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Cholinergic precursors in the treatment of cognitive impairment of vascular origin: Ineffective approaches or need for re-evaluation?

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Abstract

Inhibition of endogenous acetylcholine degradation through cholinesterase inhibitors represents a milestone in symptomatic treatment of cognitive symptoms in mild to moderate stages of Alzheimer's disease. Cholinesterase inhibitors are also under investigation for treating cognitive dysfunction of cerebrovascular origin, but to date they do not have specific indication for vascular dementia or vascular cognitive impairment. This paper reviews the main clinical studies assessing the activity of cholinergic precursors in the treatment of adult-onset dementia disorders of vascular origin. The first cholinergic precursor used phosphatidylcholine (lecithin) did not show any clear clinical benefit on symptoms of dementia disorders. The same is not true for other phospholipids involved in choline biosynthetic pathways such as cytidine 5′-diphosphocholine (CDP-choline) and choline alphoscerate for which a modest improvement of cognitive dysfunction in dementia of neurodegenerative and vascular origin is documented. Positive results obtained with selected cholinergic precursors cannot be generalized due to the small numbers of patients studied in appropriate clinical trials. However, they probably would justify reconsideration of the most promising molecules in larger carefully controlled studies.

Keywords: Cholinergic strategies; Vascular dementia; Vascular cognitive impairment; Cholinergic precursors; CDP-choline; Choline alphoscerate; Clinical trials

1. Introduction

Impaired brain cholinergic neurotransmission has a key role in the deterioration of cognitive functions in Alzheimer's disease [1–3]. Several studies have reported cholinergic deficits in brain and cerebrospinal fluid of patients with vascular dementia (VaD) [4–8]. These deficits, although are of different degree than those found in Alzheimer's disease, were suggested to be associated with VaD (for a review see [9]). In view of this, cholinergic agents were proposed for relieving symptoms of VaD [9]. To date, there are no approved treatments for VaD and the main therapeutic efforts in this field are aimed at controlling vascular risk factors for countering VaD development or progression [10–12].

2. Cholinesterase inhibitors in the treatment of vascular dementia

Cholinesterase inhibitors increase acetylcholine availability at the synaptic cleft, by slowing down its enzymatic degradation. Cholinesterase inhibitors are currently approved for the symptomatic treatment of Alzheimer's disease and were investigated in numerous clinical trials. Critical analysis of the results of the main clinical studies suggests that beneficial long-term effects of these compounds on the cognitive, functional, and behavioural symptoms of Alzheimer's disease are small and not always apparent in practice [13–15].

There have also been several trials of cholinesterase inhibitors for treatment of VaD [15]. Donepezil was assessed in 2 main randomized, double-blind, placebo-controlled, 24-week studies involving 1219 patients. The patients were randomized to receive donepezil 5 mg/day ($n=406$) or 10 mg/day (after brief titration; $n=421$) or placebo ($n=392$) and were

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assessed on cognition, global function and instrumental activities of daily living. Treated patients had modest benefits in cognition, global function and ability to perform instrumental activities of daily living, but improvements observed were on the whole rather modest [16]. Clinical data obtained with galantamine in VaD and vascular cognitive impairment (vascular dementia and mixed dementia) were recently evaluated by a meta-analysis including two main trials [17]. One study reported advantage over placebo in the areas of cognition and executive functioning, whereas no positive results were found in a second trial [17]. In both studies galantamine produced higher rates of gastrointestinal side effects [17]. The conclusion is that data on the impact of galantamine on VaD or vascular cognitive impairment are too limited and more studies are needed for demonstrating the efficacy of the drug in VaD [17]. Rivastigmine was first assessed in a small open-label investigation showing its superior benefits compared with aspirin plus nimodipine, in attention, executive function, instrumental activities of daily living, and behavioural and psychotic disturbances [18]. Rivastigmine was used in subcortical vascular dementia [19] and in vascular cognitive impairment [20] and studies in this indication were also evaluated by a Cochrane analysis [20]. Available data suggest some evidence of benefit of rivastigmine in subcortical vascular dementia and vascular cognitive impairment, but due to the small numbers of subjects examined larger studies are necessary to establish the effectiveness of the compound in dementia disorders of vascular origin [19,20].

