BRAIN HEALTH

State of the Science: Preclinical & Clinical NAD+ Research

"...Maintaining ATP level and flux via optimization of energy substrates and NAD levels may be a promising therapeutic strategy aimed at preserving brain health..." (Cuenoud et al., 2020) [1]

Executive Summary

Nicotinamide adenine dinucleotide (NAD+) is an essential molecule present in every living cell, playing a critical role in energy production, cellular stress management, and DNA repair. As research on NAD+ expands, its importance in various aspects of health, particularly brain health, is becoming increasingly evident.

The brain requires a constant supply of cellular energy to support cognitive functions such as learning, memory formation, and mood regulation [2]. Additionally, the brain must effectively manage cellular damage and inflammation caused by regular cellular activity or external stressors. Failure to regulate this stress properly can lead to neurodegeneration and cognitive decline [3].

As the brain ages, oxidative stress and DNA damage can accumulate, which, in turn, can lead to a decline in NAD+ levels [4]. Given the crucial role of NAD+ in regulating cellular stress and repair, maintaining its levels in the brain becomes increasingly important—an area that has garnered significant attention in scientific research.

Indeed, research has shown that **nicotinamide riboside (NR)**, a precursor to NAD+, can safely increase NAD+ levels in both the brain and whole blood of healthy individuals as well as those with neurodegenerative diseases, yielding positive outcomes [5–7]. For instance, NR has demonstrated neuroprotective effects in healthy older adults and in patients with subjective cognitive decline and mild cognitive impairment [8–10]. Furthermore, in patients with ataxia telangiectasia (AT) and Parkinson's disease (PD), two neurodegenerative conditions, NR has improved clinical symptoms, with Parkinson's patients benefiting from increased NAD+ levels and reduced brain inflammation [5,6,11,12].

Preclinical studies have laid the groundwork for human research by demonstrating the positive effects of NR supplementation on brain function. In cells from patients with Alpers' disease, a severe neurodegenerative disorder associated with mitochondrial dysfunction, NR improved mitochondrial function and protected against the loss of neurons [13]. In the brains of mice, NR boosted NAD+ levels, enhanced memory and learning, improved mitochondrial biogenesis and function, and reduced inflammation and oxidative stress, and stroke-induced swelling [14–17]. Additionally, NR has shown promise against depression and anxiety-like behaviors in rats and mice, highlighting its potential for improving mood [18,19]. Ongoing clinical trials are continuing to explore how NR supplementation may benefit brain health.

In conclusion, NAD+ is crucial for the function of all living cells, playing an important role in supporting brain health. The current state of the scientific literature positions NR as a safe and effective method for boosting brain NAD+ levels in healthy individuals and those with neurodegenerative conditions. As research advances, NR supplementation may emerge as a strategy for improving brain function and protecting against neurodegeneration.

Clinical Studies

Publication	Intervention	Objective	Key Outcomes
Veenhuis et al., 2021 [11] Nicotinamide Riboside Improves Ataxia Scores and Immunoglobulin Levels in Ataxia Telangiectasia CERP ChromaDex External Research Program	**Nicotinamide Riboside**	To investigate the effects of NR supplementation in patients with AT. AT is a rare, inherited disorder characterized by a variety of symptoms including neurodegeneration, immunodeficiency, premature aging, and an increased risk of cancer.	• NR improved ataxia scores. However, this improvement disappeared after NR withdrawal, indicating a temporary, symptomatic effect of NR on AT. • NR also markedly increased serum immunoglobin G in immunodeficient patients. • This is the first clinical study to investigate the effects of NR in patients with AT, and

