

# Citicoline as coadjuvant treatment of cognitive impairment in chronic degenerative Central Nervous System diseases and in ischemic stroke: A review of available data

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Citicoline (CDP-choline) is considered to have a neuroprotective effect in cerebral ischemia and neurodegenerative conditions. CDP-choline has been used in humans for decades as a treatment for cognitive impairment conditions. This molecule could have a brain repair action and neuro-protectant effect as several experimental models in acute cerebral ischaemia have suggested. There has been a growing interest for this molecule in the recent years as a supportive pharmacological treatment of chronic degenerative neurological diseases such as traumatic brain injuries, vascular dementia, Alzheimer's disease, and brain aging where it has the function of stabilizer of cell membranes and reduces the presence of free radicals. There is some evidence of a stimulating role of CDP-choline for the release of dopamine neurotransmitters in the brain suggesting a relevant role also in Parkinson disease associated dementia. CDP-choline in contrast with many other drugs that have failed in the treatment of stroke within the first 6 hours, proved to be effective when administered within 24 hours after symptom onset. In this view it could be useful to summarize the most relevant evidences available regarding the therapeutic role of CDP-choline as coadjuvant treatment of cognitive impairment in chronic degenerative central nervous system diseases and in ischemic stroke. We evaluated the available literature data regarding efficacy and safety of CDP-choline as coadjuvant treatment in chronic degenerative conditions associated with dementia such as senile dementia, Alzheimer and Parkinson disease and also data regarding its use as supportive treatment in ischemic stroke. We searched MEDLINE (1948 to May 2012), and EMBASE (1980 to May 2012) and reference lists of articles regarding CDP-choline and cognitive impairment and/or central nervous system impairment AND clinical trials and CDP-choline and ischemic Stroke and clinical trials. We found a total of 25 publications addressing the effect of CDP-choline in different neurological conditions associated to cognitive impairments. The majority of these trials have shown that the use of oral citicoline has increased the cognitive capacities of treated patients. CDP-choline could be considered a valuable coadjuvant treatment in cognitive impairment in chronic degenerative Central Nervous system diseases such as Alzheimer, Parkinson disease associated dementia and ischemic stroke.

**Keywords:** Citicoline, neuroprotection, degenerative chronic neurological diseases, ischemic stroke, review.

## INTRODUCTION

Citicoline (CDP-choline) is a compound normally present in human cells [1]. It is also an intermediate in the synthesis of phosphatidylcholine [2]. In fact CDP-choline is an essential intermediate in the biosynthetic pathway of the structural phospholipids of cell membranes [3]. This

molecule has been shown to exert neuro-protective effects in many central nervous system damage models [4]. More specifically CDP-choline has a neuroprotective effect in situations of hypoxia and ischemia, as well as improved learning and memory performance in animal

models of brain aging [5]. CDP-choline has been widespread used in humans for decades as a treatment for many types of cognitive impairment [6]. Despite this, its mechanism of action still remains unclear, but several experimental animal models suggest that it could have a brain repair action [7]. Due to the lack of significant adverse effects and its high tolerability [8], there has been a growing interest for this molecule in the recent years. Upon oral or parenteral administration, CDP-choline releases its two principle components, cytidine and choline. When administered orally, it is absorbed almost completely, and its bioavailability is approximately the same as when administered intravenously. There are several studies in literature which demonstrate the efficacy of citicoline, thanks to its neuro-protective function, for the recovery and in post-ischemic cerebral rehabilitation [9]. It has been shown that, even soon after an ischemic stroke, administration of oral citicoline (500-4000 mg/day) improves the general conditions evaluated with the Rankin scale and the National Institute of Health Stroke Scale [10]. However in this specific clinical setting, these positive results were not totally confirmed by two recent double blind placebo controlled trials [11,12]. In chronic degenerative central nervous conditions it has been shown that the CDP-choline improves the cognitive and mental performance in Alzheimer's dementia and vascular dementia [13,14]. Results show that CDP-choline seems to have beneficial impact on several cognitive domains. Fewer trials have studied its effects at medium and long-term on vascular cognitive impairment and Parkinson's disease.

