INTERNATIONAL
IV NUTRITIONAL THERAPY
GLOBAL PHYSICIAN EDUCATION

NAD+ for Acute and Chronic Disease

Advanced NAD IV
Dr. Brenden Cochran and Virginia Osborne

Three main factors are to blame for NAD^+ deficiencies:

- Stress: Lifestyle choices
- Diet / Alcohol / Drugs
- Inflammation

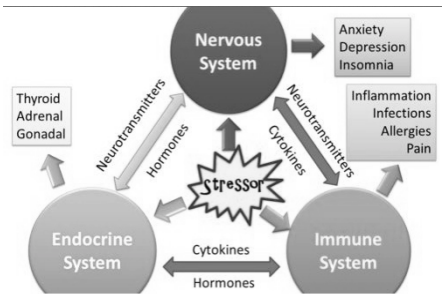
Stress:

American Psychological Association links chronic stress to the six leading causes of death: heart disease, cancer, lung ailments, accidents, cirrhosis of the liver and suicide.

Add in oxidative stress, where an imbalance between the production of free radicals and the ability of the body to counteract with antioxidants occurs, and you create an NAD^+ is being depleted environment

8-Isoprostane - biomarker of oxidative stress; a prostaglandin-like compound produced by free radical-catalyzed peroxidation. Suggested to be the most reliable approach to monitor oxidative stress. High levels of 8-isoprostane is an indication of oxidative damage and a reduction in available NAD^+.

Chronic Infections like Lyme = chronic stress = depleted NAD+ levels



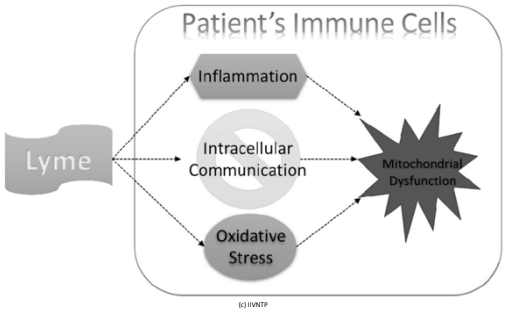
Inflammation:

Inflammation: is your body's response to stress – whether it be from diet, emotions, lifestyle, or environment.

One particular component of inflammation that is associated with NAD^+ depletion is a glycoprotein called CD38. Found on the surface of many immune cells, CD38 plays an important role in inflammation. CD38 causes migration of neutrophils and monocytes toward sites of inflammation, signals maturation of dendritic cells during inflammatory cytokine activation, and generates Ca^{2+}mobilizing metabolites. To do this though, it must consume large amounts of NAD^+.

If you have a lot of immunity issues – there's a compound called CD38. CD38 is a tremendous utilizer of NAD and it is very much involved in reducing inflammation and bolstering immunity. CD38 is also involved in oxytocin production

Lyme Dz = chronic inflammation & immune burden
=> CD38 taps NAD+ stores
=> Low Immunity & ATP levels



Causes of Oxidative Stress

Just about everything we do results in oxidation (or inflammation) producing potentially damaging free radicals!

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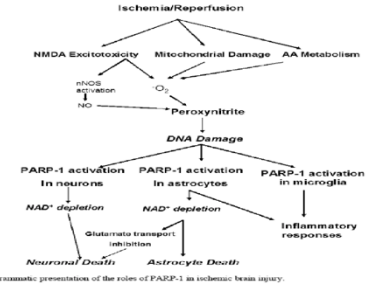

Figure 4. Diagrammatic presentation of the roles of PARP-1 in ischemic brain injury.

Ying, W. NAD+ and NADH in cellular functions and Cell Death. Frontiers in Bioscience 11, 3129, Sept. 1, 2006

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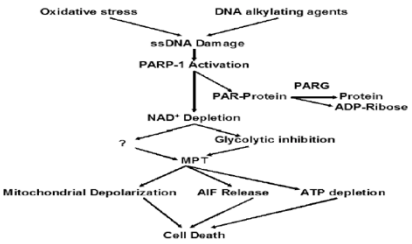

Figure 5. Diagrammatic presentation of the mechanisms of PARP-1 cytotoxicity. Abbreviations used: ssDNA damage: Single strand DNA damage. PARP-1: Poly(ADP-ribose) polymerase-1. PARG: Poly(ADP-ribose) glycohydrolase. AIF: Apoptosis inducing factor. MPT: Mitochondrial permeability transition.

Ying, W. NAD+ and NADH in cellular functions and Cell Death. Frontiers in Bioscience 11, 3129, Sept. 1, 2006

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NAD+ Metabolism and the Control of Energy Homeostasis: A Balancing Act between Mitochondria and the Nucleus

- NAD(+) has emerged as a vital cofactor that can rewire metabolism, activate sirtuins, and maintain mitochondrial fitness through mechanisms such as the mitochondrial unfolded protein response. This improved understanding of NAD(+) metabolism revived interest in NAD(+)-boosting strategies to manage a wide spectrum of diseases, ranging from diabetes to cancer. In this review, we summarize how NAD(+) metabolism links energy status with adaptive cellular and organismal responses and how this knowledge can be therapeutically exploited.

- Cantó, Carles et al. Cell Metabolism , Volume 22 , Issue 1 , 31 - 53
Cell metabolism · June 2015

(c) IIVNTP

Conclusions

- The association between metabolism, health, and lifespan have long been proposed based on similarities between metabolic dysfunction and disease (e.g., obesity, diabetes, neurodegeneration, and cancer) and the aging process. Only recently have these processes been linked so tightly by multiple proteins, including sirtuins and PARPs, all of which are tightly controlled by the regulation and subcellular balance of the metabolite NAD+. As such, we have never been so close to solving the ancient question of how we age and what we can do to slow this process while simultaneously not compromising on our quality of life. **Despite these insights, several aspects of NAD+ metabolism remain obscure. On one side, the complex detection and quantification of NAD+ metabolites and fluxes has not yet allowed us to obtain a clear picture of how different NAD+ precursors are metabolized to feed cells and tissues.** We also speculate that additional proteins controlling the supply or salvage of NAD+, along with proteins that are controlled by NAD+ levels, will be identified. Furthermore, the potential preventive and therapeutic use of NAD+-boosting strategies requires an assessment of the bioavailability and effectiveness of various precursor doses in human therapy. In addition, new NAD+ boosters are welcomed since the side effects of niacin generally lead to poor compliance, despite its known efficacy in a myriad of diseases. **Therefore, the dosing and safety of these new NAD+ boosters (e.g., NAD+ precursors, CD38 inhibitors, and PARP inhibitors) must be thoroughly assessed to translate these exciting insights into NAD+ biology toward human relevance.**

