

CITICOLINE EFFICIENCY ON COGNITIVE FUNCTION: A SYSTEMATIC REVIEW

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Abstract: *Background:* Citicoline is considered an ingredient in particular foods in the USA and is available in pharmaceutical form in Europe and Japan. It has been postulated to render positive effects on the nervous system, either by increasing levels of neurotransmitters, or by affording neuroprotection. *Methods:* Several clinical trials have shown the efficacy and safety of this biomolecule in several neurodegenerative diseases and in acute ischemic stroke. Here, we have performed a systematic review to validate the effect of citicoline on MMSE, memory, attention, and basic activity of daily living. In electronic database searches, we found 14 randomized clinical trials reporting citicoline effects on cognitive function. *Findings:* A positive effect of citicoline on MMSE in acute ischemic stroke was found, which was not evidenced for Alzheimer disease or vascular dementia. On activities of daily living, citicoline failed to exert beneficial effects in patients with acute ischemic stroke or progressive cognitive impairment. *Conclusions:* Given the present data there is no evidence that supports advising patients with cognitive alterations to take chronic citicoline supplements.

Key words: CDP-choline, cytidine, Alzheimer disease, dementia, cognition, meta-analysis, acute ischemic stroke.

Introduction

Besides being the central symptom of dementia, cognitive impairment is the principal cause of a wide range of disabilities affecting attention, mnemonic, linguistic and visuo-spatial abilities (1). Alterations in cognitive functions are present in neurodegenerative diseases, including cerebrovascular disorders such as stroke or vascular dementia (2). Among the pharmacological arsenal tested in stroke is the biomolecule Citicoline (CDP-choline or cytidine-5'-diphosphocholine) (3). Although its mode of action is far from being clarified, evidence supports citicoline roles in cellular pathways related with neural cell death prevention. Thus, citicoline increases levels of neurotransmitters, including noradrenaline, dopamine and serotonin (4). Furthermore, citicoline might enhance tolerance to ischemic brain damage by preventing cell membrane damage and impaired phospholipid metabolism described during stroke (5). Preclinical evidence supports citicoline providing efficacy and optimal neuroprotective profile in

stroke animal models (6, 7).

This neuroprotective role led the clinician to perform clinical trials aimed to ascertain the efficacy of citicoline on stroke [8-13] and other neurodegenerative diseases (8, 14, 15). However, the effect of citicoline on stroke is elusive (for literary reviews see (16-19), even more if take into account data from the latest clinical trials that failed to show beneficial results (20, 21). These neuroprotective effects lead other authors to suggest that citicoline might have beneficial impact on several cognitive domains (22), and several trials including patients of Alzheimer disease (10) or vascular dementia (23).

Meta-analysis combines findings from independent studies to assess the clinical effectiveness of healthcare interventions (22). Using this technique, the efficacy and safety of a drug (24, 25), or its lack of efficacy, such as in the case of the promising drug dimebon (26), can be determined.

The lack of a systematic review that put together all the information on citicoline effects on cognitive function was the starting point of this work. Thus in this study, we performed a systematic review of the literature on citicoline and its efficacy on impairment associated to neurodegenerative diseases such as alterations in mini-mental state examination, memory, attention and finally the plausible effects on basic activities of daily living.

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Material and Methods

We conducted a search for all clinical trials using citicoline to improve cognitive function, in patients affected by different pathologies causing neurological disorders. The studies were found by means of a MEDLINE and in the Cochrane Central Register of Controlled Trials (CENTRAL) searches using the keywords "Citicoline" AND "cognitive" (July 2014). The bibliographic references of the selected articles were also examined to locate other possible publications not found in the above-mentioned search. The trials that were included meet the following criteria. 1. Double-blind placebo controlled with random assignment to citicoline or placebo. 2. Inclusion of patient with altered cognitive function. 3. Specification of medication doses and formulation. 4. Written in English. We have found 99 studies. Of these, 73 were rejected for different reasons (figure 1). Of the 26 remaining studies, 14 were included in our systematic review (Table I and Figure 1). The quality of each study was determined by using Jadad score that considers aspect related to biases such as randomization, blinding and reporting of loss to follow-up (27). This instrument gives a score from 0 (the worst score) to 5 (the best score). Two investigators (NC-C, JJ), independently extracted those publications identified here that describe controlled studies of citicoline in cognitive impairment. Disagreements were resolved in discussion with a third investigator (JSGdP).

