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.

Thiethylperazine

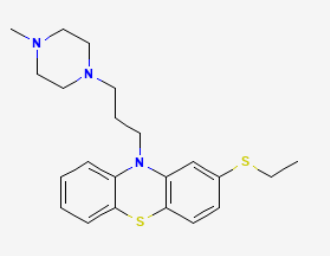
Evidence Summary

Preclinical evidence is mixed regarding the effects of thiethylperazine on Aβ clearance. Thiethylperazine can cause tardive dyskinesia and other side effects, which elderly people are particularly vulnerable to.

Neuroprotective Benefit: One study in mice reported thiethylperazine increased Aβ42 efflux, while others showed it worsened cognitive function and did not activate ABCC1. A phase 2 trial in AD was completed in 2021, but no results are available.

Aging and related health concerns: Thiethylperazine has not been tested as a standalone therapy for age-related diseases. It is used to prevent or treat nausea and vomiting following surgical procedures or cancer treatments.

Safety: Thiethylperazine can cause tardive dyskinesia even with approved doses. Other side effects include drowsiness, lightheadedness, fainting, blurred vision, dry mouth, and constipation. Children and elderly people are more vulnerable to side effects.

Availability: Rx	**Dose**: For nausea and vomiting, the oral dosage for adults is 10 mg, 1 to 3 times per day. Thiethylperazine is also available as an intramuscular injection or a rectal suppository; the dose for adults is also 10 mg, 1 to 3 times a day.	**Chemical formula:** $C_{22}H_{29}N_3S_2$ **MW**: 399.6  Source: PubChem
Half-life: elimination half-life is 12 hours	**BBB**: penetrant	
Clinical trials: The largest clinical trial of thiethylperazine enrolled a total of 663 surgical patients to test its efficacy on anti-emesis.	**Observational studies**: Most observational studies of thiethylperazine have been small; there are numerous case reports.	

What is it?

Thiethylperazine is a dopamine receptor antagonist with antiemetic properties; it is used for treating nausea and vomiting associated with anesthesia, cancer chemotherapy, radiation therapy, and toxins (DrugBank.com). Thiethylperazine is an antagonist at dopamine receptor types 1, 2, and 4, serotonin receptor types 2A and 2C, muscarinic receptors 1-5, alpha(1)-receptors, and histamine H1-receptors.

There is some renewed interest in thiethylperazine due to its potential activating effects on the ABCC1 transporter, a potential efflux mechanism for Aβ clearance across the blood-brain barrier and blood-cerebrospinal fluid barrier into the blood (Krohn et al., 2011). In humans, the ABCC1 gene encodes the multidrug resistance-associated protein 1 (MRP1), a transporter that uses ATP to transport its substrates across cellular membranes. MRP1 can transport some anticancer drugs (e.g., etoposide, vincristine, and doxorubicin) and has been implicated in tumor multidrug resistance.

Neuroprotective Benefit: One study in mice reported thiethylperazine increased Aβ42 efflux, while others showed it worsened cognitive function and did not activate ABCC1. A phase 2 trial in AD was completed in 2021, but no results are available.

Types of evidence:

- Several laboratory studies

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

No clinical trials have investigated the effects of thiethylperazine for preventing dementia or age-related cognitive decline.

Human research to suggest benefits to patients with dementia:

An open-label proof-of-mechanism clinical trial testing thiethylperazine in people with newly diagnosed early to mild dementia due to Alzheimer's disease was completed in 2021 based on ClinicalTrials.gov (NCT03417986), but no results have been posted or published in a peer-reviewed journal as of April 2026.

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

In a mouse model of rapid beta-amyloidosis (APP/PS1-21 mice), knockout of the Abcc1 gene led to a 12-14-fold increase in brain Aβ levels as compared with APP-PS1-21 mice with an intact Abcc1 gene. In a mouse model of Alzheimer's disease (young APP/PS1 mice), a preventive treatment with thiethylperazine twice daily at 3 mg/kg (intramuscular) starting at 45 days of age (prior to the appearance of plaques) and continued for 30 days significantly reduced cerebral Aβ42 levels (Krohn et al., 2011). However, in APP/PS1 mice that lacked the ABCC1 transporter (APP/PS1xAbcc1-/- mice), the same treatment with thiethylperazine failed to reduce cerebral Aβ levels, suggesting that thiethylperazine promotes clearance of Aβ42 from the brain via the ABCC1 transporter. *In vitro* studies showed that thiethylperazine activates ABCC1 transport activity by 69%. When thiethylperazine treatment (15 mg/kg, orally) was started later, from 75 days of age to 100 days of age, buffer-soluble Aβ was decreased by 65%.

