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.

Homotaurine (Tramiprosate)

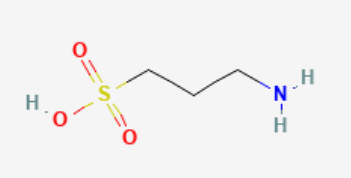
Evidence Summary

Although homotaurine failed in phase 3 clinical trials, some benefits were observed in ApoE4 carriers. ALZ-801, a prodrug with improved pharmacokinetics, tolerability, and stability, is in clinical trials.

Neuroprotective Benefit: The phase 3 clinical trials in Alzheimer's disease patients failed to show a benefit with homotaurine, but a sub-group analysis in ApoE4 homozygotes showed cognitive benefit.

Aging and related health concerns: No studies have evaluated homotaurine for age-related diseases other than neurodegenerative diseases.

Safety: Homotaurine is associated with a number of mild side effects, mostly gastrointestinal in nature, such as nausea, vomiting, and decreased weight.

Availability: OTC	**Dose**: In clinical studies, doses of 150 mg twice per day were used.	**Chemical formula:** $C_3H_9NO_3S$ **MW**: 139.18
Half-life: 4-6 hours	**BBB**: penetrant	 Source: PubChem
Clinical trials: The two phase 3 trials enrolled a total of 2,025 patients with Alzheimer's disease.	**Observational studies**: none available	

What is it?

Homotaurine (tramiprosate) was discovered in a screen for small molecules that inhibit amyloid beta aggregation. It is structurally similar to taurine except that it has an extra carbon. Homotaurine binds to soluble amyloid, leading to stabilization of Aβ42 monomers and inhibition of oligomeric and fibrillar amyloid aggregation (reviewed in Manzano et al., 2020). In addition to its actions against Aβ, homotaurine exerts anti-inflammatory effects and acts as a GABA receptor agonist.

Homotaurine was the first phase 3 study to test the 'amyloid hypothesis'. Although homotaurine failed in phase 3 clinical trials, a subgroup analysis showed that it stabilized cognition in ApoE4 carriers.

Neuroprotective Benefit*:* The phase 3 clinical trials in Alzheimer's disease patients failed to show a benefit with homotaurine, but a sub-group analysis in ApoE4 homozygotes showed cognitive benefit.

Types of evidence:

- 2 clinical trials (one phase 2 and one phase 3 study)
- Several open-label clinical studies in amnestic mild cognitive impairment
- A few laboratory studies

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

In a small open-label clinical study of 33 people with amnestic mild cognitive impairment (MCI), 11 were treated with homotaurine (50 mg daily for 2 weeks, then twice daily for the next year) for 1 year while

the remaining 22 people were untreated (Spalletta et al., 2016). Patients treated with homotaurine for 1 year showed improvement in episodic memory, as measured by the Rey 15-word list learning test immediate recall, while the untreated patients showed decreased performance. However, this difference was only observed for words appearing at the end of the 15-word list (recency effect), and not the beginning or middle (primacy and intermediate, respectively). Patients treated with homotaurine also showed less volume loss in the left and right hippocampal tail, left and right fusiform gyrus, and right inferior temporal cortex. Because this was an observational study with no placebo control group, placebo effects cannot be excluded.

A related study by the same research group reported that homotaurine supplementation (50 mg daily for 2 weeks, then twice daily for the next year) for 1 year in amnestic MCI patients significantly reduced serum levels of the proinflammatory cytokine IL-18 (total and IL-18BP unbound forms) in APOE4 carriers, though no significant differences were seen in other proinflammatory cytokines (IL-1β, TNF-α, IL-6 and TGFβ) in APOE4 carriers or noncarriers (Bossu et al., 2018).

In a more recent study by the same research group, homotaurine treatment (50 mg daily for 2 weeks, then twice daily for the next year) for 1 year in 14 amnestic MCI patients resulted in increased serum levels of the anti-inflammatory cytokines, IL-10 and IL-33 (Toppi et al., 2022). The increases in IL-10 and IL-33 were associated with an improvement in episodic memory, as measured by the delayed verbal Rey's test.