We collected data on patients' diagnosis, dosage used, duration of treatment and follow-up, inclusion and exclusion criteria and scales used for efficacy. Results were described for four domains: mini-mental state examination, memory, attention and basic activities of daily living.

- Mini-mental state examination (MMSE) (28). The MMSE is a common, validated screening instrument that is used as a general measure of cognitive function (lower score indicate greater impairment), includes questions about basic temporal and spatial orientation, attention, language, calculation, memory fixing and constructive praxis.
- Memory: Different scales were used to assess memory. Briefly, Randt memory test for longitudinal assessment of mild and/or moderate memory deficits (29), memory subscale of Alzheimer's Disease Assessment Scale (ADAS) (30) used to evaluate the severity of cognitive and noncognitive behavioral dysfunctions characteristic of persons with Alzheimer's disease, California Verbal Learning Test popular clinical and research test that claims to measure key constructs in cognitive psychology such as repetition learning, serial position effects, semantic organization, intrusions, and proactive interference (31), Logical Memory consisting in immediate repetition of short stories presented auditory (it is a subtest of Wechsler Memory Scale, a widely used clinical scale composing a number of

subtest) (32) and the Rey Auditory Verbal Learning Test (RALVT) an easy to administer test that assesses many memory domains and is, therefore, widely used in the area of clinical neuropsychology (33).

- Attention: Two tests were used for determining the subject's attention. The Toulouse-Pieron Test and the Trail Making Test are accessible neuropsychological instruments that provides the examiner with information on a wide range of cognitive skills (11).
- Basic activities of daily living (disability): two scales were used, basically for the evaluation of self-care and mobility. Barthel Index, a scoring technique that measures the patient's performance in 10 activities of daily life (34) and the Index of Activities of Daily Living (ADL) a method of classifying heterogeneous groups of people with chronic illnesses, disabilities and impairments, and of describing their health needs and outcomes (35).

The statistical analyses were performed comparing citicoline with placebo in terms of efficacy wherever such comparison was possible. The efficacy measures were expressed as odds ratio or standardized mean difference with the relevant confidence interval (IC95%). We have used a random effect where heterogeneity among studies was found. A funnel plot, if possible, were used to evaluate potential selection bias in the studies. Chi² of heterogeneity and I² inconsistency statistic were used to measure heterogeneity regarding study results. In all tests, the level of statistical significance used was $p < 0.05$. Analyses were performed using RevMan version 5.

Results

Our literature search revealed 14 clinical trials that were included in our study tested the efficacy of citicoline for improving cognitive functions in patients that were affected by altered cognition pathologies, such as vascular dementia, acute stroke, and Alzheimer disease.

Effects of citicoline on MMSE

Although we found four trials including 474 patients, of which 300 were treated with citicoline using the MMSE measure to evaluate cognitive function.

In two clinical trials, citicoline efficacy was tested in patients with vascular dementia, giving contradictory results. Chandra et al reported a marked improvement on the MMSE score compared with patients taking after two months (MMSE score: 23 in citicoline group and 14.4 in placebo group) and after 10 months (MMSE score: 23 in citicoline group and 12.2 placebo group) (12). On the other hand, Cohen et al. found no significant changes in MMSE scores at 6 and 12 months (23).