Collectively, published clinical studies suggest that in spite of hopes generated by cholinesterase inhibitors, there is no conclusive demonstration of an activity of these drugs in the treatment of vascular cognitive impairment and VaD. Similarly as reported for Alzheimer's disease [15], positive effects documented by drugs of this class are in general modest and it is complex to establish the clinical relevance of these effects [16,17,19,20].

3. Cholinergic precursors in the treatment of vascular dementia

Cholinergic precursor loading therapy was the first approach tried to relief cognitive impairment in dementia disorders. Controlled clinical trials failed to show significant improvements with choline or phosphatidylcholine (lecithin), a choline-containing phospholipid [21], alone or in association with cholinesterase inhibitors (tacrine plus choline, or physostigmine plus choline) [22]. The reasons for the lack of effect of this precursor strategy are unclear [23]. The negative effects with choline or phosphatidylcholine [22,23] cannot be generalized for all cholinergic precursors. It is thought that phosphatidylcholine increases brain choline and acetylcholine concentrations [21,24], although an effect of this precursor on neurotransmitter synthesis was not confirmed by all studies [25]. Probably phosphatidylcholine can provide choline for acetylcholine synthesis only in conditions of stimulated neurotransmitter release [26].

Other cholinergic precursors such as cytidine 5′-diphosphocholine (CDP-choline) and choline alphoscerate (alpha-glyceryl-phosphorylcholine) increase acetylcholine content and release [27–29], being choline alphoscerate more effective than CDP-choline in rising plasma choline levels [30]. The reason of the different effects of the above compounds on acetylcholine synthesis and release is unclear. It cannot be excluded that the activity observed in clinical trials with different cholinergic precursors depends from the availability of the neurotransmitter they induce [23]. The main clinical experiences with CDP-choline and choline alphoscerate in adult-onset dementia disorders with particular reference to VaD and/or vascular cognitive impairment are summarized below.

3.1. CDP-choline

Cytidine 5′-diphosphocholine (CDP-choline or citicoline) is composed by cytidine and choline linked together by a diphosphate bridge. Citicoline is the international non-proprietary name of CDP-choline. It is marketed as a prescribed drug in several European countries and in Japan and as an over-the-counter dietary supplement in USA. CDP-choline is an intermediate in the synthesis of phosphatidylcholine via the so-called Kennedy's pathway. Phosphatidylcholine is a cell membrane component that is degraded during cerebral ischemia to free fatty acids and free radicals [31,32]. Exogenous CDP-choline is hydrolyzed and absorbed as cytidine and choline [31,32].

CDP-choline enhances re-synthesis of phospholipids of cell membranes. Moreover, the compound may counter the progression of ischemic damage by reducing the release of free fatty acids [31,32]. Due to its complex pharmacological profile, as well as to an interference with adrenergic and dopaminergic neurotransmission mechanisms, CDP-choline has been proposed in several brain disorders including Parkinson's disease [31].

The main use of CDP-choline is cognitive impairment primarily related to cerebrovascular disease. Clinical studies with CDP-choline for cognitive and behavioural disturbances associated with chronic cerebral disorders in the elderly were recently reviewed and evaluated by a meta-analysis [33]. Experiences using CDP-choline in stroke, and Parkinson's disease were also reviewed [34]. There have been 13 stroke clinical trials of CDP-choline since 1980 in Europe (8 trials), Japan (1 trial) and USA (4 trials). Both European and Japanese clinical trials reported an improvement of global and neurological function and an earlier motor and cognitive recovery, whereas USA clinical trials did not clearly demonstrate beneficial effects of CDP-choline treatment [34]. On post-hoc analysis, CDP-choline in parenteral administration was effective for long-term treatments (12 week) in a subgroup of moderate-to-severe stroke cases [34]. In view of these discrepancies, further studies are essential before making any conclusions on CDP-choline activity for stroke treatment [34].

