Pharmacy Compounding Committee Review: Nicotinamide Adenine Dinucleotide (NAD+)

FAGRON NORTH AMERICA: NOMINATOR

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DIPLOMATE, ABFM

MAY 8-9TH

NAD functions

- Primarily a universal cellular electron transporter

Several recognized non-redox roles:

- Important in cell nuclear DNA repair and telomere maintenance[1]

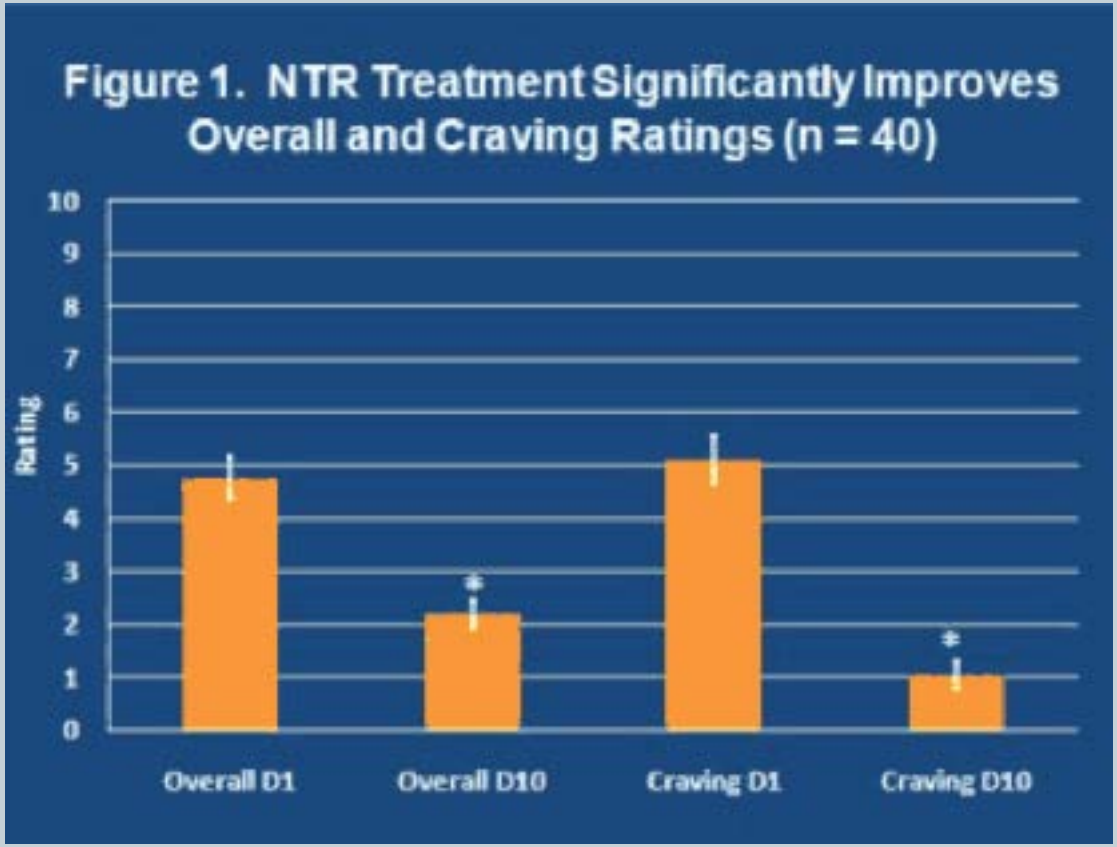
Extracellular signaling molecule:

- From neurons in blood vessels, urinary bladder[2], large intestine; and transcription regulation and aging via sirtuins[3]
- Released from neurosecretory cells and brain synaptosomes[4]

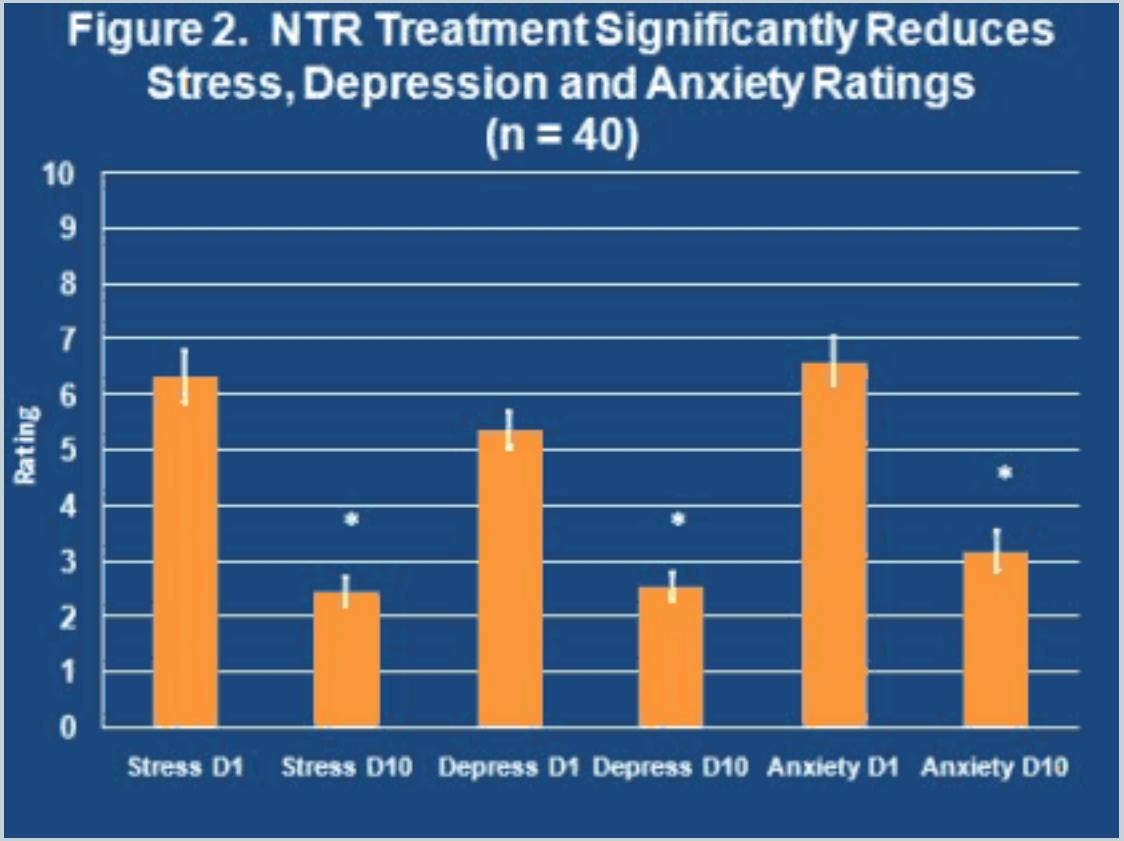
NAD history of use

- Has been used since the late 1960s in intravenous form to significantly lessen withdrawal from a variety of drugs and alcohol
- Mechanism not clear
- Limitation is that recovery tends not to be complete with IV NAD alone
- With addition of specified amino acids complex, recovery is found to be significantly more profound, complete and lasting