In patients with acute ischemic stroke, Clark et al., evaluated the effect of three daily doses of citicoline (500, 1000 and 2000 mg) versus placebo (36). At 12 weeks, citicoline increased the percentage of patients with

Table 1
Clinical trials included in this review

Author (year) [Ref]	Jadad score	Disease	Patients	Dose Daily	Via	Duration (days)	Efficacy measures
Chandra B (1992) (12)	4	Vascular dementia	146	750mg	IV	60	Ischemia Scale of Hachinski Mini-mental state examination
Piccoli F (1994) (37)	2	Chronic cerebrovascular disease	92	1000mg	IM	63	Randt Memory Test Scale of emotional and behavioral control Toulouse-Pieron Test
Spiers PA (1996) (9)	5	Aging	94	1000mg 2000mg	OV	90 60	Verbal memory
Capurso A (1996) (13)	3	Chronic cerebrovascular disease	31	1000mg	IM	63	Brane and Steen Scale Rating Scale Test Deux Barrages Randt Memory Test
Clark WM (1997) (36)	3	Acute ischemic stroke	259	500 mg 1000mg 2000mg	OV	42	Barthel Index Modified Rankin scale Mini-mental state examination
Alvarez XA (1999) [10]	3	Alzheimer disease	30	1000mg	OV	84	Mini-mental state examination Alzheimer's disease assessment scale Alzheimer's disease assessment scale-cognitive subscale
Clark WM (1999) [41]	5	Acute ischemic stroke	394	500mg	OV	84	Barthel Index Rankin scale
Clark WM (2001) [42]	5	Acute ischemic stroke	899	2000mg	OV	84	Barthel Index Clinician's Global Impressions scale
Cohen RA (2003) [23]	3	Vascular dementia	39	1000mg	OV	365	Mini-mental state examination Executive/Attention Memory Visuospatial Language Psychomotor
Brown ES (2007) [15]	4	Bipolar disorder	44	500 -2000mg	OV	84	Inventory of Depressive Symptomatology-Self-report Young Mania Rating Scale Rey Auditory Verbal Learning Test
Dávalos A (2012) [20]	4	Acute ischemic stroke	2298	2000mg	OV /IV	90	Barthel Index Modified Rankin Score
Putignano S (2012) [43]	1	Geriatric syndrome	197	500-2000 mg	IV/IM	180	NIHSS Rankin Scale Activities of Daily Living IADL
Zafonte RD (2012) [38]	5	Brain injury	1213	2000mg	OV	90	Traumatic Brain Injury Clinical Trials Network Core Battery
Alvarez-Sabin J (2013) [39]	2	Vascular dementia	347	1000mg	OV	365	Attention Temporal orientation Language Memory Spatial Perception Motor speed

an optimal outcome in the MMSE (≥ 25). Remarkably, this effect appeared not dose dependent, since it was observed at 500 and 2000 mg but not 1000 mg (36).

In Alzheimer disease patients, Alvarez et al. did not detect a difference in the MMSE score between placebo and citicoline (1000 mg, 12 weeks) (10).

Citicoline effects on memory

In table II, we have summarized the eight clinical trials, including 1890 patients, which evaluated citicoline effects on memory function (9, 10, 13, 15, 23, 37, 38).

Two trials used the Randt Memory Test to ascertain citicoline efficacy in patients with chronic cerebrovascular disease. First, Piccoli et al. revealed that citicoline induced a constant and progressive improvement ($p < 0.05$) (37).

Table 2
Clinical trials evaluating citicoline effects on memory

Author (REF)	Disease	Scale	p
Piccoli (38)	Cerebrovascular Disease	Rand Memory Test	p<0.05
Spiers (11)	Aging	Logical Memory*	N.S.
Capurso (10)	Cerebrovascular Disease	Rand Memory Test	p<0.05
Alvarez (12)	Alzheimer’s disease	Alzheimer’s disease assessment scale-Memory	N.S.
Cohen (21)	Vascular dementia	California Verbal Learning Test Logical Memory	N.S. N.S.
Brown (15)	Bipolar Disorder	RAVLT total words RAVLT delayed recall RAVLT alternative Word list	N.S. N.S. p<0.05
Zafonte (39)	Traumatic Brain Injury	California Verbal Learning Test	N.S.
Alvarez-Sabin (40)	Vascular cognitive impairment	Auditory Verbal Learning Test	N.S.

