*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 tramiprosate failed in a phase 3 clincial trial, a post-hoc analysis showed benefits in ApoE4 individuals.

**Neuroprotective Benefit:** Phase 3 studies in Alzheimer's patients failed to show a benefit with tramiprosate, but a sub-group analysis in ApoE4 individuals shows some promise.

**Aging and related health concerns:** N/A

**Safety:** Tramiprosate is associated with a number of mild side effects, mostly gastrointestinal in nature.

**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. It was the first phase 3 study to test the 'amyloid hypothesis'. Although tramiprosate failed in phase 3 clinical trials, a subgroup analysis showed that it stabilized cognition in ApoE4 individuals.

**Neuroprotective Benefit:** Phase 3 studies in Alzheimer's patients failed to show a benefit with tramiprosate, but a sub-group analysis in ApoE4 individuals shows some promise.

*Types of evidence:*

- One phase 2 and two phase 3 studies in Alzheimer's patients
- One preclinical study

A phase 2 study of 58 patients reported a dose dependent decrease in CSF Aβ42 over three months (up to 70% reduction from baseline in 150mg group) (Aisen et al, 2006). This is odd considering tramiprosate'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. In an 18 month phase 3 study of 790 patients with mild-to-moderate Alzheimer's disease, tramiprosate (100mg or 150mg bid) failed to provide cognitive benefits (Aisen et a, 2011). There was, however, a trend for less hippocampal volume loss. 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. Regardless, because of the failure in the trial, the company stopped another ongoing phase 3 study in Europe.

*In vitro* studies suggested that tramiprosate binds to amyloid to prevent its conversion to beta-sheets and subsequent aggregation. In mouse models of Alzheimer's disease, tramiprosate reduced the percentage of the cortex occupied by plaques but not the number of plaques. Preclinical studies also suggested that tramiprosate 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).

*ApoE4*
Subgroup analyses of the two phase 3 trials reported a gene-dose effect with tramiprosate, showing no cognitive effect in ApoE4 non-carriers, intermediate benefits in ApoE4 heterozygotes, and the greatest

cognitive benefit in ApoE4 homozygotes. In addition, patients on the higher dose of tramiprosate (150mg bid) and with mild (vs. moderate) Alzheimer have responded better to the drug. In fact, cognition in mild Alzheimer's ApoE4 homozygotes stabilized with tramiprosate and was 40% better than placebo, which the authors claim is clinically meaningful. The authors speculate that since tramiprosate's mechanism of action is to prevent amyloid aggregation, and since ApoE4 patients have a higher amyloid burden, it would be most beneficial in this group (Abusharkra et a, 2016; Abusharkra et al, 2017).

**Safety:** Tramiprosate is associated with a number of mild side effects, mostly gastrointestinal in nature.

*Types of evidence:*

- One phase 2 and two phase 3 studies in Alzheimer's patients

The most common side effects of tramiprosate 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). However, they tend to be mild and moderate in nature. Syncope, pneumonia, and weight loss were also more common in the drug group (occurring in 3.8%, 2.3%, and 15% of patients, respectively) (Aisen et al, 2011). 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. Tramiprosate was not associated with Amyloid Related Imaging Abnormalities (ARIA) – abnormalities present on the MRI scans of some patients with other amyloid-related drugs.

**Drug Interactions:**
There is no information on potential drug interactions.

**Availability/Dosing:**
After the failure of phase 3 clinical trials, tramiprosate began to be sold as a supplement called VIVImind (later ActiveMind from Advances Orthomolecular Research). In clinical studies best results were seen at doses of 150mg twice per day.

**Research underway:**
Alzheon purchased the rights to tramiprosate after the failed clinical trials and created a new pro-drug ALZ-801 that is reported to have improved pharmacokinetics, tolerability, and metabolic stability.

Although not listed on clinicaltrials.gov, Alzheon's website reports that it is currently in phase 2 clinical trials for ApoE4 homozygotes and heterozygotes.

**Search terms:**

Pubmed:

- Tramiprosate, homotaurine

Websites visited for Etifoxine:

- Clinicaltrials.gov
- Treato.com
- DrugAge (o)
- Geroprotectors (o)
- Drugs.com