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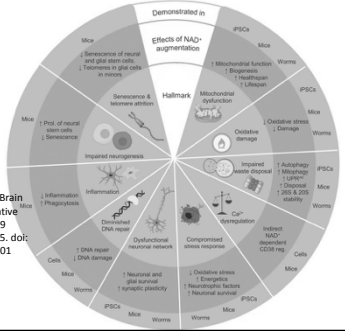

Lautrup, S et. Al. NAD+ in Brain Aging and Neurodegenerative Disorders. Cel Metab. 2019 October 01; 30(4): 630-655. doi: 10.1016/j.cemt.2019.09.001

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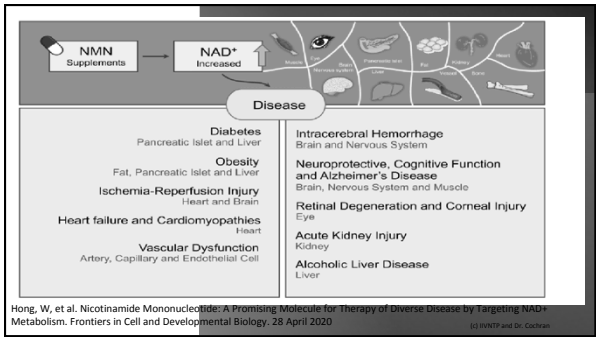


Hong, W, et al. Nicotinamide Mononucleotide: A Promising Molecule for Therapy of Diverse Disease by Targeting NAD+ Metabolism. Frontiers in Cell and Developmental Biology. 28 April 2020

Rosacea and Dermatitis

"Topical application of NADH for the treatment of rosacea and contact dermatitis.

Among many important physiological functions played by NADH (the reduced form of beta-nicotinamide adenine dinucleotide) its antioxidative properties are remarkable. Acting directly as an antioxidant, NADH can effectively protect the cell and its membrane from destruction by free radicals. **NADH can be stabilized as a suspension in hydrophobic ointments prepared in a way that prevents contact with atmosphere containing oxygen and water. We present the first report of NADH as a treatment for some inflammatory dermatoses.** It was found that topical application of 1% NADH diluted in Vaseline ointment can be very effective in the treatment of rosacea and contact dermatitis. Since no adverse effects were observed, therapy with NADH can be viewed as a potential alternative to other established treatments."[1]

1. Wojniacka A, Sysa-Jedrzejowska A, Adamus J, Gebicki J. Topical application of NADH for the treatment of rosacea and contact dermatitis. Clin Exp Dermatol. 2003 Jan;28(1):61-3.

Rosacea and Dermatitis

	Cohort	Materials	Study Length	Results
Rosacea	10 women, ages 21 - 61 with persistent disease of 1-4 years	2-3 g of 1% ointment applied BID	14 days	-30% showed 75% reduction in papules and erythema -50% showed 50% reduction in papules and erythema -20% showed slight or no clinical difference
Exogenous Eczema	4 males and 5 females, ages 20 - 48 with short-lasting allergic contact dermatitis	2-3 g of 1% ointment applied BID	14 days	-66% showed marked decrease in erythema, oedema and vesicular lesions -33% showed patients complete clearance of symptoms -No skin dryness or post-inflammatory desquamation was noticed

Wojniacka A, Sysa-Jedrzejowska A, Adamus J, Gebicki J. Topical application of NADH for the treatment of rosacea and contact dermatitis. Clin Exp Dermatol. 2003 Jan;28(1):61-3.

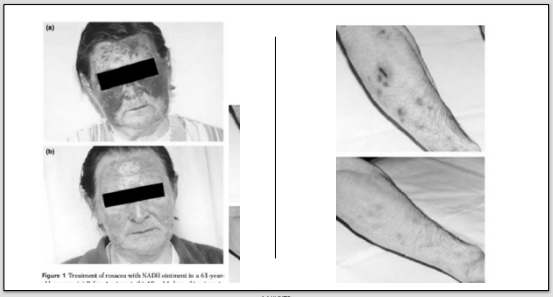


Figure 1 Treatment of rosacea with NADH ointment in a 63-year-

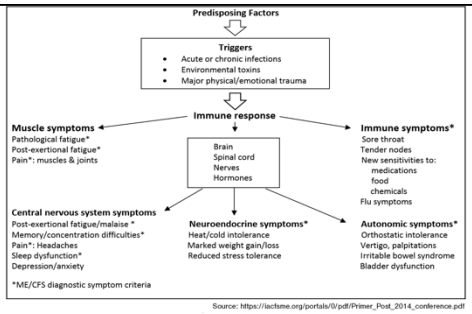
Myalgic Encephalomyelitis (Chronic Fatigue Syndrome)

The purpose of the study was to evaluate the efficacy of the reduced form of nicotinamide adenine dinucleotide (NADH), in a randomized, double-blind, placebo-controlled crossover study in patients with CFS.

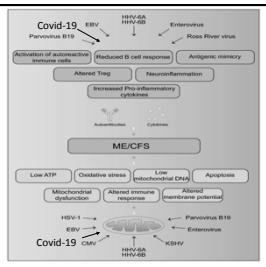
Table 2. Clinical Symptoms Presenting in Subjects

Symptom	Number of Patients (%) n = 26
Fatigue	26 (100)
Neurocognitive difficulties	26 (100)
Sleep disturbance	26 (100)
Postexertional malaise	25 (96)
Headaches	24 (92)
Muscle weakness	24 (92)
Arthralgia	22 (85)
Myalgias	21 (81)
History of allergy	21 (81)
Swelling and tenderness of lymph nodes	18 (69)

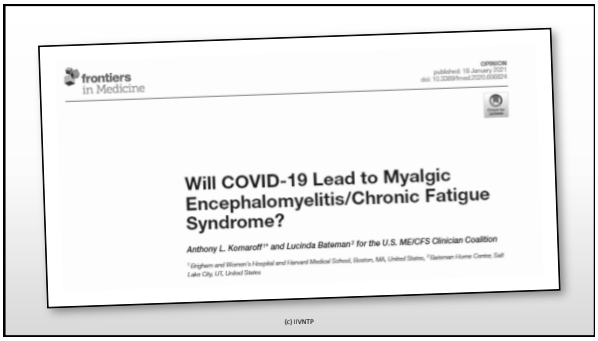
1. Forsyth LM, Preuss HG, MacDowell AL, Chiazze L Jr, Birkmayer GD, Bellanti JA. Therapeutic effects of oral NADH on the symptoms of patients with chronic fatigue syndrome. Am Allergy Asthma Immunol. 1999 Feb;82(2):185-91.



