



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.

Benfotiamine

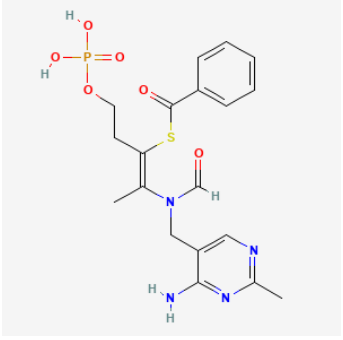
Evidence Summary

Benfotiamine appears to be safe and may protect cognitive, peripheral nerve, and vascular functions. It is generally well-tolerated at standard doses.

Neuroprotective Benefit: Benfotiamine showed a trend for slowing cognitive decline in MCI/AD while also decreasing levels of AGEs. Benefits may depend on APOE genotype.

Aging and related health concerns: Some clinical and preclinical studies suggest that benfotiamine provides some relief in diabetic peripheral neuropathy and promotes vascular function.

Safety: Benfotiamine treatment is generally well-tolerated, but due to the long elimination half-life, thiamine moderately accumulates with chronic dosing. Adverse events are generally mild and include increased liver enzymes and urinary white blood cells.

<p>Availability: OTC</p>	<p>Dose: The phase 2a clinical trial in MCI and mild Alzheimer's disease tested a benfotiamine dose of 300 mg twice daily.</p>	<p>Chemical formula: C₁₉H₂₃N₄O₆PS</p> <p>MW: 466.4</p>  <p>Source: PubChem</p>
<p>Half-life: elimination half-life of 6-14 hours</p>	<p>BBB: penetrance not directly tested in humans</p>	
<p>Clinical trials: The phase 2a trial in MCI and mild Alzheimer's included a total of 70 patients.</p>	<p>Observational studies: none available</p>	

What is it? Benfotiamine is a synthetic derivative of thiamine (vitamin B1). Thiamine is critical for glucose metabolism because its active form (thiamine diphosphate) serves as a key coenzyme for 3 enzymes involved in glucose metabolism (transketolase, pyruvate dehydrogenase, and α -ketoglutarate dehydrogenase) [1]. Thiamine is a water-soluble compound that does not penetrate the cell membranes well. Benfotiamine is not lipophilic itself, but after oral administration, it is rapidly dephosphorylated in the small intestine, yielding S-benzoylthiamine, which is a lipophilic metabolite that enters cells more easily, reaching the blood stream, and maintaining the active form of thiamine for a long period [2]. Thiamine absorption from benfotiamine is five times greater than traditional thiamine supplements [3]. Benfotiamine has been used in people with diabetes to treat peripheral neuropathies and damage to kidneys.

Benfotiamine is used as a treatment option for alcoholic neuropathy, sciatica, and other painful nerve disorders in alternative medicine [4].



Neuroprotective Benefit: Benfotiamine showed a trend for slowing cognitive decline in MCI/AD while also decreasing levels of AGEs. Benefits may depend on APOE genotype.

Types of evidence:

- 1 phase 2a randomized controlled trial in mild cognitive impairment and mild Alzheimer's
- 1 metabolomic and lipidomic analysis in the above phase 2a trial
- 1 open-label uncontrolled study
- 6 laboratory studies
- 2 reviews

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: One open-label, uncontrolled study in 5 mild-to-moderate Alzheimer's patients showed that oral benfotiamine treatment (300 mg/day) for 18 months resulted in an average increase of 3.2 points on the Mini-Mental State Examination (MMSE) [5]. All patients were A β -positive at baseline and 3 out of 5 received follow-up A β PET scan, which showed that they had a 36.7% increase in A β levels after 18 months of treatment. Thus the improvement on the MMSE scores was not due to reduction of brain amyloid accumulation.

In a phase 2a randomized controlled trial in 70 people with mild cognitive impairment (MCI) or mild Alzheimer's disease, benfotiamine treatment (300 mg, twice daily; manufactured by Advanced Orthomolecular Research, Canada) for 12 months showed a trend for a slowing of cognitive decline, the primary endpoint [6]. Cognitive decline, measured by the increase in ADAS-Cog, was 43% less in the benfotiamine-treated group than in the placebo group, though this difference did not reach statistical significance ($p=0.125$). Numerically, at 12 months, the change in ADAS-Cog was 3.26 in the placebo group while it was 1.39 in the benfotiamine group. Differences were not seen at 3, 6, or 9 months of treatment. A post-hoc analysis suggested that benfotiamine had a greater response for people with higher cognitive function at baseline (MMSE at or above 26; $p=0.027$), whereas the treatment effect was not statistically significant for people with MMSE score under 26 ($p=0.99$).

