondary outcomes were func-

Table VII. Scores (mean ± SD) obtained by patients before and after treatment.

	Group A (placebo + rehabilitation)		Group B (citicoline + rehabilitation)	
	Before	After	Before	After
Attention	95.60 ± 5.73	97.60 ± 2.19	82.00 ± 33.79	90.80 ± 20.57
Alertness	88.40 ± 8.65	96.80 ± 1.79	89.60 ± 17.74	98.80 ± 1.79
Verbal fluency	22.40 ± 9.91	23.60 ± 11.01	24.80 ± 14.65	31.80 ± 9.36 [a]
Benton test	8.20 ± 3.63	9.40 ± 6.95	8.80 ± 5.45	7.20 ± 3.70
Luria test	62.80 ± 13.24	62.00 ± 11.58	63.20 ± 17.31	71.00 ± 12.98 [a]

[a] $p < 0.05$ versus before treatment.

tional and cognitive improvement, assessed at 30, 90, and 180 days, and examination of the long-term maintenance of treatment effects. The main outcome was the functional and cognitive status, assessed at 90 days using the. Rates of favorable improvement for the Glasgow Outcome Scale-Extended were 35.4% in the citicoline group and 35.6% in the placebo group. For all other scales the rate of improvement ranged from 37.3 to 86.5% in the citicoline group and from 42.7 to 84.0% in the placebo group. The citicoline and placebo groups did not differ significantly at the 90-day evaluation –global odds ratio (OR), 0.98; 95% confidence interval (95% CI), 0.83-1.15–; in addition, there was no significant treatment effect in the two severity subgroups –global OR, 1.14 (95% CI, 0.88-1.49) and 0.89 (95% CI, 0.72-1.49) for moderate/severe and complicated mild traumatic brain injury, respectively–. At the 180-day evaluation, the citicoline and placebo groups did not differ significantly with respect to the primary outcome (global OR, 0.87; 95% CI, 0.72-1.04). According with the results obtained, the authors concluded that, among patients with traumatic brain injury, the use of citicoline compared with placebo for 90 days did not result in improvement in functional and cognitive status.

The COBRIT trial is the largest study performed with citicoline in this indication, but there are several methodological issues that question seriously the validity and applicability of the results obtained. This study was an independent study, financed by the US National Institute of Health, with a limited budget. A first point to consider is the sample size calculation. The authors chose an OR of 1.4 as the effect of the treatment, when in the most recent publications; the size of the effect of citicoline has been 1.26 in acute ischemic stroke patients, a less heterogeneous pathology than traumatic brain injury. It appears that the sample size was calculated based on the number of patients that could be afforded and then the OR of the treatment was established accordingly, rather than basing it on the effects of the drug. A more conservative and realistic OR of 1.2 or less would result in a sample size which was much higher but that would likely have been unaffordable for the authors. Another point to consider is that the authors mixed different populations, confusing mild, moderate and severe traumatic brain injury. The pathophysiology, localization, and trajectory for recovery can be very different among these groups. One means of avoiding this would have been to use a randomized, matched sample design. This mixing of lesion severity is a clear source of heterogeneity and would have to be considered an important confounding factor in the analysis and interpretation of the data. Also, the oro-enteral administration of citicoline used in this trial is completely atypical, is not approved in any country, has not previously been scientifically tested and additionally is not appropriate for many of the patients enrolled in the study. But the most controversial point is the poor compliance of the treatment. A compliance of only 44.4% of patients having taken more than 75% of the medication expected is very low and needs to be explained. Not receiving the active treatment is not the same as receiving the placebo, in terms of the standard of care being received. This means that less than half of the patients received something close to a therapeutic dose of citicoline. Thus, the COBRIT trial is not the 'definitive' study on citicoline, especially when the methodological confounds just described are taken into consideration.

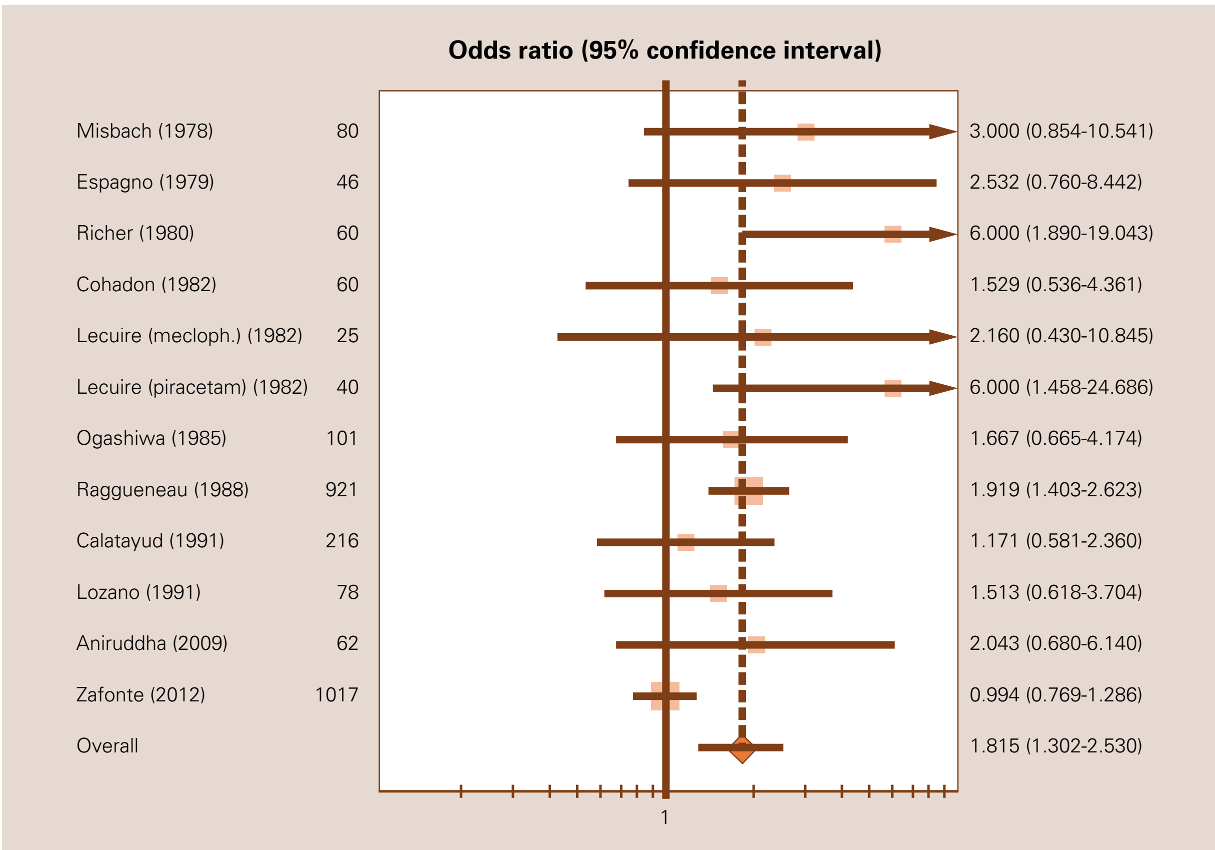
Given the controversy after the publication of the COBRIT trial, a meta-analysis has been published [482] to assess the real efficacy of citicoline in the treatment of traumatic brain injury patients. Systematic search of the relevant terms was performed on Medline, Embase, and Grupo Ferrer database (the company marketing the product in several countries) to identify all published, unconfounded, comparative clinical trials of citicoline in acute phase head injured patients. Studies were identified by searching electronic databases, scanning reference lists of articles, and consulting with experts in the field and at the pharmaceutical company (Grupo Ferrer). To be included in the meta-analysis, the trials must assess the effect of citicoline in the acute phase of traumatic brain injury, be comparative studies and have independence outcomes, evaluated with the Glasgow Outcome Scale or similar scales. All trials randomizing patients of any age or sex were included. No restrictions were applied regarding doses, route of administration or duration of treatment. No restrictions regarding language, publication date or publication status was applied. The primary efficacy measure was patient independence at the end of a scheduled follow-up period, evaluated as a Glasgow Outcome Scale score of 4-5, reflecting an excellent outcome or with mild sequelae, that guarantee an independence status after the traumatic brain injury. The systematic search detected 23 clinical trials, but only 12 were considered valid for the meta-analysis. The included studies involved 2,706 patients with mild, moderate, or severe traumatic brain injury treated in the acute phase with citicoline or not. The doses of citicoline ranged from 250 mg to 6 g per day, administered orally or parenterally. The duration of the treatment ranged from 7 to 90 days. According to the formal meta-analysis, based on random effect model (Fig. 21), the use of citicoline is associated with a significant increase in the rates of independence with an OR of 1.815 (95% CI, 1.302-2.530), but a significant heterogeneity (I^2=54.6%; p = 0.001) was detected, reflecting the time gap of 34 years between the studies included in the meta-analysis. The meta-analysis under the fixed-effects model obtains an OR of 1.451 (95% CI, 1.224-1.721), reinforcing the results obtained. But other meta-analysis with some limitations has been published [483,484] showing neutral effects of CDP-choline in the treatment of patients with traumatic brain injury.

Interesting are the results obtained by Varadaraju and Ananthakishan [485], demonstrating a certain synergistic effect when citicoline was administered together with cerebrolysin, as the patients treated with this association had a better outcome than patients treated with citicoline alone. Titov et al [486] also demonstrated a positive effect of the combination of citicoline and cerebrolysin in the management of traumatic brain injury in the acute phase. Trimmel et al [487] investigated the potential role of citicoline administration in traumatic brain injury patients treated at the Wiener Neustadt Hospital. In a retrospective subgroup analysis, they compared 67 patients at the study site treated with citicoline (3 g/day/3 weeks intravenous) and 67 matched patients from other Austrian centers not treated with citicoline. Patients with moderate to severe traumatic brain injury were included. The analysis found a significant effect of citicoline, expressed by the reduction of the rates of mortality at the intensive care unit mortality (5% versus 24%; $p < 0.01$), during the hospital stay (9% versus 24%; p = 0.035), and after six months of follow up (13% versus 28%; p = 0.031). A significant reduction in the rates of unfavorable outcome (34% versus 57%; p = 0.015) was also detected and in the observed versus expected ratio for mortality (0.42 versus 0.84) in the citicoline group (Fig. 22). Ahmadi et al [488] published a double-blind, randomized clinical trial on 30 patients with severe traumatic brain injury. According to the protocol IRCT20140611018063N7 and the abstract, patients were randomly divided into three groups: A (control), B (citicoline 0.5 g/12 hours/24 days intravenous), and C (citicoline 1.5 g/12 hours/14 días intravenous), but once the authors explained the methods in the article, these groups changed to: A (citicoline 0.5 g/12 hours/24 days intravenous), B (citicoline 1.5 g/12 hours/14 days intravenous), and C (placebo). This incongruence makes it difficult to interpret the results, because if the group assignment was the original, then a significant dose-dependent effect of citicoline can be found, but with the assignment stated in the paper, the results are difficult to interpret, but the authors concluded that citicoline had no positive effect on the outcome of such patients.

Other studies published found a significant effect of citicoline in the recovery of patients with severe head injuries [489], especially in patients with diffuse axonal injuries [490-492].

As a conclusion, it has been shown that patients who have sustained a head injury, particularly

Figure 21. Forest plot of the meta-analysis of the effects of citicoline on independence after traumatic brain injury, based on the random-effects model: odds ratio, 1.815 (95% CI: 1.302-2.530). Reprinted with permission from J.J. Secades. Citicoline *for the treatment of head injury: a systematic review and meta-analysis of controlled clinical trials*. J Trauma Treat 2014; 4: 227. doi:10.4172/2167-1222.1000227.



those with an initial Glasgow Coma Scale score of 5-7, benefit from the addition of citicoline into their therapeutic regimen because this drug accelerates cerebral oedema reabsorption and recovery of both consciousness and neurological disorders, resulting in a shorter hospital stay and improved quality of survival, with a bigger degree of independence. Agarwal and Patel [493] in their systematic review on the role of citicoline in the management of patients with traumatic brain injury concluded that functional outcomes were significantly improved by citicoline in these patients. These effects could be explained by the pharmacodynamics of the product and it pleiotropic effect on the mechanisms involved in the development of the traumatic brain injury [494,495]. Also, two complete recent reviews on the role of citicoline in the management of traumatic brain injury patients are available [496,497].

Acute cerebrovascular disease and sequelae

The neurobiological processes involved in the pathophysiology of the cerebral ischemia are extremely complex [498]. For this reason, some authors postulate the need to use multifunctional treatments for this disease [499-504], for intracerebral hemorrhages [505,506], and for the recovery phase [507,508]. As experimentally shown, citicoline is a drug having pleiotropic actions including activation of neuronal metabolism, stabilization of neuronal membranes and their function, and normalization of neurotransmission [20,39-41,180,281, 282]. Various studies with citicoline conducted in the sixties suggested its efficacy to reduce neurological symptoms in patients with cerebral ischemia [509,510].

Hazama et al [511] conducted a double-blind study to assess the effect of citicoline on functional recovery from hemiplegia in 165 patients with cerebrovascular disease. These authors showed that citicoline, at a dose of 1,000 mg/day for eight weeks, was superior to placebo, particularly for motor recovery in the upper limbs, and concluded that citicoline promotes natural recovery from hemiplegia.

Goas et al [512] conducted a double-blind study comparing citicoline (750 mg/day/10 days intravenous) versus placebo in 64 patients with cerebral infarction starting less than 48 hours before. Assessment at three months showed citicoline to be superior to placebo for improving motor deficit ($p < 0.05$), hypertonia ($p < 0.03$), gait recovery ($p < 0.02$), changes over time in electroencephalographic tracing ($p < 0.01$) and psychometric tests ($p < 0.05$), achieving a higher number of independent states (51.6% with citicoline; 24.24% with placebo) (Fig. 23). In a study with the same characteristics, Boudouresques et al [513] achieved similar results. This study included 52 patients, of whom 27 patients received citicoline (750 mg/day/10 days intravenous) and 25, placebo. An assessment was made at 10 days and showed that citicoline-treated patients had a better course as regarded consciousness disorders, with recovery of consciousness in 66.7% of cases as compared to 32.0% in the placebo group ($p < 0.01$), and deficit syndromes (82.6 and 54.5% of patients recovered with citicoline and placebo respectively; $p < 0.04$) and electroencephalographic tracings (83.3% with citicoline versus 35.3% with placebo; $p < 0.01$). In both studies, citicoline tolerability was rated as excellent by investigators.

Corso et al [514], in a double-blind study of citicoline (1 g/day/30 days intravenous) versus placebo in a sample of 33 patients, noted that at the end of the study the deficit syndrome had improved in 76.5% of patients treated with citicoline ($p < 0.01$ versus placebo), while an improved electroencephalographic tracing was seen in 70.6% of patients ($p < 0.01$ versus placebo).

Tazaki et al [515] performed a double-blind, prospective, multicentre, placebo-controlled study on the value of citicoline for the treatment of acute cerebral infarction. Sixty-three Japanese academic centers participated in this study, in which a total of 272 patients were enrolled following strict in-

Figure 22. Effect of citicoline treatment on the rates of mortality and unfavourable outcomes. ICU: intensive care unit).

