State of the Science: Preclinical & Clinical NAD+ Research (Parkinson's Disease)

"...emerging findings reveal key roles for NAD⁺ and related metabolites in the adaptation of neurons to a wide range of physiological stressors and in counteracting processes in neurodegenerative diseases, such as those occurring in Alzheimer's, Parkinson's, and Huntington diseases..." (Lautrup et al., 2019) [1]

Executive Summary

Nicotinamide adenine dinucleotide (NAD+) is an essential molecule found in every cell, playing a central role in numerous cellular processes, including energy production, DNA repair, and mitochondrial function. Extensive research underscores the importance of NAD+ in cellular health, with emerging evidence highlighting its role in protecting against age-associated neurodegenerative diseases, including Parkinson's disease (PD).

PD is a debilitating neurodegenerative disease that worsens with time. It is caused by the progressive loss of neurons in the brain, ultimately leading to motor and cognitive dysfunction [2]. At its core, PD involves complex interactions between mitochondrial dysfunction, oxidative stress, and neuroinflammation—all processes that are dependent on NAD+ [3]. As such, maintaining NAD^+ levels for the purpose of neuroprotection becomes increasingly important.

As NAD+ levels naturally decline with age, older populations become less equipped to combat the physiological disruptions caused by PD [4]. Notably, advancing age is the strongest known risk factor for PD onset, highlighting a potential link between NAD+ depletion and PD progression [5]. In this respect, restoring NAD+ levels represents a promising therapeutic approach that may enhance neuronal resilience and support the brain's ability to maintain healthy dopaminergic function in aging populations.

Indeed, research on **nicotinamide riboside (NR)**, a highly bioavailable NAD+ precursor, has provided encouraging evidence for the safety and efficacy of NR supplementation in PD patients. Research in PD patients found that NR supplementation increased cerebral NAD+ levels, improved brain metabolic patterns, produced mild but meaningful clinical improvements, and confirmed that NR was safe at high doses [6–8]. Notably, studies using NR in combination with other metabolic activators have shown promise in improving cognitive function in PD patients, especially those with lower baseline cognitive scores, suggesting that comprehensive metabolic support may offer synergistic benefits [9].

In animal models of PD, NR has demonstrated remarkable neuroprotective effects, including the preservation of dopaminergic neurons, improvement in motor function, reduction of oxidative stress, and enhancement of mitochondrial biogenesis and function [10–13]. One study using a rat model of PD found that NR improved neurological behavior and locomotor activity—effects that were amplified when NR was treated in combination with other metabolic activators [14]. Furthermore, ongoing clinical trials continue to explore the potential therapeutic effects of NR in the context of PD.

In summary, NAD+ plays a crucial role in maintaining neuronal health and function, with compelling evidence suggesting that boosting NAD+ levels through supplementation—particularly with NR—may offer therapeutic benefits for individuals with PD. As research progresses, NR supplementation may emerge as a novel and effective approach to improving outcomes for PD patients.

Ex Vivo/Clinical Studies

Publication	Intervention	Objective	Key Outcomes
Brakedal et al., 2022 [6] **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 supplementation safely increased cerebral NAD+ levels, altered brain metabolic pattern, and decreased levels of inflammatory cytokines in the cerebrospinal fluid of PD patients. • Moreover, patients experienced a mild but significant clinical improvement, and this correlated with the change in the brain's metabolic pattern.

Berven et al., 2023 [7] NR-SAFE: a randomized, double-blind safety trial of high dose nicotinamide riboside in Parkinson's disease CERP ChromaDex External Research Program	**Nicotinamide Riboside**	To assess the safety and short-term tolerability of NR and its impacts on NAD+ and the clinical severity of PD.	• High-dose NR supplementation was safe and well-tolerated with no related adverse events. • NR significantly improved clinical symptoms of PD, suggesting augmenting NAD+ levels may have a symptomatic anti-Parkinson's effect.
Gaare et al., 2023 [8] Nicotinamide riboside supplementation is not associated with altered methylation homeostasis in Parkinson's disease CERP ChromaDex External Research Program	**Nicotinamide Riboside**	To investigate the impact of NR on DNA methylation patterns in the blood cells and muscle tissues of newly diagnosed, dopaminergic treatment-naïve PD.	• NR supplementation had no impact on DNA methylation in PD patients, including those with common mutations in the MTHFR gene. • NR resulted in minor changes in the activity of metabolic pathways and patterns of DNA methylation. However, these changes were not harmful and did not disrupt normal DNA methylation.
Yulug et al., 2025 [9] Multi-omics characterization of improved cognitive functions in Parkinson's disease patients after the combined metabolic activator treatment: a randomized, double-blinded, placebo-controlled phase II trial CERP ChromaDex External Research Program	**Combined Metabolic Activator (CMA; Nicotinamide Riboside, L-serine, N-acetyl-L-cysteine, L-carnitine tartrate)**	To investigate the physical and cognitive effects of CMA supplementation in PD patients.	• CMA supplementation did not improve motor function in PD patients. • CMA significantly improved cognitive function, particularly in patients with low baseline MoCA scores, which was indicative of lower baseline cognitive function. Notably, the variability in baseline MoCA scores likely influenced the observed outcomes.