A Cochrane meta-analysis has assessed clinical efficacy of CDP-choline for the symptoms of cognitive, emotional, and behavioural impairment in older patients with dementia and cognitive impairment by evaluating 13 clinical trials made since 1978 [33]. Of these trials, 4 included 342 patients affected by neurodegenerative dementia disorders, 2 assessed 566 patients affected by VaD, one has investigated 32 patients affected by combined neurodegenerative and vascular forms of dementia and 6 included 371 patients affected by various cerebrovascular pathologies [33]. Table 1 summarizes for each trial the number of intention-to-treat subjects, treatment type and length and measures for outcome [33].

Analysis of the results of clinical studies performed with CDP-choline is difficult due to the heterogeneity of subjects for diagnosis, duration of treatment and outcomes in the domain of memory and behaviour [33]. Reaction time was assessed in 7 studies including 790 subjects and a time of treatment from 4 weeks to 12 months [33]. A little effect of CDP-choline on attention was reported. Memory was evaluated in ten studies including a total of 924 subjects, but only six studies with 675 patients affected by cognitive deficits associated with cerebrovascular disorders were comparable [33]. Meta-analysis of memory function revealed homogeneous results and there was evidence of a statistically significant positive effect on memory [33]. Behaviour was evaluated in eight studies with 844 subjects using five different scales [33]. In spite of the heterogeneous results and of some inconsistencies, meta-analysis concluded for a statistically significant but modest effect on behaviour [33]. Clinical impression was evaluated in four studies with 217 subjects, 115 in the CDP-choline group and 102 in the placebo group and no significant changes were noticeable between CDP-choline and placebo-treated subjects in terms of global clinical impression [33]. Cochrane meta-analysis concluded that CDP-choline has a positive effect on memory and behaviour in the medium term primarily in patients suffering from cognitive deficits associated with cerebrovascular disease. Further longer term studies with patients affected by cerebrovascular disease and VaD recruited with currently accepted standardised diagnostic criteria are necessary to demonstrate an activity of CDP-choline in cognitive disorders associated with cerebrovascular disease [33].

3.2. Choline alphoscerate

Choline alphoscerate (alpha-glycerylphosphorylcholine), is a phospholipid which enters in the constitution of nerve cell membranes. It is a rapidly absorbed source of choline, which does not carry the electrical charge of regular choline. This probably makes easier for the compound to cross the blood brain barrier. Choline alphoscerate raises free plasma choline more rapidly than other uncharged

Table 1
Clinical trials on CDP-choline included in the Cochrane meta-analysis of Fioravanti and Yanagi [33]

