



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.

Intranasal Glutathione

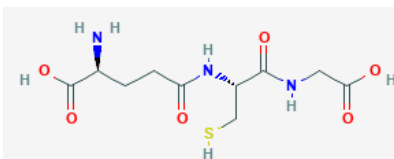
Evidence Summary

Acutely elevates brain glutathione levels, but a more comprehensive pharmacokinetic study is needed to find a dosing schedule to boost levels in disease-relevant brain regions in a clinically meaningful manner.

Neuroprotective Benefit: Intranasal glutathione was not more effective than placebo in clinical trials, but the studies were underpowered. The optimal dosing schedule to boost brain levels has not been established.

Aging and related health concerns: Intranasal glutathione has not been investigated for peripheral age-related diseases.

Safety: Primary adverse events include sinus irritation and headaches based on clinical trials up to 3 months, and outpatient use for a median of 2 years. A single case of tachycardia was reported at a high dose that may have been a treatment-related event.

Availability: Rx	Dose: Not established	Chemical formula: C ₁₀ H ₁₇ N ₃ O ₆ S MW: 307.33 g/mol  Source: PubChem
Half-life: Not established	BBB: Penetrant	
Clinical trials: Phase 1/2a (n=30) and Phase 2b (n=45) in Parkinson's disease.	Observational studies: Safety survey of patient reported outcomes (n=66).	

What is it?

Glutathione is a tripeptide of the amino acids glutamate, cysteine, and glycine. It is an **endogenous antioxidant** produced in the cytoplasm of cells that exists in reduced (GSH) and oxidized (GSSG) forms [1]. The reduced form reacts to neutralize reactive oxygen species (ROS), and the oxidized form is a byproduct of this reaction. Therefore, the ratio of the reduced (GSH) to oxidized forms (GSSG) serves as a readout of cellular oxidative stress levels. Glutathione has very poor oral bioavailability, but as a small polar molecule, it is a good candidate for intranasal administration. Intranasally administered reduced glutathione has been tested in clinical trials for Parkinson's disease, but the interpretation of the results is challenging because the full pharmacokinetic profile of this route of administration has not been established.

Neuroprotective Benefit: Intranasal glutathione was not more effective than placebo in clinical trials, but the studies were underpowered. The optimal dosing schedule to boost brain levels has not been established.

Types of evidence:

- 2 clinical trials in Parkinson's disease (Phase 1/2a n=30; Phase 2b n=45)
- 3 MRI imaging studies for brain glutathione (PD n=15; AD/MCI n=130, Healthy Elderly n=15)



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

Parkinson's disease: No clear benefit

Postmortem studies have shown that glutathione is depleted in brain regions associated with Parkinson's disease (PD)-pathology, such as the substantia nigra [2], and the results from underpowered pilot studies using intravenously administered glutathione suggested that PD patients may benefit from glutathione supplementation [3; 4].

Two small, double-blind, placebo controlled RCTs were conducted testing intranasal reduced glutathione in PD patients (Hoehn & Yahr Stage 1–3), and these studies were also not powered to determine clinical efficacy relative to placebo [5; 6]. In both studies, glutathione was administered via a 1 mL syringe attached to a Mucosal Atomization Device™ (Teleflex, following acquisition of Wolfe-Tory Medical). Patients used the device to administer saline, or saline supplemented with 100 mg or 200 mg of reduced glutathione 3 times per day (TID) for a period of 3 months. In order to minimize the circadian variation in PD symptoms, a given patient was tested at the same time of day for each study visit.

In the Phase 1/2a trial (n=30), there was a trend toward decline on the Total Unified Parkinson's Disease Rating Scale (UPDRS), however, the glutathione treated patients, especially the 600 mg/day group had, on average, worse disease severity than the placebo group, so there may have been greater ability to detect a small change in the treated group [5]. Unexpectedly, the slope of cognitive decline on the Montreal Cognitive Assessment (MoCA), became steeper between the end of treatment and the 1-month follow-up visit in the glutathione treated groups. However, it is unknown whether the rates of decline for the three groups were the same during the 3 months prior to randomization, or whether the differences observed in this short time period are clinically meaningful.

In the Phase 2b trial (n=45), all three groups (placebo, 300 mg, 600 mg) showed a similar trajectory of improvement on the Total UPDRS, and **glutathione treatment was not significantly better than placebo** on component measures of mentation (Part 1), activities of daily living (Part 2), or motor scores (Part 3) [6]. The authors attributed this finding to an unexpectedly high placebo effect, however, it appears likely that dosing may not have been adequate to meaningfully boost brain glutathione levels in disease-relevant areas. Based on ¹H-MRS measures, 300 mg/day of glutathione had no effect on levels of glutathione in the putamen, whereas 600 mg/day led to a small, non-significant increase.