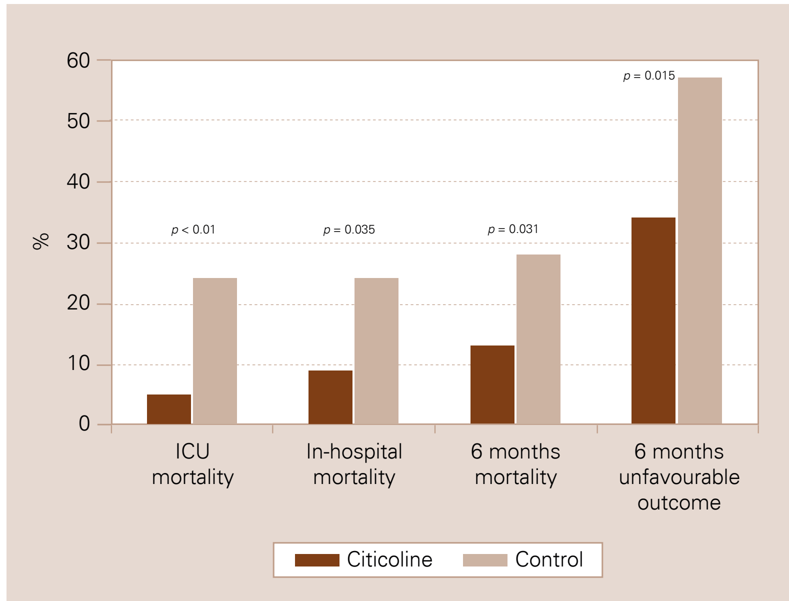
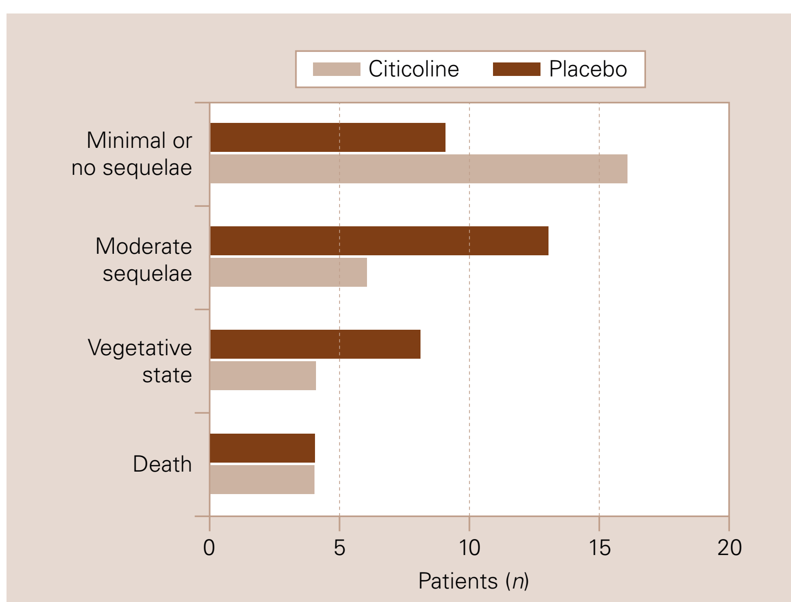


Figure 23. Outcome in relation to treatment, highlighting the number of good results achieved with citicoline compared to the control group.



clusion criteria. Patients were randomized to receive 1 g/day intravenous of citicoline or saline (placebo) for 14 days. At the end of treatment, citicoline was shown to significantly improve consciousness (51% versus 33% for placebo; $p < 0.05$) and overall improvement (52% versus 26%; $p < 0.01$) and overall usefulness rates (47% versus 24%; $p < 0.001$). In addition, fewer complications occurred in the citicoline-treated patient group (1%) as compared to the placebo group (8.1%). These authors concluded that citicoline is an effective and safe drug for the treatment of acute cerebral infarction. These results agree to those reported by other authors [516-519].

Guillén et al [520] reported a comparative, randomized study on the efficacy of citicoline for treating acute ischemic stroke as compared to conventional therapy, showing a significantly higher improvement in the citicoline group as compared to the control group. In the open label studies by Bruhwyler et al [521] and Fridman et al [522], results favoring citicoline were also achieved, with a significant clinical improvement of patients and an excellent safety profile of the drug. Alviarez and González [523] reported the beneficial effects with citicoline in a double-blind study conducted in Venezuela. León-Jiménez et al [524] evaluated the correlation between citicoline exposure and functional outcome at discharge and at 30 and 90 days post-stroke, in a retrospective case-control design on systematic descriptive databases from three referral hospitals in Mexico.

In the second half of the 90s, study of oral citicoline for the treatment of acute ischemic stroke was started in the United States. The first clinical trial was a randomized, dose-response study [525]. This double-blind, randomized, multicentre study compared three citicoline doses (500 mg, 1,000 mg, and 2,000 mg by the oral route) to placebo to document drug safety, find the optimum dose, and collect data on the efficacy of citicoline for the treatment of acute ischemic stroke. A total of 259 patients with ischemic stroke in the territory of the middle cerebral artery were recruited within 24 hours of the start of symptoms. Patients were randomized into four groups: administration of placebo or 500, 1,000, or 2,000 mg/day of oral citicoline for six weeks. Patient recovery at the end of the six-week treatment period and after a subsequent follow-up period of six additional weeks was assessed. The main efficacy endpoint was Barthel Index (BI) at 12 weeks. Secondary endpoints included the modified Rankin Scale (mRS), the National Institutes of Health Stroke Scale (NIHSS), the Mini-Mental State Examination (MMSE), hospital stay duration, and mortality. A significant difference favoring citicoline was found between the groups in functional status (BI, mRS), neurological assessment (NIHSS), and cognitive function (MMSE). In a regression analysis of BI including as covariate baseline NIHSS score, a significant effect of citicoline treatment was found at 12 weeks ($p < 0.05$). The proportions of patients who achieved a BI score ranging from 85 and 100 were 39.1% for placebo, 61.3% for the 500 mg dose, 39.4% for the 1,000 mg dose, and 52.3% for the 2,000 mg dose. Odds ratios for an improved outcome were 2.0 for the 500 mg dose and 2.1 for the 2,000 mg dose. The lack of efficacy seen in the 1,000 mg group could be due to the greater overweight of patients included in this group and their poorer neurological status at baseline. Mean score in the mRS was 3.1 with placebo, 2.5 with citicoline 500 mg, 3.1 with 1,000 mg, and 2.6 with 2,000 mg, with a significant difference being found between the 500 mg and placebo groups ($p < 0.03$). No citicoline-related serious adverse events or deaths were seen. According to these results, oral citicoline treatment achieves a better functional outcome, and 500 mg is the most effective dose of citicoline.

A second multicentre, double-blind, placebo-controlled, randomized study [526] recruited 394 patients with acute ischemic stroke arising in the middle cerebral artery less than 24 hours before and with a NIHSS score of 5 or higher. Patients were assigned oral administration of placebo (n = 127) or citicoline 500 mg/day (n = 267). Treatment was continued for six weeks, and follow-up was subsequently conducted for six additional weeks. Mean entry time was 12 hours after the stroke, and mean patient age was 71 years in the placebo group and 71 years in the citicoline group. While the mean baseline NIHSS score was similar in both groups, a greater proportion of patients had a baseline NIHSS <8 (34% versus 22%; $p < 0.01$). The planned primary endpoint (logistic regression for five BI categories) did not meet the proportional odd assumption and was therefore not reliable. No significant between-group differences were seen in any of the planned secondary variables, including a BI of 95 or higher at 12 weeks (placebo 40%, citicoline 40%) or mortality rate (placebo 18%, citicoline 17%). However, a post hoc subgroup analysis showed that in patients with moderate to severe stroke, defined by a baseline NIHSS score of 8 or higher, treatment with citicoline conferred a greater chance of achieving a complete recovery, defined as a BI ≥95 at 12 weeks (21% placebo, 33% citicoline; $p = 0.05$), while no differences were found in patients with mild stroke, i.e. with a baseline NIHSS score <8. No serious adverse events attributable to the drug were detected, which attests to its safety. Based on these data, citicoline may be considered a safe drug that may induce favorable effects in patients with moderate to severe acute ischemic stroke.

The last clinical study conducted in the US was the ECCO 2000 study [527]. This study, having similar characteristics to the previous ones, enrolled 899 patients with moderate to severe acute ischemic stroke (baseline NIHSS score ≥8) arising in the middle cerebral artery within the past 24 hours. Patients were randomized to receive citicoline 2,000 mg/day ($n = 453$) or placebo ($n = 446$) by the oral route for six weeks, with a subsequent follow-up for six additional weeks. The primary study endpoint was the proportion of patients having a reduction by 7 or more points in the NIHSS scale at 12 weeks. At the end of the study, 51% of patients in the placebo group and 52% of those in the citicoline group had achieved the reduction by 7 or more points in the NIHSS scale, with no significant between-group differences. By contrast, there was a trend favoring citicoline in achievement of a complete neurological recovery, defined by a score in the NIHSS scale of 1 or less (40% with citicoline versus 35% with placebo; $p = 0.056$), and in complete functional recovery, defined by a BI score of 95 or higher (40% with citicoline versus 35% with placebo; $p = 0.108$). With regard to mRS, 20% of patients in the placebo group achieved a complete recovery (mRS ≤1), as compared to 26% of patients in the citicoline group, the difference being statistically significant ($p = 0.025$). There were no differences between treatments in mortality or incidence of serious adverse events, but a significant decrease was seen in stroke worsening (3% with citicoline versus 6% with placebo; $p = 0.02$). On the other hand, occurrence of new stroke was decreased in patients treated with citicoline (2.9% with placebo versus 1.8% with citicoline), i.e., a 62.1% risk reduction. A post hoc analysis assessed the effect of citicoline in a multiple outcome global assessment, using the method of Generalized Estimating Equations defined by Tilley et al [528], considering the proportion of patients who had a complete recovery in all 3 scales used, i.e., achieved scores of 0-1 in the NIHSS scale, 0-1 in mRS, and ≥95 in BI at 12 weeks. Citicoline was shown to be significantly superior to placebo, achieving this complete recovery in 19% of the cases, as compared to 14% in the placebo group (OR 1.32; 1.03-1.69; $p = 0.03$).

Citicoline effects on reduction of cerebral infarction volume were investigated in parallel. The first analysis conducted was a pilot study to assess citicoline effects on lesion volume measured by diffusion-weighted magnetic resonance imaging in patients with acute cerebral infarction [529]. This study recruited 12 patients from the first clinical study on citicoline in the United States [525]. Lesion growth was seen in three of the four patients treated with placebo, while a decrease in lesion volume was noted in seven of the eight patients treated with citicoline ($p < 0.01$, with baseline NIHSS score as covariate). A second, double-blind study designed for this purpose, i.e., to measure changes in lesion volume using diffusion-weighted techniques, recruited 100 patients who were randomized to receive citicoline 500 mg/day or placebo by the oral route for six weeks [530]. These patients should be enrolled within 24 hours of symptom onset and have a baseline NIHSS score of 5 points or more and a lesion volume in cerebral grey matter of 1-120 cm^3 in diffusion-weighted magnetic resonance imaging. Neuroimaging techniques (diffusion-weighted magnetic resonance imaging, T_2-weighted magnetic resonance imaging, perfusion-weighted magnetic resonance imaging, and magnetic resonance imaging angiography) were performed at baseline and on weeks 1 and 12. Main endpoint was progression of ischemic lesion from baseline to final assessment at 12 weeks as measured by magnetic resonance imaging. The primary analysis planned could be performed in 41 patients treated with citicoline and 40 patients treated with placebo, and no significant differences were found. From baseline to 12 weeks, ischemic lesion volume expanded by 180 ± 107% in the placebo group and 34 ± 19% in the citicoline group. A secondary analysis showed that, from week 1 to week 12, lesion volume decreased by $6.9 \pm 2.8\ cm^3$ in the placebo group and by $17.2 \pm 2.6\ cm^3$ with citicoline ($p < 0.01$). A significant finding in this study was the great correlation existing, regardless of treatment, between lesion volume reduction and clinical improvement, supporting the idea of using this methodology for assessing stroke treatments. In the ECCO 2000 study [527], a substudy was conducted to assess the effects of citicoline on lesion volume [531]. This substudy had three objectives. The first objective was to assess the effects of the drug on chronic lesion volume, as measured using magnetic resonance imaging T_2 sequences in the whole patient sample, although this assessment could only be made in 676 patients. The second objective was to analyze citicoline effects on change

Table VIII. Results obtained after three months on individual scales.

	Studies (*n*)	Patients (*n*)	Peto odds ratio (95% CI)	*p*
NIHSS ≤ 1	4	1,372	1.34 (1.05-1.71)	0.020
mRS ≤ 1	4	1,351	1.45 (1.11-1.90)	0.007
BI ≥ 95	4	1,372	1.28 (1.03-1.59)	0.003

95% CI: 95% confidence interval; NIHSS: National Institutes of Health Stroke Scale; mRS: modified Rankin Scale; BI: Barthel index.

in lesion volume, using diffusion-weighted magnetic resonance imaging performed at baseline and week 12. One hundred and eighty-one patients were recruited for this second objective, of whom only 134 patients were evaluable. The third objective was methodological in nature, that is, an attempt was made to correlate clinical changes to volume changes and to check if lesion volume reduction was associated to clinical improvement. No significant differences were found in assessment of chronic lesion volume (median of 25 cm^3 for citicoline; median of 31.3 cm^3 for placebo). The diffusion-weighted study showed that in the placebo group (n = 71) lesion the increased 30.1 ± 20.5%, with a median of –8.7%, while the change occurring in the citicoline group (n = 63) was 1.3 ± 14.3%, with a median of –22.9%, a non-significant difference (p = 0.077). However, when the logarithm of change was analyzed and the baseline NIHSS score was introduced as covariate, the difference was significant (p = 0.02). In this diffusion-weighted substudy, 54% of patients in the placebo group and 675 of citicoline-treated patients were shown to have a decreased lesion volume compared to baseline, though the difference was not significant (p = 0.122). In patients having at baseline a cortical lesion with a volume ranging from 1-120 cm^3 were analyzed, a lesion increase by 40.5 ± 28.7% was seen in patients treated with placebo (n = 47), with a median of 4.5%, while in patients receiving treatment with citicoline (n = 43) the lesion increased by 7.3 ± 19.9%, with a median of –23.9%. The difference between the groups was statistically significant (p = 0.006, median comparison). In this patient subgroup with initial cortical lesions with a volume of 1-120 cm^3, a decrease in lesion volume occurred in 47% of patients in the placebo group and in 70% of patients in the citicoline group. The difference was significant, with a value of p = 0.028. The decrease in volume was also seen to be significantly correlated to the clinical improvement of patients.

Although the results obtained in studies conducted in the United States with oral citicoline for treatment of acute ischemic stroke were not conclusive for citicoline efficacy, it may be seen that, in addition to drug safety, there is a certain trend to an improved prognosis of treated patients. Since there was currently no neuroprotective drug that has been shown to be effective for the treatment of this severe condition [532], it was decided to conduct a meta-analysis of the results obtained with oral citicoline in the treatment of acute ischemic stroke to examine the effects of the drug on neurological and functional recovery of patients [533]. For this, following the methods of the Cochrane Library [534] and the guidelines of the International Conference on Harmonization [535], a comprehensive literature search was made in both Medline and our own literature database. This search found that only four double-blind, randomized clinical studies had been conducted with oral citicoline for the treatment of acute ischemic stroke, namely the four trials performed in the United States [525-527,529]. The total sample comprised 1,652 patients, 686 patients in the placebo group and 966 patients in the citicoline group (381 with 500 mg/day, 66 with 1,000 mg/day, and 519 with 2,000 mg/day). The first analysis was performed irrespective of the dose and in the total patient sample. As regards complete neurological recovery (NIHSS ≤1) at three months, the odds ratio was 1.22 (0.98; 1.52), not reaching statistical significance (p = 0.07); by contrast, significant differences favoring citicoline were obtained in an analysis of patients who achieved a virtually complete recovery in activities of daily living (BI ≥95) at three months –OR, 1.26 (95% CI, 1.02-1.55); p = 0.01– and functional recovery at three months, defined as a score of 1 or less in the mRS –OR 1.36 (95% CI, 1.06; 1.74), p = 0.01–. Since the experience gathered in the above clinical studies suggests that the drug is more effective in patients with moderate to severe acute ischemic stroke (baseline NIHSS ≥8), databases from the original studies were obtained, and patients who met this criterion and had an optimum functional status before the stroke (mRS ≤1) were selected. Of the whole sample, 1,372 patients met these criteria and therefore underwent the same assessment. In this case, the meta-analysis found statistically significant differences for all variables analyzed (Table VIII).