First author	No. of patients	Treatment	Duration	Tests used
Agnoli 1985	100 (77♂ 23♀)	1000 mg once a day	28 days	Global clinical impression
Alvarez 1999	30 (22♂ 8♀)	1000 mg once a day	84 days	ADAScog, Trial Making Test, CIBIC
Angeli 1985	40 (20♂ 20♀)	100 mg six times a day	30 days	NUDS, Birren test, anxiety and Depression scale, Global clinical judgement
Barbagallo 1988	188 (75♂ 113♀)	1000 mg once a day	42 days	Attention test, Randt memory test, BPRS rating scale
Capurso 1996	31 (23♂ 8♀)	1000 mg once a day	84 day	Randt memory test, GBS rating scale, Global clinical judgement
Cohen 2003	30 (12♂ 18♀)	500 mg twice a day	360 days	California verbal learning test, Trial a test, time, Dementia rating scale, MRI total brain volume, total hyperintensity volume.
Falchi Delitala 1984	30 ♂	500 mg twice a day	20 days	SCAG, hormonal dopaminergic responses (PRL, GH)
Madariaga 1978	32 ♀	200 mg three times a day for 10 days, 200 mg twice a day for 10 days, 200 mg once a day for 10 days	30 days	Crichton rating scale, visuo-monitoring task, EEG, neurological examination
Motta 1985	50 (25♂ 25♀)	1000 mg once a day	28 days	Parkside Behavior Rating scale, attention (Toulouse-Pieron) and cognitive (WAIS figure completion, digit span, arithmetic picture arrangement) tests, controlled clinical evaluation, global clinical impression.
Piccoli 1994	92 (51♂ 41♀)	1000 mg once a day	56 days	Toulouse-Pieron attention test, Randtmemory test, GBS, side effects
Senin 2003	536	1000 mg once a day	105 days	Toulouse-Pieron attention test, Randt memory test, GBS, side effects
Sinforiani 1986	58 ♂	1000 mg once a day	28 days	Parkside Behavior Rating scale, attention (Toulouse-Pieron) and cognitive (WAIS figure completion, digit span, arithmetic picture arrangement) test, controlled clinical evaluation.
Spiers 1996	94	500 mg twice a day	90 days	Verbal memory measures, Wechsler memory scale, Logical memory subset, Tolerability

For references of listed studies see [33].

choline precursors and is incorporated into brain phospholipids within 24 h from absorption [35].

Preclinical studies, have documented that choline alphoscerate increases the release of acetylcholine in rat hippocampus, facilitates learning and memory, counters cognitive deficit in experimental models of aging brain and reverses memory deficits induced by scopolamine administration (see [23]). Moreover, it counters brain microanatomical changes and impairment in cholinergic neurotransmission markers and receptors occurring in aged rats (see [23]). Cholinergic activity of choline alphoscerate in humans is documented *in vivo* by assessing its influence on growth hormone secretion from pituitary-hypothalamic axis [36].

The majority of clinical studies available on the effect of choline alphoscerate in neurodegenerative and cerebrovascular disorders were reviewed [37] and are summarized in Table 2. Studies published before 2001 have investigated 1570 patients, 854 of which were included in controlled trials. The patients examined were affected by dementia disorders of degenerative, vascular or combined origin, such as senile dementia of the Alzheimer's type, VaD and acute cerebrovascular diseases, such as transitory ischemic attack (TIA) and stroke [37]. Test batteries for assessing the effect of choline alphoscerate on cognitive domains were primarily the Mini Mental State Evaluation (MMSE) in neurodegenerative dementias and the Sandoz Clinical Assessment Geriatric (SCAG) scale in VaD [37].

Overall, 565 patients with degenerative dementia disorders of mild to moderate grade were enrolled. Three homogeneous-case trials evaluated 186 patients, whereas the three combined-case trials included 379 patients with degenerative dementia. In four trials, choline alphoscerate was given orally at the dose of 1200 mg/day (466 patients treated for 6 months and 39 for 3 months). In the remaining studies it was administered intramuscularly at the dose of 1000 mg/day. The duration of treatment was 3 or 6 months for oral administration and 3 months for parenteral administration. These trials documented that choline alphoscerate improved the patients' clinical condition with particular reference to memory and attention impairment [37]. Comparison between choline alphoscerate and acetyl-L-carnitine gave scores more favourable to choline alphoscerate [37].