Worsening in the Clinical Dementia Rating (CDR) was also 77% less in the benfotiamine-treated group compared to the placebo group, which was statistically significant ($p=0.034$) [6]. The change from baseline in placebo group was 0.22, whereas it was 0.05 in the benfotiamine-treated group. For

individual CDR subscores, the “home and hobbies score” was significantly different between benfotiamine and placebo groups ($p=0.032$), but other subscores were not significantly different.

No treatment effects were observed with verbal memory, as measured by the Buschke Selective Reminding Test, though the benfotiamine-treated group appeared to show more stable performance across time compared to the downward trend in the placebo-treated group [6].

Advanced glycation end products (AGEs), which are toxic protein modifications indicative of altered glucose metabolism and aging, increase in levels in the brain of Alzheimer’s patients [7]. Benfotiamine treatment significantly reduced the increase in AGEs ($p=0.044$), and this effect was stronger in APOE4 non-carriers compared to APOE4 carriers [6].

Benfotiamine treatment showed a 161-fold increase in blood thiamine levels above baseline (from 6.2 to 999 nmol/L), though there were large variations across individuals [6]. However, the blood levels of thiamine, thiamine diphosphate (active form of thiamine), and thiamine monophosphate after benfotiamine treatment did not correlate with improvement in cognitive scores or CDR ($p>0.05$ for all).

Cerebral glucose metabolism was measured using FDG-PET, but there were no differences between benfotiamine and placebo groups in the prespecified brain regions of interest [6].

Because some of the secondary endpoints and subgroup analyses were underpowered and were not corrected for multiple comparisons, a larger confirmatory trial is needed to validate these preliminary findings.

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

Benfotiamine likely exerts neuroprotective effects through multiple mechanisms. Benfotiamine has direct actions on metabolic enzymes and pathways while also exhibiting antioxidant and anti-inflammatory effects [2; 6]. Benfotiamine exerts pharmacological effects that are not completely replicated by high-dose thiamine treatment, suggesting that benfotiamine may produce distinct metabolites that act pleiotropically.

In a metabolomic and lipidomic study of the phase 2a trial in MCI and mild Alzheimer’s disease, benfotiamine treatment significantly altered metabolites involved in glucose metabolism and biosynthesis of aromatic amino acids [8]. Twenty-five metabolites showed statistically significant differences, including thiamine, tyrosine, tryptophan, lysine, and many lipid species, mostly belonging to



phosphatidylcholines. Interestingly, 10 out of 11 metabolites and 14 out of 15 lipid species showed directional changes with benfotiamine that were in the opposite direction to those reported in Alzheimer's disease progression.

In a mouse model of Alzheimer's (APP/PS1 mice), benfotiamine treatment (100-200 mg/kg/day) for 8 weeks enhanced spatial memory and reduced both amyloid plaque numbers and phosphorylated tau levels [9]. These benefits may be mediated by the ability of benfotiamine to significantly suppress the activity of GSK3, an enzyme that phosphorylates tau. Interestingly, this effect on GSK3 was not seen with other thiamine derivatives in this study. Benfotiamine also improved learning and other cognitive functions in a mouse model of stress [10]. The antidepressant/anti-stress effects of thiamine and benfotiamine were also attributed to reduced GSK-3 β levels. Similarly, in a cell culture system modeling Alzheimer's disease, benfotiamine significantly reduced A β levels and GSK-3 activity [11].

In a mouse model of tauopathy, benfotiamine treatment (200 mg/kg/day, contained in diet) improved behavior, increased lifespan by 21% (from 322 days to 390 days), reduced glycosylated tau and neurofibrillary tangles, and prevented the death of motor neurons [12]. Benfotiamine treatment also improved mitochondrial function and attenuated oxidative stress (decreased 3-NT and 4-HNE) and inflammation (iNOS, COX-2, TNF- α , IL-1 β , NF-kB). Antioxidant effects of benfotiamine were exerted through the activation of the Nrf2/ARE pathway.

