What is NAD+ (Nicotinamide Adenine Dinucleotide)

What is NAD+ used for?

- Energy production (ATP)
- DNA repair (NADPH)
- Cell signaling (Immune-CD38, CD157)
- Enzyme activity (reduction factor, NAD+ = NADH, NADP+ = NADPH)
- Increased Tankyrase activity
- Longer telomeres
Where does NAD⁺ come from? (How is it made?)

- The body needs to make it (you can not absorb it from the diet)
- Every cell in the body needs it
- Main precursors:
  - Tryptophan
  - Vitamin B3 (nicotinic acid, nicotinamide, nicotinamide riboside or nicotinamide mononucleotide)

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Main precursors:  
- Fe₂⁺  
- Renal Excretion  
- Glucose + (1, 6, 7)

The body needs to make it (you can not absorb it from the diet)
How do you raise NAD⁺ in the body?

Oral
- Nicotinamide riboside (NR)
- Nicotinamide mononucleotide (NMN)
- Nicotinic acid (Niacin)
- Nicotinamide (niacinamide)

Intravenous (IV)
- NAD⁺

Maintain NAD⁺ by:
1. Reducing oxidative damage
2. Inflammation (CD38)
3. Increasing synthesis

NAD⁺ CD38 & Inflammation

CD38 is one of the largest consumers of NAD⁺

CD38 is a glycoprotein found on the surface of many immune cells which also functions in cell adhesion, signal transduction and calcium signaling.

In humans, the CD38 gene is encoded by the CD38 gene which is located on chromosome 4.

Uses NAD⁺ to generate Ca²⁺ mobilizing metabolites.

Important role in inflammation:
- CD38 induced Ca²⁺ release causes migration of neutrophils and monocytes toward sites of inflammation.
- Increased CD38 expression signals maturation of dendritic cells during inflammatory cytokine activation.
- Decreased CD38 function is associated with impaired immunity.

NAD⁺ and social behaviour (Autism-Oxytocin)

- OXT is involved in social interactions and may promote trust, generosity, increased emotional perception and parenting behaviour.
- Autism is a spectrum disorder (ASD), which is characterized by social and communication impairments, linked to significant defects in the OXT system.

Healthy social behavior

**NAD+ & sleep / wake cycles**

Biological rhythms are established and maintained by a central clock consisting of around 20,000 pacemaker neurons in the suprachiasmatic nucleus (SCN).

NAD+ facilitates the circadian clock feedback cycle through SIRT1 and CLOCK:BMAL1.

As the levels of NAD+ oscillate over the circadian cycle, the activity of SIRT1 oscillates, linking the metabolic state of the cell through an epigenetic mechanism to the circadian clock.

Circadian dysfunction has been linked to sleep disorders, depression, bipolar disorder and changes in cognitive function and memory formation.

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**What happens as we age**

Cumulative tissue damage results in:
- structural degeneration
- functional decline, and
- age-related diseases
- Increased telomere shortening

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**Oxidative Stress:**

- Reflects an imbalance between the systemic manifestation of reactive oxygen species and a biological system's ability to readily detoxify the reactive intermediates or to repair the resulting damage.
**Oxidative Stress**

- Reactive Oxidative Species (ROS):
  - Free radicals with at least one unpaired electron in their atomic structure
  - Harmful at supra physiological concentrations
  - A delicate balance between the generation and the elimination of reactive oxidative species

**Free radicals can produce cumulative tissue damage to major cell components such as DNA**

The higher the rate of DNA damage the faster the ageing process

**Brain oxidative damage, age and NAD**
**NAD⁺ & telomere length**

Increased NAD⁺ availability can increase tankyrase removal of TRF1 improving telomerase access.

- Telomere length shortens with age.
- Critically short telomeres trigger senescence and eventually cell death.
- Shorter telomeres have been linked to:
  a) Increased incidence of disease.
  b) Poor survival.

**Conditions in which NAD⁺ can be depleted**

- Oxidative damage (with age)

**Alcohol ↓ brain NAD⁺ & ↑ inflam.**

![Graph showing changes in [NAD(H)] and inflammation with alcohol intake.](image)
EtOH effect on cultured human brain astroglial cells

Importantly: additional NAD+ prevents synaptic disconnection

![Graph showing synaptic number (%) vs. NAD+ and axon loss](image)

Figure 3. NAD+ significantly reduces axonal atrophy associated with opiate and alcohol withdrawal in mice. A: 4 days of treatment.