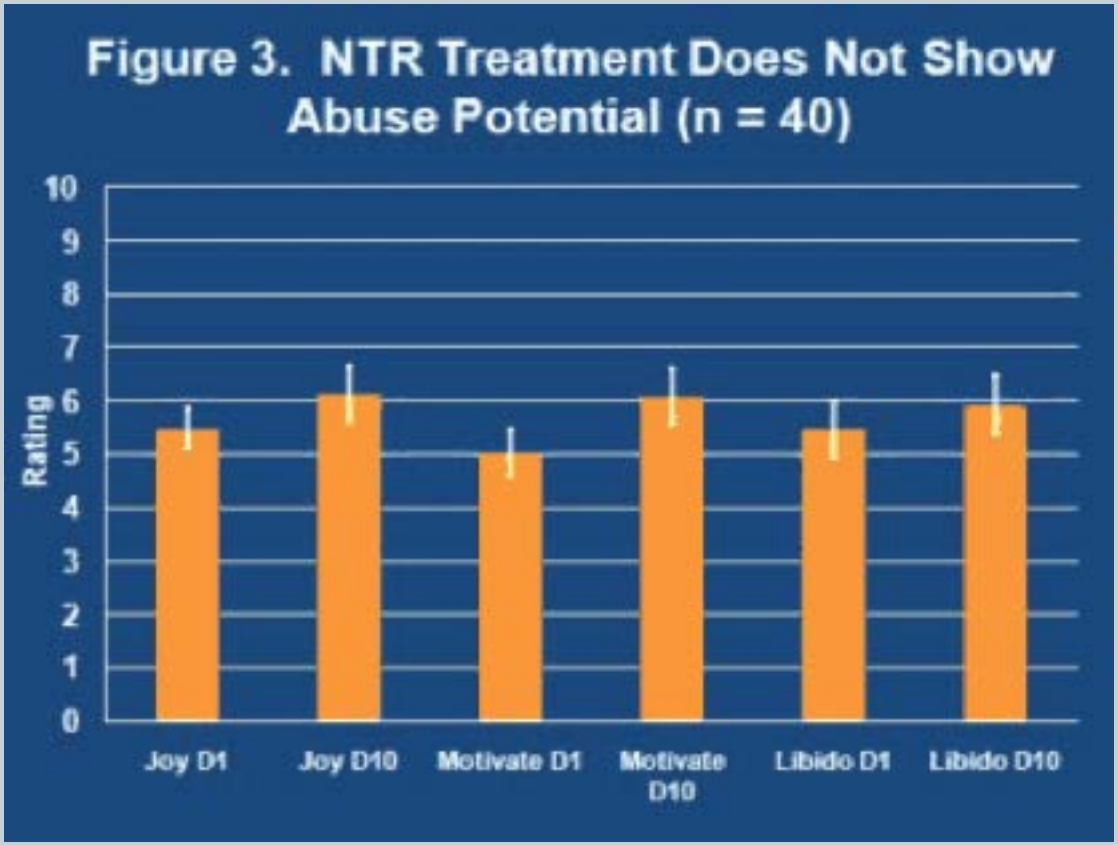
IV NAD plus amino acid outcomes



S. L. Broom, S. Owen, P. Norris, et. al.[5]



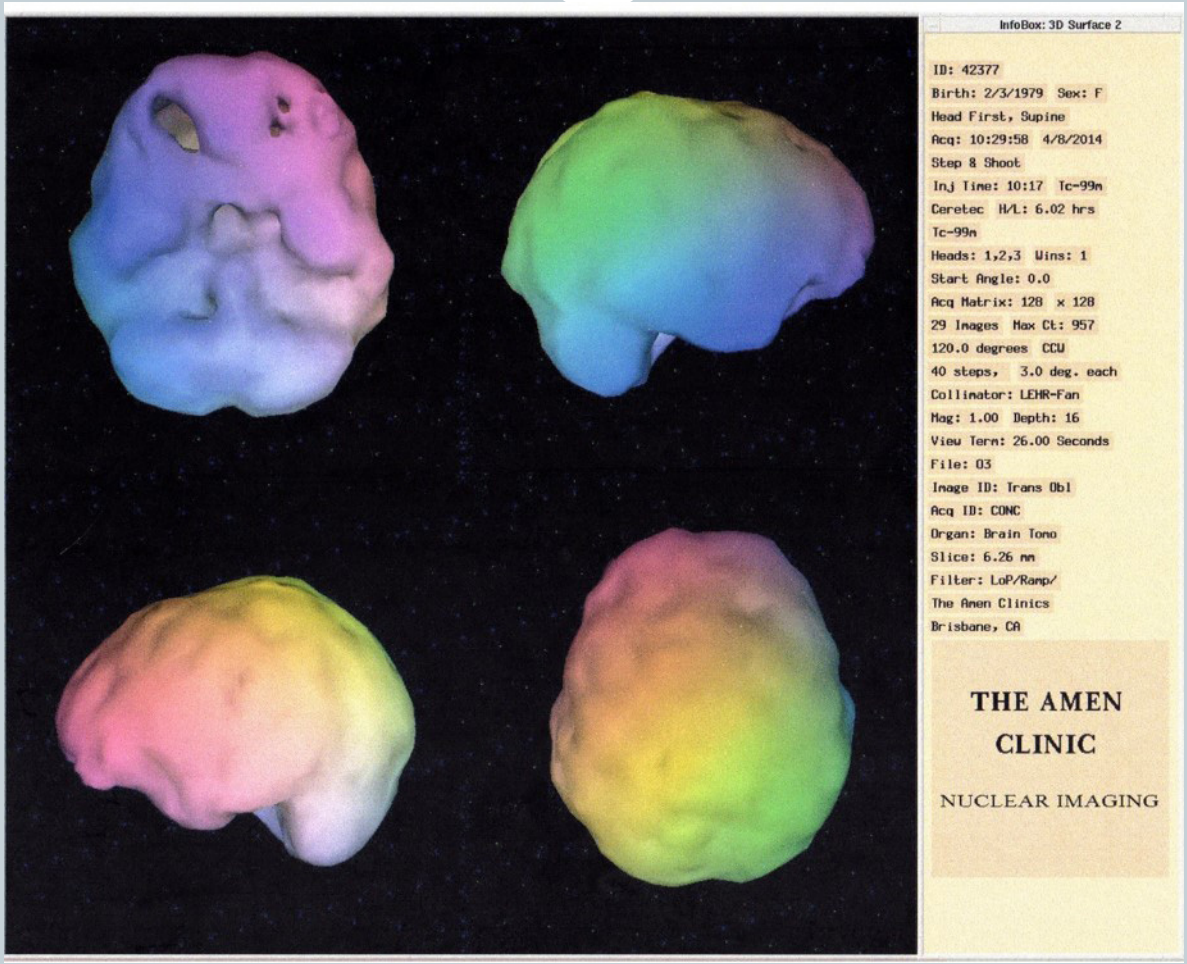
S. L. Broom, S. Owen, P. Norris, et. al.