Human research to suggest benefits to patients with dementia:

In a double-blind randomized controlled phase 2 study of 58 mild to moderate Alzheimer's patients, homotaurine treatment (100 or 150 mg BID) for 3 months showed a dose dependent decrease in CSF Aβ42 (up to 70% reduction from baseline in the 150 mg group)(Aisen et al, 2006). This is odd considering homotaurine's proposed mechanism of action is to prevent amyloid aggregation (a drug that reduced the aggregation of amyloid beta would expectedly increase CSF levels as amyloid is cleared) (Karran and Hardy, 2014). However, there were no differences in CSF Aβ40 or total tau. There were no significant effects of homotaurine on cognitive (ADAS-Cog) and clinical (CDR-sb) measures compared to placebo.

In a double-blind randomized controlled phase 3 study of 790 patients with mild-to-moderate Alzheimer's disease, homotaurine (100 mg or 150 mg bid) for 18 months failed to significantly improve cognitive functions, as measured by ADAS-Cog (p=0.098) (Aisen et a, 2011). There was no significant slowing of clinical decline with homotaurine treatment, measured by the CDR-sb. There was, however,

less hippocampal volume loss with the 100 mg (p=0.035) and 150 mg (p=0.009) homotaurine treatment compared to placebo. The study was powered to detect a 25% reduction in cognitive loss. For an unknown reason, there was a lot of variability between the study sites and the placebo group deteriorated less than is historically common. Therefore, the authors concluded that the study was insufficiently powered.

To further analyze the effects of homotaurine in Alzheimer's disease, data from the North America study (described above) and the Western Europe study were analyzed, which together, enrolled a total of 2,025 patients with mild to moderate Alzheimer's disease (Abushakra et al., 2016). The highest efficacy of homotaurine was seen in E4/E4 homozygotes receiving 150 mg BID of homotaurine, with statistically significant benefits on cognition (ADAS-Cog) and a positive trend on the clinical scale, CDR-sb. APOE4 heterozygotes showed intermediate efficacy and non-carriers showed a lack of benefit, and at some time points, significantly worse scores on cognitive (ADAS-Cog) and clinical (CDR-sb) measures.

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

In vitro studies suggested that homotaurine binds to amyloid to prevent its conversion to beta-sheets and subsequent aggregation. In mouse models of Alzheimer's disease, homotaurine reduced the percentage of the cortex occupied by plaques but not the number of plaques. Preclinical studies also suggested that homotaurine reduced the levels of soluble plasma Aβ40 and Aβ42 and reduced the levels of soluble and insoluble Aβ40 and Aβ42 in the brain (Karran and Hardy, 2014).

The primary metabolite of homotaurine (and its prodrug ALZ-801) is 3-sulfopropanoic acid (3-SPA), an endogenous molecule in the human brain that is present in the cerebrospinal fluid (CSF) of patients with Alzheimer's disease and other neurodegenerative conditions (Hey et al., 2018). 3-SPA was also present in the CSF of drug-naïve elderly people with memory deficits due to Alzheimer's disease. The levels of 3-SPA were up to 12.6-fold higher in patients with Alzheimer's disease receiving homotaurine treatment (mean, 144.7 nM; range, 112.3 to 231.8 nM) compared to drug-naïve Alzheimer's patients (11.7 ± 4.3 nM). CSF concentrations of 3-SPA was 40- to 700-fold higher than soluble Aβ42 monomers. *In vitro* studies showed an interaction of 3-SPA with monomeric Aβ42 such that it inhibited the aggregation of Aβ42 into small oligomers. In rats, 3-SPA was 100% orally bioavailable and showed 25% brain penetration.

