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Systematic Review

Activity of Choline Alphoscerate on Adult-Onset Cognitive Dysfunctions: A Systematic Review and Meta-Analysis

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Abstract.
Background: Choline alphoscerate (alpha glyceryl phosphorylcholine, α-GPC) is a choline-containing phospholipid used as a medicine or nutraceutical to improve cognitive function impairment occurring in neurological conditions including adult-onset dementia disorders. Despite its 1985 marketing authorization, there are still discrepancies between countries regarding its approval as a prescription medicine and discussions about its effectiveness.
Objective: This study aimed to evaluate the efficacy of the α-GPC compound for treating cognitive impairment in patients with adult-onset neurological disorders.
Methods: Relevant studies were identified by searching PubMed, Web of Science, and Embase. Studies that evaluated the effects of α-GPC alone or in combination with other compounds on adult-onset cognitive impairment reporting cognition, function, and behavior were considered. We assessed the risk of bias of selected studies using the Cochrane risk of bias tool.
Results: A total of 1,326 studies and 300 full-text articles were screened. We included seven randomized controlled trials (RCTs) and one prospective cohort study that met our eligibility criteria. We found significant effects of α-GPC in combination with donepezil on cognition [4 RCTs, mean difference (MD):1.72, 95% confidence interval (CI): 0.20 to 3.25], functional outcomes [3 RCTs, MD:0.79, 95% CI: 0.34 to 1.23], and behavioral outcomes [4 RCTs; MD: –7.61, 95% CI: –10.31 to –4.91]. We also observed that patients who received α-GPC had significantly better cognition than those who received either placebo or other medications [MD: 3.50, 95% CI: 0.36 to 6.63].
Conclusion: α-GPC alone or in combination with donepezil improved cognition, behavior, and functional outcomes among patients with neurological conditions associated with cerebrovascular injury.

Keywords: Alzheimer's disease, choline alphoscerate, cognitive function, dementia, donepezil

INTRODUCTION

According to the United Nations report (2020), there are 727 million older persons (65 years or older) in the world, and this number is expected to more than double by 2050 (over 1.5 billion persons) [1]. As a result of this rapid demographic aging, disease and disability will be more prevalent. Among expected age-related disorders, cognitive impairment will take a relevant place [2]. Cognitive impairment leads to the progressive loss of learning and memory capabilities, resulting in an increase in dependency and social isolation [3]. Cognitive dysfunction ranges from mild deficits to dementia. There are many

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causes of adult-onset cognitive impairment, including Alzheimer's disease (AD), vascular dementia, strokes, brain injury, Parkinson's disease dementia, and other neurodegenerative disorders [4].

It has been estimated that 10% of people diagnosed with mild cognitive impairment progress to dementia every year [5]. In 2019, 57.4 million people were living with dementia globally, and by 2050, this number will rise to 152.8 million [6]. There are many physical, psychological, social, and economic consequences associated with dementia disorders, not only for the individuals suffering from them but also for their families and society in general [7]. There is an urgent need to implement strategies to diagnose initial cognitive impairment and to stop or delay its progression into overt dementia. These efforts are aimed to mitigate this public health burden. Pharmacological treatments may have a relevant role in reducing the burden of cognitive impairment. In particular, they can contribute to delaying the transition from mild cognitive impairment into overt dementia. Choline alphoscerate (alpha glyceryl phosphorylcholine, α-GPC) is a choline-containing phospholipid with cognition enhancing capabilities, proposed for countering the cognitive impairment in AD, stroke, and other types of adult-onset dementias [8]. From a pharmacological point of view, α-GPC is considered as a parasympathetic agent, which is used both as a registered drug or as a nutraceutical in several countries. Preclinical studies have shown that α-GPC increases acetylcholine release and levels, as well as facilitates learning and memory [9]. It has been shown that α-GPC increases acetylcholine levels in the aging brain [8]. Acetylcholine is a neurotransmitter contributing to communication between nerve cells, and between neurons and their skeletal muscles and autonomic targets. It also plays a key role in the brain's ability to store and recall information [10].

In clinical studies, α-GPC was found to improve cognition, behavioral, and functional outcomes in patients with AD, stroke, and cerebral ischemic attacks [8, 11, 12]. The majority of studies have reported positive effects of the compound [13]. However, a study [14] conducted on a large sample size (12,008,977 participants) reported that α-GPC users had a higher risk for total stroke (adjusted hazard ratios [aHR], 1.43; 95% CI, 1.41–1.46), ischemic stroke (aHR, 1.34; 95% CI, 1.31–1.37), and hemorrhagic stroke (aHR, 1.37; 95% CI, 1.29–1.46). Although this paper presented a questionable and imprecise statistical analysis, it was the first one raising a safety issue for a molecule in general considered quite safe [13].

