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.

Pantethine

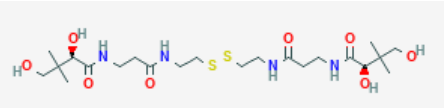
Evidence Summary

May reduce total and LDL cholesterol, though benefits are likely modest. Benefits for neuroprotection are likely limited due to pantethine's inability to cross the BBB.

Neuroprotective Benefit: The evidence is currently very limited to preclinical studies and benefits depend on many factors such as age or diet. Pantethine is not blood-brain-barrier penetrant.

Aging and related health concerns: Pantethine has reduced total and LDL cholesterol though effects have been modest. May also improve fatty liver disease.

Safety: Pantethine is generally well-tolerated but some patients have experienced diarrhea and elevated liver enzymes.

Availability: OTC.	**Dose:** Clinical trials (e.g., in people with cardiovascular disease risk) have tested pantethine treatment at 600 mg/day dose.	**Chemical formula:** $C_{22}H_{42}N_4O_8S_2$ **MW:** 554.7  Source: PubChem
Common/preferred brand: none		
Half life: not documented	**BBB:** not penetrant, but cysteamine (metabolite) is penetrant	
Clinical trials: The largest double-blind randomized controlled trial included 216 people with hyperlipidemia.	**Observational studies:** none	

What is it? Pantethine is synthesized in the body from 2 molecules of pantothenic acid (vitamin B5) linked by cysteamine. Pantethine acts as an intermediate and major precursor of coenzyme A, synthesized from pantothenic acid and cysteine. Coenzyme A is a cofactor in the metabolism of lipids and carbohydrates. Pantethine is available as a dietary supplement for lowering cholesterol and triglycerides (DrugBank). Although pantethine is considered the more biologically active form of vitamin B5, it is less stable than pantothenic acid and tends to degrade over time if it is not kept refrigerated (PubChem). Therefore, most vitamin B5 supplements are in the form of calcium pantothenate.

Neuroprotective Benefit: The evidence is currently very limited to preclinical studies and benefits depend on many factors such as age or diet. Pantethine is not blood-brain-barrier penetrant.

Types of evidence:

- A few laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?

None available.

Human research to suggest benefits to patients with dementia:

None available.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Alzheimer's models: In a mouse model of Alzheimer's disease (5xFAD mice), pantethine treatment (15 mg, i.p., 3 times per week) started at 1.5 months old and continued for 5.5 months significantly prevented behavioral impairment, reduced glial reactivity (80% and 40% reduction for GFAP and IBA1, respectively), and reduced Aβ deposition (by 85%) and Aβ-induced IL-1β release [1]. Pantethine treatment repressed many genes associated with inflammation (Aif1, Cd68, Tlr2, Tlr7, Cd14, Gfap, S100a6, Lyz, etc.), complement activation, and phagocytosis (C1qa, C1qb, C1qc, C4a, C4b, Csf1r, Trem2) that are overexpressed in 5xFAD mice. Pantethine also restored the expression of a significant number of genes involved in the regulation of Aβ processing and synaptic activities (Syn2, Gria2, Apba2, Appbp2, Grm5, Gpd2, Dgkg, Kcnma1, Nrxn1, Cacna2d1), which were downregulated in 5xFAD mice.

Although the above findings were compelling, the authors noted that when treatment was started in 4-month-old 5xFAD mice, pantethine treatment failed to show any protective benefits (data were not shown). None of the inflammation-associated genes (Aif1, Gfap, Cd68, Cd14, Lyz, Cyba, Grn, S100a6, Tyrobp, and Trem2) or genes encoding complement factors were altered by pantethine treatment.

In an astrocyte culture of 5xFAD mice, pantethine treatment reduced astrocyte reactivity and IL-1β mRNA and protein expression [2]. Pantethine treatment also increased levels of HIF-1α, which is known to reverse glial activation and glycolytic changes.

The precise mechanism of action of pantethine is unknown. It is possible that the effects observed in the young 5xFAD mice result from pantethine metabolites. Pantethine can be converted to its monomeric form (pantetheine), which is metabolized by pantetheinase to generate pantothenic acid (vitamin B5) and cysteamine. Cysteamine is known to have antioxidant effects and can cross the blood–brain-barrier and increase levels of the neurotrophic factor BDNF [3; 4]. Cysteamine is highly reactive and its oxidation leads to form cystamine, which in turn can activate Nrf2, a transcriptional factor involved in the anti-oxidant response both in cell cultures and in brain tissue [5]. Although cysteamine may appear attractive, it does cause many side effects (e.g., lethargy, vomiting, anorexia, diarrhea, etc.)(Drugs.com).