To continue with analysis of these data, it was decided to perform a pooling data analysis [536], using individual data from each patient. This additional analysis included the sample of 1,372 patients who met the established criteria of severity (baseline NIHSS ≥8), prior functional status (mRS ≤1), therapeutic window not longer than 24 hours, and consistent neuroimage. The efficacy endpoint selected was total recovery at 3 months in the three scales analyzed (mRS ≤1 + NIHSS ≤1 + BI ≥95), using the previously described Generalized Estimating Equations analysis [527]. Among the 1,372 patients, 583 received placebo and 789 citicoline (264 patients 500 mg, 40 patients 1,000 mg, and 485 patients 2,000 mg). Total recovery at three months was achieved in 25.2% of patients treated with citicoline and 20.2% of patients in the placebo group –OR, 1.33 (95% CI, 1.10-1.62); p = 0.003–, and the dose shown to be most effective was 2,000 mg. This dose resulted in complete recovery at three months in 27.9% of patients who received it –OR, 1.38 (95% CI, 1.10-1.72); p = 0.004– (Fig. 24). In addition, citicoline safety was similar to placebo.

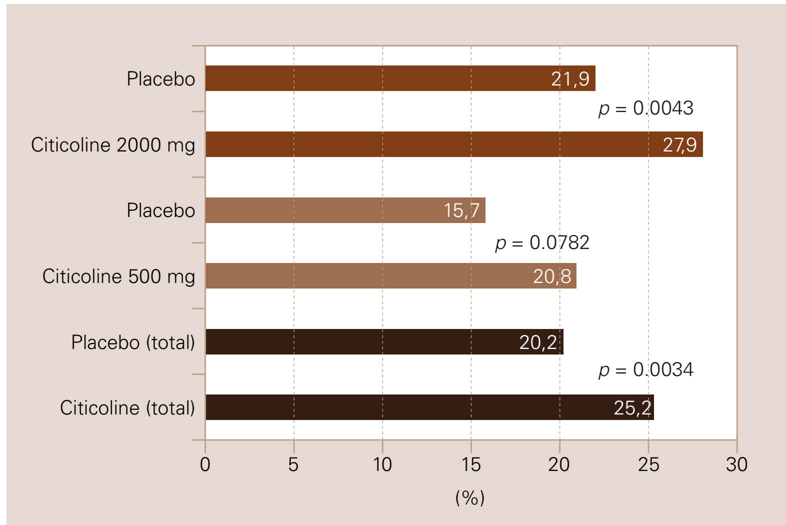
The preliminary results of a Cochrane review on the effects of choline precursors, including citicoline, in the treatment of acute and subacute stroke were reported in 2002 [537]. This meta-analysis collected data from eight double-blind studies conducted with citicoline at doses ranging from 500 and 2,000 mg daily, administered by both the oral and intravenous routes. Despite study heterogeneity, citicoline treatment was associated to decreases in late mortality and disability rates: citicoline 611/1,119 (64.6%) versus placebo 561/844 (54.4%) –OR, 0.64 (95% CI, 0.53-0.77); p < 0.00001–. In order to decrease heterogeneity, analysis was restricted to the four studies with a greater sample size (n > 100), and the positive effect seen persisted: citicoline 574/1,048 (54.58%) versus placebo 500/773 (64.7%) –OR, 0.70 (95% CI, 0.58-0.85); p < 0.0003–. In the safety analysis, no differences were found between citicoline and placebo in the mortality rate. Authors concluded that the formal meta-analysis of citicoline studies in acute and subacute stroke suggests a beneficial and substantial effect of the drug, with absolute reductions by 10%-12% in the long-term disability and mortality rate, i.e., the number of patients with a score of 3 or higher in the mRS is significantly decreased. These results agree with those previously reported for the pooled data analysis [536].

A pooled data analysis evaluating the effect of citicoline on increase of cerebral infarction size is also available [538]. Data used in this analysis come from two studies in which neuroimaging data had been obtained using magnetic resonance imaging techniques [527,530]. The primary endpoint in this analysis was percent change in infarction size from the start to the end of the study at three months. Data were available for 111 patients receiving placebo, 41 patients treated with citicoline 500 mg/day/6 weeks, and 62 patients treated with citicoline 2,000 mg/day/6 weeks. Patients receiving placebo experienced a mean increase by 84.7 ± 41.2%, while a dose-dependent effect was seen associated to citicoline: mean increase by 34.0 ± 18.5% with citicoline 500 mg and by 1.8 ± 14.5% with citicoline 2,000 mg.

These benefits shown in these systematic reviews were also associated to a reduction in the costs of integral treatment of patients with acute ischemic stroke [539]. Same results on cost-efficacy of citicoline have been obtained in Russia [540, 541].

Sobrino et al [542] investigate if an administration of citicoline, started in the acute phase of stroke, could increase the endothelial progenitor cell concentration in patients with ischemic stroke. Forty eight patients with a first-ever non-lacunar ischemic stroke were prospectively included in the study within 12 hours of symptoms onset. Patients

Figure 24. Estimated probabilities (GEE analysis) of overall recovery three months after onset of symptoms. Overall recovery is defined as a consistent and persuasive difference in the proportion of patients who achieve scores of NIHSS ≤ 1, BI ≥ 95 and mRS ≤ 1 at the same time.



received treatment ($n = 26$) or non-treatment ($n = 22$) with oral citicoline (2,000 mg/day/six weeks. Endothelial progenitor cell colonies were quantified as early outgrowth colony forming unit-endothelial cell (CFU-EC) at admission (previous to citicoline treatment) and day seven. The endothelial progenitor cell increment during the first week was defined as the difference in the number of CFU-EC between day seven and admission. CFU-EC were similar at baseline between patients treated and non-treated with citicoline (7.7 ± 6.1 versus 9.1 ± 7.3 CFU-EC; $p = 0.819$). However, patients treated with citicoline and recombinant tissue-plasminogen activator (rt-PA) had a higher endothelial progenitor cell increment compared to patients treated only with citicoline or non-treated (35.4 ± 15.9 versus 8.4 ± 8.1 versus 0.9 ± 10.2 CFUEC; $p < 0.0001$). In a logistic model, citicoline treatment (OR, 17.6; 95% CI, 2.3-137.5; $p = 0.006$) and co-treatment with citicoline and rt-PA (OR, 108.5; 95% CI, 2.9-1094.2; $p = 0.001$) were independently associated with an endothelial progenitor cell increment ≥4 CFU-EC. The authors concluded that the administration of citicoline and the co-administration of citicoline and rt-PA increase endothelial progenitor cell concentration in acute ischemic stroke. However, the molecular mechanism by which citicoline increases the concentration of endothelial progenitor cells remains to be clarified.

Regarding safety, a drug surveillance study involving 4,191 acute stroke patients treated with citicoline has been finished in South Korea [543]. The aim of this study was to determine the efficacy and safety of oral citicoline in Korean patients with acute ischemic stroke. Oral citicoline (500-4,000 mg/day) was administered within less than 24 hours after acute ischemic stroke in 3,736 patients (early group) and later than 24 hours after acute ischemic stroke in 455 patients (late group) for at least six weeks. For efficacy assessment, primary outcomes were patients' scores obtained with a short form of the National Institutes of Health Stroke Scale (s-NIHSS), a short form of the Barthel Index of activities of daily living (s-BI) and a modified Rankin Scale (mRS) at enrolment, after six weeks and at the end of therapy for those patients with extended treatment. All adverse reactions were monitored during the study period for safety assessment. All measured outcomes, including s-NIHSS, s-BI and mRS, were improved after six weeks of therapy ($p < 0.05$). Further improvement was observed in 125 patients who continued citicoline therapy for more than 12 weeks when compared with those who ended therapy at week six. Improvements were more significant in the higher dose group (≥2,000 mg/day) ($p < 0.001$). s-BI scores showed no differences between the early and late groups at the end of therapy. Citicoline safety was excellent; 37 side effects were observed in 31 patients (0.73%). The most frequent findings were nervous system-related symptoms (8 of 37, 21.62%), followed by gastrointestinal symptoms (5 of 37, 13.5%). Oral citicoline improved neurological, functional and global outcomes in patients with acute ischemic stroke without significant safety concerns.

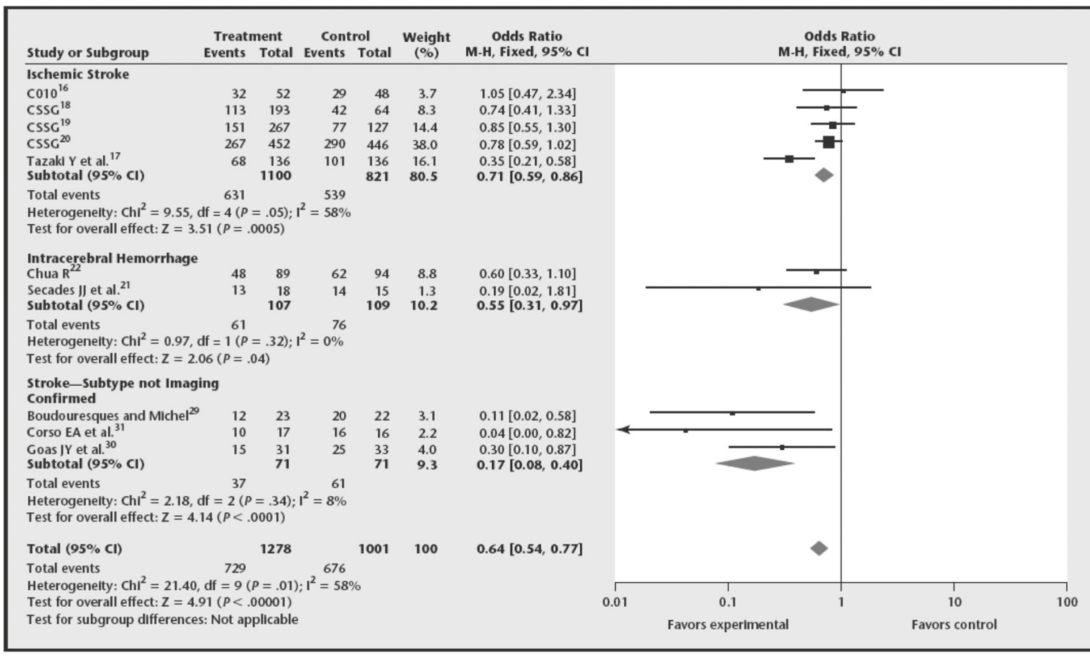
A pilot study has been published on the safety and efficacy of citicoline for the treatment of primary intracerebral hemorrhage [544]. This study recruited 38 patients aged 40 to 85 years, who should be previously independent and be enrolled within six hours of the onset of symptoms caused by primary intracerebral hemorrhage, as diagnosed by neuroimaging tests (computed tomography or magnetic resonance imaging). Patients should have a baseline severity as determined by a score higher than 8 in the Glasgow Coma Scale and higher than 7 in the NIHSS. Patients were randomized to 1 g/12 hours of citicoline or placebo by the intravenous or oral route for two weeks. The primary study objective was to assess treatment safety based on the occurrence of adverse events. The efficacy endpoint selected was the proportion of patients who had a score of 0-2 in the mRS at three months. Nineteen patients were included in each of the groups, that were perfectly matched as regarded baseline characteristics. Adverse event rate did not differ between the groups (four cases each). About efficacy, a patient from the placebo group was rated as independent (mRS <3), as compared to five patients from the citicoline group (OR, 5.38; 95% CI, 0.55-52, n.s.). As a conclusion, it may be stated that citicoline appears to be a safe drug in patients with primary intracerebral hemorrhage, which may allow citicoline to be given to patients with clinical signs suggesting stroke before neuroimaging tests are performed, at an earlier time than usual. As regards efficacy, highly promising data have been obtained, but should be confirmed in a larger study. Also, recently Eribal and Chua [545] communicated the results of the RICH trial performed in the Philippines. This study was conceived to investigate the role of neuroprotectants, particularly citicoline, in intracerebral supratentorial hemorrhage which to date, still has paucity of data on proven effective therapy. This was a randomized double-blind, placebo-controlled, multicentre, parallel group study on patients with first ever supratentorial intracerebral hemorrhage given either 4 g citicoline or placebo for 14 days from index stroke. A total of 182 patients were enrolled into the study. The mean age of both groups was similar 56.90 ± 11.45 citicoline and 57.61 ± 11.83 for placebo. Comorbidities were similar except for the significantly higher number of diabetes patients in citicoline group. Results showed there were more patients with favorable BI scores (2.2 versus 0, 9.2 versus 8.5, and 50.8 versus 31.9) in the citicoline group than in the placebo group respectively. However, the difference was only clinically significant after day 90. Patients had favorable mRS score (7.9 versus 13.4, 18.2 versus 20.3, and 46.1 versus 33.8) in the citicoline that in the placebo group only on the day 90th. This was however not statistically significant. The NIHSS did not differ in both groups with scores of 76.3 versus 75.6, 93.9 versus 91.9, and 96.8 versus 94.3 respectively. Mortality was slightly higher in the citicoline group (11 patients) than in the placebo group (10 patients) but this was not statistically significant. The incidence of adverse in both groups was not different statistically. For the authors, citicoline is effective in improving the BI, and mRS scores on the attainment of functional independence beginning on the 90th day post stroke compared to placebo. Iranmanesh and Vakilian demonstrated the efficiency of citicoline in increasing muscular strength of patients with non-traumatic cerebral hemorrhage in a double-blind randomized clinical trial [546]. Thus, citicoline could play a role in the pharmacological treatment of patients with intracerebral hemorrhages [547, 548], and also in subarachnoid hemorrhage [549]. Zhu [550] investigates the clinical efficacy of citicoline and oxiracetam in patients with cerebral hemorrhage and concludes that this therapeutic combination can affectively promote the absorption of the hematoma, improve the outcome and the quality of life of this kind of patients.

In a study-based meta-analysis, including all the double-blind studies performed with citicoline in acute stroke patients, Saver [551,552] suggests again the beneficial effect of citicoline on the long-term death and disability in this kind of patients (Fig. 25).

Several publications from different countries about the use of citicoline in the treatment of acute stroke have been published in the last years [553-563], and, in some cases, assessing the major efficacy when associated with other neuroprotective drugs [564].