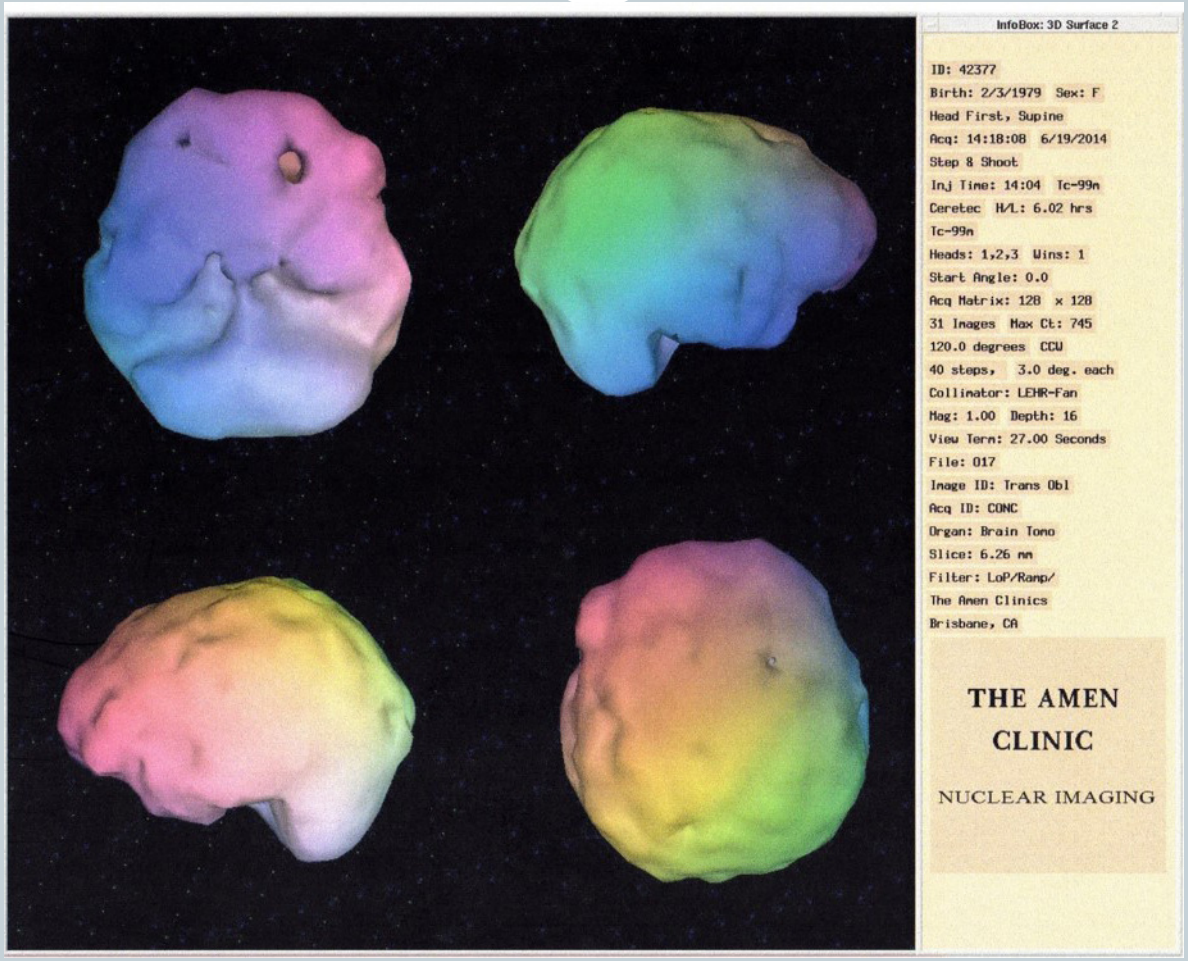
Patient J.M.

- 34-y-o woman with over 20 years of Adderall, Ritalin. Currently on antidepressants x 2 years.
- Recently a few months of Suboxone and cocaine
- Also found to be hypothyroid and adrenal insufficient
- Very spacy, very hard to feel motivated, depressed

