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.

Nicotinamide Riboside

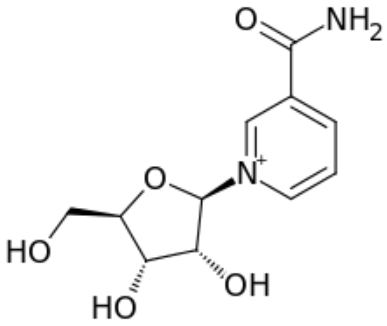
Evidence Summary

Lots of preclinical data indicate nicotinamide riboside may improve several aspects of aging, including Alzheimer's disease. No efficacy studies in humans have been conducted.

Neuroprotective Benefit: Very promising particularly for prevention, but no efficacy data in humans yet.

Aging and related health concerns: Very promising for several indications but not yet tested in humans for efficacy. Many unanswered questions, especially on dose.

Safety: No serious concerns identified but long-term human studies are limited. Some theoretical concerns exist.

Availability: OTC from Chromadex and Elysium Health	**Dose**: Clinical studies have used ~500-1000mg/day.	**Chemical formula:** $C_{11}H_{15}N_2O_5^+$ **MW**: 255.25g/mol
Half life: 2.7 hrs	**BBB**: Unknown in humans and unclear in mice	
Clinical trials: 3 safety and PK studies in 20 healthy adults (NR) and 120 elderly (Basis)	**Observational studies**: None	

What is it?

Nicotinamide adenine dinucleotide (NAD+) is a critical coenzyme that, when reduced to NADH, serves as a reducing agent to donate electrons for oxidative phosphorylation and ATP synthesis in mitochondria. NAD+ is a critical cofactor for enzymes such as sirtuins, ADP-ribosyltransferases (ARTs), and Poly [ADP-ribose] polymerases (PARPs) and is continuously consumed by these enzymes. The NAD+/NADH ratio is a critical component of the redox state of the cell. (Verdin 2015). By some counts, NAD or the related NADP participates in a quarter of all cellular reactions (Opitz Heiland 2015). There are separate compartments of NAD+ in the nucleus, mitochondria, and cytoplasm (Verdin 2015).

Nicotinamide riboside (NR) can be converted into NAD+ through an intermediate step in which it is converted into nicotinamide mononucleotide (NMN) by NR kinase (Nrk) and then to NAD+ by NMNATs. NR is naturally found in some foods but at very low quantities (e.g. low micromolar range). Historically, NR was difficult to obtain in large purified amounts, but thanks to advances in synthesis methods (Yang 2007), as of June 2013, it is sold as a dietary supplement.

Neuroprotective Benefit: Very promising particularly for prevention, no efficacy data in humans though.

Types of evidence:

- 0 meta-analyses or systematic reviews
- 0 clinical trials and 0 observational studies
- Several laboratory studies; 1 contrary study. Many related studies on NAD+ or non-NR precursors
- 1 study on human imaging of brain NAD+ decreased in aging

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

None

Human research to suggest benefits to patients with dementia.

A high-dose of 3000mg/day of nicotinamide did not improve cognition in Alzheimer's patients (Phelan et al, 2017). However, NR may be better tolerated at high doses and more effective at raising NAD+ levels in neurons. Some studies even suggest that nicotinamide can inhibit NAD+-dependent enzymes unless it is fully converted to NAD+ (Bogan Brenner 2008).

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

NAD+ is a critical and often rate-limiting factor in many aspects of mitochondrial and cellular function including DNA repair by PARPs, widespread acetylation and epigenetic effects by sirtuins, efficient production of ATP, and other pathways (Stein & Imai 2012). NAD+ levels decline with age as does the ratio of NAD+/NADH, with numerous studies suggesting that blunting this decline with NAD+ precursors or genetic manipulations can blunt fundamental features of aging (see below). The levels also decline with the high-fat diet but increase with calorie restriction and fasting (Stein & Imai 2012), leading some to argue that it can function as a calorie restriction mimetic.

Direct evidence on NR effects on the brain is rather limited to-date. In a transgenic mouse model of Alzheimer's, NR was reported to blunt cognitive deficits and reduce beta-amyloid production via PGC-1α activation and increased degradation of BACE1 through ubiquitination and proteasomal pathways (Gong 2013). Another study in Alzheimer's transgenic mice suggested that treatment with NR before the onset of symptoms decreased plaque number, improved cognition, and increased mRNA and protein levels of the mitochondrial stress response and oxidative phosphorylation (Sorrentino et al, 2017). NR also

increased neural stem cell proliferation and neurogenesis in aged mice (Zhang 2016) although another study reported that NR does not increase NAD+ levels in the brain (Canto 2012). Other NAD+ boosting strategies have been reported to block toxicity from beta-amyloid, improve synaptic (Wang 2016) and mitochondrial function (Turunc 2014, Long 2015) as well as reduce oxidative stress (Wu 2014, Wang 2016), excitoxicity-induced axonal degeneration (Vaur et al, 2017), and neuronal cell death (Wang 2016). In humans, the rationale for treatment with NAD+ precursors is supported by some but not enough studies. One pilot study reported that NAD+ levels and total NAD in the brain are lower in older adults (aged 59-68) than young adults, as measured by a recently-developed assay using noninvasive magnetic resonance spectroscopy (MRS) imaging (Zhu 2015). As yet, there are no reports of reduced NAD+ levels in Alzheimer's disease. There are reports of reduced NAD+ biosynthesis enzyme (NMNATs) in Alzheimer's, tauopathy, Parkinson's, and Huntington's disease (Ali 2013) and, in one late-onset Alzheimer's patient, copy-number variation was reported in the NAMPT gene (involved in NAD+ biosynthesis) (Villela 2014).