### Aim

In this review we evaluated the available literature data relevant to the efficacy and safety of CPD-choline as a coadjuvant treatment of central nervous system degenerative conditions such as Alzheimer Disease, Parkinson associated dementia and vascular dementia and finally also as supportive treatment in Ischemic Stroke patient.

### METHODS

We evaluated the available literature data regarding efficacy and safety of CPD-choline as a coadjuvant treatment for chronic degenerative conditions associated with dementia such as senile dementia, Alzheimer and Parkinson disease and finally ischemic stroke. We searched MEDLINE (1948 to May 2011), and EMBASE (1980 to May 2012) and reference lists of articles regarding citicoline AND cognitive impairment AND/OR central nervous system impairment AND stroke AND clinical trials. We found a total of 25 publications addressing the effect of CDP-choline in different neurological conditions associated to cognitive impairments and 4 trials conducted in ischemic stroke:

1. CPD-choline in Alzheimer disease: A total 5 trials have addressed the clinical efficacy of citicoline in Alzheimer associated dementia;
2. CPD-choline in cognitive function in Parkinson disease: A total of 6 trials have addressed the clinical efficacy of citicoline in Parkinson associated dementia;
3. CPD-choline in the cognitive impairment in the elderly (vascular dementia): a total of 14 clinical trials have been performed to investigate the clinical effect of citicoline in this clinical situation.
4. CPD-choline in the treatment of ischemic stroke: a total of 4 clinical trials have been performed to investigate the clinical effect of citicoline in the ischemic stroke.

## RESULTS

### *Citicoline in Alzheimer disease (AD)*

Based on the role of citicoline as an intermediate of phosphatidylcholine biosynthesis, it was hypothesized that citicoline could reverse age-dependent histopathological changes within the brain neuronal membrane, thereby restoring memory function [15]. Citicoline's potential as a treatment for memory impairment associated with aging was studied in a total of 5 trials [16-19] in patients with Alzheimer disease. Camargo *et al.* [16] in 1994 conducted a double-blind study with the aim to examine the effect of one-month treatment with citicoline on cognition in 20 Alzheimer's patients. Following citicoline treatment (1,000 mg/day orally), cognitive function assessed using the Mini-mental test examination (MMSE) slightly improved in an EOAD patient subgroup, as shown by small, but statistically significant ( $p < 0.005$ ) increases in MMSE scores. MMSE scores decreased in patients in later stages of the disease. Spatial-temporal orientation improved in the total group, with a more marked difference in AD patients. A double-blind, placebo-controlled trial conducted by Alvarez *et al.* [17] tested the effects of citicoline therapy on 30 patients with mild-to-moderate senile dementia of the Alzheimer's type. Citicoline was administered over a 12-week period at a daily dose of 1,000 mg. The overall results showed a non-significant difference trend between the citicoline and placebo groups in favour of the active treated group. Some studies have evaluated the effects of citicoline in brain hemodynamics in AD patients [18,19]. Citicoline was shown to slightly increase cerebral blood flow and velocities, in comparison with placebo. The mechanisms are consistent with citicoline's apparent role as a cholinergic system potentiator, via acetylcholine biosynthesis and activation of muscarinic receptors in the central nervous system. In summary, clinical data suggest that Citicoline has demonstrated a possible capability to improve cognitive performance in AD associated

dementia.