Ongoing Clinical Trials		
Trial Registry	**Intervention**	**Objective**
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 NR or NMN in healthy individuals and those with PD.
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 using NR in delaying the progression of early PD.
NCT05546567 **NOPARK Open Label Extension Study**	**Nicotinamide Riboside**	• To monitor safety, neuroprotection, and biological effects from long-term NR use in PD patients.

CERP ChromaDex External Research Program		
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.

Preclinical Studies			
Publication	**Intervention**	**Objective**	**Key Outcomes**
Schöndorf et al., 2018 [12] The NAD+ Precursor Nicotinamide Riboside Rescues Mitochondrial Defects and Neuronal Loss in iPSC and Fly Models of Parkinson's Disease CERP ChromaDex External Research Program	**Nicotinamide Riboside**	To investigate the effects of boosting mitochondrial biogenesis through NR supplementation on PD progression using PD patient neurons and a fly model of PD.	• In the neurons of PD patients, NR administration boosted NAD+ and NADH levels, improved autophagy, and ameliorated mitochondrial dysfunction by reducing oxidative stress and improving mitochondrial biogenesis. • In a fly model of PD, NR prevented the age-related decline in motor function and dopaminergic neuron count.
Turkez et al., 2022 [14] Combined metabolic activators improve metabolic functions in the animal models of neurodegenerative diseases CERP ChromaDex External Research Program	**CMA (Nicotinamide Riboside, L-serine, N-acetyl-L-cysteine, L-carnitine tartrate)**	To investigate the effects of CMA on metabolic functions in rat models of PD and AD.	• In PD rat models, CMA improved neurological behavior and locomotor activity. Notably, among the individual metabolic activators tested, NR showed the strongest effects, with CMA being the most effective overall. • In PD and AD rat models, CMA administration exhibited neuroprotective effects evidenced by reduced neuronal hyperemia, degeneration, and necrosis.
Chen et al., 2024 [10] Ablation of NAMPT in Dopaminergic Neurons Leads to Neurodegeneration and Induces Parkinson's Disease in Mouse	**Nicotinamide Riboside**	To investigate how NAMPT depletion in dopamine-producing neurons contributes to neurodegeneration and PD, and whether NR supplementation can offer neuroprotection in mice.	• NAMPT depletion led to a time-dependent loss of dopaminergic neurons, resulting in PD-like motor dysfunction in mice. • NR protected against these effects by preventing the loss of dopaminergic neurons and reducing PD-like motor dysfunction. • In a neurodegenerative cell model, NR reversed the increase in oxidative stress and mitochondrial damage induced by NAMPT depletion.
Luo et al., 2024 [11] Nicotinamide riboside ameliorates survival time and motor dysfunction in an MPTP-Induced Parkinson's	**Nicotinamide Riboside**	To investigate the neuroprotective effects of NR treatment in a zebrafish model of PD.	• NR improved motor dysfunction, extended survival time, and increased NAD+ levels in the PD zebrafish. • NR also protected neuronal health by slowing the loss of dopamine-producing and peripheral neurons.

disease zebrafish model through effects on glucose metabolism and endoplasmic reticulum stress			
Turconi et al., 2024 [13] Nicotinamide riboside first alleviates symptoms but later downregulates dopamine metabolism in proteasome inhibition mouse model of Parkinson's disease CERP ChromaDex External Research Program	**Nicotinamide Riboside**	To investigate the effects of NR supplementation on PD symptoms in *C. elegans* (worm) and mouse models of PD.	• In the worm model of PD, NR improved symptoms including mitochondrial dysfunction and defects in movement caused by the overproduction of a protein called α-synuclein, possibly by activating a response in mitochondria that helps handle cellular stress. • In the mouse model of PD, NR did not restore normal mitochondrial function and initially partially rescued behavioral dysfunction but later decreased dopamine and its gene expression in the brain.

CERP ChromaDex External Research Program *The **ChromaDex External Research Program (CERP)** is an essential component of Niagen Bioscience's R&D Program. Through CERP, Niagen Bioscience material, such as the company's patented nicotinamide riboside (NR) ingredient, Niagen®, and technical expertise is freely provided for exceptional preclinical and clinical, investigator-initiated research projects. Additionally, CERP funds research studies supporting Niagen Bioscience's business needs. Please visit https://www.chromadex.com/research/cerp/ for more information.*

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