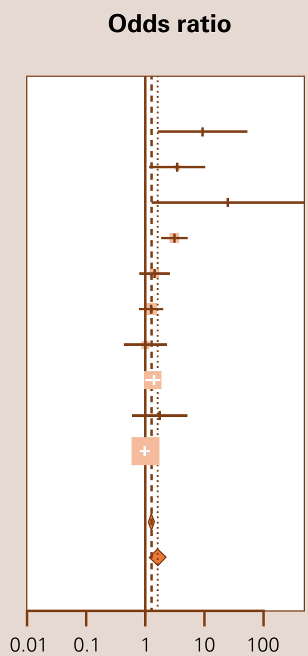
From 2006 to 2012, a large trial was conducted in Europe with the objective to corroborate the data obtained with citicoline, but under the current circumstances. This was the ICTUS trial [565-568]. It was a randomised, placebo-controlled, sequential trial in patients with moderate-to-severe acute ischemic stroke admitted at university hospitals in Germany, Portugal, and Spain. Using a centralised minimisation process, patients were randomly assigned in a 1:1 ratio to receive citicoline or placebo within 24 hours after the onset of symptoms –1,000 mg/12 hours intravenously during the first three days and orally thereafter for a total of six weeks [2 × 500 mg/12 hours–. All study participants were masked. The primary outcome was recovery at 90 days measured by a global test combining three measures of success: NIHSS ≤1, mRS ≤1, and BI ≥95 [567]. Safety endpoints included symptomatic intracranial hemorrhage in patients treated with rTPA, neurological deterioration, and mortality. This trial was registered, NCT00331890. 2,298 patients were enrolled into the study. 37 centers in Spain, 11 in Portugal, and 11 in Germany recruited patients. Of the 2,298 patients who gave informed consent and underwent randomisation, 1,148 were assigned to citicoline and 1,150 to placebo. The trial was stopped for futility at the third interim analysis on the basis of complete data from 2,078 patients. The final randomised analysis was based on data for 2,298 patients: 1,148 in citicoline group and 1,150 in placebo group. Global recovery was similar in both groups (OR, 1.03; 95% CI, 0.86-1.25; $p = 0.364$). No significant differences were reported in the safety variables nor in the rate of adverse events. Thus, under the circumstances of the ICTUS trial, citicoline is not efficacious in the treatment of moderate-to-severe acute ischaemic stroke. But when the results of the ICTUS trial were placed in the context with the previous data, the interpretation of the study was that on top of the best treatment possible, citicoline does not show any clinical improvement but, as shown an the updated fixed-effects meta-analysis included in the original paper, the effect of the drug remains significant (OR, 1.14; 95% CI, 1-1.3). Heterogeneity coming from the older studies suggests that the beneficial effect of citicoline over time was diluted in parallel with the improvement of the standard of care of acute ischaemic stroke. One of the points to consider interpreting the results of this study is that more than 46% of patients were treated with rTPA. Clinical guidelines for the treatment of ischaemic stroke should be updated in light of the salutary results of ICTUS [569].

Figure 25. Death or dependency at long-term follow-up. Forest plot meta-analysis of the effect of citicoline versus control in trials enrolling patients with ischaemic stroke, intracerebral haemorrhage and stroke without imaging confirmation of subtype. C010: citicoline 010 trial; CI: confidence interval; CSSG: Citicoline Stroke Study Group; df: degree of freedom; Fixed: fixed-effects model; M-H: Mantel-Haenszel estimate. Reprinted with permission from J.L. Saver. *Citicoline: update on a promising and widely available agent for neuroprotection and neurorepair*. Rev Neurol Dis 2008; 5: 167-77.



A new updated meta-analysis [570] was done to assess whether starting citicoline treatment within 14 days after stroke onset improves the outcome, measured as a mRS score of 0-2 or equivalent, in patients with acute ischemic stroke, as compared with placebo. Additionally, to explore if the effect of citicoline has decreased along with improvements in the standard of care. A systematic search of the adequate terms was performed on Medline, PubMed, Embase, Cochrane Specialised Register of Clinical Trials, Clinicaltrials.gov, Internet Stroke Center and Grupo Ferrer database to identify all published, unconfounded, randomized, double-blind and placebo-controlled clinical trials of citicoline initiated within the first 24 h and up to 14 days of onset in acute ischemic stroke patients. Ten randomized clinical trials (n = 4,436, but only 4,420 were valid for analysis) met the inclusion and quality criteria. The studies used citicoline with doses ranging from 500 to 2,000 mg daily administered by oral and/or intravenous route. Heterogeneity among studies was observed, reflecting the time gap of 32 years between the studies included in the meta-analysis. The administration of citicoline was associated with a higher rate of independence (Fig. 26), independently of the method of evaluation used (OR, 1.56; 95% CI, 1.12-2.16 under random effects; OR, 1.20; 95% CI, 1.06-1.36 under fixed effects). The results obtained with the subgroup of patients not treated with rtPA (OR, 1.63; 95% CI, 1.18-2.24 under random effects; OR, 1.42; 95% CI, 1.22-1.66 under fixed effects), and the results of patients not treated with rtPA and receiving the highest dose of citicoline (2g/day/6 weeks) started in the first 24 hours after onset (OR, 1.27; 95% CI, 1.05-1.53) demonstrated that the effect of citicoline is diluted when paralleled with improved standards of care. In conclusion, this systematic review shows the benefits of citicoline in the treatment of acute ischemic stroke, increasing the rate of independence. This effect is stronger in the case of patients not treated with rtPA. Yu and Zelterman [571], using a new method of parametric meta-analysis, confirmed the results re-

Figure 26. Effect estimates and 95% confidence intervals (95% CI) of the intervention with citicoline on the rates of independence (mRS score of 0-2 or equivalent) in comparison with the placebo in patients with acute ischemic stroke. Reprinted with permission from J.J. Secades, et al. Citicoline *for acute ischemic stroke: a systematic review and formal meta-analysis of randomized, double-blind, and placebo-controlled trials*. J Stroke Cerebrovasc Dis 2016; 25: 1984-96.



Study	Experimental Events	Experimental Total	Control Events	Control Total	OR	95% CI	W (fixed)	W (random)
Boudouresques 1980	11	23	2	22	9.17	1.73-48.60	0.2%	3.2%
Goas 1980	16	31	8	33	3.33	1.15-9.65	0.9%	6.4%
Corso 1982	7	17	0	16	23.57	1.21-457.36	0.1%	1.2%
Tazaki 1988	68	136	35	136	2.89	1.73-4.81	4.0%	13.0%
USA 1 1997	80	193	22	64	1.35	0.75-2.44	4.4%	11.8%
USA 2 1999	116	267	50	127	1.18	0.77-1.82	8.8%	14.3%
USA 3 2000	20	52	19	48	0.95	0.43-2.13	2.8%	8.9%
USA 4 2001	185	452	156	446	1.29	0.98-1.69	21.3%	16.8%
Alviarez 2007	13	29	10	30	1.62	0.57-4.66	1.2%	6.4%
ICTUS 2012	329	1148	343	1150	0.95	0.79-1.13	56.2%	17.9%
Fixed effect model		**2348**		**2072**	**1.20**	**[1.06; 1.36]**	**100%**	**–**
Random effects model					**1.56**	**[1.12; 2.16]**	**–**	**100%**

Heterogeneity: I^2 = 72.1%; tau^2 = 0.149; p = 0.0002

ported in this meta-analysis. Sanossian and Saver [572] replicated our previous meta-analysis and concluded that treatment with citicoline was associated with an increased frequency of functional independence at long-term follow-up, 36.4% versus 31.6%, with an OR of 1.20 (95% CI, 1.05-1.55) and p =0.02. Agarwal and Patel [493] in their systematic review on the role of citicoline in the management of patients with acute ischemic stroke concluded that functional outcomes were significantly improved by citicoline in these patients. However, another meta-analysis based only on studies published in Chinese and English, that is with an important bias, citicoline cannot reduce long-term mortality and dependence rate in the treatment of acute stroke [573], results similar to those obtained by Pinzon and Sanyasi [574]. Martí-Carvajal et al [575] published a controversial Cochrane review about the use of citicoline in the management of acute ischemic stroke. They concluded that the findings of the review suggest there may be little to no difference between citicoline and its controls regarding all-cause mortality, disability or dependence in daily activities, severe adverse events, functional recovery and the assessment of the neurological function, based on low-certainty evidence. The most relevant 'problems' with this review were: the authors were also the reviewers, the selection of trials was biased and incomplete, and some of the comments included in the review were not true, such as when the authors mention that 'citicoline has been banned in the United States and Canada', when citicoline is marketed in the United States as a medical food.

Touré et al [576] in a study performed in Senegal, confirmed the efficacy of citicoline in the management of acute stroke patients, reflected by an improvement on the functional outcome. Charan et al [577] did a comparative study of citicoline versus cerebroprotein hydrolysate in ischemic and hemorrhagic stroke patients and concluded that both treatments have a similar efficacy. Kobets [578] confirms the efficacy of citicoline in the management of acute ischaemic stroke. Sergeev et al

[579] concluded that maximal effect of citicoline is seen when it is administered as soon as possible after stroke onset in patients who are not eligible for reperfusion therapy. Seifaddini et al [580] concluded that prescription of citicoline for treatment of acute ischemic stroke is associated with hemodynamic changes in cerebral arteries and that this finding can be one of the citicoline's mechanisms of action in ischemic stroke process. Mehta et al [581] did a prospective, single center, single-blinded, and hospital-based study with the purpose to evaluate the efficacy of citicoline, edaravone, minocycline, and cerebrolysin compared with placebo in patients with a cerebral infract at the middle cerebral artery territory with 20 patients in each group. There was significant improvement in the functional outcome of patients with acute ischaemic stroke involving middle cerebral artery territory at 90 days receiving citicoline, edaravone, and cerebrolysin. However, minocycline did not offer the same efficacy as compared with other neuroprotective agents. Diana et al [582] investigate motoric improvement in acute ischemic stroke patients in Siti Khodijah Sepanjang Hospital in an observational retrospective case-control study and concluded that citicoline 500 mg/day/5 days significantly improved motor function in acute ischaemic stroke patients. Kuryata et al [583] performed a study was to estimate the effects of citicoline therapy on the levels of circulating neurospecific protein markers in serum of the patients with ischemic stroke and atrial fibrillation. The results obtained allow the authors to hypothesize that therapeutic benefit of citicoline in patients with ischemic stroke and atrial fibrillation can be mediated through increasing neuronal viability, protecting against axonal injury, decreasing the level of reactive astrogliosis, preventing deficiencies in the blood-brain integrity, and reducing the intensity of demyelination. Mazaheri et al [584] investigate the efficacy of citicoline in acute stroke patients in a randomized clinical trial on 160 patients with hemorrhagic and ischemic stroke. The participants were randomly assigned into two groups of intervention and control. The intervention group daily received 1 g citicoline injections for 10 days, in addition to the standard therapy. Regardless of the type of stroke, the severity of the disease decreased over time in both groups. However, at the end of the study (the 90^{th} day), the intervention group had lower disease severity, compared to the control group ($p < 0.05$). In terms of the ischemic stroke patients, the severity of the disease was significantly lower in the intervention group on the 90^{th} day, compared to that in the control group. According to the authors, the long-term administration of citicoline could result in significant impacts on the treatment of the patients, especially those with ischemic stroke, and improvement of their efficacy.

Agarwal et al [585] published a pilot study to determine whether administration of citicoline immediately after recanalization therapy for acute ischaemic stroke would improve clinical and radiological outcome at three months compared to standard treatment alone. They recruited participants with acute ischaemic stroke undergoing recanalization therapy and randomly assigned them to receive either citicoline or placebo in 1:1 ratio. Citicoline arm patients received citicoline 1 g intravenous twice a day for three days, followed by oral citicoline 1 g twice a day for 39 days. Placebo arm patients received 100 mL intravenous normal saline for three days, followed by multivitamin tablet twice a day for 39 days. Authors did not find any significant difference between the citicoline or placebo arms with respect to either our primary or secondary outcomes. Reasons for the failure included:

- The ceiling effect of maximum benefit achieved by thrombolysis and mechanical thrombectomy.
- The low power of the study (small sample size) to detect a meaningful difference in functional outcomes
- The study couldn't achieve the planned sample size causing a reduction in power with a possibility of type 2 error.
- Even for the surrogate outcome of the stroke volume it was not possible achieve the sample size due to poor recruitment during COVID-19 pandemic.
- Other reason could be that lacunar stroke was the common stroke subtype in the study.

Premi et al [586], in a pilot randomized, single-blind experimental study, evaluated if the treatment with citicoline was able to restore intracortical excitability measures, evaluated through transcranial magnetic stimulation protocols, in patients with acute ischemic stroke. The authors conclude that the eight-week treatment with citicoline after acute ischemic stroke may restore intracortical excitability measures, which partially depends on cholinergic transmission.

Abou Zaki and Lokin [587] communicated a meta-analysis aims to evaluate the degree of effect and safety of the neuroprotectants citicoline, cerebrolysin, edaravone and MLC601 (NeuroAid) in the recovery of patients with cerebral infarcts. The analysis showed that the outcome of patients with acute ischemic strokes improved significantly when receiving neuroprotectants versus placebo (OR, 0.29; CI 95%, 0.09-0.5). According to the authors, this study supports the use of neuroprotectants in patients with acute ischemic strokes unable to receive thrombolysis or thrombectomy to improve long term functional outcomes and ultimately quality of life.

In the sequelar phase, some studies have been shown that citicoline potentiates the effects of motor rehabilitation [511,546,588,589]. In a published meta-analysis [590], it was shown how citicoline is able to increase the efficacy of motor rehabilitation in upper limbs in hemiplegic patients after ischemic stroke. Citicoline could play a relevant role in neurorehabilitation [591]. Mushba et al [592] evaluated the effect of citicoline on the efficacy of rehabilitation measures in ischemic stroke patients and concluded that citicoline significantly improves cognitive function, which in turn has a positive effect on the efficacy of remediation and indirectly improves cerebral perfusion measured with single photon emission computed tomography in patients with hemispheric ischemic stroke. Kostenko and Petrova [593] presented the results of their own observation of the use of citicoline in the complex program of medical rehabilitation of patients after ischemic stroke describing that the high efficiency of citicoline application in complex rehabilitation of patients in the early recovery period of ischemic stroke is shown in the form of improving walking function, increasing functional independence, daily activity and quality of life. Szelenberger et al [594] postulate citicoline among the pharmacological interventions for enhancing brain self-repair and stroke recovery. Singh et al [595] did a prospective study to test the role of citicoline in stroke patients in terms of cognition, memory and post stroke disability. Patients received either a placebo (n = 40) or 500 mg/12 hours citicoline (n = 35) for 12 weeks (orally or intravenously). Citicoline shows beneficial effects in stroke in terms of cognition, memory and post stroke disability. Alizadeh et al [596] showed that citicoline is more useful drug for improving speech and language skills than piracetam in post-stroke aphasia. Shulginova et al [597] described a role of citicoline alone or in combination with other drugs in patients with chronic cerebral ischemia with disorders of the immune status.

Corallo et al [598] conducted a narrative review to investigate whether antidepressant therapy, including the use of selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors or the use of supportive drugs (i.e., citicoline or choline alfoscerate) as a substitute for antidepressant therapy, reduces depression in patients with cerebrovascular diseases. The authors concluded that the findings support the efficacy of citicoline as a treatment for depression. Arcadi et al [599] in a retrospective cohort study concluded that the administration of nootropic drugs, such as citicoline, could be a valid therapeutic strategy to manage post-stroke patients suffering from mild-moderate anxiety or anxious-depressive syndrome. Tykhomyrov et al [600] indicated for the first time that citicoline protects both astrocytes and neurons and improves angiogenic capacity through down-regulation of angiostatin in post-ischemic patients with atrial fibrillation after acute ischemic stroke.

In conclusion, it may be stated that it has been adequately shown that patients with acute stroke, as well as with sequelae, may benefit from citicoline treatment by achieving a better functional and neurological recovery, and that this is a safe and well tolerated treatment, as recognized by various authors [601-615] and some agencies [616,617].