Neuroprotective potential of thiethylperazine appear to be more mixed with longer-term treatment and/or in other rodent models. In a mouse model of Alzheimer's disease (Tg4-42 mice), thiethylperazine treatment (10 mg/kg/day, i.p.) started at 10 weeks of age and continued for 6 months restored recognition memory measured by the novel object recognition test, but worsened spatial reference memory measured by increased escape latencies in the Morris water maze task compared to untreated mice (Ruoff et al., 2026). Thiethylperazine treatment in Tg4-42 mice also significantly reduced their swimming speed, which may have affected their increased escape latencies in the water maze. Floating behavior was observed exclusively in thiethylperazine-treated Tg4-42 mice (and not in treated or untreated wild-type mice or untreated Tg4-42 mice). Thiethylperazine treatment did not affect working memory measured by the cross-maze test in Tg4-42 mice. There were no effects of chronic thiethylperazine treatment on neurogenesis, neuron count, Aβ4-42 accumulation in the hippocampus, synaptic protein levels (synaptophysin or synapsin), microgliosis, or astrogliosis. Thiethylperazine treatment significantly decreased glucose metabolism in the cortex, hippocampus, and other brain regions of Tg4-42 mice, measured by FDG-PET imaging. The thiethylperazine dose used in this study is roughly equivalent to the highest dose (52 mg/day in tablet form) used in the clinical trial in Alzheimer's patients (NCT03417986) and is approximately twice the maximum recommended dose for short-term use as an anti-emetic in humans. The authors noted that thiethylperazine's antagonism at histamine H1 and alpha-1 adrenergic receptors may have contributed to its sedative effects, impairing attention and overall cognitive performance (Ruoff et al., 2026). It is worth adding that the study did not include a vehicle (DMSO) control and used untreated animals as the control group. DMSO is generally considered safe at low concentrations but the possibility that DMSO may have contributed to some behavioral and/or metabolic effects cannot be entirely ruled out.

In wild-type mice, thiethylperazine treatment (10 mg/kg/day, i.p.) started at 10 weeks of age and continued for 6 months increased neurogenesis, but altered learning processes in the Morris water maze (less use of spatial strategies) and decreased cerebral glucose metabolism measured by FDG-PET (Ruoff et al., 2026).

In order to assess the effects of thiethylperazine (15 mg/kg/day, orally for 5 days) on the activity of the MRP1 transporter (protein encoded by the ABCC1 gene), PET imaging with the MRP1 tracer, 6-bromo-7-[11C]methylpurine, was performed in wild-type, APP/PS1-21, and Abcc1-/- mice (Wolfl-Duchek et al., 2022). Thiethylperazine treatment had no significant effects on MRP1 activity in the brain, lungs, or kidneys of wild-type, APP/PS1-21, and Abcc1-/- mice, measured by the elimination rate constant of radioactivity. It is not clear if this lack of an MRP1-stimulating effect is due to the lack of *in vivo* effects by thiethylperazine, insufficient tissue exposure to thiethylperazine, substrate-dependent effect of

thiethylperazine on MRP1 (MRP1 has at least 3 different substrate/modulating binding sites), or the limited sensitivity of the PET tracer to measure MRP1 stimulation. Based on these findings, the authors question the efficacy of this drug as an MRP1/ABCC1 stimulator in Alzheimer's disease.

APOE4 interactions:

There is currently no published information on whether thiethylperazine has differential effects based on APOE genotype.

Aging and related health concerns: Thiethylperazine has not been tested as a standalone therapy for age-related diseases. It is used to prevent or treat nausea and vomiting following surgical procedures or cancer treatments.

Types of evidence:

- 1 systematic review
- 1 clinical trial

Thiethylperazine is used to prevent or treat nausea and vomiting following surgical procedures or cancer treatments (e.g., chemotherapy and radiation), but it is not used as a standalone treatment for any age-related diseases.

In a double-blind placebo-controlled trial of 663 surgical patients, thiethylperazine treatment significantly decreased the incidence of post-surgery emetic symptoms when compared to the placebo group (23.1% in placebo, 11.1% in 5 mg thiethylperazine, and 8.1% in 10 mg thiethylperazine group)(Taylor and Stoelting, 1963).

A systematic review of 30 randomized controlled trials investigating the efficacies of cannabis versus other antiemetic treatments reported that cannabinoids were more effective than thiethylperazine, prochlorperazine, metoclopramide, chlorpromazine, haloperidol, domperidone, or alizapride (Tramer et al., 2001). However, side effects were more common with cannabinoids (e.g., euphoria, dysphoria, drowsiness, sedation, somnolence, depression, hallucinations, and paranoia) than other therapies. Given the availability of newer antiemetic medications with fewer side effects, thiethylperazine is not a first-line therapy in most guidelines.

