*Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.*

# Alpha-GPC (alfoscerate, L-alpha glycerylphosphorylcholine)

**Evidence Summary**

Several studies have suggested that alpha-GPC may slow cognitive decline in patients with Alzheimer's disease or dementia, though most of these studies were conducted before acetylcholinesterase inhibitors were in widespread use.

**Neuroprotective Benefit:** Some evidence suggests that alpha-GPC may improve cognition beyond the current Alzheimer's standard-of-care, though these results would have to be confirmed in larger trials.

**Aging and related health concerns:** Alpha-GPC is not primarily indicated as an anti-aging supplement, though one preclinical study suggested it may help with brain aging.

**Safety:** Although alpha-GPC may be associated with some mild side effects, it is relatively safe and used by many individuals as a nootropic.

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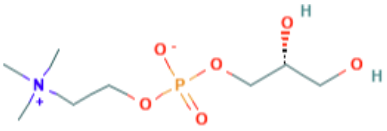
|---|---|---|
| **Availability**: Available OTC in supplement stores | **Dose**: 1200g/day (oral) in Alzheimer's study | **Molecular Formula:** $C_8H_{20}NO_6P$<br>**Molecular weight:** 257.22g/mol<br>  <br>**Source:** Pubchem |
| **Half life**: 4-6 hours (reported from websites) | **BBB**: Penetrant (in animal models) | |
| **Clinical trials**: 2 ongoing in Alzheimer's disease, 1 ongoing in diabetic elderly, 16 completed studies | **Observational studies**: 0 | |

**What is it?**

Alpha-GPC is a common nootropic. It is a choline prodrug, increasing levels of acetylcholine after administration, and may also support cellular membrane structure. The loss of acetylcholine neurons is an early event in Alzheimer's disease, and it is thought that supplementing choline may slow cognitive decline (the first set of approved Alzheimer's drugs were inhibitors of acetylcholinesterase). Several studies suggest that alpha-GPC may improve cognition in patients with Alzheimer's disease, and may even have an additional beneficial effect over donepezil. However, there is no evidence that alpha-GPC improves cognition in healthy individuals or can reduce the risk of Alzheimer's.

**Neuroprotective benefit:** Some evidence suggests that alpha-GPC may improve cognition beyond the current Alzheimer's standard-of-care, though these results would have to be confirmed in larger trials.

*Types of evidence:*

- One review of 12 studies in neurodegenerative and cerebrovascular disease
- Two studies in mild to moderate Alzheimer's
- One open-label study in patients with amnestic MCI

*Human research to suggest prevention of dementia and cognitive aging*

In patients with Alzheimer's disease, but not vascular dementia, CSF levels of glycerophosphocholine were elevated by 76% (Walter et al, 2004). This could possibly be due to the breakdown of choline-containing phospholipids. However, no studies have examined whether alpha-GPC can prevent dementia.

*Clinical research to suggest benefits to patients with dementia or cognitive aging*

In an RCT of patients with mild to moderate dementia, 261 individuals were given alpha-GPC (400mg, 3xday) or placebo over 6 months. Scores for all cognitive and functional measures (ADAS-cog, MMSE, GDS, CGI) improved in the treated group vs. the placebo (e.g. ADAS-cog better by ~6 points). A post hoc analysis reported that 46.2% of patients taking alpha-GPC and 10.1% of patients on placebo were responders (at least 4-point improvement on ADAS-cog), and 35.6% and 3.9% of individuals were complete responders (at least 7-point improvement on ADAS-cog). Note – the paper did not mention any concomitant use of acetylcholinesterase inhibitors (AChEi). This study was conducted in Mexico City, possibly before widespread use of AChEIs, the standard of care for dementia patients. Adverse events were relatively balanced (8.3% in drug, 2.3% in placebo) and mild with the most common adverse events being constipation and nervousness (Moreno, 2002).

Interim results from an RCT of 113 patients with mild to moderate Alzheimer's disease and concomitant cerebrovascular disease followed over 2 years suggested that donepezil (10mg/day) + alpha-GPC (1200mg/day) was superior to donepezil (10mg/day) + placebo. Alpha-GPC+ donepezil patients had less decline on all cognitive, functional, and behavioral measures (MMSE, ADAS-cog, BALD, IALD, NPI-f, NPI-D) (e.g. ADAS-cog better by ~6 points) (Amenta et al, 2014). The patients who responded best to alpha-GPC add-on were those with mild-to-moderate Alzheimer's.