N.S. Non-significant. RAVLT, Rey Auditory Verbal Learning Test.

Second, in a substest of this test, Capurso et al. found a significant difference in the memory index (p<0.05) (13). However, in patients with vascular dementia, citicoline failed to improve the California Verbal Learning Test (p=0.36) and Logical Memory (p=0.5) (23). Lack of citicoline-induced positive effects were also reported by Alvarez-Sabin et al. Using the Auditory Verbal Learning Test, these authors did not detect differences in patients with post-stroke vascular cognitive impairment at 6 and 12 weeks (p=0.807 y p=0.873) (39).

In the citicoline brain injury treatment trial(COBRIT), citicoline failed to afford any improvement in the California Verbal learning Test score in patients with traumatic brain injury (38). In patients with bipolar disorder with cocaine dependence, Brown et al. reported that citicoline leads to an enhancement in the RAVLT alternative Word list (p=0.006) but not in RAVLT total Word (p=0.439) or RAVLT delayed recall (p=0.105) (15). In addition, two more trials described a positive but not statistically significant tendency to improve memory in volunteering patients with relatively inefficient memory (9) or Alzheimer disease (10).

Effects of citicoline on attention

We identified five trials analyzing citicoline effects on attention, enclosing a total of 1.721 patients (23, 37-40). In patients with chronic cerebrovascular disease, citicoline induced a significant decrease in the number of incorrect responses in the Toulouse-Pieron test (p<0.05) (37). Similarly, Alvarez-Sabin, at 6 (p=0.019) and 12 (p=0.014) months of treatment, evidenced less deterioration of post-stroke vascular cognitive impairment in attention-execution (Stroop Color Word Interference test, Trails A and B and Symbol digits Modalities Test, Mental control, Digit Span) (39).

However, using the Trail Making Test scores, we did not find citicoline-induced improvements in patients affected by Alzheimer disease (p=0.74) (40), vascular dementia (p=0.58) (23) or traumatic brain injury (38).

Figure 1
Flow chart outlining the search strategy and results of the different steps

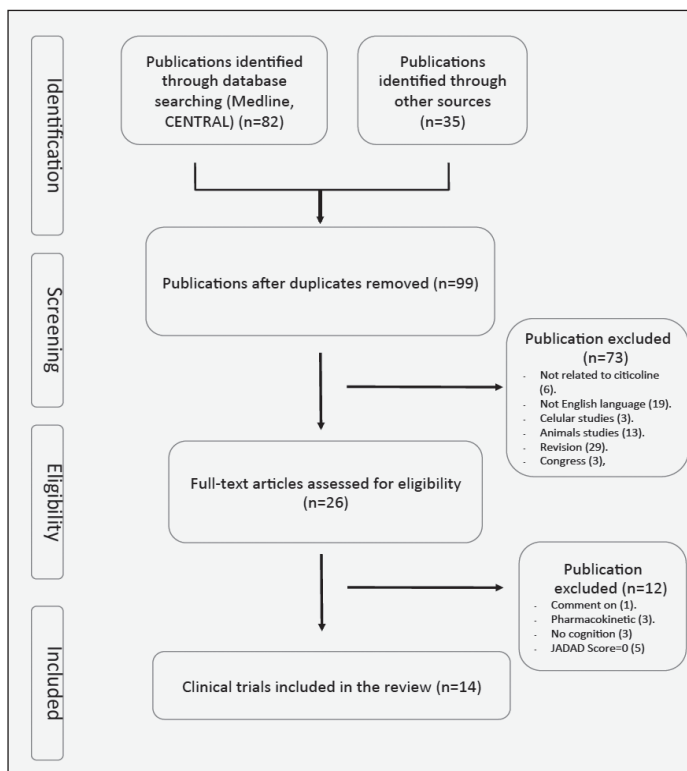
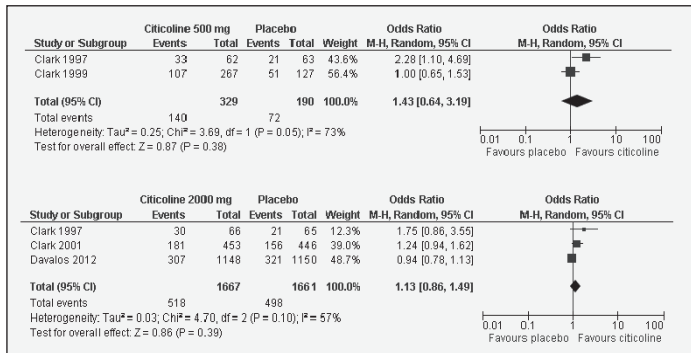