			most notably, the first clinical NR trial in children under the age of 18.
Brakedal et al., 2022 [5] The NADPARK study: A Randomized Phase I Trial of Nicotinamide Riboside Supplementation in Parkinson's Disease CERP ChromaDex External Research Program	**Nicotinamide Riboside**	To assess the safety, tolerability, and cerebral penetration of NR therapy in PD patients, as well as determine if NR has an impact on their neurometabolic profile and motor symptoms.	• NR increased cerebral NAD+ levels, altered brain metabolic pattern, and decreased levels of inflammatory cytokines in the cerebrospinal fluid of PD patients. • NR elicited a mild but significant clinical improvement which correlated with the change in the brain's metabolic pattern.
Vreones et al., 2022 [10] Oral Nicotinamide Riboside Raises NAD+ and Lowers Biomarkers of Neurodegenerative Pathology in Plasma Extracellular Vesicles Enriched for Neuronal Origin CERP ChromaDex External Research Program	**Nicotinamide Riboside**	To investigate the effects of NR supplementation on neuronal NAD+ levels and markers of neurodegeneration in plasma derived human neuronal extracellular vesicles (NEVs). Human NEVs are small particles of fluid in the blood that carry information about brain cells.	• NR increased NAD+ in plasma derived human NEVs, suggesting an increase in neuronal NAD+ levels. • In NEVs, NR also decreased levels of Aβ42, an Alzheimer's disease (AD) biomarker, as well as biomarkers pJNK and pERK1/2, which are involved in insulin resistance and neuroinflammatory pathways.
Presterud et al., 2023 [12] Long-Term Nicotinamide Riboside Use Improves Coordination and Eye Movements in Ataxia Telangiectasia CERP ChromaDex External Research Program	**Nicotinamide Riboside**	To examine the safety and efficacy of long-term NR supplementation on neuromotor function in patients with AT.	• Long-term NR supplementation was safe and well tolerated, with no serious adverse events. • Compared to historical controls, NR improved motor coordination and eye movements in AT patients. • This is the second clinical NR trial including children under the age of 18 and the longest NR supplementation study to date.
Orr et al., 2023 [8] A Randomized Placebo-Controlled trial of Nicotinamide Riboside in Older Adults with Mild Cognitive Impairment CERP ChromaDex External Research Program	**Nicotinamide Riboside**	To assess the safety of NR supplementation and investigate its effects on cognition, brain volume and functioning, and physical function in older adults with mild cognitive impairment (MCI). MCI is a transitional cognitive state between normal aging and dementia, often progressing to dementia.	• NR-supplemented subjects exhibited reduced cerebral blood flow, particularly in the default mode network, suggesting less degeneration in brain regions that typically require higher blood flow. • Cognitive function measures remained stable in both NR and placebo groups throughout the study.
Berven et al. 2023 [6] NR-SAFE: a Randomized, Double-Blind Safety Trial of High Dose Nicotinamide	**Nicotinamide Riboside**	To assess the safety of high-dose NR supplementation, its short-term tolerability, and impact on NAD+ levels in PD patients.	• High-dose NR was safe and well-tolerated with no related adverse events.

Riboside in Parkinson's Disease CERP ChromaDex External Research Program			• NR increased NAD+ levels and modified the NAD metabolome. • NR significantly improved clinical symptoms of PD, suggesting augmenting NAD+ levels may have a symptomatic anti-Parkinson's effect.
Nanga et al., 2024 [7] Acute Nicotinamide Riboside Supplementation Increases Human Cerebral NAD+ Levels in Vivo CERP ChromaDex External Research Program	**Nicotinamide Riboside**	To investigate the effects of acute NR supplementation on cerebral NAD+ levels in the healthy human brain using a specialized MRI technique called downfield proton magnetic resonance spectroscopy.	• NR increased brain NAD+ levels by about 16% compared to baseline.
Wu et al., 2025 [9] Cognitive and Alzheimer's Disease Biomarker Effects of Oral Nicotinamide Riboside (NR) Supplementation in Older Adults with Subjective Cognitive Decline and Mild Cognitive Impairment CERP ChromaDex External Research Program	**Nicotinamide Riboside**	To test the safety and efficacy of NR supplementation on cognition and AD blood biomarkers in older adults with subjective cognitive decline (SCD) and MCI.	• NR had no impact on cognition. • NR resulted in a 7% reduction in plasma $pTau^{217}$ concentrations, a biomarker for AD, while placebo resulted in an 18% increase.