Source: https://iacfsme.org/portals/0/pdf/Primer_Post_2014_conference.pdf



[i] Rasa S, Nora-Krukle Z, Henning N, Eliassen E, Shikova E, Harrer T, Scheibenbogen C, Murovska M, and Prusty BK. Chronic viral infections in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). *J Translational Med.* 2018; 16: 268, doi:10.1186/s12967-018-1644-y.


frontiers in Medicine

OPINION

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Will COVID-19 Lead to Myalgic Encephalomyelitis/Chronic Fatigue Syndrome?

Anthony L. Komaroff[1] and Lucinda Bateman[2] for the U.S. ME/CFS Clinician Coalition*

[1] Brigham and Women's Hospital and Harvard Medical School, Boston, MA, United States, [2] Bateman Horne Center, Salt Lake City, UT, United States

Myalgic Encephalomyelitis

Cohort	Study Design	Materials	Results
26 eligible female CSF patients ages 26-57	4-week randomized, double-blind, placebo-controlled crossover	Participants received either 2, 5 mg NADH tablets to be taken daily or placebo	-(31%) subjects showed 10% improvement Compared to (8%) who received placebo -(35%) subjects were able to correctly evaluate the treatment period they were on NADH -(72%) study patients thus far enrolled in a longer open label follow-up study, reported significant improvement in clinical symptomatology and energy levels. -No **severe adverse effects were observed** related to the study drug.

1. Forsyth LM, Preuss HG, MacDowell AL, Chiazze L Jr, Birkmayer GD, Bellanti JA. Therapeutic effects of oral NADH on the symptoms of patients with chronic fatigue syndrome. Ann Allergy Asthma Immunol. 1999 Feb;82(2):185-91.

Myalgic Encephalomyelitis (Chronic Fatigue Syndrome)

"Does Oral Coenzyme Q10 Plus NADH Supplementation Improve Fatigue and Biochemical Parameters in Chronic Fatigue Syndrome?

Chronic fatigue syndrome (CFS) is a chronic and extremely debilitating illness characterized by prolonged fatigue and multiple symptoms with unknown cause, diagnostic test, or universally effective treatment. Inflammation, oxidative stress, mitochondrial dysfunction, and CoQ10 deficiency have been well documented in CFS. **We conducted an 8-week, randomized, double-blind placebo-controlled trial to evaluate the benefits of oral CoQ10 (200 mg/day) plus NADH (20 mg/day) supplementation on fatigue and biochemical parameters** in 73 Spanish CFS patients. This study was registered in ClinicalTrials.gov (*NCT02063126*) [*1]

Castro-Marrero J, Cordero MD, Segundo MJ, et al. Does Oral Coenzyme Q_{10}Plus NADH Supplementation Improve Fatigue and Biochemical Parameters in Chronic Fatigue Syndrome? *Antioxidants & Redox Signaling.* 2015;23(8):679-685.

Myalgic Encephalomyelitis

Cohort	Study Design	Materials	Results
73 eligible female CFS patients ages 42-56	8-week, randomized, double-blind placebo-controlled trial	Participants received 1:1 200 mg CoQ_{10} and 20 mg NADH or placebo in gelatin capsules, given in 2 daily divided doses.	-**Fatigue impact scale:** significant reduction in total score ($p < 0.05$) was reported in treated group versus placebo. -**Biochemical parameters:** NAD+/NADH ($p < 0.001$), CoQ10 ($p < 0.05$), ATP ($p < 0.05$), and citrate synthase ($p < 0.05$) **were significantly higher** lipoperoxides ($p < 0.05$) **were significantly lower** in blood mononuclear cells of the treated group. -**No adverse events reported**

Castro-Marrero J, Cordero MD, Segundo MJ, et al. Does Oral Coenzyme Q_{10}Plus NADH Supplementation Improve Fatigue and Biochemical Parameters in Chronic Fatigue Syndrome? *Antioxidants & Redox Signaling.* 2015;23(8):679-685.

Myalgic Encephalomyelitis (Chronic Fatigue Syndrome)

"Effect of coenzyme Q10 plus nicotinamide adenine dinucleotide supplementation on maximum heart rate after exercise testing in chronic fatigue syndrome – A randomized, controlled, double-blind trial

In conclusion, this **8-week, randomized, double-blind, placebo-controlled trial** suggested that the CoQ_{10} plus NADH supplementation may be a safe, well tolerated and potentially useful treatment. Beside, **CoQ_{10} plus NADH supplementation improved significantly reducing max HR during the ergometer stress test and also on perceived fatigue in CFS.** On the contrary, CoQ_{10} plus NADH supplementation had no positive effect on pain and sleep disturbances between the intervention groups. Larger multicenter trials with longer term follow-up interventions in more homogenous CFS populations are warranted to assess these findings and to produce evidence-based guidelines regarding the potential benefits of antioxidant therapy in CFS and other chronic conditions."[1]

1. Castro-Marrero J, Sáez-Francàs N, Segundo MJ, Calvo N, Faro M, Aliste L, Fernández-de-Sevilla T, Alegre J. Effect of coenzyme Q10 plus nicotinamide adenine dinucleotide supplementation on maximum heart rate after exercise testing in chronic fatigue syndrome - A randomized, controlled, double-blind trial. Clin Nutr. 2016 Aug;35(4):828-34.

Myalgic Encephalomyelitis

Cohort	Study Design	Materials	Results
80 eligible female CFS patients ages 41-57 *73 completed the study	8-week, randomized, placebo controlled, double-blind trial	Participants were randomized to rec 100 mg CoQ_{10} and 10 mg NADH or placebo in 4 oral enteric coated tablets, given daily	-CoQ_{10} + NADH group showed a **significant reduction in max HR** during a cycle ergometer test at week 8 versus baseline (P. 0.022) -Perception of fatigue also **showed a decrease** through all follow-up visits in active group versus placebo (P . 0.03). -Pain and sleep did not improve in the active group. -Was generally **safe and well tolerated.**

1. Castro-Marrero J, Sáez-Francás N, Segundo MJ, Calvo N, Faro M, Aliste L, Fernández-de Sevilla T, Alegre J. Effect of coenzyme Q10 plus nicotinamide adenine dinucleotide supplementation on maximum heart rate after exercise testing in chronic fatigue syndrome - A randomized, controlled, double-blind trial. Clin Nutr. 2016 Aug;35(4):828-34.