Figure 2

Forest plots showing individual and pooled odd ratio (95%) for the associations between citicoline (2000 mg and 500 mg) and Barthel index (≥ 95)



Effects of citicoline on basic activities of daily living

The effect of citicoline on the patient ability to perform activities of daily living was evaluated in 5 clinical trials that included 4137 patients, 2334 of which were treated with citicoline.

In acute ischemic stroke patients, Clark et al. evaluated citicoline efficacy in three clinical trials, leading to heterogeneous results. Interestingly, in the first trial, with citicoline administered at 500, 1000, and 2000 mg, only at a daily dose of 500 mg citicoline resulted in a Barthel-index improvement ($p=0.03$) (36). Their second trial was addressed to compare citicoline (500mg) versus placebo (41), but this did not yield positive results. In the third trial, the authors compared a daily dose of 2000mg citicoline versus placebo. Although initially (at 6 weeks) a higher proportion of patients in the citicoline group showed a score higher or equal to 95 (placebo 21%, citicoline 27%; $p=0.04$), this difference was lost at 12 weeks (42). In addition, in a different trial, Davalos et al. did not find citicoline effects in this kind of patients (20). Our meta-analysis of these data shows that citicoline did not significantly alter the Barthel index at the doses of either 500mg (OR 1.43; IC 95% 0.64-3.19) or 2000mg (OR 1.13; IC 95% 0.86-1.49) (Figure 2).

Using the ADL scale in elderly patients with progressive cognitive impairment, Putignano et al., did not find effectiveness for citicoline, although, they denoted a trend towards favorable scores in the functional independence (43)

Discussion

Prompted by the fact that citicoline has been shown to be a useful treatment for neurodegenerative and cerebrovascular diseases, we have evaluated its ability to improve cognitive function by performing a systematic review. To do so, we focused on scales that measure aspects such as MMSE, memory, attention, and basic

activity of daily living.

Our data reveal a positive effect of citicoline on MMSE in acute ischemic stroke, which was not evidenced for other diseases where cognitive function is compromised, including Alzheimer disease or vascular dementia. However, this positive improvement was found in a single study, and only at a daily dose of 500 and 2000 mg but not 1000 mg. So, it will be interesting to corroborate these data in a new clinical trial. In addition, in vascular dementia, our study revealed contradictory results, which makes it difficult to draw solid conclusions. Furthermore, we found lack of evidence for citicoline effects on cognitive impairment associated to Alzheimer disease. This conclusion seems contradictory to the previous conclusion reached by Secades in a nice and elegant, but not systematic, review (17).

In addition, eight studies reporting citicoline effects on memory were found. In chronic cerebrovascular disease patients, two studies yielded favorable results. However, other studies failed to show a positive effect on post-stroke vascular cognitive impairment, AD, or aging. Unfortunately, we were unable to perform a meta-analysis as the authors used different scales with different scores and thresholds to measure sensibility. These disparities constitute a handicap to find plausible positive effects.

We have also analyzed the effects of citicoline on attention. Positive results were observed in two studies performed with post-stroke patients and chronic cerebrovascular disease. However, citicoline failed to produce this positive result when the patient suffered from Alzheimer disease, traumatic brain injury, or vascular dementia.

Our last goal was focused on the effects of citicoline on the activities of daily living. Our meta-analysis, which included four trials, revealed that citicoline failed to exert beneficial effects in patients with acute ischemic stroke (Barthel index) or progressive cognitive impairment (ADL score).