The activity of choline alphoscerate was also investigated in 789 patients with VaD. Three homogeneous-case trials evaluated 408 patients and three combined-case trials included 381 patients with VaD. In four trials, choline alphoscerate was administered orally at the dose of 1200 mg/day for 3 or 6 months, while in the other three studies it was administered by intramuscular injection at the dose of 1000 mg/day for 3 months. Of the 431 orally-treated patients, 418 received the drug over 6 months and 13 over 3 months. A total of 358 were treated intramuscularly over 3 months. In these studies, investigators thoroughly assessed, cognitive impairment, behavioural disturbances, changes of interpersonal relations, affective disorders and somatic problems. Similarly as observed in degenerative dementia disorders in all trials on VaD, treatment with choline alphoscerate improved memory and attention impairment, as well as affective and somatic symptoms (fatigue, vertigo). Effects of choline alphoscerate were superior than those of placebo and of the same extent or superior of those of reference compounds [37]. Comparison between choline alphoscerate and CDP-choline gave SCAG scores more favourable to choline alphoscerate [37]. Oxiracetam was reported to have an activity comparable with choline alphoscerate in two uncontrolled trials [37].

Choline alphoscerate was also investigated in three uncontrolled studies examining its activity in acute cerebrovascular disease [37]. Treatment consisted in the intramuscular administration of a daily dose of 1000 mg/day of choline alphoscerate in the 4 weeks following the acute event. Parenteral administration was followed by a 5-month oral administration of the drug at the dose of 1200 mg/day. In these trials, parenteral treatment with choline alphoscerate favoured cognitive, functional and motor recovery in the acute phase. The subsequent oral treatment consolidated clinical results obtained in the acute phase and positively influenced the whole clinical course. Unfortunately, the typology of these studies makes them of marginal relevance [37].

A more recent trial has evaluated 261 patients aged 72.2 ± 7.5 years (132 treated for 180 days with 400 mg tablets of choline alphoscerate 3 times a day and 129 allocated to the placebo group) affected by mild to moderate dementia of the Alzheimer's type [38]. In patients under active treatment, the mean decrease in ADAS-Cog score was 2.42 points after 90 days of treatment and 3.20 points at the end of the study (day 180), whereas in the placebo group a mean increase in ADAS-Cog score of 0.36 point < 1 after 90 days and of 2.90 points after 180 days of observation ($p < 0.001$ versus baseline) was noticeable. Other parameters assessed (MMSE, GDS, ADAS-Behav, ADAS-Total, and CGI) improved after 90 and 180 days versus baseline, whereas in the placebo group they remained unchanged or worsened. Statistically significant differences were observed between treatments after 90 and 180 days in ADAS-Cog, MMSE, GDS, ADAS-Total, and CGI scores and after 180 days of treatment in ADAS-Behav and GIS scores [38].

Table 2
Clinical trials on choline alphoscerate in dementia disorders of neurodegenerative or vascular origin and in cerebrovascular disease included in the review article of Parnetti and coworkers [37] and in the trial of Jesus Moreno [38] on Alzheimer's disease

	NDG dementia disorders	VaD	Combined NDG and vascular forms	TIA or stroke	Total
Total no. of trials	4	4	3	3	14
Controlled	4	4	1	0	9
Uncontrolled	0	0	2	3	5
Total no. of patients	826	789	216	2484	4315
Controlled	486	421	208	0	1115
Uncontrolled	340	368	8	2484	3200

NDG: Neurodegenerative; VaD: Vascular dementia; TIA: Transient ischemic attack.

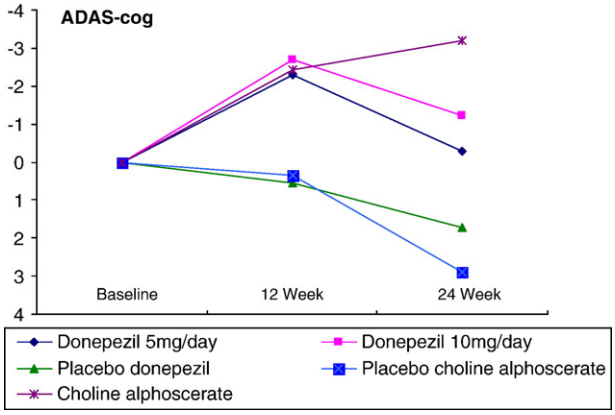

Fig. 1. Comparison of the results of ADAS-Cog test in Alzheimer's disease patients treated with choline alphoscerate or control (placebo choline alphoscerate) [38] and 5 mg/day or 10 mg/day donepezil or control (placebo donepezil). Scores for donepezil and respective control groups were obtained by pooling average data obtained in 4 trials [40–42]. Data are expressed as means of scores obtained in the ADAS-Cog test and were analyzed statistically by ANOVA. Standard error for each point was less than 5%.