In spite of the possible doubts about the preciseness and the correct statistical analysis of the above paper [14], the concerns raised suggest the need of a careful critical analysis about the clinical efficacy of α-GPC. To answer the question if α-GPC is effective in the treatment of some symptoms of adult-onset dementia disorders. We have therefore reviewed evidence from clinical studies on α-GPC on cognitive impairment of neurological origin, followed by a meta-analysis summarizing clinical data on the effects of α-GPC on cognitive function. The goal of this systematic review and meta-analysis was to determine the effects of α-GPC on cognition, functional, and behavioral symptoms assessed using different efficacy measures.

MATERIALS AND METHODS

This systematic review followed the Preferred Items for Systematic Review and Meta-analysis (PRISMA) checklists and diagrams to design and report the results [15]. A protocol for this systematic review has been registered with the International Prospective Register of Systematic Reviews (PROSPERO) and the registration number is CRD42022356965. It is available from: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=356965

Research questions

Does α-GPC improve cognitive function in terms of behavior, cognition, and the ability to perform basic daily activities in adults suffering from different pathologies with the common denominator of cognitive dysfunction?

Database search strategy and information sources

On August 2022, we conducted a comprehensive systematic search by PubMed, Web of Science, and EMBASE database using key terms of 'L-Alpha glycerylphosphorylcholine*', 'alpha-GPC*', 'choline alphoscerate*', 'Cereton*', 'α-Glycerylphosphorylcholine*', 'cognitive*', 'dementia disorders*', 'Alzheimer's disease*', 'cognitive impairment', 'cognitive dysfunction'. To combine the search terms for outcome interest, we used Boolean operators such as "AND" and "OR". Further relevant

articles were manually reviewed from the retrieved study reference lists.

Eligibility criteria and study selection process

Analysis was limited to randomized controlled trials (RCT), cohort, or case-control studies in which α-GPC was used alone or in combination with cholinergic drugs versus placebo and/or another drug on cognitive function in patients with neurological disorders of different origin. Studies with no control group were not considered in this systematic review. We included studies that considered either male or female adult patients aged 50 years and older with the diagnosis of neurological disorders with cognitive impairment and using as efficacy measures the Mini-Mental State Examination (MMSE), or the Alzheimer's Disease Assessment Scale-Cognition subscale (ADAS-Cog), Neuropsychiatric Inventory (NPI), Basic Activities of Daily Living (disability), and Instrumental activities of daily living (IADL) domains. We did not put restrictions on the route of administration, dose, duration of treatment, language, and publication date. Studies with unclear methodologies especially in terms of efficacy measurement and studies published only in abstracts and conference proceedings were excluded.

As for the selection of the studies, the title and abstract were screened based on eligibility criteria by two authors independently. We retrieved the full-text articles from the databases based on the title and abstract screening, and three authors independently reviewed the full-text articles to select studies that met our inclusion criteria. The disagreements related to article selection were resolved through discussion if any occurred.

Data extraction

From selected studies, two authors collected the following information: name of the first author, publication year, participants in the study, treatment involved in both experimental groups and control groups with details of the treatment (name of the treatment, dose, route of administration, and duration of the treatment in days), the scales that were used to determine the efficacy of the treatment, and the study design. An Excel spreadsheet was used to collect pertinent data from the included studies that were used in the subsequent analysis.

Outcome measures

The purpose of this systematic review was to investigate the effect of α-GPC on cognitive dysfunction, using the following measures: 1) cognition, measured by the MMSE or the ADAS-Cog. MMSE is a common, validated screening instrument for assessing cognitive function (a lower score indicates greater impairment) and includes questions concerning basic temporal and spatial orientation, attention, language, calculation, memory fixing, and constructive practice [16]. An ADAS-Cog score is used to determine the severity of cognitive and noncognitive impairments in persons with AD (a single scale ranging from 0 to 70 was used for evaluating the patients' performance on tasks, with higher scores indicating more severe impairments) [17]; 2) functional status, measured using the basic activities of daily living (BADL) [18] and IADL scales [18], and 3) behavior, measured by NP) [19].

Risk of bias assessments of selected studies

Our study has also investigated the risk bias in the RCTs of selected studies using the Cochrane Collaboration tool [20]. The risk of bias for the selected studies was independently assessed based on six domains by two authors. These domains include random sequence generation, allocation concealment, blinding personnel and participants, blinding outcome assessment, incomplete outcome data, selective reporting, and other biases. Based on each domain risk bias assessment, the studies were classified into three categories: low-risk bias, unclear-risk bias, and high-risk bias.