Pantothenate kinase-associated neurodegeneration model: Pantothenate kinase-associated neurodegeneration is caused by mutations in the PANK2 gene and is an autosomal recessive disorder characterized by dystonia, dysarthria, rigidity, pigmentary retinal degeneration and brain iron

accumulation. PANK2 codes for the mitochondrial enzyme pantothenate kinase type 2, which phosphorylates pantothenate (or vitamin B5) in the biosynthesis of coenzyme A. A Pank2 knockout (Pank2(-/-)) mouse model did not recapitulate the human disease but showed mitochondrial dysfunctions [6]. However, when these mice received a ketogenic diet, they developed a pantothenate kinase-associated neurodegeneration-like syndrome characterized by severe motor dysfunction, neurodegeneration and severely altered mitochondria in the central and peripheral nervous systems. These mice also showed structural alteration of muscle morphology. Pantethine treatment prevented the onset of the neuromuscular phenotype in mice and restored mitochondrial membrane potential and mitochondrial respiration in Pank2-/- neurons [6].

In a Drosophila fly model ("fumble") of pantothenate kinase-associated neurodegeneration, pantethine treatment led to the rescue of neurodegeneration and increase in lifespan [7].

APOE4 interactions: Unknown.

Aging and related health concerns: Pantethine has reduced total and LDL cholesterol though effects have been modest. May also improve fatty liver disease.

Types of evidence:

- 4 randomized controlled trials (hyperlipidemia and/or cardiovascular disease risk)
- 3 open-label studies
- Numerous laboratory studies

Hyperlipidemia: POTENTIAL BENEFIT. In a triple-blind placebo- and diet-controlled study in 120 people with low-to-moderate cardiovascular disease risk in the US, pantethine treatment (600 mg/day for the first 8 weeks, then 900 mg/day for the following 8 weeks) significantly decreased total cholesterol (by 6 mg/dL, 0.16 mmol/L, or 3% from baseline), LDL cholesterol (by 4 mg/dL, 0.10 mmol/L, or 4%), and apolipoprotein B (by 4 mg/dL, 0.04 g/L, or 5%)[8]. Pantethine supplementation significantly lowered these measures beyond the "therapeutic lifestyle change" diet alone. Although the absolute magnitudes of these effects were small (4-6 mg/dL), the results are noteworthy as prior studies have shown that, for each 1 mg/dL (0.026 mmol/L) reduction in LDL, there is a concomitant 1% reduction in overall future cardiovascular disease risk. Caveats include the limited pharmacokinetic data such as blood levels of pantethine during the course of treatment (600 or 900 mg) and that the optimal dosage requires further investigation.

In a small triple-blind placebo- and diet-controlled study in 32 people with low-to-moderate cardiovascular disease risk in the US, pantethine treatment (600 mg/day for the first 8 weeks, then 900 mg/day for the following 8 weeks) significantly decreased total cholesterol at 16 weeks (p=0.040) and LDL cholesterol at 8 and 16 weeks (p=0.020 and p=0.006, respectively) [9]. Non-HDL cholesterol was also significantly decreased by week 16 (p=0.042) in the pantethine group. An 11% decrease in LDL-C from baseline was seen in participants on pantethine, at weeks 4, 8, 12, and 16, while participants on placebo showed a 3% increase at week 16. Homocysteine levels did not change significantly from baseline to week 16 in either groups. This study showed that the Therapeutic Lifestyle Change (TLC) diet alone did not significantly affect lipid profiles but when combined with pantethine supplementation, significantly decreased lipid levels.

A few smaller older studies (from the 1980's) have reported similar results, though one study was an open-label study for which the full text was inaccessible [10] and the other study included people with different forms of hyperlipoproteinemia [11]. Both studies showed a reduction in total and LDL cholesterol levels.

In a double-blind randomized trial in 216 patients with hyperlipidemia, coenzyme A treatment (400 mg/day) and pantethine treatment (600 mg/day, taken 1 hour before meals) for 8 weeks were compared [12]. Pantethine, the stable disulfide form of pantetheine, is the major precursor of coenzyme A, which functions as an acyl group carrier and assists in transferring fatty acids from the cytoplasm to mitochondria. Pantethine significantly reduced triglyceride levels by 16.5%, but coenzyme A treatment showed greater reductions of triglyceride levels by 33.3%. Coenzyme A treatment also significantly decreased total cholesterol and non-HDL-cholesterol to a significantly greater extent than pantethine treatment, though no statistical differences were observed in the LDL cholesterol or HDL cholesterol between the pantethine and coenzyme A groups. In vivo studies have shown that insufficiency of coenzyme A influenced fatty acid β-oxidation and impaired clearance of triglycerides from the plasma [12].

Pantethine treatment has also decreased total serum cholesterol levels in rats fed a high fat diet [13].