Although this investigation did not examine patients affected by VaD, it presents the advantage of having been conducted using a modern clinical approach if compared with former investigations. On the other hand this trial, different from previous studies with choline alphoscerate [37], has used batteries of tests and time of observation comparable with studies assessing the activity of cholinesterase inhibitors [13–17]. A comparison of ADAS-Cog analysis from this investigation [38], with the results obtained on the same item in 4 trials with the cholinesterase inhibitor donepezil [39–42] revealed a more positive trend with the cholinergic precursor choline alphoscerate than with this cholinesterase inhibitor (Fig. 1).

4. Conclusion

Although clinical data obtained in the treatment of adult-onset dementias of both neurodegenerative or vascular origin do not support evidence of any clinical effect of phosphatidylcholine, the same is not true for CDP-choline and choline alphoscerate, that provided some modest symptomatic relief primarily on memory and attention. A main problem with both cholinergic precursors, is that the majority of clinical trials were carried out from 25 to 15 years ago. They therefore reflect diagnostic limits and cognitive function analysis of that time. However, the few studies comparable with trials assessing activity of more recent drugs such as cholinesterase inhibitors, do not reveal a clear advantage of these newer compounds compared with the safe and well tolerated choline alphoscerate. Of course, positive results obtained with selected cholinergic precursors cannot be generalized due to the small numbers of patients studied. However, they probably would justify reconsideration of the most active molecules in larger carefully controlled trials.

On the other hand, independently from any comparison with cholinesterase inhibitors, cholinergic precursors of proven efficacy and safety could represent a therapeutic resource in association with cholinesterase inhibitors [43] or in particular situations in which treatment with inhibitors is not tolerated or contraindicated. This is the case, for instance, of bradycardia, asthma, or of the cognitive impairment in the oldest old (>85 years), a typical condition in which very advanced age and co-morbidity may contraindicate cholinesterase inhibitor use.