Statistical analysis

The data were entered into a Microsoft Excel spreadsheet and analyzed using R-statistical software (Version 4.1.1, The R Foundation for Statistical Computing, Vienna, Austria) [21]. We used R metafor package [22] along with different arguments to calculate effect size (i.e., mean difference). To calculate the effect size (mean difference) we used change from the baseline mean (i.e., before the interventions are administrated) to the post treatment mean (final value at the end of follow-up). The mean difference was used to estimate the amount by which the experimental intervention changes the outcome on average compared with the control (comparator) intervention. As a part of the pooled analysis, mean

changes from baseline and post-intervention values along with standard deviations (SDs) of selected studies are required. For the studies that did not report SD of the mean change from the baseline, we considered the additional information from the included studies such as confidence intervals, *p*-values, *t*-values, *F*-values, and standard errors to determine the standard deviations based on the equation provided in Cochrane's Handbook for systematic reviews of interventions [20]. In cases where the above information was not available, we contacted the corresponding author(s) and requested their datasets or the mean along with standard deviation changes between baseline and post-intervention. When corresponding authors did not provide their datasets or mean change along with SD from baseline values, the SD change value was calculated by adding 0.7 to the correlation coefficient (r) in the formula $[SDchange = SD^2_{baseline} + SD^2_{final} - (2^*r^*SD^*_{baseline}SD_{final})]^{1/2}$ to provide a conservative estimate as previously undertaken by different systematic reviews [23, 24].

To generate the summary measures of effect in the form of mean difference (MD), random effects models with the inverse variance method were used [25]. Heterogeneity between studies was assessed using Cochrane's Q test [26] and I^2 test statistics [27]. The degree of heterogeneity was considered as low, moderate, and high based on I^2 values of less than 25%, 25% to 75%, and more than 75%, respectively [28].

RESULTS

Literature search

In our literature search, we found 1,326 records, of which 826 records were excluded because of duplicate records. As a result of title and abstract screening, 200 records were excluded. Three hundred full-text articles were found to be potentially relevant for inclusion. Based on the screening of full-text articles, 292 studies were excluded. We identified eight studies that met our eligibility criteria (Fig. 1). One of the included studies was a prospective cohort study [29], and the other seven were RCTs [30–36].

Study characteristics

All of the included studies (eight studies) were conducted between 1993 and 2022 in Russia (one study) [29], Italy (six studies) [30–35], and Mexico (one study) [36] (Table 1). In four RCTs, α-GPC was combined with the cholinesterase inhibitor (ChE-I) donepezil [30, 31, 33, 35]. In one RCT, α-GPC was evaluated in combination with nimodipine [34], and the effects of α-GPC were examined in three RCTs without any combination of treatments [29, 32, 36]. In four RCTs, α-GPC and donepezil were compared to placebo and donepezil; in one RCT, α-GPC and nimodipine were compared to placebo and nimodipine. In three studies (two RCTs and one prospective cohort study), α-GPC was compared to either placebo or another active drug (Table 1). The number of participants in included studies ranged from 56 to 261.

Effect of choline alphoscerate on cognition

We identified three studies that evaluated the effects of α-GPC versus placebo or other drugs on cognitive function using the MMSE [29, 32, 36]. In these three RCTs, there were a total of 449 participants ($n = 227$ in the experimental group and $n = 222$ in the control group). Our meta-analysis showed that patients who received α-GPC had significantly better cognition as measured by the MMSE than those who received either placebo capsules or other medications (MD 3.50, 95% CI: 0.36 to 6.63, $I^2 = 98\%$; Fig. 2).

Four RCTs assessed the effectiveness of α-GPC combined with the ChEI donepezil on cognition as measured by the MMSE test [30, 31, 33, 35], while three RCTs used as a cognitive measure the ADAS-Cog test [30, 31, 33]. These four RCTs included 175 participants in the active treatment group (with α-GPC) and 175 participants in the control group. The pooled effect estimate showed that patients who received α-GPC and donepezil had significantly improved cognitive function than those who received donepezil and placebo as measured by MMSE (4 RCTs, MD: 1.72, 95% CI: 0.20 to 3.25, $I^2 = 61\%$, Fig. 3). Significant differences in cognition between the patients who received α-GPC and donepezil compared to the patients who received donepezil and placebo as measured by the ADAS-Cog were observed (3 RCTs, MD: –5.76, 95% CI: –8.07 to –3.46, $I^2 = 0.0\%$, Fig. 4). After 180 days of follow-up, a significant difference was observed between patients who received α-GPC and those who received placebo, in a single RCT [36] that assessed cognition outcomes using the ADAS-Cog (MD: –6.10, 95% CI: –7.51 to –4.69).