Another RCT of 126 patients with probable mild to moderate senile dementia comparing alpha-GPC (800mg in morning and 400mg in afternoon) to acetyl-*l*-carnitine (1000mg in morning and 500mg in afternoon) reported improved cognitive function in both groups after six months with no difference between groups. Improvements in apathy and affective disorders were greater in the alpha-GPC group. Again, this study was conducted before the use of AChE inhibitors (Parnetti et al, 1993).

An open-label study in 50 patients with amnestic MCI tested the effect of alpha-GPC (1200mg/day in 3 daily doses) over three months. Memory improved after three months, though these benefits were reduced 6 months after treatment ended (Gavrilova et al, 2018 – abstract only, in Russian).

In a review of trials in dementia or vascular dementia (most of the studies are in Italian, published in the 1990's, and inaccessible), alpha-GPC improved cognition (measured with the MMSE) from baseline and was usually numerically superior to a comparator drug (oxiracetam, acetyl-L-carnitine, citicoline, or placebo) (Parnetti et al, 2001).

*Mechanisms of action from preclinical research*

Alpha-GPC restored acetylcholine levels and improved cognition in a scopolamine model of cognitive dysfunction (Lopez et al, 1991). It has also been reported to improve memory in models of brain aging (Moreno, 2002 – original references in Italian).

APOE4 Interactions:

One study reported that alpha-GPC was most effective in non-carriers (data were not accessible- Gavrilova et al, 2018 – abstract only, in Russian).

**Aging and related health concerns:** Alpha-GPC is not primarily indicated as an anti-aging supplement, though one preclinical study suggested it may help with brain aging.

*Types of evidence:*

- One preclinical study in SAMP8 mice

In SAMP8 mice, administration of alpha-GPC was associated with reduced levels of phenotypic senescence at 36 weeks (but not 44 weeks), a reduction of number of cortices with deposition of transthyretin but no change in transthyretin plaque load, a reduction in joint degeneration, and no change in amyloid plaque load or measures of anxiety (Matsubara et al, 2018).

**Safety:** Although alpha-GPC may be associated with some mild side effects, it is relatively safe and used by many individuals as a nootropic.

*Types of evidence:*

- Safety data from two clinical trials
- Case reports online

Reports on the side effect of alpha-GPC in clinical studies has been sparse. Moreno, 2002 reported that of 132 patients, 8.3% treated with alpha-GPC experience side effects (constipation and nervousness) though these were mild in severity. Parnetti et al, 1993 reported that of 65 patients there were three side effects (insomnia, gastralgia, and restlessness). Examine.com reports that the estimated No Observed Adverse Effect Level (NOAEL) for humans as extrapolated from dog studies would be 150mg/kg for 26 weeks, well above the doses used in clinical trials. There are also some case reports online that alpha-GPC may cause dizziness and hypotension in some individuals (link).

***Drug interactions***:
Drug interactions have not been reported. Although alpha-GPC is a choline supplement, evidence suggests it may be beneficial as an add-on therapy to Alzheimer's acetylcholine esterase inhibitors. The only reported drug interaction is with scopolamine (which reduces cholinergic transmission).

**Sources and dosing**:
Alpha-GPC is available in supplement stores and is a common ingredient added to nootropic stacks. The doses used in clinical trials for Alzheimer's patients was 1200mg/day.

**Research underway:**
One study is testing the effect of alpha-GPC with nimodipine versus nimodipine alone in patients with vascular cognitive impairment (NCT03228498). The study was recently completed, though no results have been published. An open-label trial in Alzheimer's patients is ongoing in Korea and is expected to be completed in the middle of 2020 (NCT03441516). One study is examining cognitive function in elderly diabetic patients. The trial was recently completed (NCT03249259). One study examined the physical and cognitive performance in volleyball players. The trial was completed in Decebmer 2016, though no results have been reported (NCT02886130).

**Search terms:**
alpha gpc + alzheimer, cognition, cardiovascular, lifespan, aging, cancer, neuropathy, hypotension, alphoscerate + alzheimer, cognition, memory, cardiovascular, lifespan, aging, cancer, neuropathy, hypotension

**Websites visited:**
- Clinicaltrials.gov
- Pubmed

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*If you have suggestions for drugs, drugs-in-development, supplements, nutraceuticals, or food/drink with neuroprotective properties that warrant in-depth reviews by ADDF's Aging and Alzheimer's Prevention Program, please contact INFO@alzdiscovery.org. To view our official ratings, visit Cognitive Vitality's Rating page.*