Diabetes/Obesity

- NAD+ plays a crucial role in insulin sensitivity and secretion
- NAD+ biosynthesis is critical for proper Beta cell function
- 500 mg/kg/day of NMN for 12 months was shown in mice to ameliorate age-associated decreased insulin sensitivity
- 100 and 300 mg/kg/day of NMN for 12 months was show to reduce weight by 4% and 9% respectively compared to the control.

Hong, W, et al. Nicotinamide Mononucleotide: A Promising Molecule for Therapy of Diverse Disease by Targeting NAD+ Metabolism. Frontiers in Cell and Developmental Biology. 28 April 2020

Alcoholic Liver Dz.

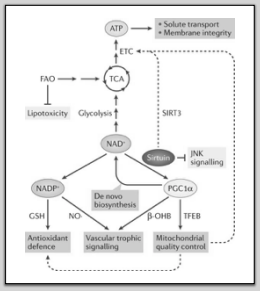
500 mg/kg NMN every other day for 6 weeks

Prevented ethanol-induced elevation of plasma ALT and AST

Hong, W, et al. Nicotinamide Mononucleotide: A Promising Molecule for Therapy of Diverse Disease by Targeting NAD+ Metabolism. Frontiers in Cell and Developmental Biology. 28 April 2020

Acute Kidney Injury

- Cisplatin-induced or ischemic injury leading to acute kidney injury
- Reduced PG1a triggers damage to kidneys
- Treatment NMN 500 mg/kg x 4 days



NAD⁺ homeostasis in renal health and disease

Kenneth M. Ralto[1], Eugene P. Rhee[2] and Samir M. Parikh[3]

Abstract | The mammalian kidney relies on abundant mitochondria in the renal tubule to generate sufficient ATP to provide the energy required for constant reclamation of solutes from crude blood filtrate. The highly metabolically active cells of the renal tubule also pair their energetic needs to the regulation of diverse cellular processes, including energy generation, antioxidant responses, autophagy and mitochondrial quality control. Nicotinamide adenine dinucleotide (NAD^+)is essential not only for the harvesting of energy from substrates but also for an array of regulatory reactions that determine cellular health. In acute kidney injury (AKI), substantial decreases in the levels of NAD^+ impair energy generation and, ultimately, the core kidney function of selective solute transport. Conversely, augmentation of NAD^+ may protect the kidney tubule against diverse acute stressors. For example, NAD^+ augmentation can ameliorate experimental AKI triggered by ischaemia–reperfusion, toxic injury and systemic inflammation. NAD^+-dependent maintenance of renal tubular metabolic health may also attenuate long-term profibrotic responses that could lead to chronic kidney disease. Further understanding of the genetic, environmental and nutritional factors that influence NAD^+ biosynthesis and renal resilience may lead to novel approaches for the prevention and treatment of kidney disease.

Heart Failure and Cardiomyopathies

- NMN supplementation reduced lactate production and inhibited glycolysis improving cardiac expenditure and function.
- NMN blocks fatty acid oxidation and serum triglyceride in heart failure models
- Preclinically shows promise for heart failure and cardiomyopathies

Hong, W, et al. Nicotinamide Mononucleotide: A Promising Molecule for Therapy of Diverse Disease by Targeting NAD+ Metabolism. Frontiers in Cell and Developmental Biology. 28 April 2020

CLINICAL MEDICINE — The Journal of Clinical Investigation

Boosting NAD level suppresses inflammatory activation of PBMCs in heart failure

Bo Zhou,[1] Dennis Ding-Hwa Wang,[2] Vanhua Qiu,[1] Sophia Airhart,[2] Yaxin Liu,[1] April Stempien-Otero,[2] Kevin D. O'Brien,[2] and Rong Tian[1]

[1]Mitochondria and Metabolism Center, Department of Anesthesiology and Pain Medicine and [2]Division of Cardiology, Department of Medicine, University of Washington School of Medicine, Seattle, Washington, USA.

BACKGROUND. While mitochondria play an important role in innate immunity, the relationship between mitochondrial dysfunction and inflammation in heart failure (HF) is poorly understood. In this study we aimed to investigate the mechanistic link between mitochondrial dysfunction and inflammatory activation in peripheral blood mononuclear cells (PBMCs), and the potential antiinflammatory effect of boosting the NAD level.

METHODS. We compared the PBMC mitochondrial respiration of 19 hospitalized patients with stage D HF with that of 19 healthy participants. We then created an in vitro model of sterile inflammation by treating healthy PBMCs with mitochondrial damage–associated molecular patterns (MitoDAMPs) isolated from human heart tissue. Last, we enrolled patients with stage D HF and sampled their blood before and after taking 5 to 9 days of oral nicotinamide riboside (NR), a NAD precursor.

RESULTS. We demonstrated that HF is associated with both reduced respiratory capacity and elevated proinflammatory cytokine gene expressions. In our in vitro model, MitoDAMP-treated PBMCs secreted IL-6 that impaired mitochondrial respiration by reducing complex I activity. Last, oral NR administration enhanced PBMC respiration and reduced proinflammatory cytokine gene expression in 4 subjects with HF.

CONCLUSION. These findings suggest that systemic inflammation in patients with HF is causally linked to mitochondrial function of the PBMCs. Increasing NAD levels may have the potential to improve mitochondrial respiration and attenuate proinflammatory activation of PBMCs in HF.

TRIAL REGISTRATION. ClinicalTrials.gov NCT03727646.

FUNDING. This study was funded by the NIH, the University of Washington, and the American Heart Association.

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NAD and Eye Health

Review Article

Implications of NAD+ Metabolism in the Aging Retina and Retinal Degeneration

Ravirajsinh N. Jadeja, Menaka C. Thounaojam, Manuela Bartoli, and Pamela M. Martin

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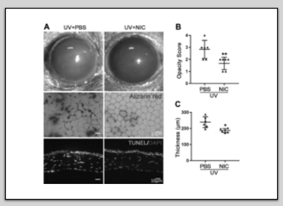
NAD and corneal regeneration



RESEARCH ARTICLE

NAD+ precursors protect corneal endothelial cells from UVB-induced apoptosis

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Cancer support

- It is postulated that a decrease in NAD concentration has a primary association with carcinogenesis. The following observations have been discovered:
- 1. NAD & ATP concentrations are lower in cancer cells
- 2. Chemical carcinogens and radiation can cause a lowering of NAD concentration in precancerous cells
- 3. Biosynthesis of NAD in certain tumor cells is altered
- 4. NAD is involved in regulating deoxyribonucleic acid (DNA) synthesis.
- The lowering of NAD concentration would lead to the expression of oncogene and/or virogene according to the *protovirus hypothesis*, and the cellular characteristics of cancer cells can also be explained through the lowering of cellular NAD."