APOE4 interactions:
No data available

Aging and related health concerns: Very promising for several indications but not yet tested in humans for efficacy. Many unanswered questions, especially on dose

Types of evidence:

- 0 meta-analyses or systematic reviews
- 0 clinical trials and 0 observational studies on NR but a Phase III trials on NA in cancer prevention
- Numerous laboratory studies on NR. Many other studies on NAD+ or non-NR precursors
- 3 studies of reduced NAD+ levels in elderly humans

Details:
It has been suggested that age-related decreases in NAD+ and the NAD+/NADH ratio advance aging and age-related diseases because of widespread influence on mitochondrial function, metabolism, senescence, epigenetics, and signaling pathways like sirtuins (Imai & Guarente 2014). Age-related decreases in NAD+ has been reported in rodents and (by small studies) in humans in red-blood cells (Chaleckis 2016), liver (Zhou 2016), and the brain (Zhu 2015). NR treatment reverses this decrease and has been reported, when starting in old mice (22-month-old), to extend lifespan slightly (mean 829 +/-

12d vs 868 d +/- 12.4d) (Zhang 2016). In rodents, NAD+ levels decline with high-fat diet but increase with calorie restriction or fasting (Stein & Imai 2012), leading some to argue that it can function as a calorie restriction mimetic. Cell culture studies report that the effects of calorie restriction on replicative lifespan require an increase in NAD+ (Yang 2015).

NR treatment in rodents increased stem cell proliferation in three different tissues, reduced markers of inflammation and senescence in muscle stem cells, and increased oxidative respiration and unfolded protein response pathways (Zhang 2016). Other studies have reported benefits in mouse models of metabolic disease/obesity (Canto 2012), non-alcoholic fatty liver disease (Gariani 2015, Zhou 2016), diabetes (Lee 2015), diabetic neuropathy (Trammell et al, 2016), heart failure (Diguet et al, 2017), chemotherapy-induced peripheral neuropathy (Hamity et al, 2017), noise-induced hearing loss (Brown 2014), and liver tumor genesis (Tummala 2014). Some effects are reported dependent on SIRT1 or SIRT3. Meanwhile, the NAD+ precursor NMN was reported to help animal models of diabetes (Yoshino 2011), vascular dysfunction (de Picciotto 2016) and ischemia (Yamamoto 2014), with improvements in mitochondrial function (Gomes 2013) and restoration of youthful levels of BubR1 checkpoint kinase (North 2014).

Frederick et al (2016) reported decreased levels of NAD+ and ATP synthesis in an animal model with NAMPT (an enzyme important in the NAD+ salvage pathway) knocked out in skeletal muscles. In old mice, there were muscular deficiencies and increased expression of p16ink4a in skeletal muscles, suggesting a senescent phenotype. NR treatment reversed the muscle pathology.

Despite this promise, much remains to be done. Most of these treatments used doses that did not simply restore youthful levels of NAD+ but raised it to artificially high levels (e.g. Zhang 2016, North 2014). There are some concerns, albeit theoretical, in cancer and other diseases.

Safety: No serious concerns identified but long-term human studies are limited. Some theoretical concerns exist.

Types of evidence:

- 0 meta-analyses or systematic reviews
- 3 clinical trials completed on NR pharmacokinetics
- 0 observational studies on NR.
- Some ad-hoc reports by consumers

- Toxicology animal report by Chromadex

Details.
NR is a dietary supplement generally considered safe (GRAS status from the FDA).

Three PK/safety studies using NR or Basis were published. One open-label clinical study of 8 patients reported an increase in NR levels after 9 days of administration (1000mg 2x/day). The change in NR levels were very variable, ranging from -10% to 127%. NR is unstable in the blood and could have contributed to this variability.

Although blood NR concentrations peaked and then fell, by day two NAD+ levels reached a steady state concentration that persisted throughout the 24 hours it was measured after day 9. NAD+ levels are modulated by the circadian rhythm in animal models. It is not clear what this means for supplementation in humans. NAD+ increases were also highly variable and somewhat reflected peak NR concentrations observed. There was a slight but statistically significant decrease in hematocrit, hemoglobin, and platelet count – though these levels were still within the normal range (Airhart et al, 2017).

A randomized three-arm cross over trial (100mg, 300mg, and 1000mg NR) in 12 healthy adults reported that NR increased levels of many NAD+ metabolites and suggested that nicotinic acid adenine dinucleotide (NAAD) is a unique biomarker for NR supplementation, as it is below detectable levels without supplementation (Trammell et al, 2016).