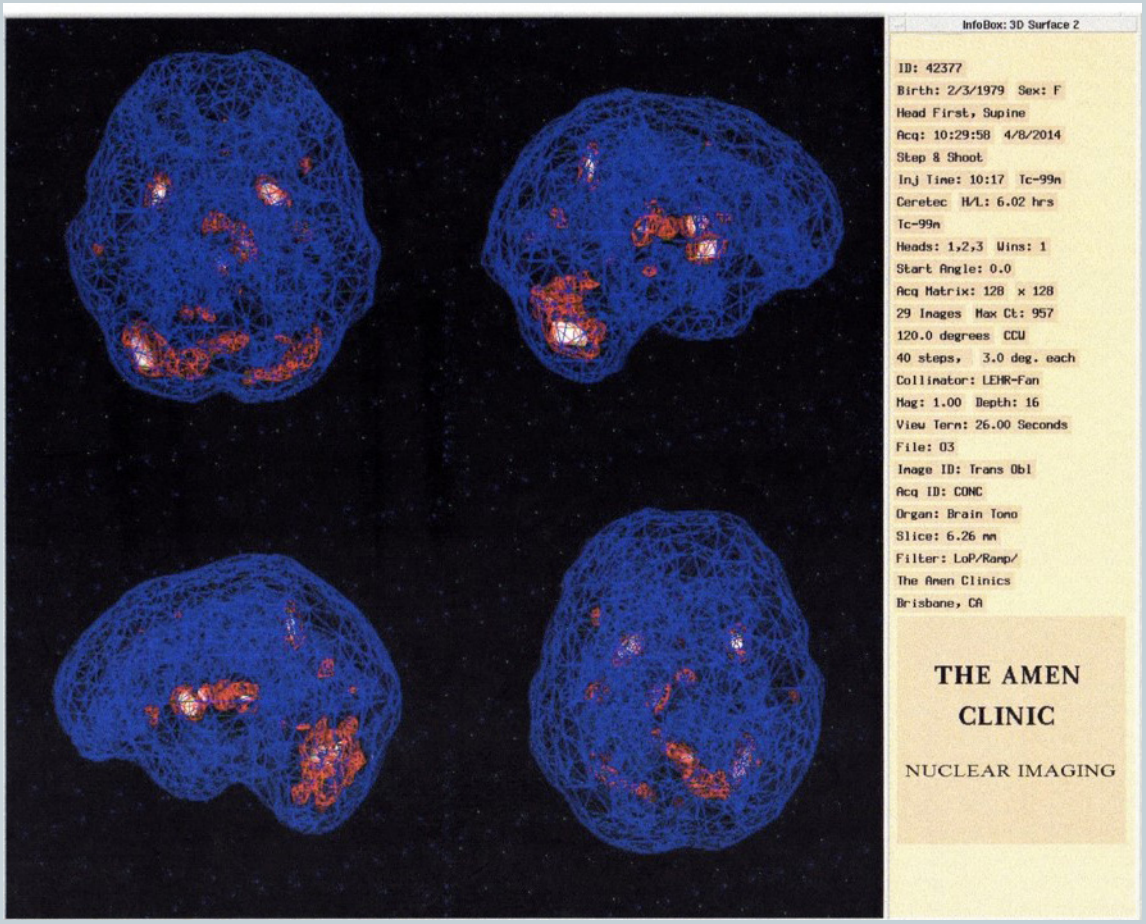
Patient J.M. – before treatment



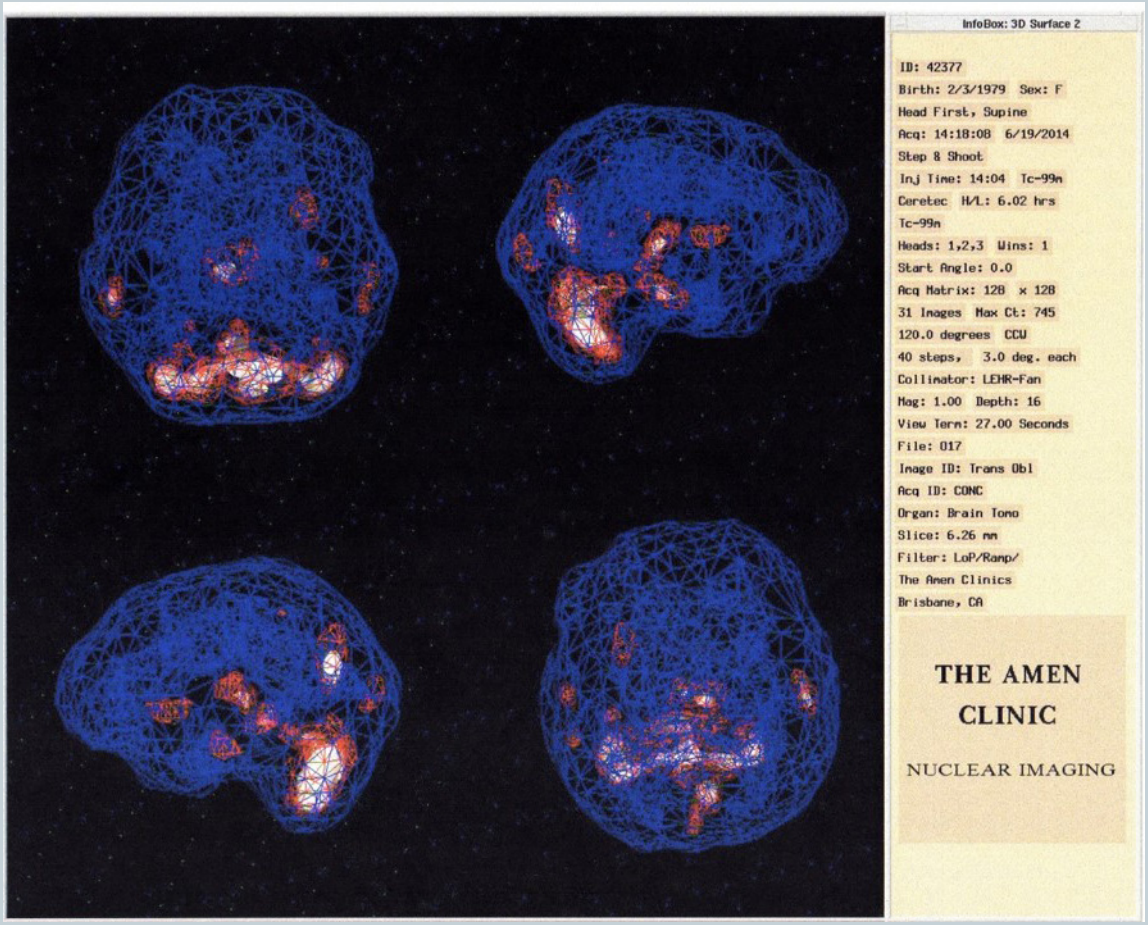
Patient J.M. – after treatment



Patient J.M. – before treatment



Patient J.M. – after treatment



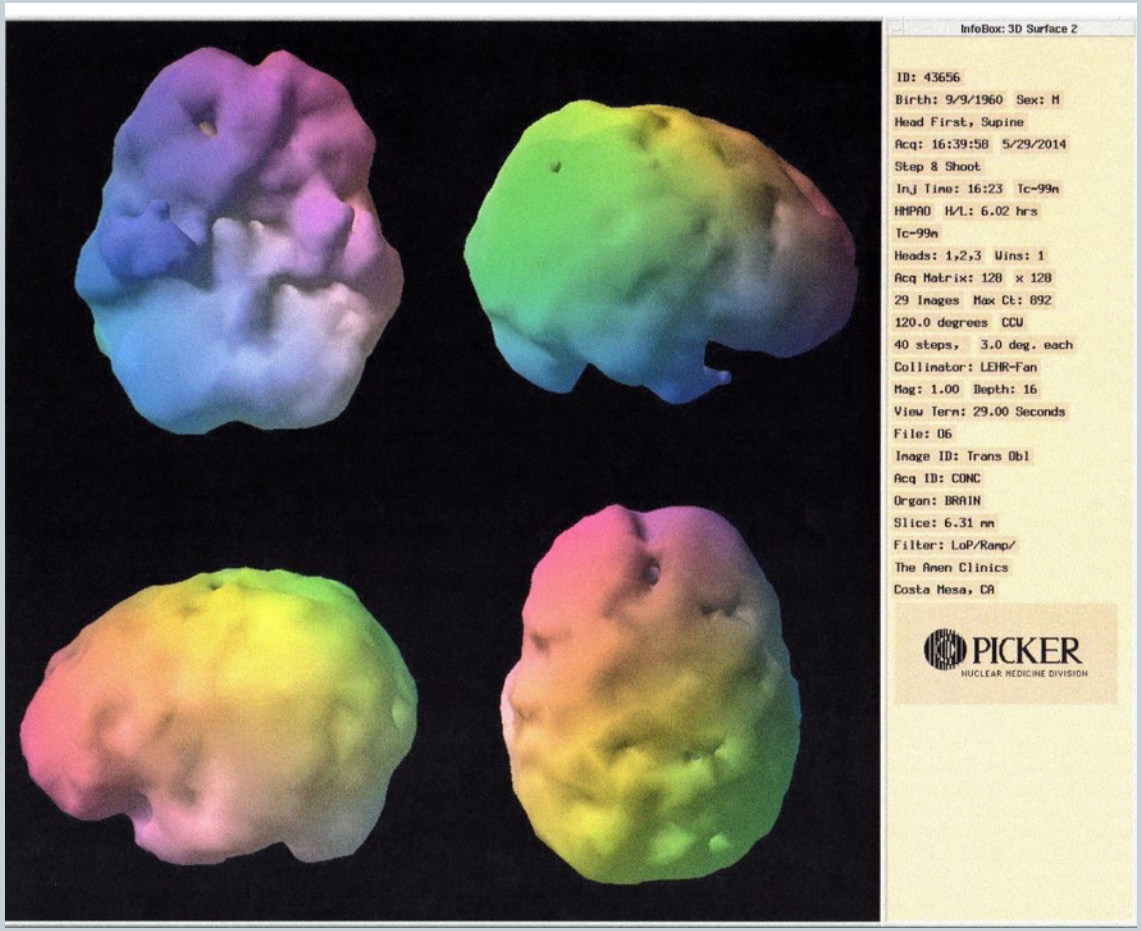
Patient J. M.