The primary difficulty in interpreting these results is that while levels in the healthy brain are estimated to be approximately 1 to 2 mM, **the reported normal range of glutathione in the brain is extremely**



variable, and differs based on age, sex, and brain region [7]. Additionally, the presence of disease-related pathology may lead to higher levels of oxidative stress, and thus a higher demand for antioxidant capacity. Therefore, it is difficult to determine what level of glutathione supplementation would be needed for restoration of brain levels, and consequently impedes the ability to test the hypothesis that restoration of brain glutathione levels benefits cognitive function.

Human research to suggest benefits to patients with dementia:

Alzheimer's disease: Unknown

Intranasal glutathione has not yet been clinically tested in patients with Alzheimer's disease (AD), but there is evidence to indicate that there is an increased burden of oxidative stress, and decrease in glutathione levels in brain regions with AD-associated pathology.

Postmortem studies have indicated decreased glutathione levels in the brains of AD patients [8], more recently, the use of magnetic resonance spectroscopy ($^1\text{H-MRS}$) with the MEGA-PRESS sequence has allowed for the detection of brain glutathione levels in living patients, in a non-invasive manner. One study examining glutathione levels in the hippocampus (n=66) or frontal cortex (n=64) of participants with AD, mild cognitive impairment (MCI), or healthy older adults found that there were region specific alternations in glutathione in AD and MCI [9]. Both MCI and AD patients had lower levels of GSH in the hippocampus, but levels were only significantly changed in the frontal cortex in AD. Meanwhile, neither group had a significant change in glutathione levels in a brain region unaffected by AD pathology, the cerebellum, suggesting that the decrease in the levels of this endogenous antioxidant may contribute to disease progression. Cognitive function, based on Mini-Mental State Examination (MMSE) and Clinical Dementia Rating (CDR), was also inversely associated with glutathione levels in the frontal and temporal cortices, in cognitively impaired individuals.

A separate $^1\text{H-MRS}$ study in cognitively normal healthy older adults (n=15) found that **decreased levels of glutathione were associated with greater levels of amyloid**, based on PIB PET imaging, in the temporal lobe [8]. However, the timing of the relationship has not been established, so it is not known whether regions with high oxidative stress and low glutathione are likely to promote amyloid pathology, or if amyloid-induced oxidative stress leads to depletion of glutathione, or both.

Since it is not clear whether the loss of glutathione plays a causal role, or is a byproduct of other brain changes associated with AD, it is **not clear whether boosting brain levels of glutathione would meaningfully slow disease progression**. Furthermore, it is not known how well the intranasal



administration of glutathione could reliably boost glutathione levels specifically in the hippocampus and frontal cortices, where it is depleted in AD patients.

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

Glutathione is an endogenous antioxidant involved in the scavenging of ROS, and thus protects cells from oxidative stress damage [1]. Levels of glutathione have been shown to decrease with age, in conjunction with the increased susceptibility to oxidative stress damage [7]. Therefore, glutathione supplementation has been hypothesized as a way to protect cells against this damage. Orally administered glutathione has very poor bioavailability, while frequent intravenous administration is burdensome.

Intranasal administration allows therapeutics to access the brain directly via the olfactory nerve and epithelium, and indirectly by crossing the blood-brain barrier (BBB) following entry into the systemic circulation [10]. Since the surface area of the nasal cavity region that contributes to the systemic circulation is larger, more of the drug is typically diverted to this path, but the therapeutic agent will also be more extensively diluted, and thus may not reach biologically meaningful doses in peripheral organ systems. The effectiveness of transport to the brain is heavily influenced by the physiological environment of the nasal cavity, such as the pH.

An ¹H-MRS imaging study in PD patients (n=15) found that intranasal administration of reduced glutathione led to an increase in brain levels of glutathione from 20 to 45 minutes after administration [11]. However, there was considerable variation in the baseline levels and magnitude of increase, and there were also some within-subject fluctuations.

Since 60 minutes was the last time point assessed in this study, and it was only assessed in one subject, it is not known how long glutathione levels remain elevated in the brain. Additionally, this study used a region of interest centered over the left dorsal putamen, and it has not been established whether the glutathione distributes uniformly, or preferentially within certain brain regions. **A more comprehensive pharmacokinetic study is needed** to determine a dosing schedule that leads to consistently elevated glutathione levels in the brain regions of interest.