Chung, K.T. (1982). An association of carcinogenesis and decrease of cellular NAD concentration. Chung Hua Min Kuo Wei Sheng Wu Chi Mien I Hsueh Tsa Chih 1982 Nov;15(4):309-18

(c) IIVNTP

Cancer support

- These folks need mitochondrial support just as much if not more so than immune support
- NAD+ helps with "chemo brain" if Hx of Chemo
- Tx: 250-500mg NAD+ in 500NS 2-3x/mo
- F/U: energy & mental clarity pick up dramatically as does general quality of life

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Oncology – Not a linear consideration!

- Genomic stress is the root of all cancers, and so maintaining genome integrity is an essential tool for the prevention of cancer. The fact that PARPs and several sirtuin enzymes are key for genomic maintenance suggests that the regulation of NAD+ **could have** an impact on cancer susceptibility and development (Cantó et al., 2013).

(c) IIVNTP

Roy K, et. al. NADPH oxidases and cancer.
Clin Sci (Lond). 2015 Jun;128(12):863-75. doi: 10.1042/CS20140542.

- * Nobody wants to really read this paper… trust me.
- But it underscores that we know likely 5-10% of what NAD biology and cancer have to do with one another.

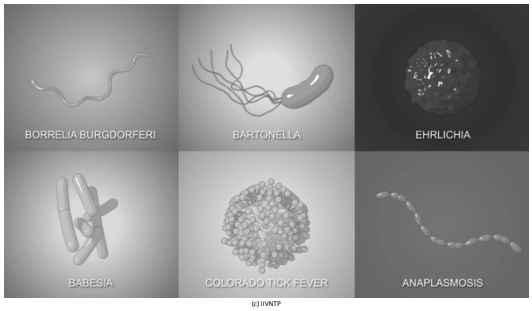
Hong SM, Hwang SW, Wang T, et al. **Increased nicotinamide adenine dinucleotide pool promotes colon cancer progression by suppressing reactive oxygen species level.** Cancer Sci. 2018;110(2):629–638. doi: 10.1111/cas.13886

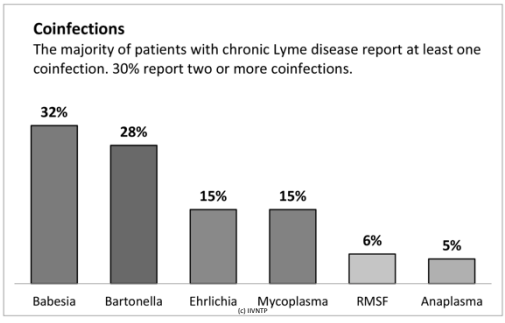
- **Cancer cells require significantly more NAD+ than normal cells due to their elevated metabolic needs.** The cytosolic NAD+/NADH ratio was reported to downregulate in cancer cell lines such as H1299, U87 and MDA-MB468, as observed by genetically engineered fluorescent biosensors that can measure protein-unbound species of NAD(H)
- We confirmed that the **NAD(H) pool size and NAD+/NADH ratio could increase during CRC progression due to the increasing influx of NAD+, which was mediated by NAMPT**. NAMPT-mediated increases in the NAD(H) pool size should promote inflammation-induced CRC progression by decreasing the detrimental effects associated with excessive ROS accumulation.

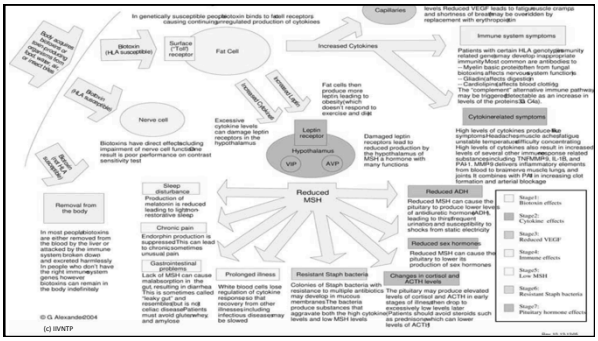
Oncology – So what do we do?

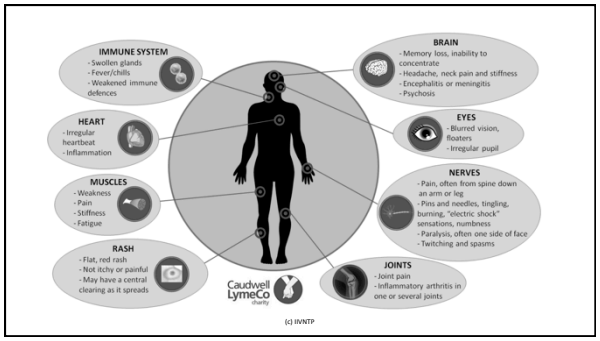
- **Think of it like glutathione and cancer:**

1. It isn't "one way or the other" (all good or all bad)
2. It is actually both!
3. Lower doses as support are fine during active and recovery phases of oncology therapies.
4. Higher doses would not be recommended during those time periods (generally)
5. And, just like glutathione, in a true primary prevention (i.e. no occult cancer) setting optimized NAD cycling is likely protective against oncogenesis.





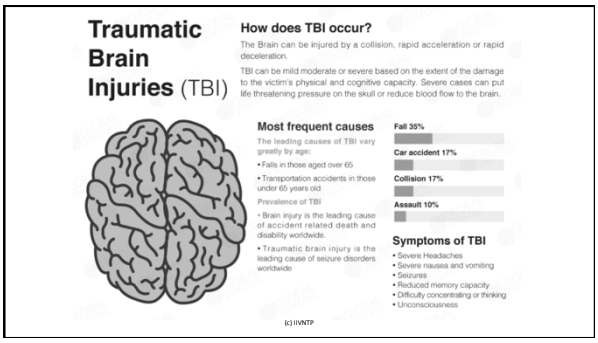


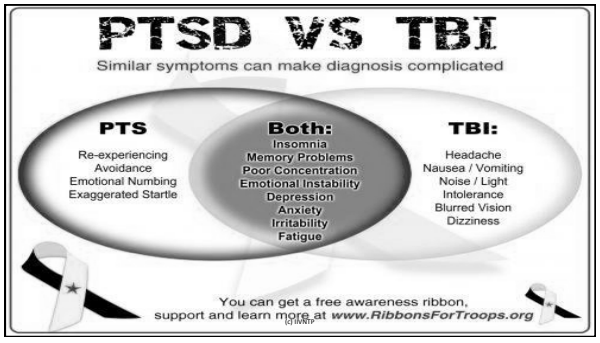


NAD Tx in Lyme Disease

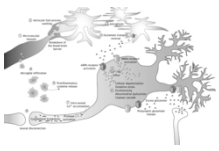
- Sx: Fatigue, Dizziness, Photosensitivity, Blurred Vision, Insomnia just to name a few
- Tx: WIDE range from 100mg NAD up to 1000mg x 5-7 days depending on tolerance of the patient
- F/U:
  - Markedly improved energy, clarity & sleep (from 4-5 hrs/nt to 7-8 hrs/nt)
  - Decreased photosensitivity & dizziness > could drive again!
  - Multiple patients went from not even being able to read an Ad in a magazine to free reading by day 4