In preclinical studies, a 1000-fold molar excess of homotaurine fully inhibited the formation of Aβ oligomers from monomers, while 100-fold excess partially reduced the number of Aβ oligomers (Kocis et

al., 2017). Thus, it is proposed that homotaurine, when present in large excess, envelopes soluble Aβ monomers and prevents assembly into neurotoxic oligomer species and subsequent aggregation.

APOE4 interactions:

Subgroup analyses of the two phase 3 trials in ApoE4 carriers versus non-carriers reported a gene-dose effect with homotaurine showing no cognitive effect in non-carriers, intermediate effect in ApoE4 heterozygotes, and some cognitive benefit in ApoE4 homozygotes (Abusharkra et a, 2016; Abusharkra et al, 2017). In addition, patients on the higher dose of homotaurine (150 mg bid) and with mild (vs. moderate) Alzheimer's disease responded more favorably to the drug. Cognition in mild Alzheimer's ApoE4 homozygotes stabilized with homotaurine and was 40% better than placebo, which the authors claim is clinically meaningful. The authors speculate that since homotaurine's mechanism of action is to prevent amyloid aggregation and since ApoE4 patients have a higher amyloid burden, homotaurine would be most beneficial in this group.

Aging and health-related concerns*:* No studies have evaluated homotaurine for age-related diseases other than neurodegenerative diseases.

Types of evidence:

- No studies

There have not been any preclinical or clinical studies testing homotaurine for age-related diseases.

Safety: Homotaurine is associated with a number of mild side effects, mostly gastrointestinal in nature, such as nausea, vomiting, and decreased weight.

Types of evidence:

- 2 clinical trials
- Several small open-label clinical studies
- A few laboratory studies

The most common side effects of homotaurine are gastrointestinal in nature (nausea and vomiting) and can occur in up to 23% of the patients on the drug (compared to 13% in placebo). In the phase 2 study of

58 mild to moderate Alzheimer's patients, 7 patients receiving homotaurine treatment discontinued because of side effects, though there were no serious adverse events (Aisen et al, 2006). Syncope, pneumonia, and weight loss were also more common in the homotaurine group (occurring in 3.8%, 2.3%, and 15% of patients, respectively) (Aisen et al, 2011). The two phase 3 studies in North America and the Western Europe, which together, enrolled a total of 2,025 patients with mild to moderate Alzheimer's disease, reported that the most common adverse events with homotaurine were nausea, vomiting, and decreased weight (Abushakra et al., 2016). ApoE4 homozygotes also had an increased incidence of depression (13% vs. 9% for placebo)(Abusharkra et al, 2017). It is unclear what caused these drug effects in patients. Based on an MRI analysis that included a total of 409 patients with scans at screening and at week 78, homotaurine was not associated with Amyloid Related Imaging Abnormalities (ARIA)– abnormalities present on the MRI scans of some patients with other amyloid-related drugs; there was only one APOE4/4 subject with possible ARIA-E in the placebo group (Abushakra et al., 2016).

***Drug Interactions*:**

There is no information on potential drug interactions, although there was no exclusion criteria for patients taking other drugs in the phase 2 and 3 clinical trials.

Sources and dosing:

After the failure of phase 3 clinical trials, homotaurine began to be sold as a supplement called Vivimind. However, in 2011, the FDA refused to permit sales of Vivimind in the US because while homotaurine is naturally found in seaweed, the homotaurine in Vivimind is made synthetically (SupplementCounsel.com). In clinical studies, doses of 100-150 mg twice per day have been tested (Aisen et al, 2006).

Research underway:

There are currently no ongoing clinical trials testing homotaurine, based on ClinicalTrials.gov. Alzheon purchased the rights to homotaurine after the failed clinical trials and created a new pro-drug ALZ-801 that is reported to have improved pharmacokinetics, tolerability, and metabolic stability.

Search terms:

Pubmed:

- Tramiprosate, homotaurine

Websites visited for Etifoxine:

- Clinicaltrials.gov (none ongoing)
- DrugAge (0)
- Geroprotectors (0)
- Drugs.com (0)
- PubChem
- DrugBank