Ongoing Clinical Trials		
Trial Registry	**Intervention**	**Objective**
NCT03568968 A Randomized Controlled Trial of Nicotinamide Riboside Supplementation in Early Parkinson's Disease (NOPARK) CERP ChromaDex External Research Program	**Nicotinamide Riboside**	To assess the efficacy of NAD-replenishment therapy in the form of oral NR in delaying the progression of early PD.
NCT05589766 N-DOSE: A Dose Optimization Trial of Nicotinamide Riboside in Parkinson's Disease CERP ChromaDex External Research Program	**Nicotinamide Riboside**	To determine the optimal biological dose of NR in individuals with PD.
NCT04870866 NAD Supplementation to Prevent Progressive Neurological Disease in Ataxia Telangiectasia CERP ChromaDex External Research Program	**Nicotinamide Riboside**	To investigate the effect of NR supplementation in children with AT, with a focus on neurological symptoms.

NCT06162013 The NADAPT Study: a Randomized Double-blind Trial of NAD Replenishment Therapy for Atypical Parkinsonism (NADAPT)	**Nicotinamide Riboside**	To test the neuroprotective effects of NR treatment on atypical parkinsonism in patients with progressive supranuclear palsy, multiple system atrophy, and corticobasal syndrome.
NCT05740722 Nicotinamide Riboside Supplementation in Progressive Multiple Sclerosis (Norseman)	**Nicotinamide Riboside**	To assess the safety and efficacy of NR treatment in patients with progressive multiple sclerosis.
NCT05698771 NAD-Brain: a Pharmacokinetic Study of NAD Replenishment Therapy (NAD-brain)	**Nicotinamide Riboside**	To determine the blood and brain pharmacokinetics of NAD+ replenishment therapy using treatment with NR and nicotinamide mononucleotide (NMN).
NCT04430517 Effects of Nicotinamide Riboside on Bioenergetics and Oxidative Stress in Mild Cognitive Impairment/Alzheimer's Dementia CERP ChromaDex External Research Program	**Nicotinamide Riboside**	To investigate the effects of NR on brain energy metabolism, oxidative stress, and cognitive function in individuals with MCI and mild AD.
NCT05500170 Benefits of Nicotinamide Riboside Upon Cognition and Sleep	**Nicotinamide Riboside**	To examine the benefits of NR supplementation on sleep and cognitive function in older adults.
NCT05483465 The Effect of NAD Supplementation on Brain Vascular Health in Aging	**Nicotinamide Riboside**	To investigate the effects of NR on brain vascular health.
NCT03482167 NAD Therapy for Improving Memory and Brain Blood Flow in Older Adults with Mild Cognitive Impairment CERP ChromaDex External Research Program	**Nicotinamide Riboside**	To investigate whether NR can reduce arterial stiffness and improve arterial function within the brain and restore brain function and memory in patients with “amnestic” MCI.
NCT02721537 Use of 31P MRS to Assess Brain NAD+ in Healthy Current and Former Collegiate Athletes (TRMC-004) CERP ChromaDex External Research Program	**Nicotinamide Riboside**	To assess whether NR can affect the levels of brain NAD+ in healthy current and former collegiate athletes.

Preclinical Studies			
Publication	**Intervention**	**Objective**	**Key Outcomes**
Lee & Yang, 2019 [14]	**Nicotinamide Riboside**	To investigate the effects of NR treatment on inflammation and	• In diabetic mice, NR increased the weight of the brain and reduced and normalized