- Bone pain, restless legs and anxiety from Suboxone gone on day 7
- Brain zaps from antidepressant withdrawal resolved
- All cravings resolved by day 7
- Texted a month post-treatment that she is feeling great, with no relapses

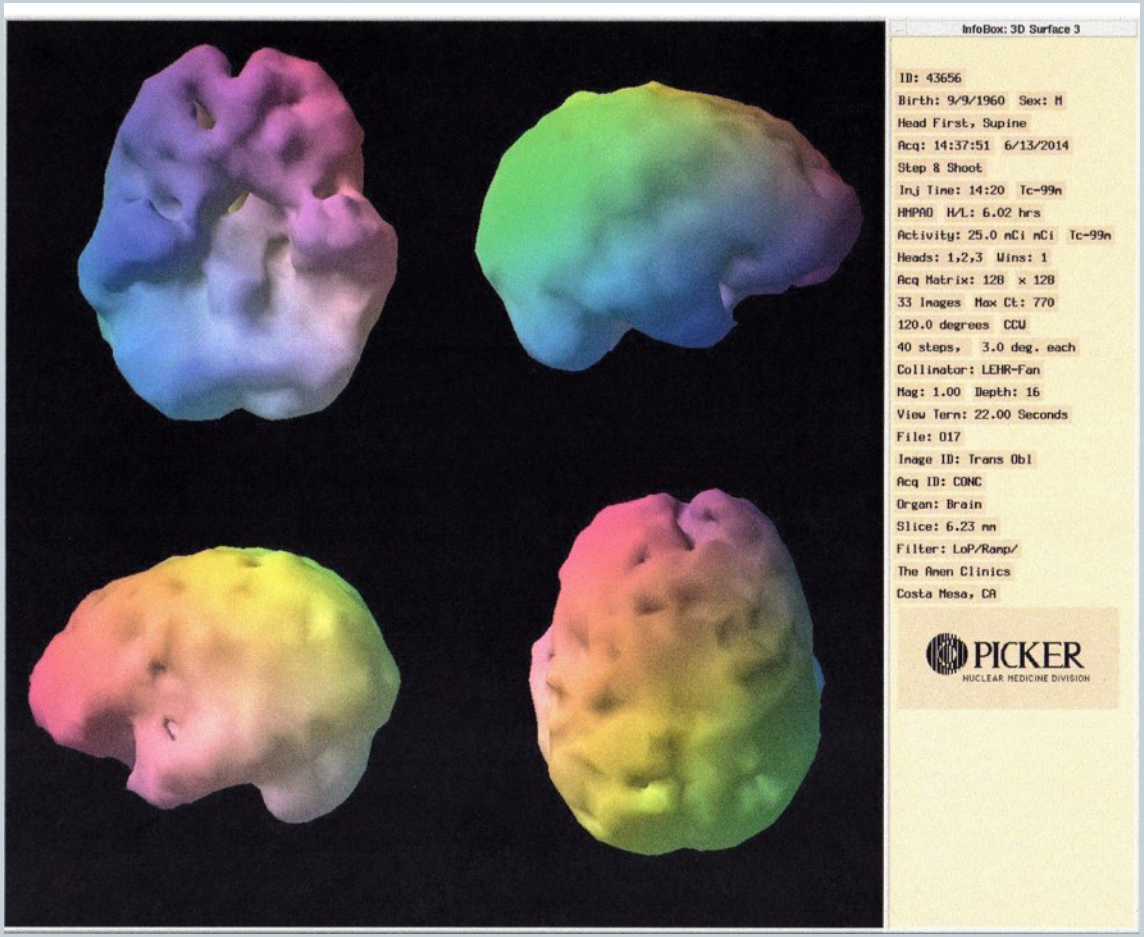
Patient M. L.

- 54-y-o man with history of years of cocaine use
- Pornography always accompanied cocaine (together they “make me feel alive again”)
- Using marijuana lately to calm down paranoia from cocaine
- Arrhythmia not going away as in past