Cognitive disorders

Various experimental investigations on the so-called brain aging have led in recent years to give an increasing importance to changes in neuronal metabolism as a factor involved in the pathophysiology of this process. In the senile brain there is a general decrease in enzyme activities related to energy metabolism, and more specific biochemical changes affecting lipid and nucleic acid metabolism. It has also been shown that specific changes in certain neurotransmitters (dopamine, acetylcholine) and hormones (growth hormone, prolactin) are associated in both aging processes and certain presenile and senile diseases [618], and more recently there are several publications showing an increasing evidence of vascular risk factors as key mechanisms in the development of cognitive impairment and dementia [619-622].

As shown in the various experimental studies analyzed, citicoline increases phospholipid synthesis and glucose uptake in the brain in conditions in which these processes are decreased. Citicoline also influences metabolism of neurotransmitters and has been shown to increase dopamine synthesis in certain brain regions. Based on these facts, many clinical trials have been conducted to assess

Table IX. Percentage remission and symptomatic improvement ($p < 0.001$ for each symptom in relation to the onset of treatment).

	Patients (*n*)	Remission	Improvement
State of mood	1521	38.2%	40.9%
Emotivity	1559	36.9%	39.7%
Restlessness	1504	41.3%	34.1%
Own initiative	1378	35.8%	32.9%
Short-term memory	1614	26.0%	45.5%
Interest in the environment	1410	38.3%	34.5%
Appearance	1132	40.0%	26.9%
Vertigo	1463	59.4%	31.3%
Mobility	1234	35.2%	30.5%
Headache	1425	57.7%	31.2%

the efficacy of citicoline in the treatment of cognitive disorders associated to brain aging, chronic cerebral vascular disease, and dementia [623]. Using magnetic resonance spectroscopy techniques, citicoline has been shown to stimulate phosphatidylcholine synthesis in the brain [624-627] and improves the energetic cerebral metabolism of elderly subjects [628], which is related to an improvement in their cognitive capacities [629], particularly memory [630-632] and reaction time [633]. In healthy volunteers, the administration of citicoline has been associated with improvement in attention [634,635], memory [636,637] and in some neurophysiological parameters [638-641]. Some authors emphasize the role of citicoline in the management of vascular cognitive impairment [642], specially as a sirtuin-activating compound, considering this a relevant action on the neuroinflammation involved in cognitive impairment [643]. Baumel et al [644] considered the utility of a uridine/choline supplementation in the management of mild cognitive impairment. Gromova et al [413] consider that the pharmacological effects of CDP-choline are mediated through multiple molecular mechanisms that contribute to the nootropic action of this molecule and its effectiveness in the management of cognitive disorders. Farooq et al [645] included citicoline among the pharmacotherapy for vascular cognitive impairment. Lewis et al [646] included citicoline among the nutrients and phytonutrients with effect on cognitive function.

In one of the early studies conducted in this field, Madariaga et al [647] showed that, in a group of female senile patients, treatment with citicoline induced improvements in memory, cooperation, and capacity of relationship to the environment. Fassio et al [648] discussed the value of citicoline in psychogeriatrics and stressed that use of citicoline as background treatment allows for reducing dosage of psychoactive drugs routinely used in psychogeriatrics. Many studies have shown the value of citicoline for the treatment of the so-called senile cerebral involution, decreasing its characteristics symptoms [649-658]. Lingetti et al [649], in an open-label, controlled study conducted on a group of 30 patients with senile involutive brain disease, achieved symptomatic improvements in 83.3% of cases and emphasized the absence of treatment-related side effects. Stramba-Badiale and Scillieri [650] were able to show a significant improvement in scores of the Fishback's *Mental Status Questionnaire* in a group of 24 elderly subjects after 20 days of treatment with citicoline 500 mg/day intramuscular. Bonavita et al [651] emphasized the efficacy of citicoline for promoting changes in some neuropsychiatric symptoms, such as memory and attention, in senile patients without causing side effects. Lozano et al [652] reviewed a series of 2,067 elderly patients treated with citicoline at doses of 300-600 mg/day for two months. Table IX gives the results obtained based on remission and improvement of certain neuropsychic symptoms. Palleschi and Capobianco [653] showed significant improvements in scores of the Sandoz Clinical Assessment-Geriatric (SCAG) and MMSE scales in patients with pathological brain aging following citicoline treatment. In a multicentre study in which 502 senile patients participated, Schergna and Lupo [654] showed citicoline to induce significant improvements in attention, behavior, relational life, and independence. No side effects occurred associated to this treatment. Suryani et al [655] showed citicoline to be effective for the treatment of memory deficits in the elderly, achieving significant and progressive improvements in all parameters analyzed (Table X). Citicoline has been able to improve scores of senile patients in various scales, such as the Plutchik scale [656], *Trail Making Test*, Randt memory test, and Toulouse-Piéron attention test [657,658].

Administration of citicoline to healthy adult individuals was shown to act upon the anterior pitu-

Table X. Scores for the repetition of digits, an adaptation by Wechsler of the Stanford-Benet logical history test, the Bali image memorisation test and memory deficits and physical disorders reported by patients before and after treatment with citicoline. Values are expressed as means ± SD.

	Baseline (n = 10)	After treatment		
		1 week (n = 10)	2 weeks (n = 10)	3 weeks (n = 6)
Direct repetition of digits	14.6 ± 4.6	19.6 ± 5.6 [b]	20.2 ± 4.5 [b]	22.8 ± 6.0 [b]
Reverse repetition of digits	5.60 ± 4.1	7.30 ± 3.4 [b]	11.3 ± 7.1 [b]	12.1 ± 7.7 [b]
Logic history test	6.10 ± 4.4	9.60 ± 3.8 [b]	12.7 ± 3.7 [b]	13.6 ± 4.8 [b]
Bali images test	5.20 ± 3.2	9.30 ± 3.5 [b]	11.7 ± 3.4 [b]	12.0 ± 2.4 [b]
Memory deficits	2.5 ± 0.9	1.00 ± 0.9 [a]	0.30 ± 0.4 [b]	0.30 ± 0.5 [b]
Physical disorders	2.3 ± 0.9	1.00 ± 0.8 [a]	0.20 ± 0.6 [b]	0.10 ± 0.4 [b]

[a] $p < 0.05$; [b] $p < 0.01$, versus baseline values.

itary gland, inducing an increased growth hormone secretion and a decreased prolactin secretion thanks to the activation of the dopaminergic system induced [659,660]. Ceda et al [661] showed that citicoline is able to increase growth hormone secretion, both basal and stimulated by the growth hormone-releasing hormone, in elderly patients. This secretion is impaired in such individuals and, to a greater extent, in patients with degenerative brain diseases.

One of the main causes of cognitive impairment in the elderly is chronic cerebral vascular disease, also called cerebral insufficiency, whose maximum degree of clinical expression is vascular dementia. A multicentre, randomized, double-blind study versus placebo assessed the efficacy of citicoline for the treatment of patients with chronic vascular disease [662]. In this study, 33 patients received treatment with citicoline 1 g/day or saline as an intravenous infusion for 28 days. At the end of the treatment period, significant improvements were noted in the citicoline-treated group in the Bender-Gestalt test, Hamilton scale for depression, Parkside scale, neurological assessment scale, and attention test. Falchi Delitalia et al [663] and Moglia et al [664] noted that the clinical improvement seen was associated to an improved electroencephalogram tracing in these patients. Merchan et al [665] showed a gradual improvement in symptoms associated to cerebrovascular insufficiency in a group of 40 elderly patients treated with citicoline at a dose of 1 g/day intramuscular for 60 days.

Agnoli et al [666] conducted a double-blind study in 100 patients with chronic cerebral vascular disease, in whom effectiveness of administration of citicoline 1 g/day/28 days intravenous compared to placebo was assessed. After the treatment period, the group of citicoline-treated patients showed statistically significant improvements in the scores obtained in the Hamilton scale for depression and in the modified Parkside behavior rating scale, as well as in the psychometric and observational tests used. It was concluded that citicoline improved perceptual-motor capacity and attention in these patients, in addition to having a stabilizing effect on behavior. Sinforani et al [667], Motta et al [668], and Rossi and Zanardi [669] achieved very similar results in their respective studies. The best clinical and behavioral results were seen in patients with a diffuse cerebral vascular disease [670-675].

Eberhardt and Derr [676] conducted a double-blind, crossover study to assess the efficacy and tolerability of citicoline in patients with senile cerebral insufficiency. This study enrolled 111 patients with a mean age of 74.6 ± 6.9 years and a clinical diagnosis of senile cerebral insufficiency. After a placebo washout period, two homogeneous groups were formed, one of which received treatment with citicoline 600 mg/day orally for five weeks and placebo for five additional weeks, with a placebo washout period between both treatments. The reverse administration order was used in the other group. Controls were performed at 2, 7, 9, and 12 weeks. Citicoline significantly improved the

Table XI. Percentage of patients who improved in each group in relation to treatment initiation with citicoline or placebo.

	Group I		Group II	
	Citicoline	Placebo	Placebo	Citicoline
Numerical counting	47	31	21	52
Labyrinth	73	69	71	83
Numerical connection	67	76	67	87
NAS	57	41	44	69
NAB	63	57	48	67
SCAG	80	73	65	83

NAS: Neuropsychological Self-Assessment Scale; NAB: Gerontopsychological Observation Scale; SCAG: Sandoz Clinical Assessment Geriatric Scale.

clinical status in all six tests used (number recall, labyrinth, number connection, neuropsychological assessment scale, geriatric observation scale, and SCAG) as initial treatment, and provided a statistically significant additional improvement as second treatment after placebo, that achieved some degree of improvement in five of the six tests. Between-subject comparisons also showed a superior efficacy of citicoline. Table XI shows the proportions of patients who improved in each treatment phase in both groups. No treatment-associated severe side effects were seen. Authors concluded that these results support the efficacy of citicoline for the treatment of senile cerebral insufficiency and its excellent tolerability in geriatric patients. Such benefits would be due to the capacity of citicoline to inhibit degradation of phospholipids in neuronal membranes, increase choline plasma levels, and activate the synthesis of structural phospholipids and the synthesis and release of catecholamines. Citicoline effects on test improvement were also shown to persist after switching to placebo, suggesting that they are related to the neuronal metabolic process tending to restore and maintain neuron function.

Chandra [677] reported the results of a double-blind study on the treatment of multi-infarction dementia with citicoline. The study enrolled 146 patients who were randomized into two groups, one of which received treatment with citicoline, 750 mg/day intravenous, and the other saline for two months, though follow-up was prolonged up to 10 months. At the end of the treatment period, citicoline-treated patients showed significant improvements in the MMSE scores. By contrast, such scores slightly worsened in the placebo group. After 10 months, citicoline-treated patients had a sustained improvement, while patients in the placebo group continued to worsen.

Piccoli et al [678] reported the results of a double-blind study conducted in 92 patients with chronic cerebral vascular disease treated with citicoline (1,000 mg/day intramuscular) or placebo in two treatment cycles of four weeks each separated by a one-week interval. Forty-six patients were randomized to each group, and both groups were fully matched as regarded cognitive impairment. Psychometric assessment was performed using the Toulouse-Piéron test (attention to non-verbal stimuli), Randt memory test, and SCAG scale (a measure of behavior and emotional control). A between-group comparison revealed significant improvements in the citicoline group in attention tests, with fewer wrong answers in the Toulouse-Piéron test ($p < 0.05$), in mnesic capacities according to the general information subtest of the Randt memory test ($p < 0.05$), and in the affective disorder score in the SCAG scale ($p < 0.02$). In addition to being clinically effective, citicoline was shown to be a very safe drug, as no adverse effects associated to treatment were detected.

Capurso et al [679] assessed the efficacy of citicoline for the treatment of chronic cerebrovascular disease in a multicentre, double-blind, placebo-controlled study. Cognitive and behavioral functions were assessed using psychometric scales and tests in 31 patients, who were randomized to receive citicoline (17 cases) or placebo (16 cases). After a two-week washout period, three treatment periods, each lasting 28 days, were started. Patients were given 1 g/day of citicoline or placebo by the intramuscular route. A one-week washout period was left between each treatment cycle. Various cognitive functions improved in the group of citicoline-treated patients, particularly short and long-term memory. The Randt memory test showed a constant improvement in several subtests, and cognitive and attention efficiency also significantly improved. The Glasgow-Blatchford scale, assessing behavioral indices, also showed improvements associated to citicoline treatment. Authors concluded that patients treated with citicoline showed a significant improvement in cognitive functions, while placebo-treated patients showed no favourable trends. On the other hand, good tolerability of the drug was also reported.

However, in patients with vascular dementia according to current diagnostic criteria, Cohen et al [680] were not able to show any beneficial effect of citicoline in their pilot study.

Using positron emission tomography, Tanaka et al [681] correlated cognitive improvement to a significant increase in cerebral blood flow in patients with vascular dementia who received treatment with citicoline (1 g/day/1 week intravenous).

Lozano [682] reported the results of a study conducted by the Iberian-American Group for the Study of Alzheimer's Disease and Longevity (GIAL), aimed at assessing the status and course, after one year, of a group of patients with dementia-like psychic and organic impairment following diagnosis and classification of its cause as degenerative, vascular or mixed, and treatment with oral citicoline. Citicoline 600 mg/day orally was administered for one year to 314 patients with a mean age of 75.02 ± 7.72 years to assess the course of their dementia during that time. Dementia was rated as degenerative in 41.1% of cases, while vascular dementia accounted for 39.5% of cases and mixed dementia for 11.4%. The MMSE and BI were used for assessment, and controls were performed at months 1, 3, and 12. MMSE scores were seen to significantly improve in vascular and mixed dementia and to remain stable, with a certain trend to improve, in degenerative dementia. Scores in the BI showed statistically significant improvements in each of the controls and for each type of dementia. These results suggest that citicoline has a beneficial effect of long-term course of dementia and is also a safe treatment.

Corona et al [683] pointed that citicoline benefits in the treatment of patients with dementia would be partly due to the ability of the drug to improve activity of the noradrenergic, dopaminergic, and serotonergic systems, as shown by them in a study assessing changes over time in cerebrospinal fluid and urinary levels of metabolites from the monoamines involved in these systems during treatment of patients with senile dementia of the Alzheimer type.

