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, though much of the evidence comes from people with diabetes.

Neuroprotective Benefit: Benfotiamine may be neuroprotective, though the evidence is based on a small open-label study and a few preclinical models.

Aging and related health concerns: Some clinical and preclinical studies suggest that benfotiamine protects from peripheral neuropathy and promotes vascular function.

Safety: Benfotiamine treatment is generally regarded as safe for most people when taken at standard doses, but long-term studies are lacking.

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, whereas benfotiamine enters cells more easily and maintains the active form of thiamine for longer periods. Thiamine absorption from benfotiamine is five times greater than traditional thiamine supplements [2]. Benfotiamine has been used in people with diabetes to treat peripheral neuropathies and damage to kidneys.

Neuroprotective Benefit: Benfotiamine may be neuroprotective, though the evidence is based on a small open-label study and a few preclinical models.

Types of evidence:

- 1 open-label uncontrolled study
- 3 laboratory studies
- 1 review

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) [3]. All patients were Aβ-positive at baseline and 3 out of 5 received follow-up Aβ PET scan, which showed that they had a 36.7% increase in Aβ levels after 18 months of treatment. Thus the improvement on the MMSE scores was not due to reduction of brain amyloid accumulation.

Mechanisms of action for neuroprotection identified from laboratory and clinical research. In a mouse model of Alzheimer's (APP/PS1 mice), benfotiamine treatment for 8 weeks enhanced spatial memory and reduced both amyloid plaque numbers and phosphorylated tau levels [4]. 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 [5]. The antidepressant/anti-stress effects of thiamine and benfotiamine were also attributed to

reduced GSK-3β levels. Similarly, in a cell culture system modeling Alzheimer's disease, benfotiamine significantly reduced Aβ levels and GSK-3 activity [6].

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 [7]. The mean brain thiamine level after benfotiamine treatment was at least 3-fold higher than the mean thiamine level for control. Also, a more recent study in Alzheimer's mice showed that benfotiamine treatment significantly increased thiamine levels in the brain [4].

APOE4 interactions: Unknown.

Aging and related health concerns: Some clinical and preclinical studies suggest that benfotiamine protects from peripheral neuropathy and promotes vascular function**.**

Types of evidence:

- 1 meta-analysis examining vitamin B or its derivatives in diabetic kidney disease
- 8 randomized clinical trials: 3 in diabetes, 2 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
- 3 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 [8]. 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 [9] and alcoholic polyneuropathy [10].

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) [11], 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 [12].

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 [13].

Although some clinical trials have shown benefit with benfotiamine, clinical guidelines for painful diabetic neuropathy do not include benfotiamine [14]. 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.

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 [15]. In culture systems, benfotiamine suppresses the activation of microglia and decreases the production of pro-inflammatory mediators [16; 17], 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 [18]. 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) [19]. 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 [20].

While the evidence is mixed, potential mechanisms of action of benfotiamine include reduction of endogenous AGEs and dicarbonyl production as well as reduction of oxidative stress [19]. In diabetic mice, benfotiamine improved diastolic and systolic function and cardiac perfusion, while reducing cardiomyocyte apoptosis and interstitial fibrosis [21]. In diabetic mice with ischemic limbs, benfotiamine improved healing through stimulation of reparative angiogensis and inhibition of endothelial cell

apoptosis, and these therapeutic effects were mediated by activation of protein kinase B and Akt [22]. Benfotiamine also restored 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 [11]. A randomized controlled trial of 82 patients with diabetic nephropathy also reported that benfotiamine treatment did not significantly change inflammation markers [20].

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 [16; 17]. 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 [23].

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 [20]. 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 [19]. In a rodent model of diabetes with ischemic limbs, benfotiamine prevented vascular accumulation of AGE products [22].

Safety: Benfotiamine treatment is generally regarded as safe for most people when taken at standard doses, but long-term studies are lacking.

Types of evidence:

- 1 meta-analysis testing vitamin B or its derivatives in patients with diabetic kidney disease
- 4 randomized clinical trials: 1 in patients with diabetes, 2 in diabetic polyneuropathy, and 1 in alcoholic polyneuropathy
- A few laboratory studies

Details. The largest randomized controlled trial testing benfotiamine was for diabetic polyneuropathy and included 165 patients [8]. 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 [24], diabetic polyneuropathy [9], and alcoholic polyneuropathy [10] 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 [25].

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 [26].

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 [3]. Most studies in clinical populations used doses ranging from 200-600 mg/day [8; 9; 11], though higher doses of 1050 mg/day have been used in short-term studies (a few days) in diabetics and smokers [18; 19].

Research underway: A phase II clinical trial is testing the effects of benfotiamine in patients with mild cognitive impairment or mild Alzheimer's disease (NCT02292238). ADDF is funding this trial led by Dr. Gary Gibson at the Burke Medical Research Institute in NY. It is scheduled to be completed in late 2018. Another clinical trial is testing the effects of benfotiamine on advanced glycation end products (AGEs) in patients with type 2 diabetes (NCT02772926).

Search terms:
Pubmed, Google: benfotiamine or thiamine

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

Clinicaltrials.gov, DrugAge: benfotiamine

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