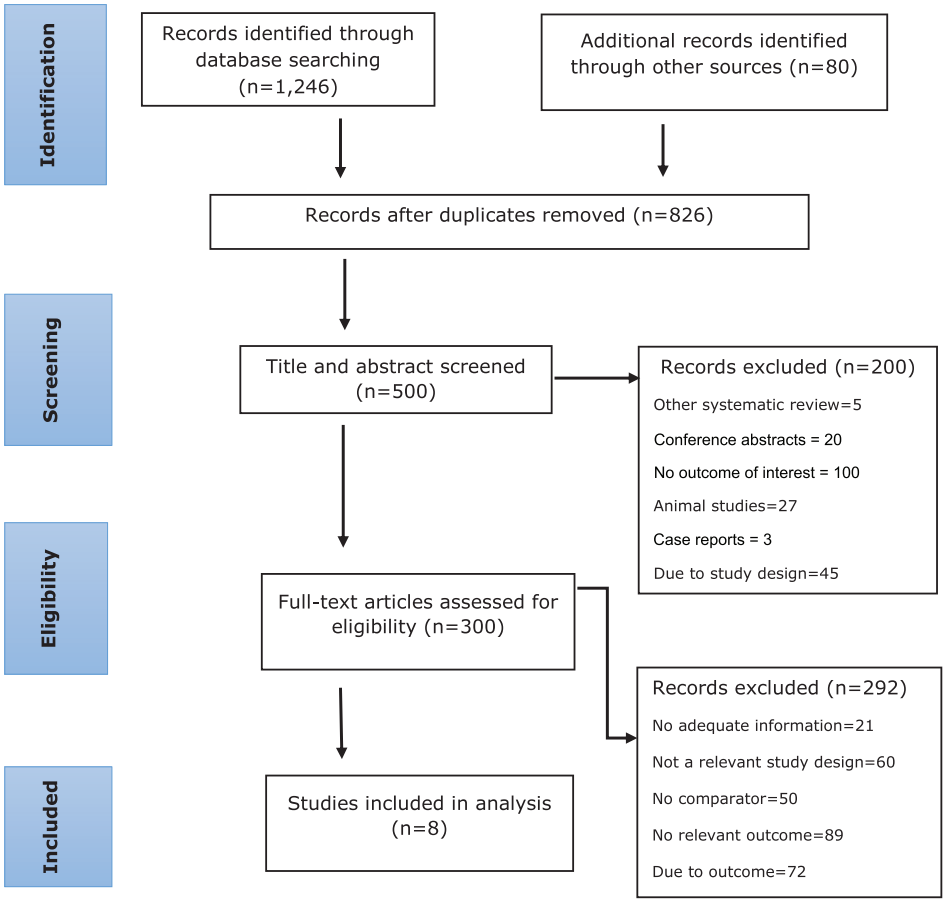

Fig. 1. Selection of eligible studies.

Effect of choline alphoscerate on functional outcomes

In three RCTs [30, 31, 33] and one RCT [34], α-GPC was evaluated in combination with donepezil and nimodipine, respectively to determine its effect on the functional status in patients with cognitive dysfunction as assessed by the BADL and IADL. According to the pooled effect estimate, we observed no significant difference in functional outcomes, as measured by the BADL between patients who received α-GPC and donepezil when compared with those who received donepezil and placebo [3 RCTs, MD: 0.46, 95% CI: –0.21 to 1.13, $I^2 = 66\%$, Fig. 5).

Similarly, in the single RCT that reported functional outcomes based on both the activities of daily living and instrumental activities of daily living scales [34], after 360 days of follow-up, no significant difference was observed between patients who received α-GPC and nimodipine and those who received nimodipine and placebo as measured by the both ADL (MD:0.00, 95% CI: –0.51 to 0.51), and IADL (MD: –0.30, 95% CI: –1.54 to 0.94).

On the other hand, the pooled effect estimate showed that patients who received α-GPC and donepezil had significantly improved functional status than those who received donepezil and placebo as assessed by the IADL after follow-up periods ranging from 360 days to 720 days [3 RCTs, MD: 0.79, 95% CI: 0.34 to 1.23, $I^2 = 0\%$, Fig. 6).

Effect of choline alphoscerate on behavioral outcomes

Four [30, 31, 33, 35] of the seven RCTs examined the effect of α-GPC in combination with donepezil on the behavioral status of patients with cognitive impairments using the NPI. The pooled effect estimate showed that patients treated with α-GPC and donepezil had a significantly reduced behavioral symptoms severity and caregiver distress as measured by the NPI, compared to those treated