References

[1] Davies P, Maloney AJ. Selective loss of central cholinergic neurons in Alzheimer's disease. Lancet 1976;2:1403.
[2] Bowen DM. Biochemistry of dementias. Proc R Soc Med 1977;70:351–3.
[3] Bartus RT, Dean RL, Pontecorvo MJ, Flicker C. The cholinergic hypothesis: a historical overview, current perspective, and future directions. Ann NY Acad Sci 1985;444:332–58.
[4] Perry EK, Gibson PH, Blessed G, Perry RH, Tomlinson PE. Neurotransmitter enzyme abnormalities in senile dementia. Choline acetyltransferase and glutamic acid decarboxylase activities in necropsy brain tissue. J Neurol Sci 1977;34:247–65.
[5] Gottfries CG, Blennow K, Karlsson I, Wallin A. The neurochemistry of vascular dementia. Dementia 1994;5:163–7.
[6] Martin-Ruiz C, Court J, Lee M, Piggott M, Johnson M, Ballard C, et al. Nicotinic receptors in dementia of Alzheimer. Lewy body and vascular types. Acta Neurol Scand 2000;176:34–41.
[7] Tohgi H, Abe T, Kimura M, Saheki M, Takahashi S. Cerebrospinal fluid acetylcholine and choline in vascular dementia of Binswanger and multiple small infarct types as compared with Alzheimer-type dementia. J Neural Transm 1996;103:1211–20.
[8] Wallin A, Sjögren M, Blennow K, Davidsson P. Decreased cerebrospinal fluid acetylcholinesterase in patients with subcortical vascular dementia. Dement Geriatr Cogn Disord 2003;16:200–7.
[9] Roman GC. Cholinergic dysfunction in vascular dementia. Curr Psychiatry Rep 2005;7:18–26.
[10] Sachdev PS, Brodaty H, Looi JC. Vascular dementia: diagnosis, management and possible prevention. Med J Aust 1999;170:81–5.
[11] Roman GC. Vascular dementia revisited: diagnosis, pathogenesis, treatment and prevention. Med Clin North Am 2002;86:477–99.
[12] O'Brien JT, Erkinjuntti T, Reisberg B, Roman G, Sawada T, Pantoni L, et al. Vascular cognitive impairment. Lancet Neurol 2003;2:89–98.
[13] Birks J. Cholinesterase inhibitors for Alzheimer's disease. Cochrane Database Syst Rev 2006;1:CD005593.
[14] Birks J, Harvey R. Donepezil for dementia due to Alzheimer's disease. Cochrane Database Syst Rev 2006;1:CD001190.
[15] Kaduszkiewicz H, Zimmermann T, Beck-Bornholdt HP, van den Bussche H. Cholinesterase inhibitors for patients with Alzheimer's disease: systematic review of randomised clinical trials. BMJ 2005;331:321–7.
[16] Roman GC, Wilkinson DG, Doody RS, Black SE, Salloway SP, Schindler RJ. Donepezil in vascular dementia: combined analysis of two large-scale clinical trials. Dement Geriatr Cogn Disord 2005;20:338–44.
[17] Craig D, Birks J. Galantamine for vascular cognitive impairment. Cochrane Database Syst Rev 2006;1:CD004746.
[18] Moretti R, Torre P, Antonello RM, Cazzato G, Griggio S, Ukmar M, et al. Rivastigmine superior to aspirin plus nimodipine in subcortical vascular dementia: an open, 16-month, comparative study. Int J Clin Pract 2004;58:346–53.
[19] Roman GC. Rivastigmine for subcortical vascular dementia. Expert Rev Neurother 2005;5:309–13.
[20] Craig D, Birks J. Rivastigmine for vascular cognitive impairment. Cochrane Database Syst Rev 2005;2:CD004744.