Safety: Thiethylperazine can cause tardive dyskinesia even with approved doses. Other side effects include drowsiness, lightheadedness, fainting, blurred vision, dry mouth, and constipation. Children and elderly people are more vulnerable to side effects.

Types of evidence:

- Several clinical trials
- Numerous observational studies
- Numerous case reports
- Numerous laboratory studies

Thiethylperazine can cause some people to have blurred vision or become dizzy, lightheaded, drowsy, or less alert than usual (Drugs.com). Other less common side effects include constipation, dryness of the mouth/nose/throat, fainting, fever, headache, ringing in ears, and skin rash. Children and elderly people are usually more sensitive to the effects of thiethylperazine. In people with asthma or other lung diseases, thiethylperazine may cause secretions to become thick so it might be difficult to cough them up. In people with blood disease or heart or blood vessel disease, thiethylperazine may cause more serious adverse events. In people with difficulty urinating or enlarged prostate, thiethylperazine may cause urinary problems to get worse. Thiethylperazine may cause an increase in intraocular pressure, relevant to glaucoma risk. In people with Parkinson's disease or seizure disorders, thiethylperazine may have a greater chance of causing seizures or uncontrolled movements.

In a double-blind placebo-controlled trial of 663 surgical patients, a 10 mg dose of thiethylperazine more frequently decreased systolic blood pressure by more than 30 mmHg compared to placebo or the 5 mg dose (Taylor and Stoelting, 1963). Thiethylperazine treatment also slightly prolonged postanesthetic somnolence. There was no significant effect of thiethylperazine treatment on pulse rate, restlessness, or rigidity.

Over a 14-month period in an outpatient department of a geriatric hospital, 7 female patients over 75 years old were identified with tardive dyskinesia (involuntary repetitive movements) associated with the use of thiethylperazine (Sulkava, 1984). These patients were prescribed thiethylperazine for vertigo or dizziness due to arteriosclerosis, disturbances in the vertebrobasilar circulation, orthostatic hypotension, or aging. Tardive dyskinesia appeared after a treatment period as short as 3 weeks and up to 6 years. The Committee for Side Effects of Drugs in Sweden issued a warning against the use of thiethylperazine

in elderly patients. The lowest total dosage of thiethylperazine needed to induce tardive dyskinesia was 140 mg.

In a retrospective study of 105 patients with drug-induced parkinsonism in a Movement Disorders Unit, causal drugs included calcium-channel blockers (61 cases), antipsychotic drugs (29 cases), thiethylperazine (18 cases), clebopride (14 cases), and sulpiride (10 cases)(Jimenez-Jimenez et al., 1996). When compared to Parkinson's disease patients, drug-induced parkinsonism occurred predominantly in women and at an older age. Only 39% (41 patients) had parkinsonian signs disappear completely after withdrawal of the drug that induced parkinsonism.

A case report described a 47-year-old woman with vertigo due to vestibular dysfunction, who developed parkinsonism 1 month after starting thiethylperazine treatment (20 mg/day), which included severe bradykinesia, rigidity, hypophonia, facial hypomimia, and mild postural tremor (Briani et al., 2004). Thiethylperazine was withdrawn and in a few weeks her gait was back to normal, with only a slightly reduced swing of the arms. Bradykinesia and tremor disappeared. Two months after withdrawal of the drug, she underwent cerebral SPECT scan (123I-IBZM), which is specific to dopamine D2 receptor binding. The scan showed reduced postsynaptic D2 receptor activity by 45% in the basal ganglia. This finding suggests that even after thiethylperazine is stopped and parkinsonism symptoms have disappeared, there may be persistent changes in the dopamine system.

A case report described a 19-year-old with metastatic mixed follicular and papillary carcinoma of the thyroid, who was administered thiethylperazine (10 mg suppositories every 8 hours) due to the development of severe nausea and vomiting after radiation therapy (Khanderia, 1985). Following the sixth dose of thiethylperazine, the patient developed a fixed upward stare, sudden abdominal cramping and flank pain, oculogyric crisis (acute involuntary sustained upward deviation of the eyes), and involuntary protrusion of the tongue. Symptoms were relieved by i.v. diphenhydramine 50 mg. No further doses of thiethylperazine were administered. Approximately 23 hours after the drug was discontinued, the patient experienced another attack of dystonia that was more severe than the initial reaction (in addition to earlier symptoms, the patient developed spastic torticollis [involuntary neck muscle contractions], opisthotonos [rigid spasm of the back, neck, and head causing backward arching], facial grimacing, "thickened" tongue, inability to swallow, and generalized rigidity). A third attack occurred 35 hours after thiethylperazine discontinuation and was similar to the previous episode. Symptoms of these attacks were reversed with diphenhydramine (two 50 mg doses given i.v. at 5-minute intervals). No further episodes occurred. The author noted that diphenhydramine reversed these dystonic symptoms by restoring the balance between dopaminergic and cholinergic pathways.