Table 1
Characteristics of the included studies

Study, year [Ref]	Disease	Number of participants	Treatment	Dose	Via	Duration	Efficacy measures	Study design
Selezneva et al., 2020 [29]	Alzheimer's disease	$N = 62$ $N = 30$ [Intervention group (E)] $n = 32$ [Control group (C)]	choline alphoscerate (E) and placebo (C)	E = 1200 mg (CA) C = placebo	PO	90 days	MMSE and MoCA	Prospective cohort
Salvadori et al., 2021 [34]	Cerebral small vessel disease	$N = 62$ $n = 31$(E) $n = 31$(C)	choline alphoscerate and nimodipine (E), nimodipine and placebo (C)	E = 1200 mg (CA) and NI = 90 mg (NI) C = 90 mg (NI) and placebo capsule (BID)	PO	360 days	MoCA, ADL, IADL, DAD, RAVL	RCT
Parnetti et al., 1993 [32]	Dementia	$N = 126$ $n = 65$ (E) $n = 61$ (C)	choline alphoscerate (E) and ST200 (acetyl-L-carnitine) (C)	E = 1200 mg (CA) C = 1500 mg	PO	180 days	GDS, SCAG, GBS, MMSE	RCT
Moreno et al., 2003 [36]	Alzheimer's disease	$N = 261$ $n = 132$ (E) $n = 129$ (C)	choline alphoscerate (E) and placebo (C)	E = 1200 mg (CA) C = placebo capsule	PO	180 days	MMSE, ADAS-Cog, CGI, GDS, ADAS-Behav, ADAS_Total	RCT
Amenta et al., 2012 [30]	Alzheimer's disease	$N = 91$ $n = 44$ (E) $n = 47$ (C)	choline alphoscerate and donepezil (E), donepezil and placebo (C)	E = 1200 mg (CA) + 10 mg (DP) C = 10 mg (DP) + placebo	PO	360 days	MMSE, ADAS-Cog, BADL, IADL, NPI	RCT
Amenta et al., 2014 [31]	Alzheimer's disease + Cerebrovascular injury	$N = 113$ $n = 57$ (E) $n = 56$ (C)	choline alphoscerate and donepezil (E), donepezil and placebo (C)	E = 1200 mg (CA) + 10 mg (DP) C = 10 mg (DP) + placebo	PO	720 days	MMSE, ADAS-Cog, BADL, IADL, NPI	RCT
Traini et al., 2020 [33]	Alzheimer's disease	$N = 56$ $n = 29$ (E) $n = 27$ (C)	choline alphoscerate and donepezil (E), donepezil and placebo (C)	E = 1200 mg (CA) + 10 mg (DP) C = 10 mg (DP) + placebo	PO	720 days	MMSE, ADAS-Cog, BADL, IADL, NPI	RCT
Carotenuto et al., 2022 [35]	Depression	$N = 90$ $n = 45$ (E) $n = 45$ (C)	choline alphoscerate and donepezil (E), donepezil and placebo (C)	E = 1200 mg (CA) + 10 mg (DP) C = 10 mg (DP) + placebo	PO	720 days	MMSE NPI	RCT

MoCA, Montreal Cognitive Assessment; ADL, activities of daily living; DAD, Disability Assessment in Dementia; RAVL, Rey Auditory-Verbal Learning Test; GDS, Global Deterioration Scale; SCAG, Sandoz Clinical Assessment Geriatric scale; GBS, Gottfries-Bfllne-Steen Rating Scale; CGI, Clinical Global Impression.

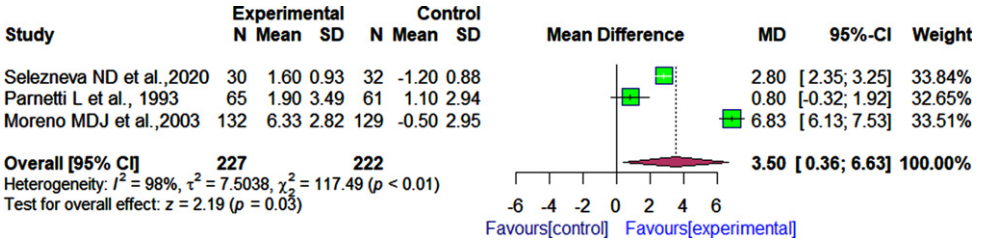

Fig. 2. Comparison of effects of choline alphoscerate (1,200 mg per day) and placebo or acetyl-L-carnitine (1,500 mg per day) on patient cognition as measured by the MMSE after follow-up periods ranging from 90 days to 180 days.

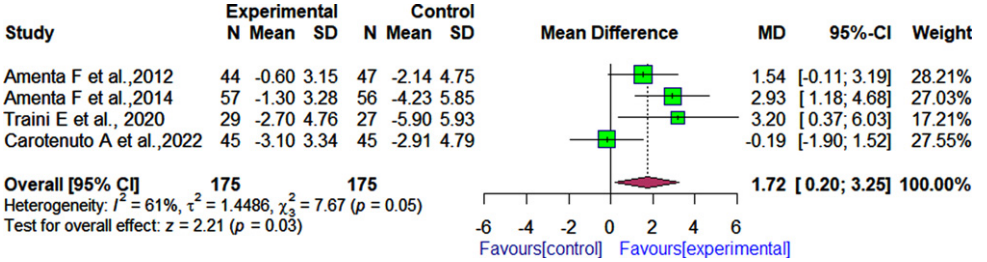

Fig. 3. Comparison of the effects of choline alphoscerate (1,200 mg/day) and donepezil (10 mg/day), and placebo and donepezil (10 mg/day) on patient cognition as measured by the MMSE after follow-up periods ranging from 360 days to 720 days.