- CTL: control
- NAD+: NAD+ treatment
- Axon loss: axonal degeneration

- NAD+ prevents axon (Wallerian) degeneration

Quantification of cortical presynaptic structures affixed to MAP-2-positive striatal dendrites after cortical axotomy. NAD+ delays cortical synaptic loss (ANOVA 2, *p-value, 0.05, **p-value, 0.01). Deleglise et al PLoS ONE 8(8): e71103. doi:10.1371/journal.pone.0071103

Deleglise et al Experimental Neurology 251 (2014) 91–100 Importantly: additional NAD+ prevents synaptic disconnection

- Axonal degeneration at different time points in presence or absence of [NAD]. In vitro-Dorsal root ganglion cells (DRG)
- NAD+ prevents axon (Wallerian) degeneration

- Implications for neurodegenerative disease (e.g. alcoholism, AD)

- *p-value, 0.05
- **p-value, 0.01

- Importance: additional NAD+ prevents synaptic disconnection
Isoprostanes

- The isoprostanes are prostaglandin-like compounds formed in vivo from the free radical-catalyzed peroxidation of essential fatty acids (primarily arachidonic acid) without the direct action of cyclooxygenase (COX) enzymes.
- 8-Isoprostane is a prostaglandin (PG)-F₂-like compound belonging to the F₂-isoprostane class that is produced in vivo by the free radical-catalyzed peroxidation of arachidonic acid. 8-Isoprostane is a biomarker of oxidative stress.

Response to Intravenous NAD BR+ Therapy in Subjects Treated for Opiate Abuse

(n = 11 Subjects)

Response to Intravenous NAD BR+ Therapy in Subjects Treated for Alcohol Abuse

(n = 19 Subjects)
What research is still needed to be done?

We do not yet know:
1. The best dose regimen (how much and for how long) for many conditions and any of the NAD+ enhancing substances.
2. If there are combinations of pharmacologic (molecular) that may enhance the NAD+ effect.

Need to assess the effectiveness of NAD+ therapy alone or in combination in multiple clinical health-performance conditions/valuations such as:
- Addiction medicine
- Neurodegenerative disease (AD, PD)
- Depression
- Chronic fatigue
- PTSD
- Traumatic brain injury - CTE
- Metabolic disease (Diabetes, mitochondrialopathies)
END
PRESENTATION
Questions?
**Introduction:** Treatment of substance abuse disorders continues to challenge clinicians and "cravings" for the abused substance are often impediments to sobriety. Nicotinamide Adenine Dinucleotide (NAD) has been used in the past with claims of having anti-craving properties. Previous data from this clinic using a similar formulation of NAD support the use of NAD as a valid treatment for drug cravings.

This pilot study retrospectively examined the anti-craving properties of NAD in a group of 60 patients. Additionally, patients were assessed on severity of cravings and relapse episodes at 12-20 months post treatment.

The patients were adult males and females with addictions to primarily opiates or alcohol (N=60). Six patients were omitted due to incomplete data. The treatment Brain Restoration Plus (BR+) comprised of IV infusions of NAD as well as vitamins, oral amino acids, NAC and variable PRN medications for an average of 10 consecutive days ranging from 5 to 10 hours daily at a dose range of 500mg-1500mg each day. Self-reported craving ratings (0-10 Scale) were collected on Day 1 (before starting treatment), Day 5, and on Day 10 (last day of treatment). Follow up phone surveys were conducted from 12-20 months post treatment (N= 27). Patients reported severity of cravings (1-5) and number of relapse episodes at the present time.

**Method:**

Thank you to Springfield Wellness Center for providing patient data. Thank you to William Carey University for providing a Professional Development Grant in support of this project.

**Results:**

1. NAD is an effective detox treatment for alcohol and opiate addicts as evidenced by a significant reduction in craving ratings.
2. NAD was effective in reducing and maintaining the number of relapse episodes, as well as severity of drug cravings.
3. NAD shows potential as a long-term therapy in maintaining sobriety through minimizing drug cravings and preventing relapse.

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Aging: Lifespan

Ataxia-telangiectasia (A-T) is a rare "accelerated aging" degenerative disorder affecting multiple body systems but especially the brain and the immune system.

NAD+ therapy improves A-T (animal model)

NAD+ is low in brain and tissue in A-T

NAD+ therapy (NR/NMN) increased

- DNA repair
- Mitophagy
- Mitochondrial function
- NAD+ salvaged neurodegeneration
- Improved behavior and memory to normal levels
- Markedly extending lifespan

Response to Intravenous NAD+ Therapy in Subjects Treated for Opiate Abuse

(n = 10 Subjects)
Response to Intravenous NAD+ Therapy in Subjects Treated for Alcohol Abuse

n = 12 Subjects

[Graph showing response over time with data points and error bars]