### ***Citicoline in cognitive function in Parkinson disease***

The effect of CPD-choline in Parkinson disease was evaluated in 6 controlled clinical studies involving more than 160 patients [20-25]. Garcia [20] *et al.* have performed a study investigating the EEG effects of CPD-choline in patients with Parkinson disease. Two groups of patients with idiopathic Parkinson's disease underwent quantitative electroencephalography (EEGq) using Fast Fourier Transform (FFT) to assess the effects of treatment with citicholine. Specifically, differences were found in the overall potentials of the delta and alpha bands, in the alpha/theta index, in posterior activity, in the anteriorization index of the delta and alpha rhythms, and in the spatialization index of the alpha rhythm. Agnoli *et al.* [26] have studied the effect of CPD-choline in a double blind placebo controlled trial. All patients were already treated with L-dopa + dopa decarboxylase inhibitor. Clinical evaluations were carried out using the Webster Rating Scale (WRS), the Northwestern University Disability Scale (NUDS) and a semiquantitative rating scale for tremor, rigidity and bradykinesia. CDP-choline treatment showed a significant improvement of rigidity and bradykinesia and a less important amelioration of tremor. Comparing the results obtained with placebo, the authors found that the actual clinical efficacy of CDP-choline regards mainly bradykinesia and rigidity (23 and 33% improvement, respectively). Authors' conclusions were that positive effect of CDP-choline on parkinsonian patients already treated with L-dopa + dopa decarboxylase inhibitor stands for a possible action on the DA receptor through an activation of the phospholipid metabolism. In 1991, Marti and Urtasun [21] conducted a study in 20 patients with Parkinson disease. Patients were aged 52 to 76 years and the duration of the disease ranged from four to 25 years. All the patients were receiving levodopa alone or in combination with tricyclic antidepressants, amantadine, bromocriptine, anticholinergic agents, or lisuride. Each patient received 1,000 mg of citicoline intramuscularly daily for 15 days and then 500 mg daily for 15 days. After 30 days of treatment, the scores on the Columbia rating scale showed an improvement of 7.3%; rigidity was improved of 18.8%; times to walk 10 m and turn over were reduced of 17.5% and 37.4%; and the handwriting test scores improved of 19.7%. No side effects were reported. Between 1982 and 1990 additional studies and review [23-25] underlined the clinical efficacy of citicoline in this clinical condition. In particular Eberhart *et al.* [22] has studied 85 patients with an established diagnosis of primary Parkinson's disease; patients were randomly assigned to receive their usual dose of levodopa (mean, 381 mg daily) plus 1,200 mg of citicoline daily or half their usual dose of levodopa (mean, 196 mg daily) plus the citicoline. A significant larger number of patients receiving

citicoline and "low dose" (i.e 50% of the usual dose) of levodopa shown improvements on the tests in comparison with the group receiving full usual levodopa dose plus citicoline. In conclusion: levodopa-saving effect of citicoline could be used to decrease the incidence of side effects and retard the loss of efficacy of levodopa in long-term treatment.

### ***Citicoline in the cognitive impairment in the elderly (vascular dementia)***

A recent meta-analysis examined data relevant to published, double-blind, randomized trials on citicoline and cognitive impairment in patients with chronic cerebral vascular disorders [27]. This meta-analysis included a total of fourteen studies enrolling more than 800 subjects. Studies were included only when they were performed according to a randomized placebo controlled design. In some studies, treatment was given continuously while in other studies cycles of treatment were administered. Usually treatment cycles were of three weeks duration, interspersed by a treatment free period of the same length. Seven of the included studies were performed on patients affected exclusively by chronic cerebrovascular disorders. Twelve of the fourteen studies (for references see [25]) were performed with a dosage of 1000 mg per day (in 5 intravenous route administration, 4 intramuscular, and 3 oral), and two other studies were performed with a total daily dosage of 600 mg in one administration given orally and intramuscularly respectively. The meta-analysis of CPD-choline effects on memory function revealed homogeneous results and there was evidence of a statistically significant positive effect on this clinical parameter. It was concluded that citicoline improves memory and behavioral outcomes. Agnoli *et al.* [26] have conducted a trial on 84 elderly patients with mild-to-moderate memory loss. The subjects, who all exhibited memory loss as assessed by scores on the Mini Mental State Examination (MMSE), took 1,000 mg citicoline daily or placebo for six weeks. The Randt Memory Test was administered after three weeks and at the end of the treatment period. In addition to memory factors such as immediate recall, delayed recall, and global memory efficiency, the Randt test measures three cognitive function parameters: encoding and organization (E-O), cognitive efficiency (CE), and acquisition efficiency (AE). The results showed that AE improved while E-O and CE remained unchanged. Because AE is specifically related to attention, the researchers postulated this finding evidenced a dopaminergic effect of citicoline, based on an association between dopaminergic stimulation and improvement in attention-related cognitive mechanisms. Improvements in global memory efficiency were also observed. Citicoline therapy improved verbal memory functioning in older individuals with relatively inefficient memory. Citicoline may prove to be effective in treating age-related cognitive