The data are mixed in terms of the blood-brain-barrier penetrance of benfotiamine, though a few studies suggest benfotiamine does get into the brain. Although one study reported that oral benfotiamine treatment in mice did not increase thiamine levels in the brain, this was likely due to the small sample size and large error bars [13]. The mean brain thiamine level after benfotiamine treatment was at least 3-fold higher than the mean thiamine level for control. In a different study in Alzheimer's mice, benfotiamine treatment significantly increased thiamine levels in the brain [9]. In the most recent study in a rat model of sporadic Alzheimer's (induced by intracerebroventricular injection of streptozotocin), benfotiamine treatment (150 mg/kg) for 30 days significantly increased the concentrations of thiamine diphosphate in the hippocampus and entorhinal cortex while improving cognitive deficits [14]. This was accompanied by improved mitochondrial enzymes and insulin signaling, decreased inflammation, and increased GluN2B subunit of glutamate NMDA receptors.

In a mouse model of memory impairment (induced by streptozotocin), co-administration of benfotiamine (100 mg/kg) and citicoline (50, 100, and 250 mg/kg) for 3 weeks significantly improved learning and memory as measured by the passive avoidance test, more than either treatment alone

[15]. Although both benfotiamine and citicoline treatments improved object recognition memory, the effects of a combination therapy were not significantly greater than either treatment alone.

APOE4 interactions: In a phase 2a randomized controlled trial in 70 people with mild cognitive impairment (MCI) or mild Alzheimer's disease, benfotiamine treatment (300 mg, twice daily; manufactured by Advanced Orthomolecular Research, Canada) for 12 months appeared to benefit APOE4 non-carriers more than APOE4 carriers [6]. Benfotiamine treatment slowed the worsening of the Clinical Dementia Rating (CDR) score compared to the placebo group ($p=0.034$), and this effect was stronger in the APOE4 non-carriers than APOE4 carriers. Benfotiamine treatment also significantly reduced levels of AGEs ($p = 0.044$), and this effect was stronger in the APOE4 non-carriers compared to APOE4 carriers. The reasons for the differences by APOE genotype are currently unknown. It is worth noting that for other measures, such as ADAS-Cog, there were no significant differences by APOE genotype.

Aging and related health concerns: Some clinical and preclinical studies suggest that benfotiamine provides some relief in diabetic peripheral neuropathy and promotes vascular function.

Types of evidence:

- 1 meta-analysis examining vitamin B or its derivatives in diabetic kidney disease
- 9 randomized clinical trials: 3 in diabetes, 3 in diabetic polyneuropathy, 1 in diabetic nephropathy, 1 in alcoholic polyneuropathy, and 1 in smokers
- 1 case study in type 1 diabetes with acute neuropathy
- 7 reviews
- Numerous laboratory studies

Peripheral neuropathy: BENEFIT.

In a double-blind randomized controlled trial of 165 patients with diabetic polyneuropathy, those receiving benfotiamine treatment (600 mg/day) for 6 weeks had better neuropathy symptom score compared to those receiving placebo [16]. Although the total symptom score (combined scores for pain, numbness, burning, and paresthesia) was not significantly different in the treatment groups compared to placebo, the group receiving 600 mg improved the most compared to other groups and also compared to baseline. The best improvement was found for pain, followed by numbness, burning, and paresthesia (tingling/prickling sensation). Two other smaller studies also reported significant



improvement with benfotiamine treatment in symptoms of diabetic polyneuropathy [17] and alcoholic polyneuropathy [18].

One double-blind randomized controlled trial in type 1 diabetics failed to show significant improvement in peripheral nerve function with 2 years of benfotiamine treatment (300 mg/day) [19], though a commentary on this study noted that the study design was questionable as the patients had almost normal nerve function, leaving no room for a meaningful improvement [20].

In a 12-year-old girl with type 1 diabetes and acute painful neuropathy, a combination therapy of benfotiamine, carbamazepine (anticonvulsant and analgesic), and NSAID for 9 months resulted in complete recovery [21].

Although some clinical trials have shown benefit with benfotiamine, clinical guidelines for painful diabetic neuropathy do not include benfotiamine [22]. Recommendations are atypical analgesics for pain relief, including duloxetine and amitriptyline; γ -aminobutyric acid (GABA) analogues gabapentin and pregabalin; opioids, including Tapentadol; and topical agents such as lidocaine and capsaicin. No single effective treatment exists for painful diabetic peripheral neuropathy. A number of novel potential candidates, including erythropoietin analogues and angiotensin II type 2 receptor antagonists are currently being evaluated in phase II clinical trials.