Supplementation with Nicotinamide Riboside Reduces Brain Inflammation and Improves Cognitive Function in Diabetic Mice CERP ChromaDex External Research Program		cognitive function in diabetic mice.	inflammation and markers of neurodegeneration. • NR also improved spatial recognition memory, movement activity, and hippocampal function. The hippocampus is a region of the brain responsible for memory and learning.
Joshi et al., 2020 [15] Targeting Sirtuin Activity with Nicotinamide Riboside Reduces Neuroinflammation in a GWI Mouse Model	**Nicotinamide Riboside**	To investigate the effects of NR supplementation on brain bioenergetics in a mouse model of Gulf War Illness (GWI)—an illness that causes pain, fatigue, and memory loss in veterans from the Gulf War.	• NR protected against the GWI-induced decrease in plasma NAD+ levels and increased brain NAD+ levels in both GWI and healthy mice. • NR protected against GWI-induced fatigue-like behavior and normalized brain inflammation. • NR increased markers of mitochondrial biogenesis in the brains of GWI and healthy mice and normalized markers of mitochondrial function in the brains of GWI mice.
Wang et al., 2022 [19] Potential Therapeutic Effects of NAMPT-Mediated NAD Biosynthesis in Depression In Vivo	**Nicotinamide Riboside**	To investigate the effects of NR supplementation on the activity of nicotinamide phosphoribosyltransferase (NAMPT), an NAD-regulating enzyme, and its consequences on depression in rats.	• NR treatment normalized NAMPT levels in the brains of depressed rats, with a more pronounced effect on the prefrontal cortex, a brain region primarily responsible for executive functioning and higher-order cognitive processes. • NR reversed depressive and anxiety-like symptoms, regulated a marker of brain plasticity, and improved locomotor activity and cognitive function in depressed rats.
Hong et al., 2024 [13] The NAD$^+$ Precursor Nicotinamide Riboside Rescues Mitochondrial Defects and Neuronal Loss in iPSC derived Cortical Organoid of Alpers' Disease	**Nicotinamide Riboside**	To develop a model of Alpers' syndrome using cells from an Alpers' patient to investigate the disease's progression and evaluate the potential of NR treatment as a therapeutic strategy. Alpers' disease is a rare, severe neurodegenerative disorder that typically manifests in childhood and is associated with dysfunctional mitochondria.	• Patient-derived cells and their differentiated forms, such as neural stem cells (NSCs) and cortical organoids (small brain-like structures), exhibited mitochondrial abnormalities, which were more severe in the NSCs. • NR improved mitochondrial function and neuronal health, as evidenced by an increase in glial cells, a reduction in neuronal loss, and decreased mitochondrial damage in the cortical organoids.
Wang et al., 2024 [20] Nicotinamide Riboside Alleviates Brain Dysfunction Induced by Chronic Cerebral Hypoperfusion Via	**Nicotinamide Riboside**	To investigate the neuroprotective effects of NR administration in a rat model of chronic cerebral hypoperfusion (CCH)-induced vascular dementia. CCH is a long-term reduction in blood flow to the brain, leading	• In mice with vascular dementia, NR increased NAD+ levels in both the blood and brain. • NR improved memory retention, recognition, and spatial learning, while also enhancing cognitive function and brain oxygen use. • NR protected brain cells from death, preserved neural connections, and maintained mitochondrial function and

Protecting Mitochondria		to cognitive decline and vascular dementia.	structure, supporting energy production and preventing cellular damage.
She et al., 2024 [16] Nicotinamide Riboside Restores Nicotinamide Adenine Dinucleotide Levels and Alleviates Brain Injury by Inhibiting Oxidative Stress and Neuroinflammation in a Mouse Model of Intracerebral Hemorrhage	**Nicotinamide Riboside**	To explore whether intravenously increasing NAD+ with NR could protect against hemorrhagic stroke in mice.	• In a mouse model of hemorrhagic stroke, NAD+ levels decreased, while neuroinflammation and oxidative stress increased, leading to impaired brain function. • NR reduced brain bleeding, swelling, and tissue damage, while also promoting neurological recovery, and reducing oxidative stress and neuroinflammation.
Jiang et al., 2025 [18] Nicotinamide Riboside Alleviates Sweeteners-Induced Brain and Cognitive Impairments in Immature Mice	**Nicotinamide Riboside**	To investigate the effects of sugar and sugar-free sweet beverages on the brain and cognition of mice and assess the potential protective effects of NR supplementation.	• NR protected against impairments in cognition, sociability, and the increase in depressive and anxiety-like behaviors induced by sucrose or aspartame. • NR protected the brains of mice from inflammation induced by exposure to sucrose or aspartame. • NR attenuated the increase in oxidative stress and dysregulation of programmed cell death induced by sucrose or aspartame exposure.

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