decline that may be the precursor of dementia. The majority of these trials have shown that the use of oral citicoline has increased the cognitive capacities of treated patients. The effect of citicoline on verbal memory in the elderly was tested in a double-blind trial using 95 healthy volunteers ages 50-85 years [28]. This study took place in two phases. In the initial phase, all subjects took 1,000 mg citicoline or placebo daily for three months. Analysis of the data revealed a subgroup with relatively poor memory. These subjects were recruited for the second crossover trial phase and given either placebo or 2,000 mg citicoline daily for three months. After the initial phase, improvement with citicoline occurred only in the poor-memory subgroup, which showed gains in delayed recall and logical memory. At the end of the second phase, greater improvements occurred in the citicoline group, suggesting that 2,000 mg per day is a more effective dose for age-associated memory impairment. In a double-blind, crossover trial, performed by Alvarez *et al.* [17] citicoline was administered orally to 24 memory impaired elderly subjects for four weeks. Citicoline was given alone at 500 or 1,000 mg doses, or combined with nimodipine, a calcium channel blocker used to treat neurological deficits in brain hemorrhage patients (citicoline 300 mg/day plus nimodipine 90 mg/day). Pre- and post-treatment memory performance was evaluated. The results showed that citicoline improved the ability to recall words and objects after viewing them for two seconds each. In tests of recognition, where subjects attempt to identify previously viewed words and objects randomly mixed with non-viewed items, no improvement was observed. Positive results occurred in all three treatment groups. In summary these clinical data suggest that Citicoline seems to have beneficial impact on several cognitive domains in vascular associate dementia.

### ***Citicoline in the treatment of ischemic stroke***

Stroke is a medical emergency with a mortality rate higher than most forms of cancer. It is the second leading cause of death in developed countries and the most common cause of serious, long-term disability in adults. Numerous experimental studies with citicoline have shown improved outcome and reduced infarct size in ischemic stroke models. Citicoline has been studied worldwide ischemic clinical stroke with excellent safety and possibly efficacy found in several trials [29]. Citicoline was found to be beneficial in 113 patients post-stroke [30]. In an observational study, patients suffering a stroke began citicoline therapy within 48 hours. Citicoline 2 g was administered intravenously for the first 5 days and intramuscularly thereafter (from day 6 to day 9) at 1 g daily. Using the Canadian Neurological scale, 5.3% of patients showed improvement. Adverse effects (most common: headache, vertigo, dizziness) were seen in 7.4% of patients. In a randomized, double-blind, placebo-controlled study, three different dosages of oral citicoline

(500 milligrams (mg) once daily, 500 mg twice daily, and 1000 mg twice daily) started within 24 hours of stroke onset and continued for 6 weeks were reported to improve functional outcome and reduce neurologic deficit compared to placebo in a study of 259 patients [31]. In a double-blind, placebo-controlled study [17] of 267 patients, intravenous citicoline 1000 milligrams daily for 2 weeks was associated with improvement in the level of consciousness in patients with acute cerebral infarction (onset within 14 days). Superiority of citicoline over placebo was also seen in global improvement rating (GIR), which assesses 6 categories based on changes in consciousness, individual neurologic signs, and general condition of the patient. However, differences between placebo and citicoline were significant only on days 7 and 14 of treatment for improved level of consciousness. Rates of improvement in the level of consciousness were statistically significant (51% with citicoline, 33% for placebo). The greatest improvement in the GIR was seen on day 14 (54% and 29% with citicoline and placebo, respectively). Although details of follow-up were not provided, the authors suggested that prognosis appeared better in the citicoline group during assessments made for 18 months after therapy (based on fatal strokes cardiopulmonary events).