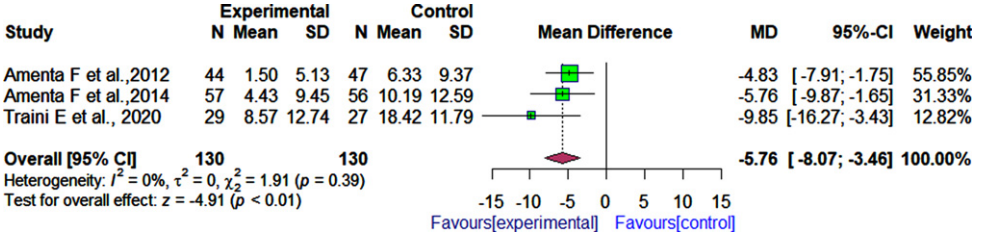

Fig. 4. Comparison of effects of choline alphoscerate (1,200 mg/day) and donepezil (10 mg/day), and placebo and donepezil (10 mg/day) on patient cognition as measured by the ADAS-Cog after follow-up periods ranging from 360 days to 720 days.

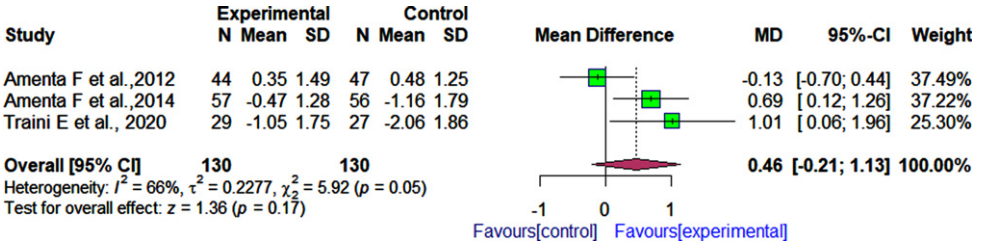

Fig. 5. Comparison of effects of choline alphoscerate (1,200 mg/day) and donepezil (10 mg/day), and placebo and donepezil (10 mg/day) on patient functional outcomes as measured by the BADL after follow-up periods ranging from 360 days to 720 days.

with donepezil and placebo after follow-up periods ranging from 360 days to 720 days (4 RCTs; MD: –7.61, 95% CI: –10.31 to –4.91, I^2 = 42%, Fig. 7). Regarding the severity of behavioral symptoms (NPI-Fxs), we observed significant differences in patients who received α-GPC and donepezil, and those who received placebo and donepezil [MD: –7.74; 95% CI: –12.69 to –2.79, I^2 = 52%, Fig. 7). In terms of caregiver distress, the pooled effect estimate indicated that caregiver distress (NPI-D) was reduced significantly in patients treated with donepezil and α-GPC in comparison to patients treated with placebo and donepezil [4 RCTs; MD: –7.37; 95% CI: –10.90 to –3.83, I^2 = 46%].

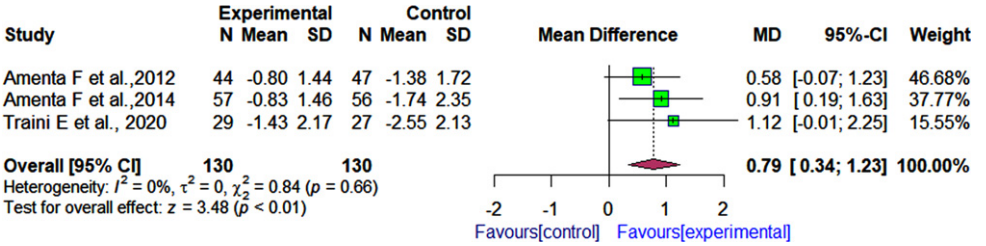

Fig. 6. Comparison of effects of choline alphoscerate (1200 mg/day) and donepezil (10 mg/day), and placebo and donepezil (10 mg/day) on patient functional outcomes as measured by the IADL after follow-up periods ranging from 360 days to 720 days.