Why citicoline improves some cognitive impairments but fails to do so with others remains unknown (43, 44, 45) Pre-clinical evidence supports citicoline efficacy and an optimal neuroprotective profile in stroke animal models (7). In a recent review, Overgaard concluded that citicoline is the only drug that, in different clinical stroke trials, continuously showed neuroprotective effects (3).

However, we cannot ignore that often important causes of irreproducibility of experimental results in clinical settings are the use of large drug doses in most animal experiments (18) or the lack of methodological rigor, and these lead to an inflated treatment effect (46) Considering that citicoline is an essential intermediate in the synthesis of structural phospholipids of cell membranes and its formation from phosphorylcholine is the rate-limiting step of this biosynthetic pathway, one could hypothesize that it needs to have a strict control. In fact, citicoline is hydrolysed into choline and

cytidine to be resynthesized later in the brain (47). In this scenario, long treatment periods would result in a negative feedback and result in readjustment of the available citicoline levels, yielding a non-efficient drug. Supporting this idea, Baab et al. found that phospholipid synthesis and turnover were stimulated at 6 but not 12 weeks of oral citicoline treatment. Moreover, these authors correlated results from the California Verbal learning test with an increase in phosphodiesterases (48). Then, only under acute damage (e.g. acute stroke), where this homeostatic response does not efficiently regulate endogenous values, citicoline administration results in an efficient protection. On the other hand, in acute events citicoline might result in an inhibition of cell death pathways. For instance, in an experimental model, citicoline markedly lowered brain edema and blood-brain barrier permeability, enhanced the activities of superoxide dismutase, increased glutathione levels, and reduced the levels of malondialdehyde and lactic acid (49). Other mechanisms suggested to be involved include prevention of phospholipase A2 activation (50), which is involved in transient cerebral ischemia (51).

There is a Cochrane's Systematic review about this topic performed by Fioravanti M and Yanagi M, that yielded different results (52). The authors concluded that there was some evidence that CDP-choline has a positive effect on memory and behaviour. The effect on attention measures was not significant ($p=0.22$). Nonetheless, the characteristics of this review are different from ours since the outcome analyzed differ. For instance, the effect of citicoline on the MMSE and on activities of daily living is novel in our review. We have to acknowledge that our study presents limitations related to the difficult process of selecting trials using citicoline. In addition, our systematic review shows the heterogeneity of trials using citicoline. This heterogeneity is present in parameters such as treatment duration, the number of patients, the follow-up period, and the scores used. Moreover, we were negatively surprised by the way the authors of the trials had reported their results. Whereas some authors gave mean scores, others categorized them when they referred to the same scale. Indeed, we found that 5 reached a Jadad score of zero (8, 14, 21, 53, 54), which is indicative of a lack of answer to relevant key questions such as «Was the study described as randomized, or as double blind?», «Was there a description of withdrawals and dropouts?» Due to these discrepancies, it is difficult to make a thorough analysis of the data and might easily lead to wrong interpretations.

Finally, although our study was not undertaken to determine citicoline safety, we validate the general idea that citicoline presents a good safety profile. Ten of the trials included in our study described adverse events. Enclosing 2254 patients in total, 1400 were treated with citicoline. The side effects most frequently reported were effects on the central nervous system in both the citicoline (127 events, 10%) and the placebo (103 events, 13%)

groups. However, we did not find significant differences between these groups.

In summary, our data suggests that citicoline may improve MMSE in acute stroke patients. However, to reach a solid conclusion for this and other chronic diseases such as Alzheimer disease and vascular dementia, we need to reach an agreement on the test scales and how to report the scores before performing more trials. Awaiting the completion of new clinical trials including higher numbers of patients in order to obtain more consistent results, we would not advise the use of citicoline as effective treatment in patients with cognitive impairment.

Ethical Standards: None disclosed.

Conflicts of Interest: The authors declare that they have not conflicts of interest.

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