### **DISCUSSION**

CDP-choline activates the biosynthesis of structural phospholipids in the neuronal membranes, increases cerebral metabolism and acts on the levels of various neurotransmitters [32]. Thus, it has been experimentally proven that CDP-choline increases noradrenaline and dopamine levels in the CNS. Due to these pharmacological activities, CDP-choline has a neuroprotective effect in situations of hypoxia and ischemia, as well as improved learning and memory performance in animal models [33] of brain aging. Furthermore, it has been demonstrated that CDP-choline restores the activity of mitochondrial ATPase and of membranal Na<sup>+</sup>/K<sup>+</sup> ATPase, inhibits the activation of phospholipase A2 and accelerates the reabsorption of cerebral edema in various experimental models [34]. Citicoline metabolites such as choline, methionine, betaine, and cytidine-derived nucleotides enter a number of metabolic pathways [35]. Evidence of citicoline's role as a phosphatidylcholine precursor has been found in animal studies [36]. Biochemical markers of cholinergic nerve transmission are known to be deficient in conditions characterized by degeneration of cholinergic neurons, such as Alzheimer's disease (AD). Choline precursors promote repair and growth of cell membranes and hold promise in a variety of neurologic diseases, including ischemic and hemorrhagic stroke [37]. Citicoline, the most well-studied choline agent precursor, is widely prescribed [38]. In experimental stroke models,

citicoline conferred acute neuro-protection and enhanced neuroplasticity and neuro-repair in the sub-acute period. Although individual human stroke trials have been inconclusive, meta-analysis of 10 trials enrolling 2279 patients suggest that patients receiving citicoline had significant reduced frequency of death and disability [39]. Citicoline modestly improves cognitive function in AD by serving as an acetylcholine precursor. The brain uses choline preferentially for acetylcholine synthesis, which can limit the amount of choline available for phosphatidylcholine production. CDP-choline is a safe drug, as toxicological tests have shown [10]; it has no serious effects on the cholinergic system and it is perfectly tolerated. CDP-choline has been widespread used in humans for decades as a treatment for many types of cognitive impairment. Despite this, its mechanism of action still remains unclear, but several experimental models in acute cerebral ischaemia suggest that it could have a brain repair action [40]. Due to the lack of significant adverse effects and its high tolerability, there has been a growing interest for this molecule in recent years. In this article, a review of the most significant published clinical trials in cognitive decline has been made. A few Citicoline trials have studied its effects at medium and long-term on vascular cognitive impairment and Alzheimer's disease. Results show that Citicoline seems to have beneficial impact on several cognitive domains, but the methodological heterogeneity of these studies makes it difficult to draw conclusions about these effects. New trials with a greater number of patients, uniform diagnostic criteria for inclusion and standardized neuropsychological assessment are needed to evidence with much more consistency the citicoline efficacy upon cognitive disorders. The use of new neuroimaging procedures in current trials could be of great interest. Citicoline pharmacological characteristics, combined with its mechanisms of action, suggest that this drug may be suitable for the treatment of cerebral vascular disease, head trauma of varying severity and cognitive disorders of diverse etiology [41]. In this review, we have focused the latest publications on the major ongoing experimental and clinical projects involving citicoline in Parkinson-associated dementia. A recent Cochrane meta-analysis [27] evaluating the role of CPD-choline for cognitive and behavioral disturbances associated with chronic cerebral disorders in the elderly concluded that there was some evidence that CDP-choline has a positive effect on memory and behavior in at least the short to medium term. The evidence of benefit from global impression was stronger. CPD-choline is the only neuroprotector that has shown positive results in all randomized trials and has also demonstrated efficacy in meta-analysis with an overall safety profile similar to placebo.

## Conclusion

Citicoline could be considered a valuable coadjuvant

treatment in cognitive impairment in chronic degenerative Central Nervous System diseases such as Alzheimer and Parkinson disease associated dementia. Citicoline also proved to be a valid neuroprotectant drug with some beneficial effects in human ischemic stroke with an excellent safety profile. Moreover in the majority of trials conducted to demonstrate the clinical efficacy of citicoline the intravenous administration route was more effective compared to the oral administration.

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