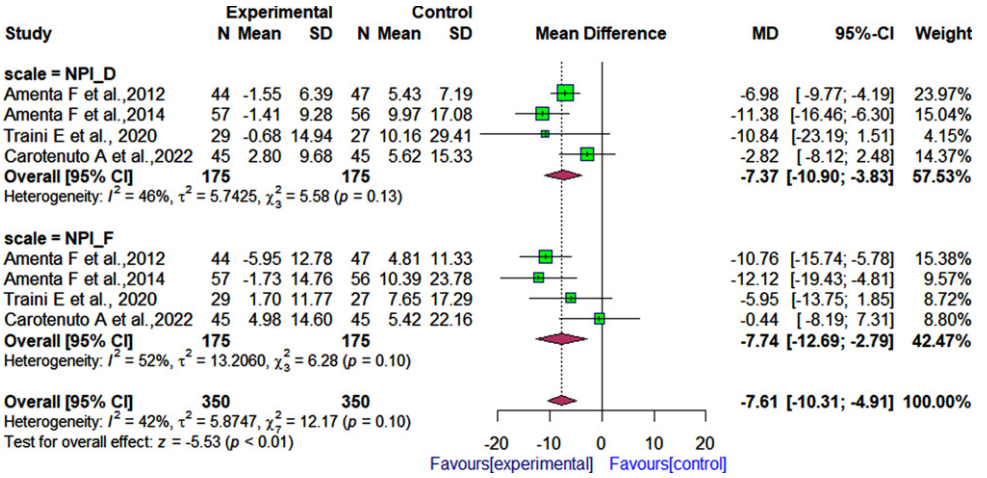

Fig. 7. Comparison of effects of choline alphoscerate (1,200 mg/day) and donepezil (10 mg/day), and placebo and donepezil (10 mg/day) on patient behavioral outcomes as measured by the NPI after follow-up periods ranging from 360 days to 720 days.

Methodological quality of included studies

In accordance with the Cochrane risk of the bias assessment tool, five studies were evaluated as having a low risk of bias on six of seven items (Table 2). In the remaining studies, at least two criteria were unclear regarding the risk of bias (Table 2).

DISCUSSION

In the present systematic review and meta-analysis, the effects of α-GPC alone or in combination with other drugs on cognitive function in patients with adult-onset dementia disorders of neurological origin caused by different pathologies compared to a placebo and/or other drugs were evaluated.

We synthesized eight studies (seven RCTs and one a prospective cohort study) with a total of 861 study participants (433 in the intervention group and 428 in the control group) between 1993 and 2022 that met the eligibility criteria in order to evaluate the effects of α-GPC on cognitive, functional, and behavioral domains in patients with neurological conditions.

Analysis of the effects of α-GPC on cognitive dysfunction was focused on scales measuring cognition such as MMSE and ADAS-Cog. Our work has demonstrated a positive effect of α-GPC on MMSE. Patients receiving α-GPC had significantly improved cognition compared to those treated with placebo or other drugs [3 RCTs; MD:3.50, 95% CI: 0.36 to 6.63]. This positive improvement was found in patients affected by AD. In three RCTs, α-GPC was administered orally at a dose of 1,200 mg per day for follow-up periods ranging from 90 to 180 days [29, 32, 36]. In two of three trials, α-GPC was compared to placebo [29, 36], whereas in one study it was compared to ST200 (acetyl-L-Carnitine) [32]. The results of this study are in line with the conclusions of the review of Parnetti and co-workers [8] on the effects of α-GPC on cognitive decline as measured by the MMSE. This study has shown that α-GPC improved the cognitive function of patients with degenerative dementia disorders in terms of orientation, mem-

Table 2
Assessment of risk of bias of the included studies using the Cochrane risk-of-bias tool

Study	Risk of bias						
	Random sequence generation	Allocation concealment	Blinding of participants, personnel	Blinding of outcome assessors	Incomplete outcome data	Selective reporting	Others
Selezneva et al., 2020 [29]	Unclear	Low	Unclear	Unclear	Low	Unclear	Unclear
Salvadori et al., 2021 [34]	Low	Low	Low	Low	Low	Low	Unclear
Parnetti et al., 1993 [32]	Low	Low	Low	Unclear	Unclear	Low	Unclear
Moreno et al., 2003 [36]	Low	Unclear	Low	Low	Low	Low	Low
Amenta et al., 2012 [30]	Low	Low	Low	Unclear	Low	Low	Low
Amenta et al., 2014 [31]	Low	Unclear	Low	Low	Low	Low	Unclear
Traini et al., 2020 [33]	Low	Unclear	Low	Low	Low	Low	Low
Carotenuto et al., 2022 [35]	Low	Low	Low	Unclear	Low	Low	Low

Low, low risk of bias; unclear, unclear about the risk of bias.

ory, and language [8]. Our findings are consistent with previous studies which reported that α-GPC was beneficial in improving cognitive performance compared to placebo [29, 36] and acetyl-L-Carnitine [32].