(c) IIVNTP





TBI / Concussion / CTE



- Documented decrease in NAD levels
- Shift to pentose pathway
- Decrease in PDH
- Hopeful pilot study with NFL w/ - NAD, HBOT, PEMF & Stem Cells

(c) IIVNTP

TBI/CTE

- TBI- Traumatic Brain Injury
- CTE- Chronic Traumatic Encephalopathy
- Hx: Concussion from various trauma
- Sx: agitation/ dizziness / low-grade nausea & depression/ acute dementia
- Tx: 1000mg NAD+ in 1000NS x 4-5 days
  - PEMF to prefrontal cortex qd x 15 min
  - HBOT 3 days/wk x 6-8 weeks @ 3ATM
- F/U on 5 cases:
  - All patients reported marked improvement of symptoms & were able to return to work

Ischemic Injury Brain

- NMN alleviates cerebral infarction size, neurological deficit and neuronal cell death.
- NMN supplements for 7 days with first administration at 12 hours after cerebral ischemia improved post-ischemic regenerative neurogenesis.
- Is dose dependent 62.5 mg/kg was optimal
- Dosages of 500, 250, 125 mg showed adverse effects on post-ischemic neurons.
- NMN accumulation in injured nerves promotes axonal degeneration

Regenerative Neurogenesis After Ischemic Stroke Promoted by Nicotinamide Phosphoribosyltransferase–Nicotinamide Adenine Dinucleotide Cascade

Yan Zhao, MD, PhD*; Yun-Feng Guan, BSc*; Xiao-Ming Zhou, MD*; Guo-Qiang Li, MD; Zhi-Yong Li, MD, PhD; Can-Can Zhou, BSc; Pei Wang, MD, PhD; Chao-Yu Miao, MD, PhD

Background and Purpose—Nicotinamide adenine dinucleotide (NAD) is a ubiquitous fundamental metabolite. Nicotinamide phosphoribosyltransferase (Nampt) is the rate-limiting enzyme for mammalian NAD salvage synthesis and has been shown to protect against acute ischemic stroke. In this study, we investigated the role of Nampt–NAD cascade in brain regeneration after ischemic stroke.

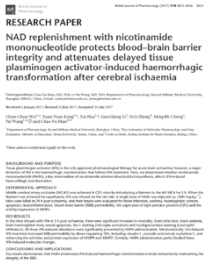
Methods—Nampt transgenic (Nampt-Tg) mice and H247A mutant enzymatic-dead Nampt transgenic (ΔNampt-Tg) mice were subjected with experimental cerebral ischemia by middle cerebral artery occlusion. Activation of neural stem cells, neurogenesis, and neurological function recovery were measured. Besides, nicotinamide mononucleotide and NAD, two chemical enzymatic product of Nampt, were administrated in vivo and in vitro.

Results—Compared with wild-type mice, Nampt-Tg mice showed enhanced number of neural stem cells, improved neural functional recovery, increased survival rate, and accelerated body weight gain after middle cerebral artery occlusion, which were not observed in ΔNampt-Tg mice. A delayed nicotinamide mononucleotide administration for 7 days with the first dose at 12 hours post middle cerebral artery occlusion did not protect acute brain infarction and neuronal deficit; however, it still improved postischemic regenerative neurogenesis. Nicotinamide mononucleotide and NAD+ promoted proliferation and differentiation of neural stem cells in vitro. Knockdown of NAD-dependent deacetylase sirtuin 1 (SIRT1) and SIRT2 inhibited the progrowth action of Nampt–NAD axis, whereas knockdown of SIRT1, SIRT2, and SIRT6 compromised the prodifferentiation effect of Nampt–NAD axis.

Conclusions—Our data demonstrate that the Nampt–NAD cascade may act as a centralizing switch in postischemic regeneration through controlling different sirtuins and therefore represent a promising therapeutic target for long-term recovery of ischemic stroke. (***Stroke***. 2015;46:1966-1974. DOI: 10.1161/STROKEAHA.115.009216.)

Key Words: ischemic stroke ■ NAD ■ neurogenesis ■ neural stem cells ■ sirtuin

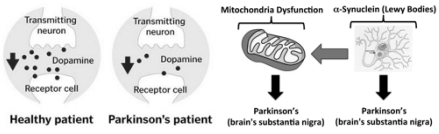
How about with hemorrhagic stroke or tPa induced hemorrhage?

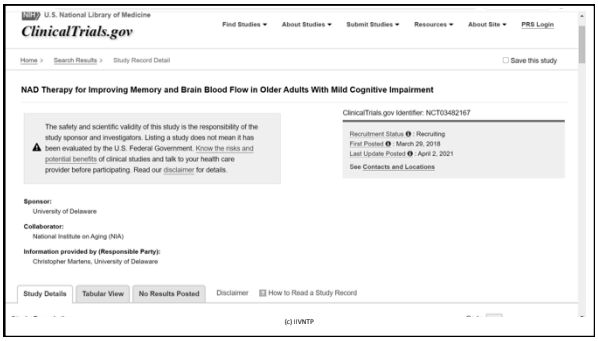


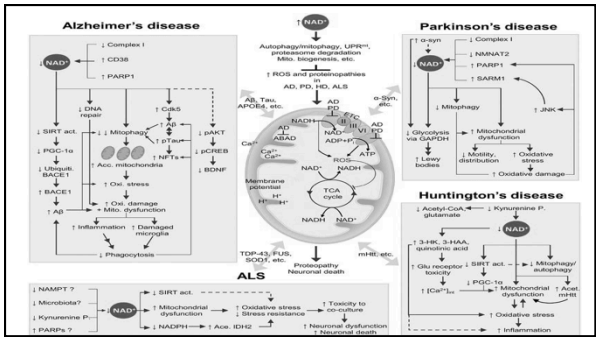
RESEARCH PAPER

NAD replenishment with nicotinamide mononucleotide protects blood–brain barrier integrity and attenuates delayed tissue plasminogen activator-induced haemorrhagic transformation after cerebral ischaemia

Dementia / Parkinson's







NAD+ in Brain Aging and Neurodegenerative Disorders

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Abstract

NAD+ is a pivotal metabolite involved in cellular bioenergetics, genomic stability, mitochondrial homeostasis, adaptive stress responses, and cell survival. Multiple NAD+-dependent enzymes are involved in synaptic plasticity and neuronal stress resistance. Here, we review emerging findings that 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, and amyotrophic lateral sclerosis. Advances in understanding the molecular and cellular mechanisms of NAD+-based neuronal resilience will lead to novel approaches for facilitating healthy brain aging and for the treatment of a range of neurological disorders.