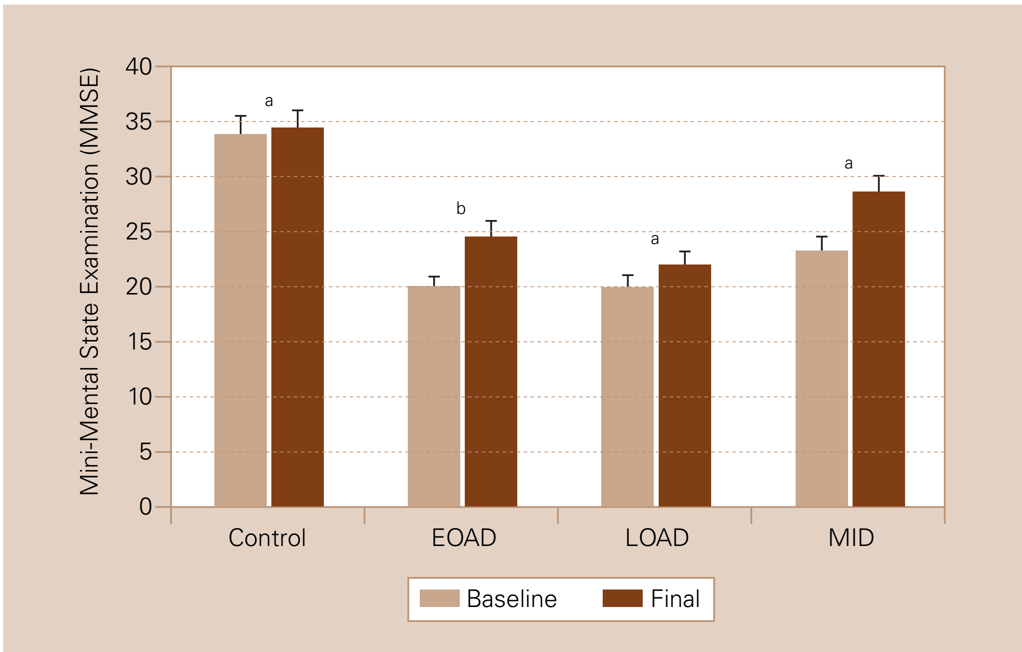
Cacabelos et al [684] conducted a study to assess the therapeutic effects of citicoline in dementia patients. This study recruited 40 patients, who were distributed into four groups a) 10 healthy elderly subjects; b) 10 patients with early onset Alzheimer's disease; c) 10 patients with late onset Alzheimer's disease; and d) 10 patients with multi-infarction dementia. These patients received treatment with citicoline at a dose of 1 g/day orally for three months. After this treatment period, all groups experienced a significant improvement in MMSE scores (Fig. 27) and a significant antidepressant effect, as assessed by the Hamilton scale for depression (Fig. 28). Patients with early onset Alzheimer's disease were also found to have significantly higher interleukin 1β plasma levels at baseline as compared to all other groups, revealing the participation of a neuroimmune change in the pathophysiology of Alzheimer's disease. After citicoline treatment, interleukin 1β plasma levels were normalized, which suggests that this drug has a certain immunomodulatory action. In a subsequent phase of their study, this same investigating group showed that, in patients with Alzheimer's disease, citicoline not only improved cognitive function, but also cerebrovascular function, as assessed using transcranial Doppler ultrasonography [685]. The neuroimmune effect of the drug was demonstrated by the findings that citicoline therapy decreased histamine plasma levels that are abnormally elevated in patients with Alzheimer's disease [686] and increases plasma levels of tumor necrosis factor alpha [687].

This same investigating group recently published the results of a double-blind, randomized, placebo-controlled, pilot study where citicoline (1 g/day/12 weeks orally) or placebo was administered to 30 patients with mild to moderate senile dementia of the Alzheimer type [688]. As compared to the 17 patients treated with placebo, patients receiving citicoline who had a positive APOE ε4 genotype showed a significant improvement in their cognitive capacity as assessed with the Alzheimer's disease assessment scale ($p < 0.05$). As previously seen, citicoline was also shown to increase cerebral blood flow and improve bioelectric activity in the brain.

Soto et al [689] showed the value of the therapeutic association of citicoline, piracetam, and a dihydropyridine calcium channel blocker, either nicardipine or nimodipine, for the treatment of senile dementia of the Alzheimer type. Cacabelos et al [690] also advocated a multifactorial treatment, that would include citicoline, for Alzheimer's disease in genotyped patients. Zhuravin et al [691] demonstrated that the activities of blood serum acetylcholinesterase, butyrylcholinesterase and neprilysin reflect the level of cognitive dysfunction in patients with Alzheimer's disease and can be used as prognostic biomarkers of the level of dementia progression, and that the treatment with citicoline can modify positively these levels.

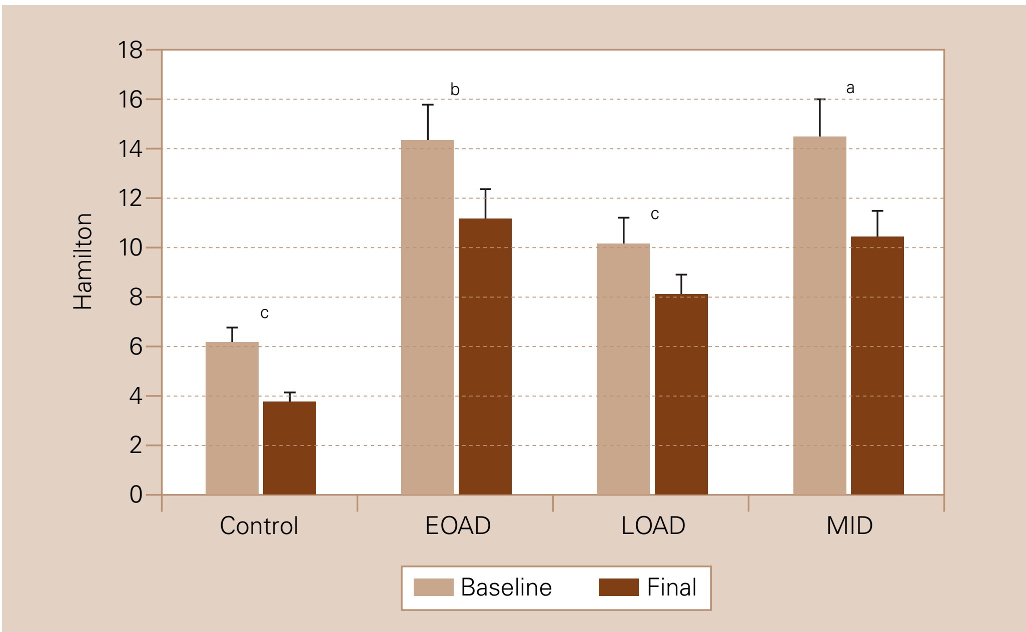
In a systematic review published by the Cochrane Library, Fioravanti and Yanagi [692] exam-

Figure 27. Effects of citicoline on cognitive function assessed using the MMSE in healthy older subjects (control), patients with early-onset Alzheimer's disease (EOAD) or late-onset Alzheimer's disease (LOAD) and patients with multi-infarct dementia (MID). [a] $p < 0.02$; [b] $p < 0.01$.



ined the effects of citicoline in the treatment of cognitive, emotional, and behavioral deficits associated to chronic brain disorders in the elderly. Fourteen studies were included in this review. Some of the included studies did not present numerical data suitable for analysis. Description of participants varied over the years and by type of disorders and severity and ranged from aged individuals with subjective memory disorders to patients with vascular cognitive impairment (mild to moderate), vascular dementia or senile dementia (mild to moderate). Seven of the included studies observed the subjects for a period between 20 to 30 days, one study was of six weeks duration, four studies used periods extending over two and three months, one study observed continuous administration over three months and one study was prolonged, with 12 months of observation. The studies were heterogeneous in dose, modalities of administration, inclusion criteria for subjects, and outcome measures. Results were reported for the domains of attention, memory testing, behavioural rating scales, global clinical impression and tolerability. Reaction time was used as a measure of attention, and the results were obtained from seven of the included studies with a total of 790 subjects, 384 in the citicoline group and 406 in the placebo group. Using the standardised mean difference (SMD) and fixed-effect model, the summary effect size is –0.09 [–0.23, 0.05], then there was evidence of little effect of CDP-choline on attention. The meta-analysis of the memory tests from ten studies included a total of 924 subjects, 456 in the citicoline group and 468 in the placebo group. The effect size on memory was 0.38 [0.11, 0.65] which was statistically significant. Using the six studies which reported memory test results in 675 participants with cognitive deficits associated with cerebrovascular disorders, the meta-analysis of memory function revealed homogeneous results and there was evidence of a statistically significant positive effect on memory (SMD = 0.22; 0.07,0.37). Behaviour was measured using five different scales in eight studies with 844 subjects, 412 in the citicoline group and 432 in the placebo group. There was evidence of a positive effect of citicoline on behaviour (SMD = –0.60; –1.05, –0.15) using the random-effects model. The evidence of benefit

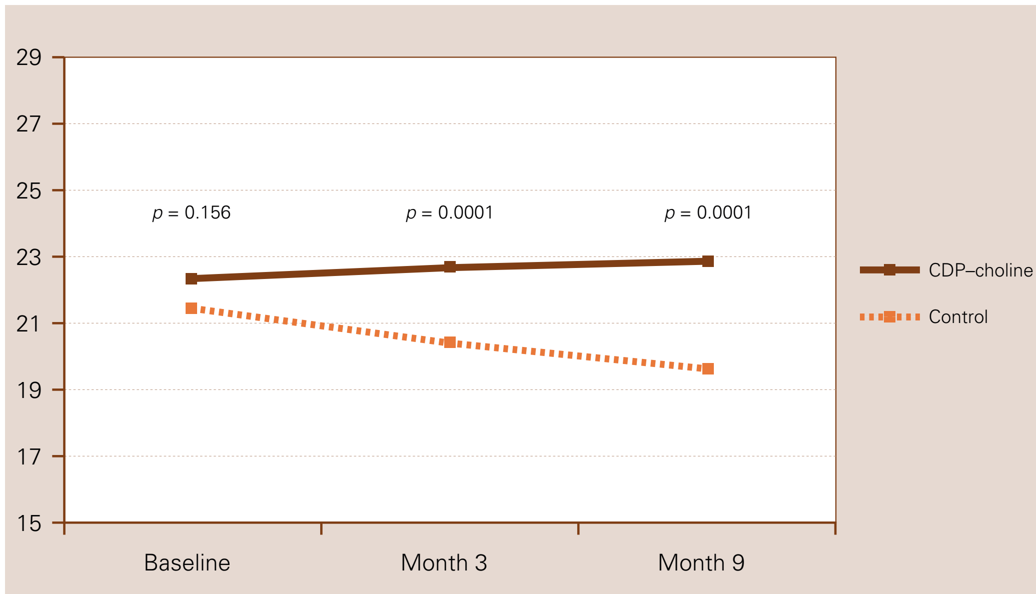
Figure 28. Antidepressive effects of citicoline in healthy older subjects (control) and in patients with Alzheimer's disease or multi-infarct dementia (MID), evaluated with the Hamilton Depression Scale. EOAD: early-onset Alzheimer's disease; LOAD: late-onset Alzheimer's disease. [a] $p < 0.02$; [b] $p < 0.01$; [c] $p < 0.05$.



from global impression was stronger; using a fixed-effect model, the Peto odds ratio for improvement in the subjects treated with citicoline as opposed to the subjects treated with placebo was 8.89 [5.19, 15.22]. Relevant was the finding that citicoline tended to be associated with fewer adverse effects than placebo, but this was not statistically significant. According to the authors, further research with citicoline should focus on longer term studies in subjects who have been diagnosed with currently accepted standardised criteria, especially vascular mild cognitive impairment or vascular dementia.

Deutsch et al [693, 694] are studying the association citicoline plus galantamine in schizophrenia. Also, recently some positive effects of citicoline in the prevention of postoperative cognitive dysfunction during total intravenous anesthesia have been reported [695-698]. Li et al [699] demonstrated the effect of citicoline as adjuvant therapy on mild cognitive impairment in Parkinson's disease. Putignano et al published the VITA study [700], a retrospective and observational study performed to assess the efficacy of citicoline in elderly patients suffering from stupor related to complex geriatric syndrome, showing that there was an improvement in key measures of performance after the treatment. The same team published the IDEALE study [701]. The IDEALE study was an open multicentre Italian study, the aim of which was to assess the effectiveness and safety of oral citicoline in elderly people with mild vascular cognitive impairment. The study was performed in 349 patients. The active or citicoline group was composed of 265 patients and included 122 men and 143 women of mean age 79.9 ± 7.8 years selected from six Italian regions. Inclusion criteria were age ≥65 years, Mini-Mental State Examination (MMSE) score ≥21, subjective memory complaints but no evidence of deficits on MMSE, and evidence of vascular lesions on neuroradiology. Those with probable Alzheimer's disease were excluded. The control group consisted of 84 patients, including 36 men and 48 women of mean age 78.9 ± 7.01 (range 67-90) years. Patients included in the study underwent brain computed tomography or magnetic resonance imaging, and plasma dosage of vitamin B_{12}, folate, and thyroid hormones. Functional depen-

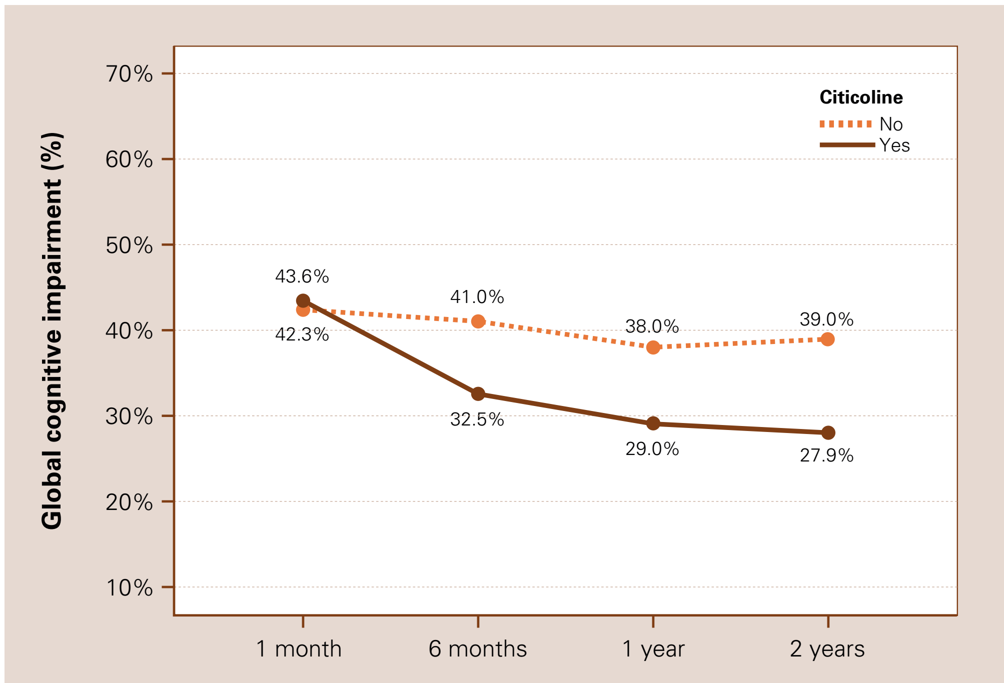
Figure 29. Comparison of corrected Mini-Mental State Examination levels between citicoline group and controls.



dence was investigated by scores on the activities of daily living (ADL) and instrumental activities of daily living (IADL) scales, mood was assessed by the Geriatric Depression Scale (GDS), and behavioral disorders using the Neuropsychiatric Inventory scale. Comorbidity was assessed using the Cumulative Illness Rating Scale. An assessment was made at baseline (T0), after three months (T1), and after nine months (T2, i.e., six months after T1). The main outcomes were an improvement in MMSE, ADL, and IADL scores in the study group compared with the control group. Side effects were also investigated. The study group was administered oral citicoline 500 mg twice a day throughout the study. MMSE scores remained unchanged over time (22.4 ± 4 at T0; 22.7 ± 4 at T1; 22.9 ± 4 at T2), whereas a significant difference was found between the study and control groups, both in T1 and in T2 (Fig. 29). No differences were found in ADL and IADL scores between the two groups. A slight but not statistically significant difference was found in GDS score between the study and control groups ($p = 0.06$). No adverse events were recorded. In this study, citicoline was effective and well tolerated in patients with mild vascular cognitive impairment. Recently the same team published the CITIRIVAD study [702], with the aim to show the effectiveness of oral citicoline plus rivastigmine in patients with Alzheimer's disease and mixed dementia. The results show the effectiveness and safety of combined administration versus rivastigmine alone, mainly in slowing disease progression and consequently in disease management, both in Alzheimer's disease and in mixed dementia. Gareri et al [703] published the Citicholinage Study and concluded that patients treated with citicoline plus an acetylcholinesterase inhibitor showed a statistically significant improvement in cognitive function. The association citicoline plus donepezil showed to be still better than citicoline plus rivastigmine. Definitely the present study showed that a cholinergic precursor such as citicoline plus an acetylcholinesterase inhibitor is able to slow down disease progression in Alzheimer's disease patients [704]. Gareri et al [705,706] in the CITIMEM study showed the effectiveness of oral citicoline plus memantine in patients affected with Alzheimer's disease and mixed dementia and encourage the role of this combined therapy in disease management and in slowing down the progression of disease. Castagna et al [707] studied on the benefits of combined treatment with citicoline, memantine, and an acetylcholinesterase inhibitor in older patients affected with Alzheimer's disease, and concluded that this triple therapy with citicoline, memantine, and an acetylcholinesterase inhibitor was more effective than memantine and an acetylcholinesterase inhibitor without citicoline in maintaining the MMSE total score after 12 months. Castagna et al [708] published the CITIMERIVA study (CITIcoline plus MEmantina plus RIVAstigmine) in older patients affected with Alzheimer's disease. This was a multicentre, retrospective case-control study conducted in Italian centers for cognitive impairment and dementia on consecutive patients aged 65 years or older affected with Alzheimer's disease. Overall, 104 patients were recruited (27% male; mean age, 76.04 ± 4.92 years); 41 (39.42%) treated with citicoline 1,000 mg/day given orally + memantine + rivastigmine (cases) and 63 (60.58%) treated with memantine + rivastigmine (controls). In the case group (triple therapy) there was a statistically significant increase in the MMSE score between the baseline and the end of the study. Gareri et al [709], in the CITIDEMAGE study, showed the effectiveness of oral citicoline plus acetylcholinesterase inhibitors plus memantine in outpatients with Alzheimer's disease. Gareri et al [710] reported an overview of the studies about combination treatment with citicoline of Alzheimer's disease and mixed dementia and demonstrated the benefits in terms of delay in cognitive worsening. Piamonte et al [711] in their review concluded that that citicoline used in adjunct with acetylcholinesterase inhibitors in the treatment of Alzheimer's disease was well-tolerated and showed improvement in cognition, mood, and behavioral symptoms compared to treating with acetylcholinesterase inhibitors alone.