Evidence gathered from the four RCTs in this meta-analysis indicates that α-GPC in association with the ChEI donepezil was more effective in terms of cognition as measured by the MMSE versus donepezil and placebo in patients with AD, AD disease with depression and cerebrovascular injury [4 RCTs, MD: 1.72, 95% CI: 0.20 to 3.25]. In general, the results of this study confirm the findings of a previous study, which indicated that α-GPC has significant cognitive effects with a good safety and tolerability profile [13]. We have also found significant differences between patients treated with α-GPC and donepezil as assessed by the ADAS-Cog and those treated with donepezil and placebo regarding cognition outcomes [3RCTs; MD: –5.76, 95% CI: –8.07 to –3.46]. In a single study, we observed that α-GPC significantly improved the cognitive function in patients with mild to moderate AD compared to patients treated with placebo as assessed by ADAS-Cog [MD: –6.10, 95% CI: –7.51 to –4.69].

The present systematic review has found that α-GPC was effective either in combination with donepezil or alone in improving cognitive function in patients with adult-onset dementia disorders as measured by both MMSE and ADAS-Cog when compared to those treated with either ChE-I or placebo. In terms of cognitive function outcomes our results are consistent with those of a previous review, which concluded that α-GPC improved cognitive performance in patients suffering from dementia disorders of neurodegenerative or vascular origin either in combination with ChEIs or alone [8, 37].

Analysis of functional outcomes included three randomized controlled trials with 260 participants divided into two groups (130 in the experimental group and 130 in the control group). These three studies evaluated the effects of α-GPC in combination with donepezil on the functional status of patients with AD and AD associated with cerebrovascular injury using both BADLs and ADLs. Our pooled analysis found no significant difference between patients treated with α-GPC plus donepezil compared to patients treated with donepezil and placebo as measured by the BADL [3 RCTs, MD: 0.46, 95% CI: –0.21 to 1.13]. From the functional point of view, our conclusion contradicted the findings of previous review, which reported that α-GPC could improve functional status in patients affected by AD or other forms dementia disorders of neurological origin in combination with other active treatments or as an independent treatment [8]. This inconsistency could be due to methodological differences and different efficacy measurement approaches. Our study used meta-analysis and the BADL to measure the effects of α-GPC, whereas the study by Parnetti and his colleagues [8], to which one of the co-authors of the present work has contributed was a review analyz-

ing examined studies using the Matthew's scale to measure functional outcomes.

We have also found a single randomized controlled trials, reporting no significant differences between patients receiving α-GPC in combination with nimodipine and those who received nimodipine and placebo as assessed by both the ADL [MD:0.00, 95% CI: –0.51 to 0.51] and IADL [MD: –0.30, 95% CI: –1.54 to 0.94] after 12 months follow-up periods. As measured by the IADL, however, there was a significant difference between patients treated with α-GPC plus donepezil and those treated with donepezil plus placebo [3 RCTs, MD: 0.79, 95% CI: 0.34 to 1.23). In terms of functional outcomes assessed by the IADL, our results are consistent with those of previous reviews on the effects of α-GPC on cognitive dysfunction [8, 13, 37].

As for the effect on NPI, we observed a significant reduction of behavioral symptoms severity and caregiver distress for patients treated with the combination α-GPC and donepezil when compared to those treated with placebo and donepezil after 12 to 24 months of follow-up periods [4 RCTs; MD: –7.61, 95% CI: –10.31 to –4.91]. These findings are consistent with those of the study conducted by Rea and his colleagues, which assessed the severity of apathy, behavioral symptoms among 113 study participants with mild-moderate AD randomized to receive α-GPC plus donepezil or donepezil plus placebo [38]. Based on follow-up results after 360 and 720 days, the authors found that patients treated with a combination (donepezil and α-GPC) experienced less apathy than those treated with donepezil and placebo [38]. Our study reached the same conclusion of previous randomized controlled trials [38, 39].

Strength and weakness of the present study

To our knowledge, this is the first systematic review with meta-analysis to evaluate the effects of cholinergic precursor α-GPC in combination with the ChE-I donepezil or alone in patients with adult-onset dementia disorders interfering with cognitive function. Considering this, it is essential to note that the results obtained through this systematic review will assist in making evidence-based decisions regarding the safety of α-GPC in patients with neurological disorders. Regarding the weakness of the study, we considered an assigned value of 0.7 in the formula to calculate the SD change for two studies. This may limit the certainty of our pooled findings.

Conclusion

In conclusion, the results of this study support the use of α-GPC in combination with the ChE-I donepezil or alone to improve cognition, functional, and behavioral status, but not BADL of patients with AD and other dementia disorders of neurological origin. Based on our pooled analysis from randomized controlled trials, we can conclude that α-GPC is effective in improving cognitive function in patients with adult-onset dementia disorders associated with cerebrovascular involvement. The above findings suggest the need of further and larger studies to confirm the interest of α-GPC in the treatment of the pathologies in which the compound has shown promising results.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

DATA AVAILABILITY

All relevant data are included in the article or provided as supplementary materials. All extracted data are available upon request from the corresponding author.

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