In a population-based observational study based on the Hungarian Case-Control Surveillance of Congenital Abnormalities, there were 38,151 newborn infants between 1980 and 1996, of whom 746 (2.0%) had mothers who were treated with thiethylperazine (Czeizel and Vargha, 2003). When the pairs of cases with congenital abnormalities and their matched controls without congenital abnormalities were compared, thiethylperazine treatment during the first trimester of gestation in usual therapeutic doses showed a higher rate of cleft lip and/or palate (OR=2.0, 95% CI, 1.0 to 4.0). The authors noted that this did not indicate a clear teratogenic effect of thiethylperazine, but a weak association with cleft lip/palate that needed confirmation with further studies.

A case report described a 15-year-old girl who experienced an anaphylactic reaction followed by an extrapyramidal syndrome and relapse of respiratory distress following 3 tablets of thiethylperazine maleate (adequate dose for her weight)(Rossetti et al., 2005). Three hours after the last tablet, she developed face and tongue edema, speech difficulties, and dysphagia. Upon physical examination, she showed an angioedema and erythema of the face, the upper thorax, and the tongue. Respiratory rate was increased with diffuse wheezing. After an aerosol of epinephrine and albuterol, intravenous rehydration with saline solution, and 2 mg of clemastine fumarate, the symptoms improved within minutes. Two hours later, she had lower jaw dyskinesia and her respiratory distress relapsed. Her lower jaw moved to the right except when she kept her teeth firmly closed, and she was clenching her mouth and hands. Extrapyramidal syndrome was suspected and the patient was treated with i.v. biperiden hydrochloride, which promptly resolved all extrapyramidal symptoms.

Drug interactions: Thiethylperazine should not be taken with saquinavir (Drugs.com). Other drugs that are usually not recommended to be taken with thiethylperazine include antihistamines, allergy medications, cold medicine, sedatives, tranquilizers, sleep medications, prescription pain medications, narcotics, barbiturates, seizure medications, muscle relaxants, and anesthetics. Some examples include alprazolam, buprenorphine, bupropion, cannabidiol, cannabis, cetirizine, clonazepam, codeine, daridorexant, dihydrocodeine, donepezil, duloxetine, epinephrine, esketamine, fentanyl, gabapentin, hydrocodone, ketamine, lemborexant, levocetirizine, methadone, metoclopramide, morphine, olanzapine, oxycodone, oxymorphone, pregabalin, tramadol, zolpidem, and others (for full list, see Drugs.com). Using thiethylperazine with the following medicines may cause an increased risk of some side effects: aminolevulinic acid, belladonna, betel nut, evening primrose, and phenylalanine. If thiethylperazine is taken with alcohol, blood pressure may be reduced and central nervous system depressant effects may occur, including severe drowsiness.

Sources and dosing:

Thiethylperazine is available as a prescription drug and is used for treating nausea and vomiting associated with anesthesia, cancer chemotherapy, radiation therapy, and toxins (DrugBank.com). For nausea and vomiting, the oral dosage for adults is 10 mg, 1 to 3 times per day (Drugs.com). Thiethylperazine is also available as an intramuscular injection or a rectal suppository; the dose for adults is 10 mg, 1 to 3 times a day.

Research underway:

There are no ongoing clinical trials testing the effects of thiethylperazine in neurodegenerative conditions, based on ClinicalTrials.gov.

Search terms:

Pubmed, Google: thiethylperazine

Websites visited for thiethylperazine:

- Clinicaltrials.gov
- NIH RePORTER (0)
- DrugAge (0)
- Drugs.com
- WebMD.com (0)
- PubChem
- DrugBank.ca
- Cafepharma (0)
- Pharmapro.com (0)

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If you have suggestions for drugs, drugs-in-development, supplements, nutraceuticals, or food/drink with neuroprotective properties that warrant in-depth reviews by ADDF's Aging and Alzheimer's Prevention Program, please contact INFO@alzdiscovery.org. To view our official ratings, visit Cognitive Vitality's Rating page.