Liver disease: POTENTIAL BENEFIT. In a small controlled trial of 32 patients with fatty liver and hypertriglyceridemia, 16 patients were treated with pantethine (600 mg/day) for 6 months or longer and 16 patients were untreated [14]. Nine of the 16 pantethine-treated patients were no longer diagnosed as having fatty liver after the study period. At the same time, the visceral fat calculated from the CT image was also significantly reduced. In contrast, the subcutaneous fat area tended to increase,

so the ratio of the visceral-to-subcutaneous fat area was reduced significantly. The authors speculated that triglycerides may be pooled in the body as hepato-visceral fat and subcutaneous fat, and that pantethine may promote transfer of fat from the liver and viscera to the subcutaneous tissue. Control patients, on the other hand, did not show any change in fatty liver or fat distribution over the 6 months.

In a small controlled trial of 16 patients with non-alcoholic steatohepatitis (NASH) and hyperlipidemia, a combination of pantethine (600 mg/day) and probucol (lipid-lowering antioxidant agent; 500 mg/day) for 48 weeks significantly reduced levels of liver enzymes (AST reduced from 66 to 33 IU/L, and ALT reduced from 113 to 51 IU/L, or by 58%) [15]. Total cholesterol level was also significantly decreased ($p<0.01$). Additionally, the mean serum TGF-β level was significantly decreased, while the mean serum level of high molecular adiponectin was increased. Other cytokines did not change significantly with this combination treatment. In 8 patients, liver biopsy was performed both before and after treatment; in 4 patients, inflammation was improved, and in 2 patients, fibrosis was improved. The mean non-alcoholic fatty liver disease (NAFLD) activity score also decreased from 6.6 ± 1.1 to 5.8 ± 1.2, but the difference was not statistically significant. Immunoreactive insulin, fasting blood sugar, mean BMI, and serum albumin levels did not change with treatment. While HOMA–IR showed a slight decrease after treatment, the change was not statistically significant.

Cytokines, oxidative stress, and lipid peroxidation are thought to play key roles in NASH. Although the precise mechanism of action is unclear, pantethine is thought to promote fatty acid oxidation in relation to choline metabolism and reduces serum triglyceride.

Cancer: POTENTIAL BENEFIT BASED ON RODENT MODELS. In a mouse model of ovarian tumor, pantethine treatment (750 mg/kg/day, i.p.) for 4 weeks resulted in slower tumor progression, decreased levels of phosphocholine and phosphatidylcholine, and reduced occurrences of metastases and ascites [16]. After 4 weeks of treatment, liver metastases occurred in 86% of control mice (6/7), but only in 43% of treated mice (2/7). Lung metastases occurred in 29% of control mice (2/7) and none in treated mice. Ascites occurred in 86% of control mice (6/7) and 29% of treated mice (2/7). Higher levels of caspase-3 (more than 3-fold) were measured in the treated tumors compared to control tumors. A significant decrease of phosphocholine in the treated tumors was also observed.

Pantethine inhibits fatty acid synthase (FAS), which synthesizes fatty acids using 4′-phospho-pantetheine, which acts as a universal mechanism of transport of intermediates [16]. High FAS activity is observed in most ovarian cancers and is strongly associated with high aggressiveness and poor

prognosis. Inhibition of FAS activity has been shown to be cytotoxic to human cancer cells *in vitro* and *in vivo* [17].

In a mouse model of lymphoma (NK/Ly lymphoma-bearing mice), D-pantethine treatment (500 mg/kg) for 30 days partially reduced the negative side effects (leukocytopenia and erythropenia) of doxorubicin (5 mg/kg) [18]. This increased animal survival time from 47-48 to 60+ days. D-pantethine exerted these effects via hepatoprotective and immunomodulating activities. D-pantethine also restored the levels of acid-soluble and free CoA in the liver of tumor-bearing animals. Both compounds decreased glutathione level in the liver, which was induced by doxorubicin. It is worth noting that D-pantethine treatment failed to improve outcomes in mice treated with higher doses of doxorubicin (10 mg/kg), which by itself cured 100% animals with NK/Ly lymphoma (survival >60 days). D-pantethine treatment failed to increase survival of animals treated with high dose doxorubicin and only 33% of the mice survived longer than 60 days.

Cataract: UNKNOWN. In a review on drugs for cataract prevention, pantethine was discussed on the basis of its ability to lower the phase separation temperature of γ-crystallin, which in turn enhances the efficacy of the lens molecular chaperone, α-crystallin [19]. Pantethine has shown preventive effects in several animal models of cataract, though many showed benefit when pantethine was administered before the cataractogenic agent, or within a limited timeframe after the insult.

Eventually pantethine eye drops were tested in a clinical trial and the subjects were patients who had undergone vitrectomy; these patients were chosen because they develop cataract within 12 to 18 months of surgery [19]. Unfortunately, the trial had to be stopped because the eye drops irritated the eyes of patients who had undergone vitrectomy. It is possible that the vitrectomy procedure had sensitized the eyes. It is also unknown whether necessary levels of pantethine could reach the lens following topical application.