Cognitive disorders are common stroke sequelae and can impair functional recovery [712]. Ischemic stroke is a significant risk factor for vascular cognitive impairment and vascular dementia [713]. In this context, Alvarez-Sabín et al performed a study to assess the safety of long-term administration and its possible efficacy of citicoline in preventing poststroke cognitive decline in patients with first-ever ischemic stroke [714], following an open-label, randomized, and parallel design to compare citicoline versus usual treatment. All subjects were selected six weeks after suffering a qualifying stroke and randomized by age, sex, education and stroke type into parallel arms of citicoline (1 g/day) for 12 months versus no citicoline (control group). Medical management was similar otherwise. All patients underwent neuropsychological evaluation at one month, six months and 12 months after stroke. Tests results were combined to give indexes of six neurocognitive domains: attention and executive function, memory, language, spatial perception, motor speed and temporal orientation. Using adjusted logistic regression models the association between citicoline treatment and cognitive decline for each neurocognitive domain at six and 12 months was determined. 347 subjects were recruited (mean age 67.2 years; 186 male, 56.6%; mean education 5.7 years); 172 (49.6%) received citicoline for 12 months. Demographic data, risk factors, initial stroke severity, clinical and etiological classification were similar in both groups. Only 37 subjects (10.7%) discontinued treatment (10.5% citicoline versus 10.9% control) at six months; 30 (8.6%) due to death –16 (9.3%) citicoline versus 14 (8.0%) control; $p = 0.740$–, seven lost to follow-up or incorrect treatment, and four (2.3%) had adverse events from citicoline without discontinuation. 199 patients underwent neuropsychological evaluation at 12 months. Cognitive functions improved six and 12 months after stroke in the entire group but in comparison with controls, citicoline-treated patients showed better outcome in attention-executive functions (OR, 1.721; 95% CI, 1.065-2.781; $p = 0.027$ at six months; OR, 2.379; 95% CI, 1.269-4.462; $p = 0.007$ at 12 months) and temporal orientation (OR, 1.780; 95% CI, 1.020-3.104; $p = 0.042$ at six months; OR, 2.155; 95% CI, 1.017-4.566; $p = 0.045$ at 12 months) during the follow-up. Moreover, citicoline group showed a better functional outcome (mRS ≤2) at 12 months (57.3 versus 48.7%) without statistically significant differences ($p = 0.186$). The authors concluded that citicoline treatment for 12 months in patients with first-ever ischemic stroke is safe and probably effective in improving poststroke cognitive decline. Citicoline appears to be a promising agent to improve recovery after stroke. Recently, the authors published the follow-up of this study after two years of treatment with citicoline [715], adding an evaluation of the quality of life, using the EuroQoL-5D questionnaire, to the cognitive assessment. 163 patients were followed for two years. The mean age was 67.5 years-old, and 50.9% were women. Age and absence of citicoline treatment were independent predictors of both utility and poor quality of life. Patients with cognitive impairment had a poorer quality of life at two years (0.55 versus 0.66 in utility; $p = 0.015$). Citicoline treatment improved significantly cognitive status during follow-up ($p = 0.005$), showing a gradual improvement across the time (Fig. 30).

Figure 30. Global cognitive impairment during follow-up. Patients treated with citicoline show a significant improvement in cognitive status during follow-up (p = 0.005). After the first year, only citicoline-treated patients continue to improve cognitive status. Reprinted from J. Álvarez-Sabín, et al. *Long-term treatment with citicoline prevents cognitive decline and predicts a better quality of life after a first ischemic stroke*. Int J Mol Sci 2016; 17: 390.



Other authors communicated beneficial effects of citicoline in the treatment of post-stroke cognitive disturbances [716,717].

Feng et al [718] investigated the effects of citicoline therapy on the network connectivity of the corpus callosum in patients with leukoaraiosis by diffusion tension imaging. After one year of treatment, citicoline was able to delay the disruption of the network connectivity of the corpus callosum in those patients. Kovalenko and Lytvyn [719] showed that citicoline treatment in patients with hypertensive dyscirculatory encephalopathy and concomitant hypothyroidism significantly improves the performance of brain electrogenesis. Mashin et al [720] concluded that treatment with citicoline in patients with chronic cerebrovascular pathologies improved cognitive function, memory and visuospatial coordination, and decreased depression severity. Chutko et al [721] indicated that the use of citicoline in the treatment of patients with somatoform dysfunction of the autonomic nervous system was highly effective (improvements occurred in 67.4% of patients), including cognitive function. Qureshi et al [722] consider that citicoline will be the cost-effective way to be administered for hyperhomocysteinemia.

Turana et al [723] described in detail the potential citicoline mechanisms as adjunctive therapy and prevention of COVID-19-related cognitive decline and other neurologic complications through citicoline properties of anti-inflammation, anti-viral, neuroprotection, neurorestorative, and acetylcholine neurotransmitter synthesis, and provide a recommendation for future clinical trials.

Also, recent studies found positive effects in healthy people [724-727]. Choueiry et al [724] did a randomized, double-blind, placebo-controlled and counterbalanced pilot study in healthy humans to assess the speech P50 gating indices effects of an alpha 7 nicotinic acetylcholine receptor strategy combining citicoline with galantamine, and obtained positive results with this combination. Nemkova et al [725] showed that the use of citicoline has a positive effect on compensation of autonomic and asthenic disorders, improves cognitive status, corrects psycho-emotional disorders in university students and teachers. Nakazaki et al [726,727] showed in a randomized, double-blind, placebo-controlled trial that citicoline improved overall memory performance, especially episodic memory, in healthy males and females with age-associated memory impairment.

The drug may be more effective for mild cognitive disorders [728-730] and cases related with vascular pathologies [731-734]. In addition, citicoline has been shown to have beneficial effects on neurophysiological and neuroimmune changes [734].

Other clinical experiences

Parkinson's disease

While levodopa continues to be the central therapeutic agent in Parkinson's disease, it has well-known limitations, the main of which is a progressive loss of efficacy, that is often already evident at 3-5 years of treatment. It seems therefore warranted to use other drugs that, associated to levodopa, allow for decreasing its dosage or may even be administered as the only medication in the early stages of the disease. In this regard, use of citicoline has been tested because of its previously analyzed capacity to increase dopamine availability in the striatum and to act as a dopaminergic agonist. Citicoline has been shown to be effective in various experimental models, and its use in Parkinson's disease is therefore accepted [735].

Ruggieri et al [736], in a double-blind, crossover study conducted on 28 parkinsonian patients comparing citicoline 600 mg/day/10 days intravenous to placebo, showed citicoline to be an effective treatment for these patients, achieving improvements in the assessment of bradykinesia, rigidity, and tremor, and also in the scores of the Webster scale and the Northwestern University disability scale. These same investigators later obtained very similar results in an extension of the above [737]. They subsequently tested the effects of citicoline in two groups of patients with Parkinson's disease [738]. The first group included 28 patients who had not previously received treatment, while the second group included 30 patients who were already receiving treatment with levodopa and carbidopa since at least two months before, and in whom dosage had been stabilized at the minimum effective level. The same methods as in previous studies by these investigators were used, that is, a double-blind, crossover study comparative to placebo. Treatment was administered for 20 days at a dose of 500 mg/day by the parenteral route. Clinical assessments were performed on days 10 and 20, coinciding with change in treatment, according to the study design. Treatment with citicoline provided statistically significant improvements in Webster scale, Northwestern University disability scale, and assessment of bradykinesia in both patient groups. Rigidity also improved in both groups, although this improvement only reached statistical significance in the previously treated group of patients. Tremor also improved in both groups, but the desired statistical significance was not reached.

Eberhardt et al [739-741] have shown that association of citicoline to levodopa treatment allows for reducing levodopa dose by 50%, thus minimizing the side effects associated to levodopa therapy. Thus, for this group of investigators, citicoline represents a useful alternative in patients requiring a reduction in levodopa doses and, moreover, addition of citicoline to a treatment with levodopa may relieve decompensation states in the course of parkinsonism [742].

Loeb et al [743] conducted a multicentre, double-blind study with citicoline for the treatment of parkinsonian patients. In this study, 65 patients were randomized to a group to which citicoline 1 g/day intravenous was added or to a placebo group. Treatment lasted 21 days. All patients continued their underlying treatment with levodopa plus mianserin or benserazide for at least eight weeks. Authors found significant differences between citicoline and placebo at the controls performed after 14 and 21 days of treatment in all parameters assessed by the Webster and Northwestern University disability scales. They also noted that patients treated with citicoline experienced a significant worsening 45 days after the medication was discontinued, thus showing the efficacy of citicoline as adjuvant treatment to levodopa in patients with Parkinson's disease.

Acosta et al [744] treated with citicoline 61 parkinsonian patients, of whom 48 patients were already receiving treatment with levodopa. Each patient received two treatment courses. In the first 10-day phase, citicoline 500 mg daily were administered by the intramuscular route. This was followed in a second phase by oral treatment at the same dose for 14 weeks. Patients treated with levodopa continued taking this medication at the same dose in a first period, after which an attempt was made to decrease it. Parkinsonian symptoms were assessed using the Webster scale. Among patients receiving levodopa, 36% improved when citicoline was added, with the greater percent improvements being obtained in bradykinesia, rigidity, posture, gait, and limb sway. In patients who had been treated with levodopa for less than two years, percent improvements amounted to 42.12%, as compared to 19.08% of improvements in patients with more than two years of levodopa therapy. Levodopa doses could be decreased by 20 to 100% in 35.3% of patients with less than two years of treatment. In patients with more than two years of levodopa treatment, levodopa dose could be reduced by 25-33% in 10% of the cases. Authors concluded that citicoline treatment allows for delaying the start of levodopa therapy in the early disease stages, and for decreasing or maintaining levodopa dosage in already treated subjects.

Cubells and Hernando [745] tested citicoline in 30 parkinsonian patients who were already being treated with levodopa. The dose administered was 500 mg/day by the intramuscular route for two months and was reduced to a third at the end of the first month of treatment. Changes in parkinsonian symptoms, according to the Yahr scale, showed after the first month of treatment a moderate improvement in facial expression and digital skills, and an obvious improvement in postural stability, motor changes and bradykinesia. A greater stabilization of therapeutic response was also seen, with a decreased incidence of 'wearing-off' and 'on-off' phenomena, although dyskinesia increased. When levodopa dose was decreased during the second study month, clinical improvement was maintained, and incidence of dyskinesia was decreased. Measurements of various electrophysiological parameters using an original technique by the authors revealed recovery from hyporeflexia and hypotonia after one month of treatment with citicoline, and a major improvement in active muscle contraction, decreased muscle fatigue, and an obvious recovery of contractile speed, a parameter that was greatly decreased before treatment with citicoline was started. Authors stated that the increase in levodopa plasma levels was so significant that it could not be interpreted as due only to an increased release of dopamine stored in presynaptic vesicles. They therefore assumed that citicoline exerts an action upon the synthetic mechanism of dopamine, acting through the tyrosine hydroxylase enzymatic system. In addition, the increase in dopamine receptors quantified in lymphocytes suggests, according to authors, a promoting role of citicoline upon the availability of postsynaptic dopamine receptors.

Martí-Massó and Urtasun [746] examined the effects of citicoline in 20 parkinsonian patients treated with levodopa for more than two years. These patients were administered citicoline 1 g/day/15 days intramuscular, and then continued with half the dose for 15 additional days. A progressive symptom improvement was achieved. Thus, 4.16% and 7.26% overall improvements were achieved in the Columbia University scale at 15 days and at the end of treatment respectively. Partial improvements achieved in ambulation, turning time in bed, and writing time should be particularly noted. In assessment conducted by relatives, improvements achieved in agility, ambulation, and general patient status deserved special mention.

García-Mas et al [747] conducted a study with quantified electroencephalography using fast Fourier transforms in two groups of patients with idiopathic Parkinson's disease, one of which showed cortical cognitive impairment. Study of specific quantified electroencephalography indices allowed for establishing some parameters differentiating patients with and without cortical impairment. Specifically, differences were found in global potencies of delta and alpha rhythms, the alpha/theta index, posterior activities, anteriorization index of delta and alpha rhythms and finally, spatialization index of alpha rhythm. Administration of citicoline 2 g intravenous in these patients achieves a global increase in potencies corresponding to posterior rhythms, particularly alpha rhythm, that is a marker of cognitive activity in dementia processes. As shown previously, citicoline is an adjuvant therapy on mild cognitive impairment in Parkinson's disease [699]. On the other hand, citicoline significantly improved essential tremor [748].

Based on the reported and discussed studies, it may be stated that citicoline represents an effective treatment for Parkinson's disease in both untreated patients and patients already treated with levodopa, in whom it also allows for reducing levodopa dose. In patients with Parkinson's disease and cognitive impairment, administration of citicoline induces a trend to normalization of deficits and the main electrophysiological parameters altered. Que and Jamora [749] did a systematic review with the aim to synthesize current existing evidence on the efficacy of citicoline adjunctive therapy in improving Parkinson's disease symptoms and concluded that citicoline adjuvant therapy has beneficial effects as an adjuvant therapy in patients with Parkinson's disease. However, due to the heterogeneity of the studies, there is a need for more high-quality studies.

Alcoholism and drug addiction

Clinical experience with citicoline in alcoholism and drug addictions is not very extensive, but there is some evidence of its efficacy in these applications.

Chinchilla et al [750] conducted a randomized, double-blind study on the effects of citicoline in 20 patients with alcohol withdrawal syndrome. At the end of the study, i.e., at two months, a significant improvement in attention-concentration and time and space orientation in the group of patients receiving citicoline suggesting, according to the authors, that the drug may be useful for the treatment of chronic alcoholism. Brown et al [751] reported a neutral study in patients with alcohol use disorder. Kang and Choi [752], despite the neutral results of the study by Brown et al [751], consider that the use of citicoline in the management of alcohol use disorder remains at investigational stages and needs further studies, and Shen [753] considers citicoline among the anticraving therapies for alcohol use disorder.