A double-blind randomized controlled trial of 22 subjects with diabetic sensorimotor polyneuropathy testing the efficacy of benfotiamine treatment (600 mg/day for 3 months, followed by 300 mg/day) for 12 months was prematurely terminated due to “technical reasons” [23]. After 6 months of treatment, the benfotiamine-treated group showed reduced neuropathic symptoms compared to the placebo group ($p=0.036$), though this trend was not significant at 12 months ($p=0.17$), possibly due to the smaller sample size at 12 months compared to 6 months.

Recent international expert consensus recommendations on diabetic sensorimotor polyneuropathy noted that benfotiamine is licensed as a drug and approved for treatment in several countries worldwide, though additional long-term randomized controlled trials could further strengthen the evidence and rationale for use in clinical practice [24]. To date, there have not been any head-to-head clinical trials that compared benfotiamine treatment with first-line treatments for diabetic polyneuropathy [4].



Mechanisms of action for polyneuropathy, as well as effective treatments, may be different depending on the type of polyneuropathy. In rodent models of diabetic and non-diabetic neuropathic pain, benfotiamine reduces inflammatory and neuropathic pain [25]. In culture systems, benfotiamine suppresses the activation of microglia and decreases the production of pro-inflammatory mediators [26; 27], which in turn may prevent damage to neighboring neurons.

Vascular function: MIXED.

In a small randomized controlled trial of 20 healthy smokers, benfotiamine pretreatment (1050 mg/day) for 3 days before smoking a cigarette was associated with protection of vascular function [28]. Benfotiamine partly prevented the reduction in vascular blood flow and the elevation of an inflammatory marker (sVCAM-1). Also, in a small clinical study including 13 patients with type 2 diabetes, benfotiamine prevented the micro- and macrovascular dysfunction induced by eating a meal rich in advanced glycation endproducts (AGEs) [29]. However, a larger randomized controlled trial of 82 patients with diabetic nephropathy showed that benfotiamine treatment (300 mg, 3 times per day) for 12 weeks did not significantly change markers of endothelial functions, including sVCAM-1 [30].

While the evidence is mixed, potential mechanisms of action of benfotiamine include reduction of endogenous AGEs and dicarbonyls production as well as reduction of oxidative stress [29]. In diabetic mice, benfotiamine improved diastolic and systolic function and cardiac perfusion, while reducing cardiomyocyte apoptosis and interstitial fibrosis [31]. In diabetic mice with ischemic limbs, benfotiamine improves healing through stimulation of reparative angiogenesis and inhibition of endothelial cell apoptosis, and these therapeutic effects are mediated by activation of protein kinase B and Akt [32]. Benfotiamine also restores endothelial progenitor cells that are lost with diabetes. Because much of the clinical and preclinical studies were on diabetes, it is unknown how or whether benfotiamine influences vascular function in healthy adults.

Inflammation: NO BENEFIT.

In a double-blind randomized controlled trial in type 1 diabetics, benfotiamine treatment (300 mg/day) for 2 years failed to show significant effects on inflammatory biomarkers [19]. A randomized controlled trial of 82 patients with diabetic nephropathy also reported that benfotiamine treatment did not significantly change inflammation markers [30].

In preclinical studies, benfotiamine appears to exert anti-inflammatory effects. In microglia cultures, benfotiamine decreases microglia activation and levels of reactive oxygen species, lipid peroxidation, and pro-inflammatory markers (e.g., TNF- α , IL-6, COX-2, etc), while enhancing anti-inflammatory

markers [26; 27]. A study in a macrophage culture also suggests that benfotiamine exerts anti-inflammatory effects peripherally; benfotiamine blocked COX-2 and lipoxygenase (LOX)-5 among other enzymes and prevented macrophage death and monocyte adhesion to endothelial cells [33].

AGEs: MIXED.

A randomized controlled trial of 82 patients with diabetic nephropathy showed that benfotiamine treatment (300 mg, 3 times per day) for 12 weeks did not significantly reduce plasma or urinary levels of AGEs [30]. However, in a small clinical study in patients with type 2 diabetes, benfotiamine prevented the increase in AGE levels induced by an AGE-rich meal [29]. In a rodent model of diabetes with ischemic limbs, benfotiamine prevents vascular accumulation of AGE products [32].

Safety: Benfotiamine treatment is generally well-tolerated, but due to the long elimination half-life, thiamine moderately accumulates with chronic dosing. Adverse events are generally mild and include increased liver enzymes and urinary white blood cells.