Table 2.

A Summary of Clinical Trials with NAD+ Precursors: Focusing on Cognitive Function and Neurodegenerative Diseases

Disease	NAD+ Precursor	Dose and Treatment Duration	Main Endpoints	Status and Results	References/NCT
AD and MCI	NAM	1,500 mg twice daily, orally for 48 weeks	effect on P-tau[181] and total tau in CSF	recruiting, no results	
		1,500 mg twice daily for 6 months	Alzheimer's Disease Assessment Scale-Cognitive Subscale (cognitive function)	completed, no effect reported	Flanka et al., 2022
	NR	dose escalation, 250–1,000 mg for 10 weeks	change in cognitive assessments, cerebral blood flow, plasma NAD levels, and physical performances in MCI patients	recruiting, no results	
		500 mg twice daily for 12 weeks	memory, brain blood flow, and cognitive function	recruiting, no results	
	NADH	10 mg/day for 8–12 weeks (i.v.)	cognitive score (MMSE)	completed, no effect on cognitive score	Reiser et al., 2000
			cognitive score (MMSE)	completed, improved cognitive score	Birkmayer, 1996
PD	NR	1,000 mg/day for 32 weeks	MDS-UPDRS, levels of NAD metabolites in blood	not yet recruiting, no results	
		500 mg/day for 30 days	changes in PD related pattern, neurometabolic profile, and motor function	recruiting, no results	
	NA or NAM	100 mg twice daily for 18 months	unified PD rating scale changes, cognitive function (MMSE), sleep, niacin changes, and inflammatory markers in CSF	not yet recruiting, no results	
	NADH	25–50 mg/day, i.v. or i.m.	changes in PD-related disabilities, including movements	completed, benefits on PD-related disabilities like movement	Birkmayer et al., 1989, 1993
		25 mg/day/4 days i.v., after 2–4 weeks 25 mg/day/4 days i.m.	unified PD rating scale changes including disabilities and movements	completed, no effects of treatment	Dietzie et al., 1994

Parenteral application of NADH in Parkinson's disease: clinical improvement partially due to stimulation of endogenous levodopa biosynthesis

W Kuhn [1], T Müller, R Winkel, S Danielczik, A Gerstner, R Hacker, C Mattern, H Przuntek

Affiliations + expand
PMID: 9013405 DOI: 10.1007/BF01271203

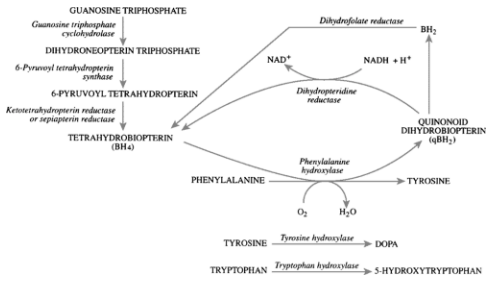
Abstract

Exogenous application of levodopa is conventionally used to equalize the striatal dopamine deficit in idiopathic Parkinson's disease (PD). The stimulation of endogenous biosynthesis of levodopa via activation of tyrosine hydroxylase (TH) has been proposed as new therapeutic concept in PD. This may be achieved by exogenous supply with the reduced coenzyme nicotinamide adenine dinucleotide (NADH). Aim of this open prospective study was to investigate (1) the efficacy of a new developed, parenteral application form of NADH on Parkinsonian symptoms and (2) the influence of bioavailability of levodopa. 15 patients, suffering from idiopathic PD (11 male, 4 female, age: 61.40[mean] +/- 10.27[SD] range: 44-74 years, Hoehn and Yahr stage: 3.03 +/- 0.69, range 2-4) received intravenous infusions of NADH (10 mg a' 30 min) over a period of 7 days in addition to conventional Parkinsonian pharmacotherapy. Parkinsonian symptoms were scored before (day 1) and after NADH treatment (day 8). Levodopa plasma levels were estimated over a period of four hours on the day before and on the first day of NADH application by HPLC. Parkinsonian patients showed a significant response, evaluated by the Unified Parkinson's Disease Rating Scale Version 3.0 (p = 0.025; Wilcoxon test). Moreover application of NADH significantly increased bioavailability of plasma levodopa (AUC, p = 0.035; Cmax p = 0.025). In conclusion NADH in used galenic form may be a potent stimulator of endogenous levodopa biosynthesis with clinical benefit for Parkinsonian patients.

Kuhn W, et al. **Parenteral application of NADH in Parkinson's disease:** clinical improvement partially due to stimulation of endogenous levodopa biosynthesis. J Neural Transm (Vienna). 1996. PMID 9013405

Abstract

Exogenous application of levodopa is conventionally used to equalize the striatal dopamine deficit in idiopathic Parkinson's disease (PD). The stimulation of endogenous biosynthesis of levodopa via activation of tyrosine hydroxylase (TH) has been proposed as new therapeutic concept in PD. This may be achieved by exogenous supply with the reduced coenzyme nicotinamide adenine dinucleotide (NADH). Aim of this open prospective study was to investigate (1) the efficacy of a new developed, parenteral application form of NADH on Parkinsonian symptoms and (2) the influence of bioavailability of levodopa. 15 patients, suffering from idiopathic PD (11 male, 4 female, age: 61.40[mean] +/- 10.27[SD] range: 44-74 years, Hoehn and Yahr stage: 3.03 +/- 0.69, range 2-4) received intravenous infusions of NADH (10 mg a' 30 min) over a period of 7 days in addition to conventional Parkinsonian pharmacotherapy. Parkinsonian symptoms were scored before (day 1) and after NADH treatment (day 8). Levodopa plasma levels were estimated over a period of four hours on the day before and on the first day of NADH application by HPLC. Parkinsonian patients showed a significant response, evaluated by the Unified Parkinson's Disease Rating Scale Version 3.0 (p = 0.025; Wilcoxon test). Moreover application of NADH significantly increased bioavailability of plasma levodopa (AUC, p = 0.035; Cmax p = 0.025). In conclusion NADH in used galenic form may be a potent stimulator of endogenous levodopa biosynthesis with clinical benefit for Parkinsonian patients.