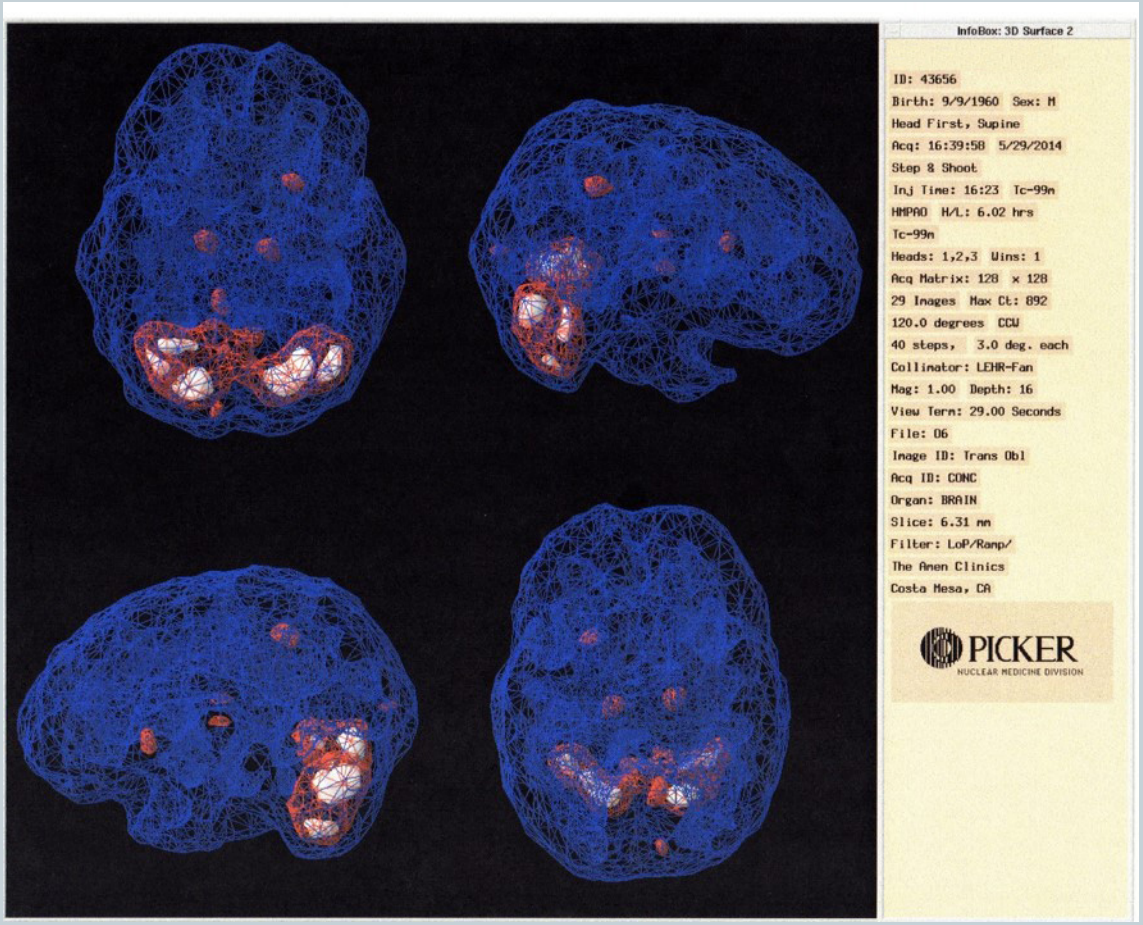
Patient M. L. – before treatment



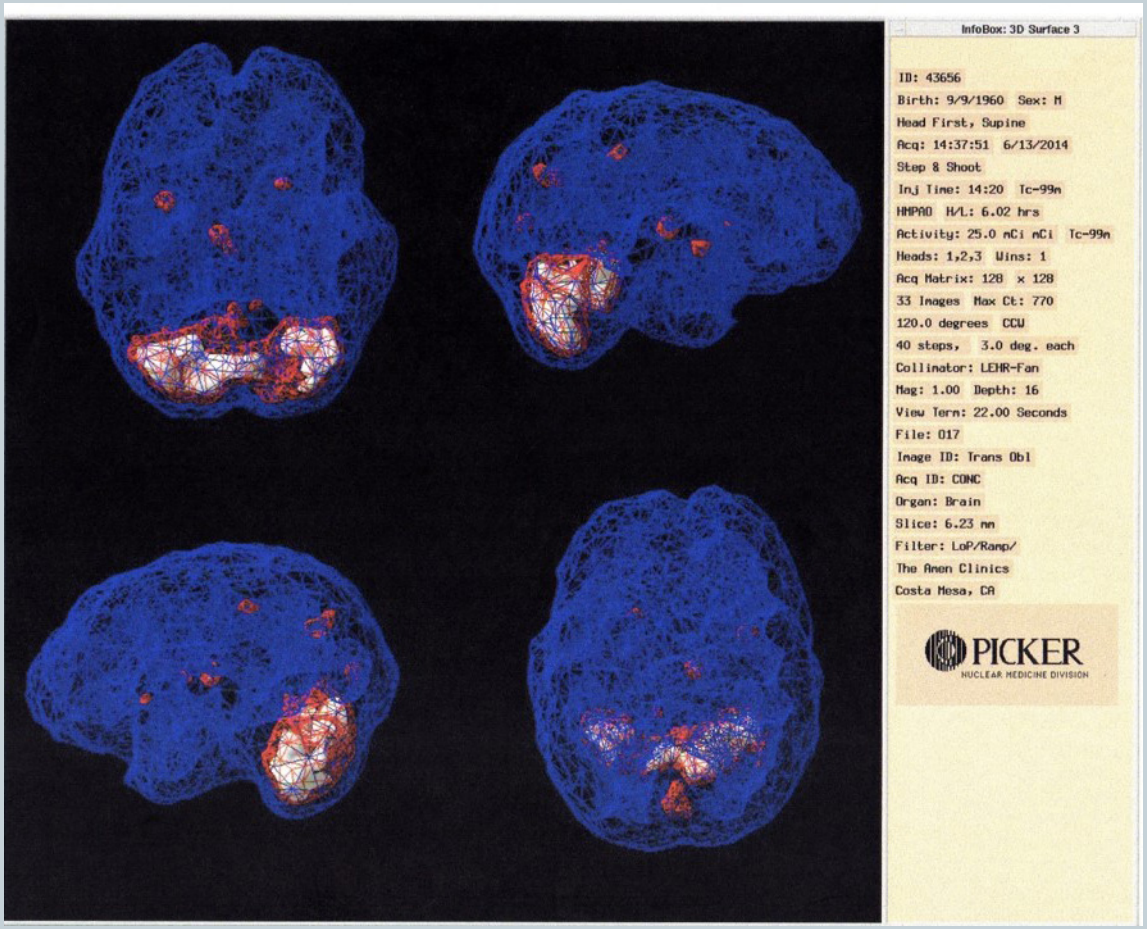
Patient M. L. – after treatment



Patient M. L. – before treatment



Patient M. L. – after treatment



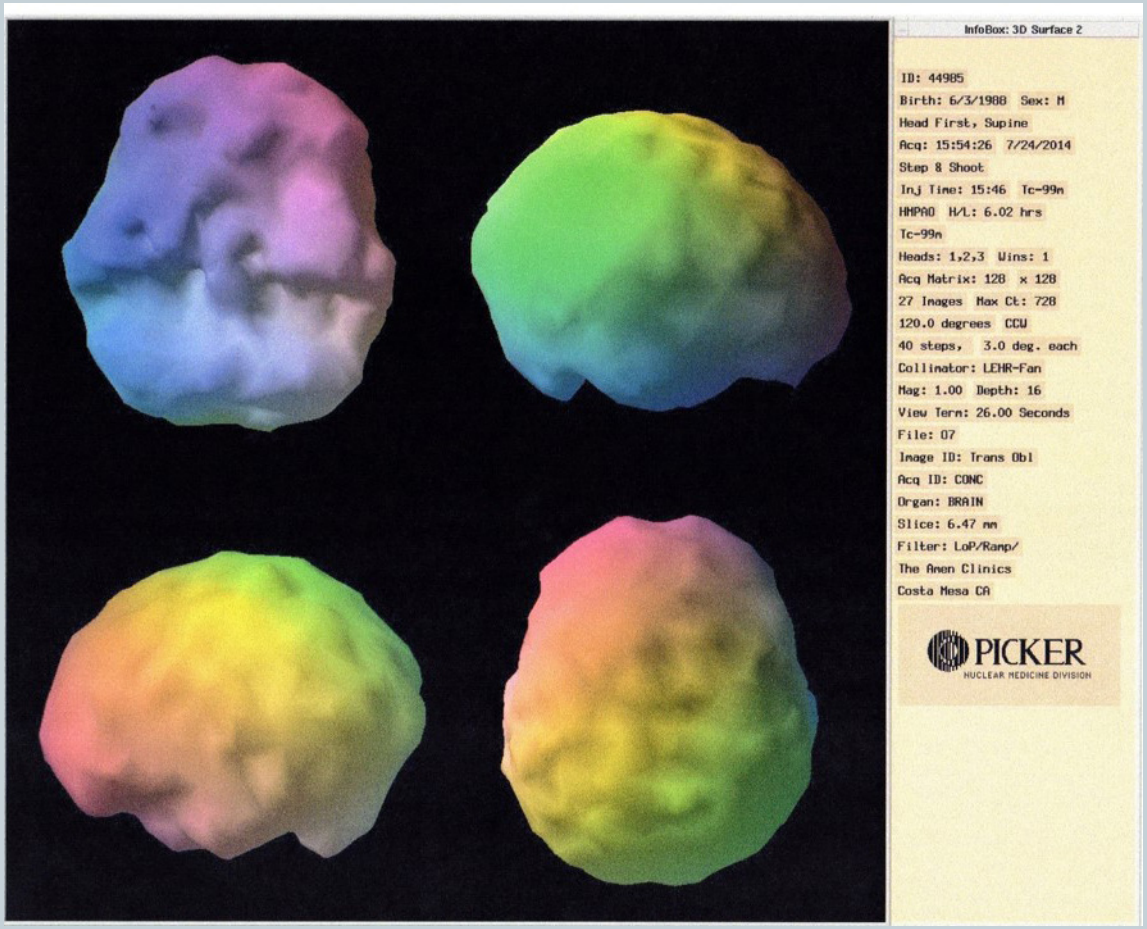
Patient M. L.