Lifespan: UNKNOWN. No studies have examined whether pantethine treatment may increase lifespan in people. A mouse model of pantothenate kinase-associated neurodegeneration (Pank2 -/- mice) fed a ketogenic diet died after 2 months, but when pantethine was administered (15 mg/kg/day in drinking water), the mice survived for up to 5 months [6]. Similarly, a Drosophila fly model ("fumble") of PANK also had prolonged lifespan with pantethine treatment [7].

Safety: Pantethine is generally well-tolerated but some patients have experienced diarrhea and elevated liver enzymes.

Types of evidence:

- 3 randomized controlled trials (hyperlipidemia and cardiovascular disease risk)
- 2 open-label studies
- A few laboratory studies

Pantethine was generally well-tolerated and incidences and types of adverse events were similar to people taking the placebo [8; 9].

Clinical trials: In a triple-blind placebo- and diet-controlled study of 120 people with low-to-moderate cardiovascular disease risk in the US that tested the efficacy of pantethine treatment (600 mg/day for the first 8 weeks, then 900 mg/day for the following 8 weeks), a total of 14 symptoms were experienced by 12 subjects in the placebo group, and a total of 9 symptoms were experienced by 8 subjects in the pantethine group [8]. A single and resolved episode of neutropenia was found in a placebo subject. Headache was reported twice in placebo subjects and not reported in any of the pantethine subjects. Bloating, heartburn, nausea, loose stools, and upset stomach was reported 8 times in the placebo group and 8 times in the pantethine group. Loose stools accounted for only 1 of these symptoms in the placebo group but 6 times in the pantethine group. All but 1 subject reporting loose stools/diarrhea regardless of treatment arm recovered spontaneously and remained in the study. One subject in the pantethine group reported severe symptoms and was withdrawn from the study.

In a small triple-blind placebo- and diet-controlled study in 32 people with low-to-moderate cardiovascular disease risk in the US, pantethine treatment (600 mg/day for the first 8 weeks, then 900 mg/day for the following 8 weeks) did not result in statistical differences in blood pressure, heart rate, waist circumference, or body mass index (BMI) compared to the placebo group [9]. The biochemistry and clinical chemistry of the participants showed there were no clinically relevant differences between the participants in the pantethine and placebo groups. A total of 1 symptom was recorded in one participant in the placebo group. A total of 2 symptoms (diarrhea and flatulence) were reported by participants on pantethine. The diarrhea was moderate in intensity, experienced for 3 days during the 600 mg/day dosage period, and did not recur when the dosage was escalated. The flatulence reported by 1 participant was experienced during both dosage periods, was mild in intensity, and resolved prior to the end of the study. A single mild episode of neutropenia was found in a participant on placebo.

In a double-blind randomized trial in 216 patients with hyperlipidemia, coenzyme A treatment (400 mg/day) and pantethine treatment (600 mg/day, taken 1 hour before meals) for 8 weeks were compared [12]. They found no significant differences in any of the indices for liver and kidney function after either 4 or 8 weeks of treatment compared with baseline (P>0.05). No difference was observed in the incidence of myopathy or gastrointestinal (GI) tract symptoms after either 4 or 8 weeks compared with baseline (P>0.05) or between the 2 groups. In the pantethine group, the most common adverse events were elevated ALT and AST and GI tract symptoms, but none of these differed significantly between the pantethine and coenzyme A groups.

Preclinical studies: In a mouse model of ovarian tumors, pantethine treatment (750 mg/kg/day, i.p., in saline) for 4 weeks did not result in any observable side effects or weight loss [16]. Blood analysis performed at the end of the treatment period revealed neither hepatic nor renal toxicity, as shown by the absence of significant differences in the levels of BUN, creatinine, AST, and ALT between control and pantethine-treated mice. Pantethine was rapidly eliminated into the urine.

Drug interactions: Drug interactions with pantethine are not well-documented.

Sources and dosing: Pantethine is available over-the-counter in capsule and tablet forms. Clinical trials (e.g., in people with cardiovascular disease risk) have tested pantethine treatment at a dose of 600 mg/day [8; 9; 12].

Research underway: No clinical trials testing pantethine are currently underway based on ClinicalTrials.gov.

Search terms:
Pubmed, Google: pantethine

- + cognitive, + APOE, + Alzheimer, + clinical trial, + lifespan, + mortality

Websites visited for pantethine:

- Clinicaltrials.gov
- Examine.com
- DrugAge (0)
- Geroprotectors (0)
- Drugs.com
- WebMD.com (0)

- PubChem
- DrugBank.ca
- Labdoor.com (0)
- ConsumerLab.com (0)
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- Pharmapro.com (0)

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