https://musculoskeletalkey.com/disorders-of-amino-acid-and-organic-acid-metabolism/#F2-385

Birkmayer JG, et al. Nicotinamide adenine dinucleotide **(NADH)--a new therapeutic approach to Parkinson's disease. Comparison of oral and parenteral application.** Acta Neurol Scand Suppl. 1993. PMID 8101414

Abstract

The reduced coenzyme nicotinamide adenine dinucleotide (NADH) has been used as medication in 885 parkinsonian patients in an open label trial. About half of the patients received NADH by intravenous infusion, the other part orally by capsules. In about 80% of the patients a beneficial clinical effect was observed: 19.3% of the patients showed a very good (30-50%) improvement of disability, 58.8% a moderate (10-30%) improvement. 21.8% did not respond to NADH. Statistical analysis of the improvement in correlation with the disability prior to treatment, the duration of the disease and the age of the patients revealed the following results: All these 3 parameters have a significant although weak influence on the improvement. The disability before the treatment has a positive regression coefficient (t value < 0.01). The duration of the disease has a negative regression coefficient (< 0.01) and so has the age a negative regression coefficient (t value < 0.05). **In other words younger patients and patients with a shorter duration of disease have a better chance to gain a marked improvement than older patients and patients with longer duration of the disease. The orally applied form of NADH yielded an overall improvement in the disability which was comparable to that of the parenterally applied form.**

Parkinson's Case: JL 72 yo female

- Sx: pill rolling tremor, shuffling gait, shaky speech & fine motor skills, cognitive impairment
- Hx: 7-8 yrs of gradual progression of disease; had tried L-Dopa in the past but didn't like it; Hx of opiate use
- Tx: 1,500mg NAD+ in 1000NS x 2 days, 1000mg in 750NS x 3 days then 750mg in 500NS x 2 days
- Oral NR: 300 mg BID between infusions
- Eval:
  - Tremors - nearly gone by day 4; Gait improved drastically
  - Memory improved slightly by day 3 & significantly by day 7

Serum nicotinamide adenine dinucleotide levels through disease course in multiple sclerosis.

- **Abstract**
- The levels of the essential pyridine nucleotide, NAD(+) and its reduced form NADH have not been documented in MS patients. We aimed to investigate NAD(+) and NADH levels in serum in patients with different disease stages and forms of MS. NAD(+) and NADH levels were measured in the serum from 209 patients with relapsing remitting MS (RRMS), 136 with secondary progressive MS (SPMS), 51 with primary progressive MS (PPMS), and 99 healthy controls. All patients were in a clinically stable phase. Serum NAD(+) levels declined by at least 50% in patients with MS compared to controls (17.9 ± 3.2 μg/ml; p=0.0012). Within the MS sub-groups NAD(+) levels were higher in RRMS (9.9 ± 2.9 μg/ml; p=0.001) compared to PPMS (6.3 ± 2.1 μg/ml; p=0.003) and SPMS (7.8 ± 2.0 μg/ml; p=0.005). A two-fold increase in NADH levels (p=0.002) and at least three-fold reduction in the NAD(+)/NADH ratio (p=0.009) were observed in MS patients compared to controls. Serum NAD(+) and NADH levels are may be associated with disease progression in MS. Given the importance of NAD(+) in the maintenance of normal cellular function, it is likely that this molecule is of therapeutic relevance in MS.

- Serum nicotinamide adenine dinucleotide levels through disease course in multiple sclerosis. Braidy N., Lim CK, Grant R, Brew BJ, Guillemin GJ. Brain Res. 2013 Nov 6;1537:267-72. doi: 10.1016/j.brainres.2013.08.025. Epub 2013 Aug 21. PMID: 23973746

Human Clinical Trials (NMN)

TABLE 2 | Human clinical trials of NMN.

Molecule	Objectives	Subjects and sample size	Intervention	Study design	Region and Institute	Phase	Trial number
NMN	Evaluate the safety and kinetics of NMN in healthy volunteers	Healthy men 40–60 years (n = 10)	NMN P.O. single time	Non-randomized non-label uncontrolled	Keio University School of Medicine in Japan	I	UMIN000021309
NMN	Evaluate the safety and kinetics of long-term NMN and its effect on glucose metabolism in healthy volunteers.	Healthy men 40–60 years (n = 30)	NMN P.O. 8 weeks	Non-randomized non-label uncontrolled	Keio University School of Medicine in Japan.	II	UMIN000030609
NMN	Evaluate the effect of the dietary (NMN) on key cardiovascular and metabolic functions in healthy women.	Postmenopausal women pre-diabetic BMI 25.0–44.9 55–75 years (n = 25)	Placebo or 250 mg/day NMN P.O. 8 weeks	Randomized double-blinded placebo-controlled	Washington University School of Medicine in United States of America	Active, not recruiting	NCT03151239
NMN	Evaluate the safety and effect of long-term NMN on various hormonal levels in healthy human.	Healthy men and women 50–70 years (n = 20)	100 or 200 mg/day NMN P.O. 24 weeks	Randomized double-blinded dose comparison	Hiroshima University in Japan	Not applicable	UMIN000025739
NMN	Evaluate the effect of NMN on the body composition in the elder	Healthy men no smoking BMI 22–28 ~65 years (n = 42)	Placebo or 250 mg/day NMN P.O. 12 weeks	Randomized double-blind placebo-controlled	The University of Tokyo Hospital in Japan	Not applicable	UMIN000036321

There is no panacea…

- PO, TD, IM NAD+ ongoing after treatment &/or…
- 1-Day IV NAD Booster q 2-3 months depending on case
- Amino Acids & nutrients to support NT imbalances
- IV Ozone Therapy/MAH to indirectly ^ NAD levels
- Integrate in other supportive therapies IV with the line in > Meyer's, GSH, etc.
- HBOT > TBI/CTEs
- AA/NA &/or Individual Counseling for Addicts

SUMMARY OF BENEFITS

- Rebalances neurotransmitters & optimizes mitochondrial function
- Reduces cravings & withdrawl symptoms of substance detox
- Improves mental clarity and cognitive function
- Accelerates recovery of psycho-emotional issues
- Reduces oxidative stress
- Slows & possibly reverses the aging process
- Activates PARPs which detects & repair damaged DNA
- Activates SIRTs, which helps increase metabolism, decrease inflammation, extend cell life, and prevent neurodegeneration
- Activates cell signaling which alerts the immune response when the cell is under stress or when there is inflammation