- Did ten days of cocaine formula, and two days of marijuana formula
- Cocaine cravings resolved by day 4
- Became more social during treatment
- Two months later had had two brief relapses (one or two days each)

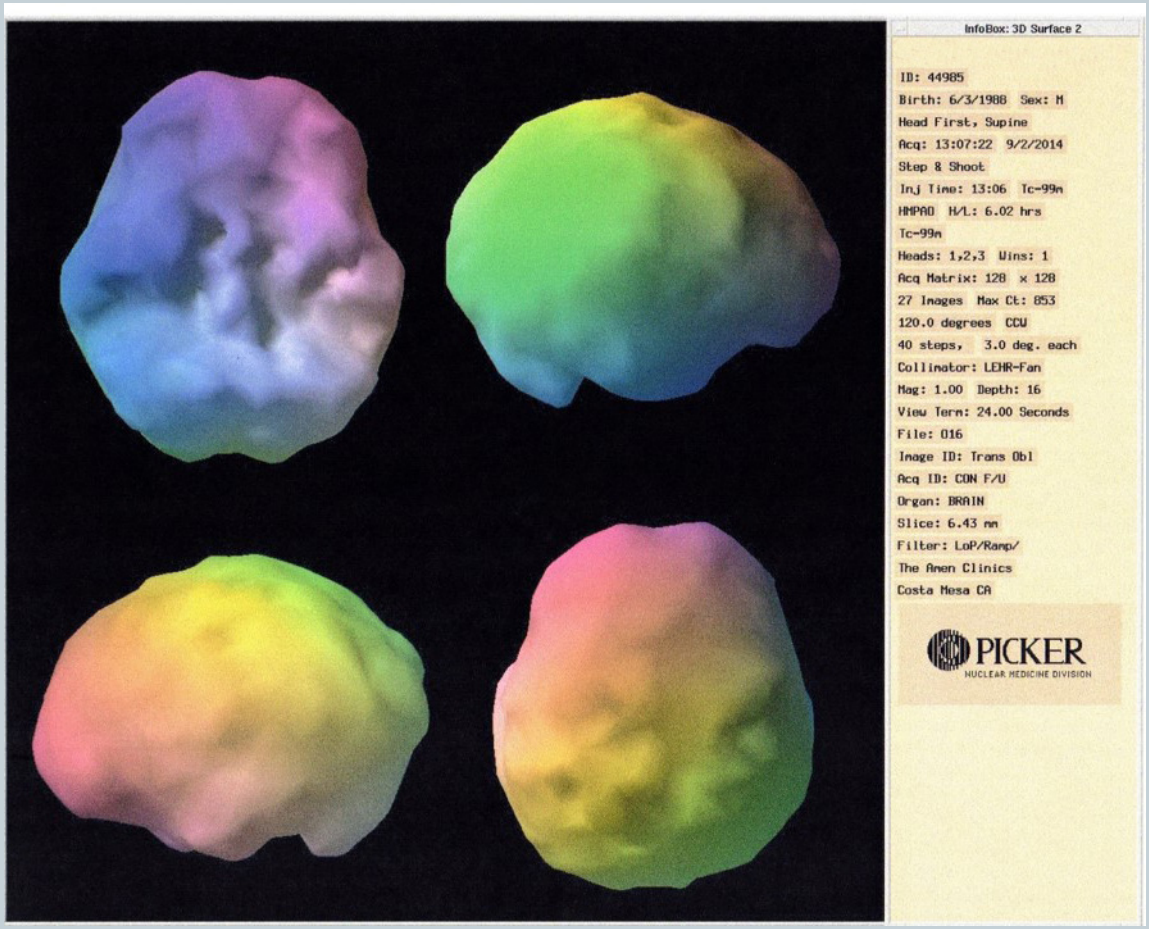
Patient C. R.