APOE4 interactions:

Brain tissue from ApoE4 carrier AD patients was found to have higher levels of oxidative stress and lower levels of reduced glutathione relative to ApoE3 carriers [12], suggesting that ApoE4 carriers may preferentially benefit from glutathione supplementation and/or that they would require higher doses



for efficacy. However, the efficacy of intranasal glutathione for AD patients with or without ApoE4 has not been tested.

Aging and related health concerns: Intranasal glutathione has not been investigated for peripheral age-related diseases.

Types of evidence:

- None

Reduced glutathione (GSH) levels decrease with age in conjunction with the rise in oxidative stress, leading to the hypothesis that supplementation of reduced glutathione could prevent age-related oxidative stress damage [13]. However, the pharmacokinetics and pharmacodynamics of intranasal glutathione have not been fully characterized, so it is not known how much enters the peripheral circulation relative to the amount that enters the brain. Furthermore, **it is unclear if the concentration of glutathione that reaches peripheral organ systems following intranasal administration is high enough to exert biologically meaningful activity**. The peripheral contribution is likely to vary from person to person depending on nasal architecture and physiochemistry [10].

Safety: Primary adverse events include sinus irritation and headaches based on clinical trials up to 3 months, and outpatient use for a median of 2 years. A single case of tachycardia was reported at a high dose that may have been a treatment-related event.

Types of evidence:

- 2 clinical trials in Parkinson's disease (Phase 1/2a n=30 + 4; Phase 2b n=45)
- 1 observational safety survey from pharmacy database (n=66)

A safety survey was conducted to assess patient-reported outcomes for intranasal glutathione [14]. Three hundred people from twenty states were randomly selected from the Key Pharmacy database, of which 70 completed the survey, and 66 had filled a prescription for intranasal glutathione. The treatment indications included multiple chemical sensitivity (n=29), allergies/sinusitis (n=25), Parkinson's disease (n=7), Lyme disease (n=3), fatigue (n=2), or other (n=10). The intranasal glutathione was used for a median of 24 months (25th percentile to 75th percentile: 10 to 56 months). 78.8% (n=52)



reported an overall positive experience, with 62.1% (n=41) attributing health benefits to intranasal glutathione use. 12.1% (n=8) reported experiencing **adverse events, which primarily related to the route of administration, including sinus irritation, headaches, or bloody nose.**

In the Phase 1/2a trial in PD patients (n=30), placebo and glutathione treated groups had similar levels of sinus irritation, both of which were greater than in the watchful waiting group (n=4) that did not receive any treatment [5]. None of the patients showed a significant difference in measured laboratory events, including complete blood count (CBC), white blood cell (WBC) count with differential, liver enzymes (ALT, AST), creatine, blood urea, nitrogen, uric acid, or urinalysis.

In the Phase 2b trial in PD patients (n=45), one patient receiving 600 mg glutathione/day withdrew from the study due to newly diagnosed cardiomyopathy following the onset of treatment [6]. The patient's tachycardia resolved after treatment cessation, suggesting this was a treatment-related event. The study investigators state that the cardiac side effect may be related to the finding in rodent studies that high levels of antioxidants can lead to reductive stress that injures cardiomyocytes. This suggests that taking high doses of glutathione in combination with other potent antioxidants may increase the risk for adverse events.

Sources and dosing:

The clinical trials testing intranasal glutathione used powdered glutathione from [MEDISCA](#) that was compounded by Key Pharmacy (Kent, Washington), and administered three times per day at doses of 100 or 200 mg/day in 1mL of saline in a syringe attached to a Mucosal Atomization Device™ (Teleflex). Neither dose was associated with significant increases in brain glutathione levels or clinical efficacy over the course of 3 months, and the optimal dosing schedule for neurodegenerative conditions has not been established. The glutathione used in the safety survey was also compounded through Key Pharmacy, but it is not known whether the same glutathione source or the nasal administration device supplied by the pharmacy was the same for all prescriptions. The compounded glutathione used a stabilization formula resulting in >97.4% stability after 30 days, and >94% stability after 60 days [14].

Research underway:

There are no reported planned or ongoing trials for intranasal glutathione.

Search terms:

Pubmed, Google: Intranasal glutathione

- Alzheimer's disease, Parkinson's disease, neurodegeneration, aging, clinical trials, safety

Websites visited for Intranasal Glutathione:

- Clinicaltrials.gov (intranasal glutathione)
- DrugAge (glutathione)
- Examine.com (glutathione)
- Geroprotectors (glutathione)
- Drugs.com (glutathione)
- WebMD.com (glutathione)
- PubChem (glutathione)
- DrugBank.ca (glutathione)

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