Types of evidence:

- 1 meta-analysis testing vitamin B or its derivatives in patients with diabetic kidney disease
- 5 randomized clinical trials: 1 in patients with MCI/AD, 1 in patients with diabetes, 2 in diabetic polyneuropathy, and 1 in alcoholic polyneuropathy
- 1 double-blind randomized controlled phase 1 study in healthy subjects
- A few laboratory studies

The largest randomized controlled trial testing benfotiamine was for diabetic polyneuropathy and included 165 patients [16]. This trial reported that treatment (300 or 600 mg/day) for 6 weeks was well-tolerated in all patients and no clinically relevant changes were noted in fasting glucose, laboratory values, blood pressure, heart rate, or urine chemistry. The only treatment-related side effects were slight gastrointestinal issues (6 patients) and skin/allergic reactions (2 patients). Numbers of patients experiencing adverse events were similar across placebo and the two treatment groups. Other randomized controlled trials in patients with diabetes [34], diabetic polyneuropathy [17], and alcoholic polyneuropathy [18] also reported that benfotiamine was well-tolerated and no serious adverse effects were seen. A meta-analysis that examined treatment with vitamin B or its derivatives in diabetic kidney disease also reported that vitamin B therapy (monotherapy or combination) was well-tolerated with mild side effects in studies lasting over 6 months [35].



In a phase 2a randomized controlled trial in 70 people with MCI or mild Alzheimer's disease, benfotiamine treatment (300 mg, twice daily) for 12 months did not result in any subjects withdrawing from the study [6]. No adverse events were observed in patients receiving benfotiamine.

In a phase 1 double-blind randomized controlled trial testing the safety and tolerability of single- and multiple-ascending doses of benfotiamine in 28 healthy Chinese subjects, the incidence and severity of adverse events were similar between benfotiamine and placebo [36]. Benfotiamine was generally safe and well-tolerated over the dose range tested (150, 300, 600, 900, or 1200 mg for the single-ascending dose study; 150, 300, and 600 mg for multiple-ascending dose study). Commonly reported treatment-related adverse events were increased liver enzyme (ALT; 4% of subjects receiving benfotiamine, 10% of subjects receiving placebo) and urinary white blood cells (4% of subjects receiving benfotiamine). Twelve subject reported adverse events that were considered to be drug-related, including 9 out of 50 (18%) receiving benfotiamine and 3 out of 10 (30%) receiving placebo.

Following multiple doses, 17 out of 48 subjects (35%) reported a total of 23 adverse events: 150 mg (4/12), 300 mg (5/12), 600 mg (3/12) benfotiamine, and placebo (5/12). The most frequently reported drug-related adverse event was increased blood pressure, reported by 3% (1 out of 36) of subjects who received benfotiamine and 25% (3 out of 12) of subjects who received the placebo treatment. Sinus bradycardia and urinary red blood cells were reported by 3 (8%) and 2 (6%) out of 36 subjects who received benfotiamine, respectively. Increased pulse rate, increased white blood cells, urinary white blood cells, proteinuria, and increased ALT were each reported in 1 (3%) of 36 subjects who received benfotiamine. All reported adverse events were mild or moderate in severity. There were no serious adverse events.

With repeated administration of benfotiamine, thiamine and thiamine diphosphate exhibited moderate accumulation due to the long elimination half-life. For thiamine, accumulation ratio was 1.60 to 1.88 following 7 days of multiple dosing.

Drug interactions: Drug interactions with benfotiamine are unknown. Because benfotiamine gets converted to thiamine, and thiamine may cause low blood pressure or low blood glucose, people taking drugs to lower blood pressure or blood glucose should exercise caution [37].

Sources and dosing: Benfotiamine supplements are available commercially, often in capsules containing 150-300 mg. No studies have directly compared products of different brands. The open-label trial that showed cognitive improvement in Alzheimer's disease patients used a dose of 300 mg per day [5]. Most



studies in clinical populations used doses ranging from 200-600 mg/day [16; 17; 19], though higher doses of 1050 mg/day have been used in short-term studies (a few days) in diabetics and smokers [28; 29].

Research underway: A randomized double-blind placebo-controlled trial in Germany is testing the effects of benfotiamine on clinical measures in patients with type 2 diabetes with symptomatic polyneuropathy [38]. Patients will be treated with benfotiamine (300 mg, twice daily) or placebo for 12 months. The primary outcome is the change in corneal nerve fiber length, and the secondary outcomes include skin biopsy, function indices, somatic and autonomic nerve function tests, and other variables.

Search terms:

Pubmed, Google: benfotiamine or thiamine

- + cognitive, + meta-analysis, + clinical trial, + safety, + neuropathy, + lifespan

Clinicaltrials.gov, DrugAge: benfotiamine

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