Renshaw et al [754-756] published a double-blind pilot study of patients addicted to cocaine, showing that after 14 days of treatment with 500 mg/12 hours of citicoline or placebo, the patients in the citicoline group experienced a reduction in craving for cocaine. Consequently, citicoline appears to be a promising therapy for this type of affliction, that do not perturb sleep/wake cycles [757] and may decrease cocaine use and enhance cognition [758]. But Licata et al [759] reported that citicoline is not an effective treatment reducing craving for heavy cocaine users. Also have been reported positive effects in patients with mood disorders related with the use of cocaine [760,761], antidepressant properties in methamphetamine dependence [762], and a role facilitating the treatment of marijuana use disorders by improving the cognitive skills necessary to fully engage in comprehensive treatment programs [763]. There is a clear implication of the cerebral metabolism in the drug addiction pathophysiology [764,765].

The application of brain imaging to study drug addictions has offered new insights into the fundamental factors that contribute to their use and abuse [766]. That is the case of Jeong et al [767], who performed a randomized, double-blind, placebo-controlled study to assess the effects of citicoline on the brain structures and their associations with craving and methamphetamine use. Methamphetamine users (n = 44) were randomized to receive 2 g/day of citicoline (n = 22) or placebo (n = 22) for eight weeks. Patients underwent brain magnetic resonance imaging at baseline and eight-week follow-up. Healthy individuals (n = 27) were also examined using brain magnetic resonance imaging at the same interval. Voxel-based morphometry analysis was conducted to examine changes in gray matter volumes and their associations with craving and methamphetamine use. Craving for methamphetamine was significantly reduced after the eight-week treatment with citicoline (p = 0.01), but not with the placebo treatment (p = 0.10). There was no significant difference in the total number of methamphetamine negative urine samples between the two groups (p = 0.19). With citicoline treatment, gray matter volumes in the left middle frontal gyrus (p = 0.001), right hippocampus (p = 0.009), and left precuneus (p = 0.001) were significantly increased compared to the placebo and control groups. Increased gray matter volumes in the left middle frontal gyrus with citicoline treatment were associated with reduced craving for methamphetamine (Spearman's ρ = 0.56; p = 0.03). In addition, the right hippocampal volume increases were positively associated with the total number of methamphetamine -negative urine results in the citicoline group (Spearman's ρ = 0.67; p = 0.006). Then, these results suggest that citicoline-induced gray matter volume increases may contribute to decreases in methamphetamine use and craving.

And there is some data suggesting a potential usefulness of citicoline in modulating appetite [768]. Preuss et al [769] consider citicoline among the therapies for bipolar disorder and comorbid use of illicit substances. Despite the limited research on the efficacy of citicoline for addictive disorders, the available literature suggests promising results [770].

Amblyopia and glaucoma

There is clinical evidence that citicoline improves visual acuity in patients with amblyopia [771-786], visual function in patients with glaucoma [787-814], in patients with non-arteritic ischemic optic neuropathy [815,816], and in early diabetic retinopathy [817].

Now there are citicoline in eye drops formulations for the management of glaucoma [818-821]. Tokuc et al [822] demonstrate the protective effects of citicoline eye drops on ultraviolet B radiation-induced corneal oxidative damage in a rat model. Parisi et al [823] reported the results of a pilot study evaluating the long-term efficacy of citicoline and vitamin B_{12} eye drops on macular function in patients with type 1 diabetes with mild signs of non-proliferative diabetic retinopathy. Treatment with citicoline and vitamin B_{12} eye drops for a 36-month period achieved an improvement of the macular bioelectrical responses, whereas, during the same period of follow-up, patients treated with placebo showed a worsening of the macular function. Topical citicoline and vitamin B_{12} ameliorated both morphology and function of corneal nerves in patients with diabetic neuropathy [824]. Topically administered citicoline eye drops had beneficial effects in the early recovery of corneal sensitivity during the first six weeks after LASIK, suggesting that citicoline may play a significant role in accelerating corneal reinnervation [825]. Despite their neuroprotective effect, topical citicoline drops had no significant effect on the superficial and deep microvascular structures of the retina or choriocapillaris [826].

Oddone et al [827] recently published an extensive review on the role of citicoline in ophthalmological neurodegenerative disease.

Other uses

There are positive results reported for citicoline in the treatment of facial neuritis [828], X-chromosome-linked ichthyosis [829], delayed-onset encephalopathy caused by carbon monoxide poisoning [830], epilepsy [831], vertigo [832], major depressive disorder [833,834], schizophrenia [835-837], fragile X-associated tremor/ataxia syndrome [838], an COVID-19 [839]. Recently, a new mechanism to enhance central nervous system remyelination via the choline pathway has been described. Due to its regenerative action combined with an excellent safety profile, CDP-choline could become a promising substance for patients with multiple sclerosis as an add-on therapy [840-844].

Pediatric use. The experience in children is limited; therefore, it may only be administered when the expected therapeutically benefit is higher than any possible risk.

There are some studies published in pediatric populations with citicoline in traumatic brain injuries [456], organic brain syndromes [845-847], neonatal hypoxic-ischaemic encephalopathy [848-852], visual impairment [853], refractive amblyopia [854], neurophysiologic abnormalities in developmental dysphasias [855], choline kinase beta deficiency [856], children with post cardiac arrest [857], learning disturbances [858,859], and autism and Asperger's syndrome [860]. There is a review on the use of citicoline in pediatric neurology and pediatric psychiatry [861]. No safety concerns related with the use of citicoline were reported in these studies.

Safety

Dinsdale et al [862] administered citicoline or placebo to 12 healthy volunteers in two oral regimens repeated at short-term intervals (600 mg/day and 1 g/day), every day for five days. The only adverse effects that appeared were self-limiting headaches in four and five subjects with high and low doses, respectively and in one subject who was given placebo. The results of hematological and clinical analyses did not show any abnormality associated to citicoline administration. No clinically significant electrocardiogram and electroencephalogram abnormalities were registered. Empirical neurological tests, tendon reflexes, blood pressure and heart rate were not affected by any dose of the drug or placebo.

In addition to an excellent tolerability in healthy individuals, as demonstrated in the above study, all of the authors of clinical trials using citicoline that have been reviewed in this present article, agree in rating the safety of this drug as excellent without serious side effects being reported. In some cases, the appearance of digestive intolerance has been reported and occasional excitability or restlessness in the first days of treatment. For instance, Lozano [863] monitored a study of the efficacy and safety of citicoline in 2,817 patients of all ages, with a predominance of patients between 60 and 80 years, who had different neurological processes, mostly cognitive disorders of diverse origin. The duration of citicoline Treatment ranged from 15 to 60 days and the mean dose administered was 600 mg/day orally. Only 5.01% of the patients had collateral effects associated with citicoline treatment, most often digestive intolerance (3.6%). In no case was it necessary to interrupt treatment for side effects attributable to citicoline use.

In the pooled analysis of citicoline in the treatment of acute ischemic stroke in the United States [536], there were few adverse events that were reported in more than the 5 %. These adverse events are listed in table XII.

In the South Korean drug surveillance study [543], the safety of the product was considered as excellent, with only 37 side effects in 31 cases among the 4,191 patients treated, that is a rate of side effects of 0.73 %.

Also, in the Cochrane review [692], it was demonstrated a lower rate on the incidence of adverse events related with citicoline in comparison with placebo.

In front of the question: Can citicoline cause depression?, Tardner [864] did a literature review and conclude that not only are there no recorded cases of citicoline causing depression in anybody, regardless of medical or psychiatric history. If anything, the clinical evidence suggests that citicoline may have antidepressant properties.

Synoradzki and Grieb [865] explained why, on a molar mass basis, citicoline is significantly less toxic than choline that has been associated with concerning its contribution to normal lipid metabolism, maintenance of normal liver function, and normal homocysteine metabolism. Choline in citicoline is less prone to conversion to trimethylamine and its putative atherogenic N-oxide, then the choline supplementation with citicoline may be safer and more efficacious.

In conclusion, the tolerability of citicoline is excellent and the side effects attributable to this drug are infrequent. In any case, side effects are never severe and consist, mainly, in gastrointestinal discomfort and restlessness.

Conclusions

Cytidine 5'-diphosphocholine, CDP-choline or citicoline is an essential intermediate in the biosynthetic pathway of structural phospholipids in cell membranes, particularly phosphatidylcholine. Following administration by both the oral and parenteral routes, citicoline releases its two main components, cytidine and choline. Absorption by the oral route is virtually complete, and bioavailability by the oral route is therefore approximately the same as by the intravenous route. Once absorbed, citicoline is widely distributed throughout the body, crosses the blood-brain barrier and reaches the central nervous system, where it is incorporated into the membrane and microsomal phospholipid fraction. Citicoline activates biosynthesis of structural phospholipids of neuronal membranes, increases brain metabolism, and acts upon the levels of different neurotransmitters. Thus, citicoline has been experimentally shown to increase norepinephrine and dopamine levels in the central nervous system. Owing to these pharmacological mechanisms, citicoline has a neuroprotective effect in hypoxic and ischemic conditions, and also improves learning and memory performance in animal models of brain aging. In addition, citicoline has been shown to restore the activity of mitochondrial ATPase and membrane Na^+/K^+ATPase, to inhibit activation of phospholipase A_2, and to accelerate reabsorption of cerebral edema in various experimental models. Citicoline is a safe drug, as shown by the toxicological tests conducted, that has no significant systemic cholinergic effects and is a well-tolerated product. These pharmacological characteristics and the action mechanisms of citicoline suggest that this product may be indicated for treatment of cerebral vascular disease, head injury of varying severity, and cognitive disorders of different causes. In studies conducted in the treatment of patients with head injury, citicoline was able to accelerate recovery from post-traumatic coma and improve gait, achieving an improved final functional outcome and shortening hospital stay in these patients. Citicoline also improved the mnesic and cognitive disorders seen after head injury of minor severity that constitute the so-called post-concussional syndrome. In the treatment of patients with acute ischemic cerebral vascular disease, citicoline accelerates recovery of consciousness and motor deficit, achieves a better outcome, and facilitates rehabilitation of these patients. The other major indication of citicoline is for the treatment of senile cognitive impairment, either secondary to degenerative diseases or to chronic cerebral vascular disease. In patients with vascular cognitive impairment, citicoline improves scores in cognitive rating scales, while in patients with senile dementia of the Alzheimer type it stops the course of disease, and neuroendocrine, neuroimmunodulatory, and neurophysiological benefits have been reported. Moreover, citicoline has also been shown to be effective as adjuvant therapy in Parkinson's disease. No serious side effects have occurred in any series of patients treated with citicoline, which attests to the safety of treatment with citicoline [866,867].

Agarwal and Patel [493] pointed out that the use of citicoline is associated with improved functional outcomes significantly, but the positive role of this drug in neurological recovery, domestic adaptation, and cognitive outcomes is still a topic of discussion for future. Putilina [868] concluded that the various mechanisms of the action of citicoline enable to recommend it as a drug effective both in the acute phase of the disease and in the delayed period, giving it the status of a universal nootropic compound. Jasielski et al [869] in their systematic review, concluded that citicoline has a wide range of effects and could be an essential substance in the treatment of many neurological diseases and its positive impact on learning and cognitive functions among the healthy population is also worth noting. Piotrowska et al [870] concluded that the application of citicoline improves the health status of persons diagnosed with a stroke, brain trauma, as well as in patients with cognitive impairment,

Table XII. Safety analysis in the pooling data analysis of acute ischaemic stroke patients treated with citicoline. The table shows adverse events that were reported in more than 5% of cases. n.s.: no significative.

	Placebo		Citicoline		
	n	%	*n*	%	*p*
Adverse events with incidence > 5% in the citicoline group					
Anxiety	58	9.95	108	13.69	0.036
Leg oedema	38	6.52	77	9.76	0.032
Adverse events with incidence > 5%					
Accidental injury	86	14.75	135	17.11	n.s.
Agitation	78	13.38	113	14.32	n.s.
Constipation	228	39.11	286	36.25	n.s.
Coughing	81	13.89	105	13.31	n.s.
Diarrhoea	81	13.89	117	14.83	n.s.
Dizziness	46	7.89	72	9.13	n.s.
ECG abnormality	57	9.78	74	9.38	n.s.
Fever	182	31.22	241	30.54	n.s.
Auricular fibrillation	65	11.15	92	11.66	n.s.
Headache	186	31.90	261	33.08	n.s.
Haematuria	53	9.09	91	11.53	n.s.
Hypertension	88	15.09	131	16.60	n.s.
Hypokalemia	71	12.18	119	15.08	n.s.
Hypotension	55	9.43	90	11.41	n.s.
Urinary tract infection	235	40.31	298	37.77	n.s.
Insomnia	103	17.67	145	18.38	n.s.
Joint pain	48	8.23	78	9.89	n.s.
Nausea	111	19.04	157	19.90	n.s.
Pain	180	30.87	227	28.77	n.s.
Back pain	45	7.72	74	9.38	n.s.
Chest pain	55	9.43	82	10.39	n.s.
Rash	79	13.55	112	14.20	n.s.
Restlessness	49	8.40	74	9.38	n.s.
Shoulder pain	75	12.86	105	13.31	n.s.
Vomiting	89	15.27	111	14.07	n.s.
Adverse events with incidence > 5% in the placebo group					
Depression	160	27.44	178	22.56	0.038
Falling down	109	18.70	99	12.55	0.002
Urinary incontinence	82	14.07	83	10.52	0.047

and it is also effective in Parkinson's disease, glaucoma and addictions, highlighting its low toxicity, which has been confirmed via animal testing and clinical studies.

Kopka and Sochacki [871] concluded that in the light of currently available scientific reports, citicoline can be consider as a safe and useful substance for many indications and it is also characterized by a lack serious side effects as well as very good tolerance among patients. Thus, there are 10 reasons why to use citicoline:

- Improves prognosis in stroke.
- Improves memory and attention in healthy people.
- Improves memory in patients with vascular dementia.
- Has a beneficial influence on cognitive functions in Alzheimer's disease.
- Improves prognosis after head injuries.
- Reduces the severity of bradykinesia and muscle stiffness in individuals with Parkinson's disease.
- Slows down the progression of the disease in patients with glaucoma.
- Improves visual acuity in patients with the lazy eye syndrome.
- Has an useful safety profile.
- Reduces the craving for cocaine.

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Citicolina: revisión farmacológica y clínica, actualización 2022

Resumen. Esta revisión se basa en la publicada en 2016 –Secades JJ. Citicolina: revisión farmacológica y clínica, actualización 2016. Rev Neurol 2016; 63 (Supl 3): S1-S73–, e incorpora 176 nuevas referencias aparecidas desde entonces, con toda la información disponible para facilitar el acceso a toda la información en un único documento. La revisión se centra en las principales indicaciones del fármaco, como los accidentes cerebrovasculares agudos y sus secuelas, incluyendo el deterioro cognitivo, y los traumatismos craneoencefálicos y sus secuelas. Se recogen los principales aspectos experimentales y clínicos en estas indicaciones.

Palabras clave. Alcoholismo. Ambliopía. Apoptosis. CDP-colina. Citicolina. Demencia senil. Drogodependencia. Edema cerebral. Enfermedad de Alzheimer. Enfermedad de Parkinson. Fosfatidilcolina. Fosfolipasa. Fosfolípidos estructurales. Glaucoma. Ictus. Isquemia cerebral. Lesión cerebral traumática. Membrana neuronal. Memoria. Neuroplasticidad. Neuroprotección. Neurorreparación. Neurotransmisión. Remielinización. Trastorno cognitivo. Traumatismo craneoencefálico.