[21] Blusztajn JK, Liscovitch M, Mauron C, Richardson UI, Wurtman RJ. Phosphatidylcholine as a precursor of choline for acetylcholine synthesis. J Neural Transm Suppl 1987;24:247–59.
[22] Higgins JP, Flicker L. Lecithin for dementia and cognitive impairment. Cochrane Database Syst Rev 2003:CD001015.
[23] Amenta F, Parnetti L, Gallai V, Wallin A. Treatment of cognitive dysfunction associated with Alzheimer's disease with cholinergic precursors. Ineffective treatments or inappropriate approaches? Mech Ageing Dev 2001;122:2025–40.
[24] Chung SY, Moriyama T, Uezu E, Uezu K, Hirata R, Yohena N, et al. Administration of phosphatidylcholine increases brain acetylcholine concentration and improves memory in mice with dementia. J Nutr 1995;125:1484–9.
[25] Domino EF, Mathews BN, Tait SK, Ortiz A. Effects of oral phosphatidylcholine on mouse brain choline and acetylcholine. Arch Int Pharmacodyn Ther 1983;265:49–54.
[26] Jope RS. Effects of phosphatidylcholine administration to rats on choline in blood and choline and acetylcholine in brain. J Pharmacol Exp Ther 1982;220:322–8.
[27] Sigala S, Imperato A, Rizzonelli P, Casolini P, Missale C, Spano P. L-alpha-glycerylphosphorylcholine antagonizes scopolamine-induced amnesia and enhances hippocampal cholinergic transmission in the rat. Eur J Pharmacol 1992;211:351–8.
[28] Pinardi G, Pelissier T, Kramer V, Paeile C, Miranda HF. Effects of CDP-choline on acetylcholine-induced relaxation of the perfused carotid vascular beds of the rat. Gen Pharmacol 1994;25:635–8.
[29] Dixon CE, Ma X, Marion DW. Effects of CDP-choline treatment on neurobehavioral deficits after TBI and on hippocampal and neocortical acetylcholine release. J Neurotrauma 1997;14:161–9.
[30] Gatti G, Barzaghi N, Acuto G, Abbiati G, Fossati T, Perucca E. A comparative study of free plasma choline levels following intramuscular administration of L-alpha-glycerylphosphorylcholine and citicoline in normal volunteers. Int J Clin Pharmacol Ther Toxicol 1992;30: 331–5.
[31] Secades JJ. CDP-choline: update and review of its pharmacology and clinical use. Methods Find Exp Clin Pharmacol 2002;24:1–53.
[32] Adibhatla RM, Hatcher JF, Dempsey RJ. Cytidine-5′-diphosphocholine (CDP-choline) affects CTP: phosphocholine cytidylyltransferase and lyso-phosphatidylcholine after transient brain ischemia. J Neurosci Res 2004;76:390–6.
[33] Fioravanti M, Yanagi M. Cytidinediphosphocholine (CDP-choline) for cognitive and behavioural disturbances associated with chronic cerebral disorders in the elderly. Cochrane Database Syst Rev 2005;2: CD000269.
[34] Adibhatla RM, Hatcher JF. Cytidine 5′-diphosphocholine (CDP-choline) in stroke and other CNS disorders. Neurochem Res 2005;30: 15–23.
[35] Abbiati G, Fossati T, Lachmann G, Bergamaschi M, Castiglioni C. Absorption, tissue distribution and excretion of radiolabelled compounds in rats after administration of [14C]-L-alpha-glycerylphosphorylcholine. Eur J Drug Metab Pharmacokinet 1993;18:173–80.
[36] Ceda GP, Ceresini G, Denti L, Marzani G, Piovani E, Banchini A, et al. alpha-Glycerylphosphorylcholine administration increases the GH responses to GHRH of young and elderly subjects. Horm Metab Res 1992;24:119–21.
[37] Parnetti L, Amenta F, Gallai V. Choline alphoscerate in cognitive decline and in acute cerebrovascular disease: an analysis of published clinical data. Mech Ageing Dev 2001;122:2041–55.
[38] De Jesus Moreno Moreno M. Cognitive improvement in mild to moderate Alzheimer's dementia after treatment with the acetylcholine precursor choline alfoscerate: a multicenter, double-blind, randomized, placebo-controlled trial. Clin Ther 2003;25:178–93.
[39] Rogers SL, Friedhoff LT, the Donepezil Study Group. The efficacy and safety of donepezil in patients with Alzheimer's disease: results of a US muhicentre, randomized, double-blind, placebo-controlled trial. Dementia 1996;7:293–303.
[40] Rogers SL, Doody RS, Mohs RC, Friedhoff LT, for the Donepezil Study Group. Donepezil improves cognition and global function in Alzheimer disease, a 15-week, double-blind, placebo-controlled study. Arch Intern Med 1998;158:1021–31.
[41] Rogers SL, Farlow MR, Doody RS, Mohs R, Friedhoff LT. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Neurology 1998;50:136–45.
[42] Burns A, Rossor M, Hecker J, Gauthier S, Petit H, Moller HJ, et al. The effects of donepezil in Alzheimer's disease-results from a multinational trial. Dement Geriatr Cogn Disord 1999;10:237–44.
[43] Amenta F, Tayebati SK, Vitali D, Di Tullio MA. Association with the cholinergic precursor choline alphoscerate and the cholinesterase inhibitor rivastigmine: an approach for enhancing cholinergic neurotransmission. Mech Ageing Dev 2006;127:173–9.