A placebo-controlled clinical study in 120 healthy elderly individuals (60-80 years) of Basis (250mg NR/50mg pterostilbene) over 8 weeks reported no adverse events related to the study drug. Whole blood NAD+ levels increased at the regular dose (40%) and with double the regular dose (90%) at 4 weeks. Levels were maintained with the regular dose over 8 weeks. In the double dose, levels were initially higher after four weeks (90%) and returned to levels seen with the regular dose (+ 55%) after 8 weeks.

There was a decrease in alanine transaminase with the regular dose. Hematology measures (hematocrit, hemoglobin, and platelet count) were not different between placebo in the two study groups. Individuals with the double dose had improvements in measures of mobility (6-minute walk test and 30-second chair stand test). There was an increase in LDL-c, specifically in overweight patients. The authors

suggested this could be due to differences in LDL particle size or an increase in reverse cholesterol transport (Dellinger et al, 2017).

Another placebo-controlled randomized cross-over study in 24 healthy middle-aged and older adults reported that NR (1000mg/day) was safe and well-tolerated. There were no changes in blood chemistry measures. The study reported improvements in blood pressure and pulse wave velocity in a subset of patients with stage 1 hypertension (120-139/80-89), but was not powered to determine significance (Martens et al, 2018).

NAD+ levels are often tightly regulated which raises concern for artificially high level that have been achieved by the NR and NMN mouse studies (Zhang 2016, North 2014). Also, NAD+ levels may change at different times of day, raising concern that supplementation might disrupt healthy circadian signaling (see first clinical study above) (Peek et al 2013). However, these concerns are theoretical. So far, a toxicology report by Chromadex reported no adverse effects below 1000 mg/kg in rodents (Conze 2016).

One limited concern is *cancer*. The depletion of NAD+ via NAMPT inhibitors has been proposed as a strategy to treat cancer, which might suggest concern for NAD+ precursors. However, such inhibitors have so far met with limited success in clinical trials and the mechanism – reduced PARP activity to reduce genomic stability in cancer cells – may in contrast reduce the risk of incident cancer by increasing genomic stability in normal cells (Montecucco, 2013, Sauve 2007). The risk of non-melanoma skin cancer in high-risk patients was reportedly decreased by 23% in a Phase III trial with nicotinamide (Chen 2015). It is unclear whether NR might have similar or opposing effects. Although NR and nicotinamide are similar in structure, nicotinamide can inhibit NAD+-dependent enzymes unless it is fully converted to NAD+ (Bogan Brenner 2008).

NAD+ depletion via NAMPT inhibitors has also been proposed as a potential therapy for inflammatory and cardiovascular diseases (Montecucco, 2013). Osteoporosis and calcium homeostasis is another potential concern. NAD+ in the extracellular space may encourage bone breakdown (e.g. Iqbal & Zaidi 2014). This risk is very theoretical with no robust data. Other side effects reported by consumers include a sudden fatigue and dizziness after several days of positive effects and pain after sublingual use. All information is anecdotal, with no published studies on safety (or efficacy) in humans.

Sources and dosing:
Chromadex holds the patent for NR synthesis and manufactures the ingredient for other suppliers, sometimes with the brand name Niagen. Chromadex recommends a dose at 100mg-250mg. Assuming a

160lb adult, that dose is equivalent to 42.3 mg/kg in the mouse, considerably lower than the roughly estimated 400-500 mg/kg/d used in many mouse studies. From a biological perspective, the goal should be to supplement enough to reverse the age-dependent decrease, not to cause artificially high NAD+ levels as most of the rodent studies have achieved (eg. Zhang 2016).

NR is unlikely to have much immediate benefit in people whose NAD+ levels have not fallen, for example in younger healthy adults. The pilot studies in humans to-date do not adequately inform when NAD+ levels are likely to fall but tentatively suggest a very slow decline starting in the 20's without reaching significance until after the 40's (Zhu 2015). In mice, NAD+ levels have a circadian rhythm with a peak in NAD+ levels at the end of the rest cycle (Peek 2013). This circadian regulation of NAD+ levels needs to be confirmed for humans but, if true, suggests that NR should be taken at the same time each day, perhaps immediately on waking.

Research underway:
This is a rapidly moving field. There are currently 8 clinical trials ongoing. Bauer from the Mayo Clinic is testing 750mg/d NR in college football players for 12 weeks to look at effects on NAD+ in the brain. Another two trials are looking at NR effects in healthy older adults and obese men; a 3rd small study is looking at brain function in patients with mild cognitive impairment (only 26 patients) (NCT02942888).

Search terms (not a complete list):
Pubmed:

- nicotinamide riboside;
- nicotinamide riboside with pterostilbene or resveratrol;
- NAD with aging, human, apolipoprotein E;
- nicotinamide or NAD with centenarian or Alzheimer

Google – NAD, circadian; NAD levels, human
PatientsLikeMe & ALSUntangled – no reports on either
Clinicaltrials.gov – nicotinamide riboside

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