- 25-y-o man on Lyrica (pregabalin) for 2 years for foot neuropathy from combat injury
- History of alcoholism in high school, Navy
- Unusually sharp night vision has faded in recent months. Irritable, fatigued, depressed, angry outbursts

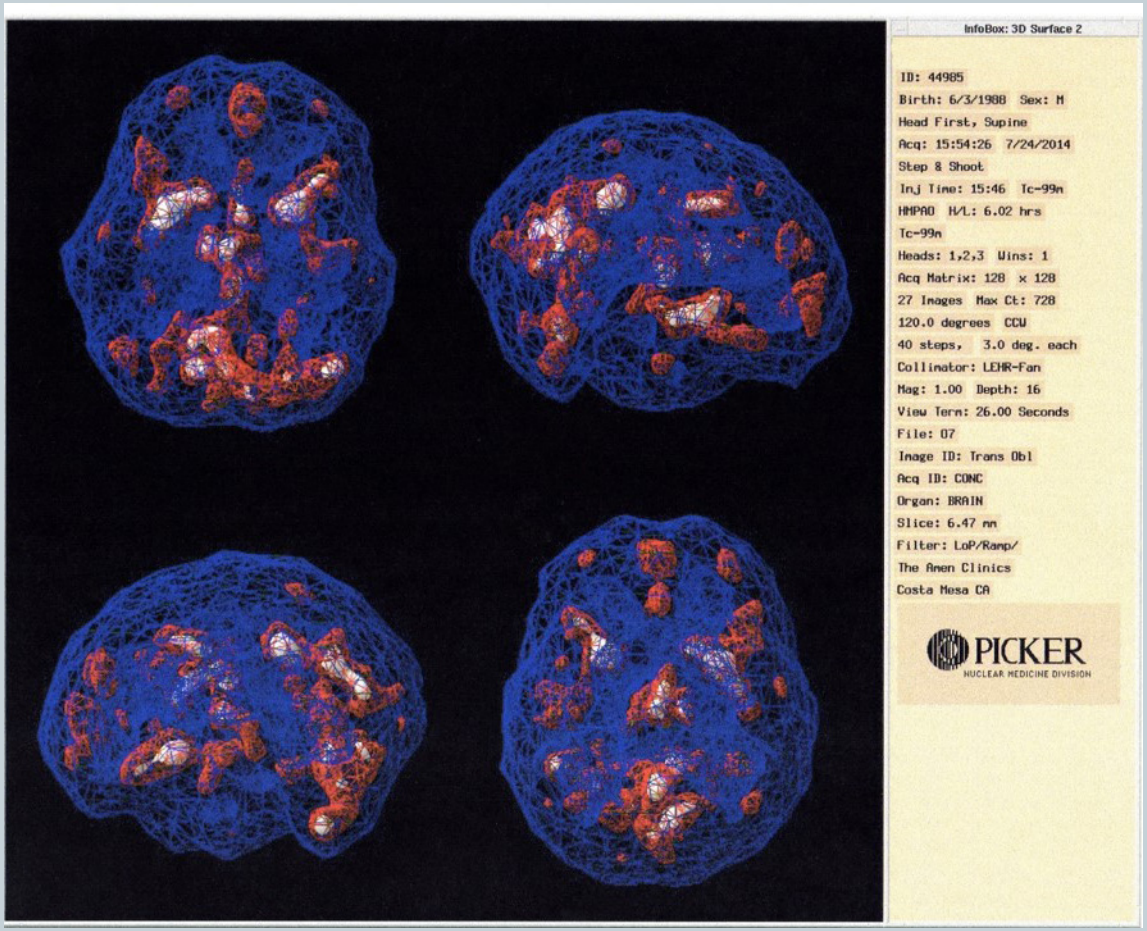
Patient C. R. – before treatment



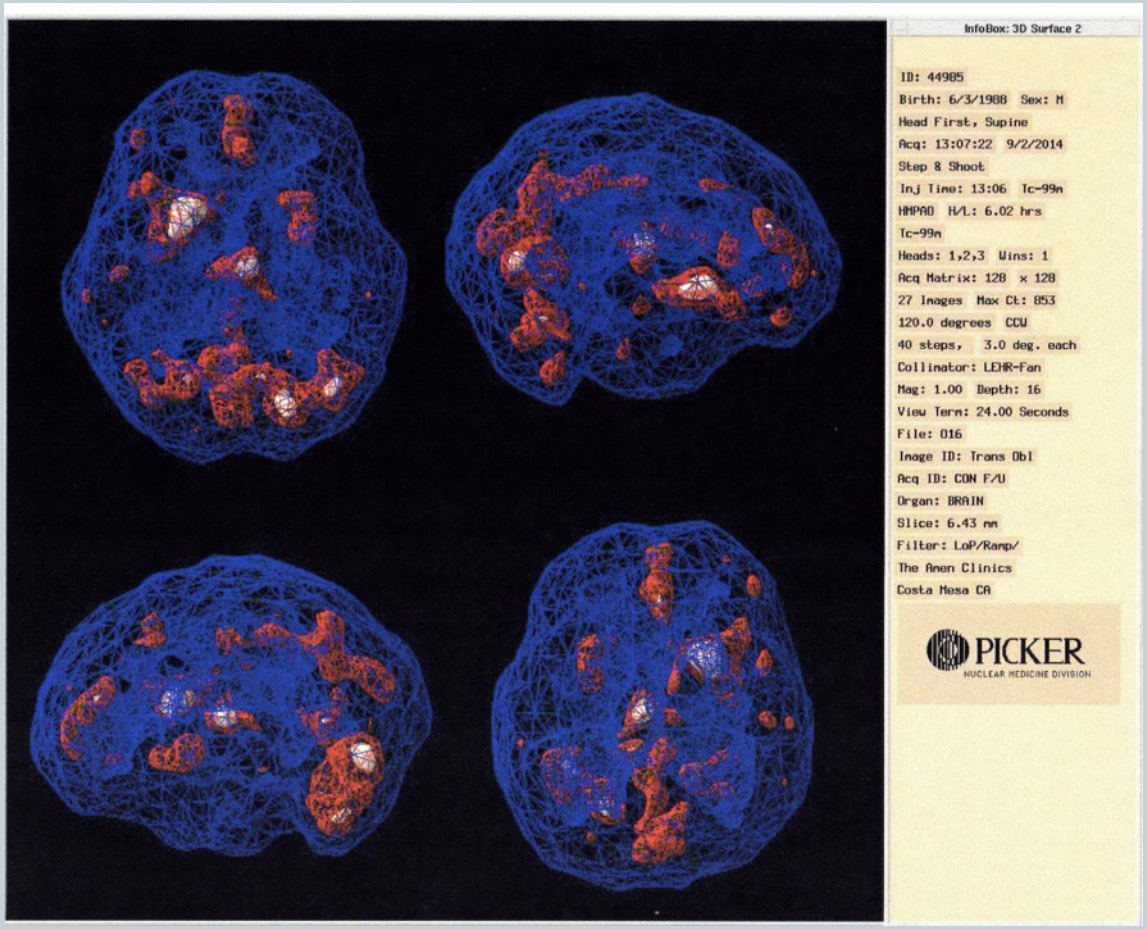
Patient C. R. – after treatment



Patient C. R. – before treatment



Patient C. R. – after treatment



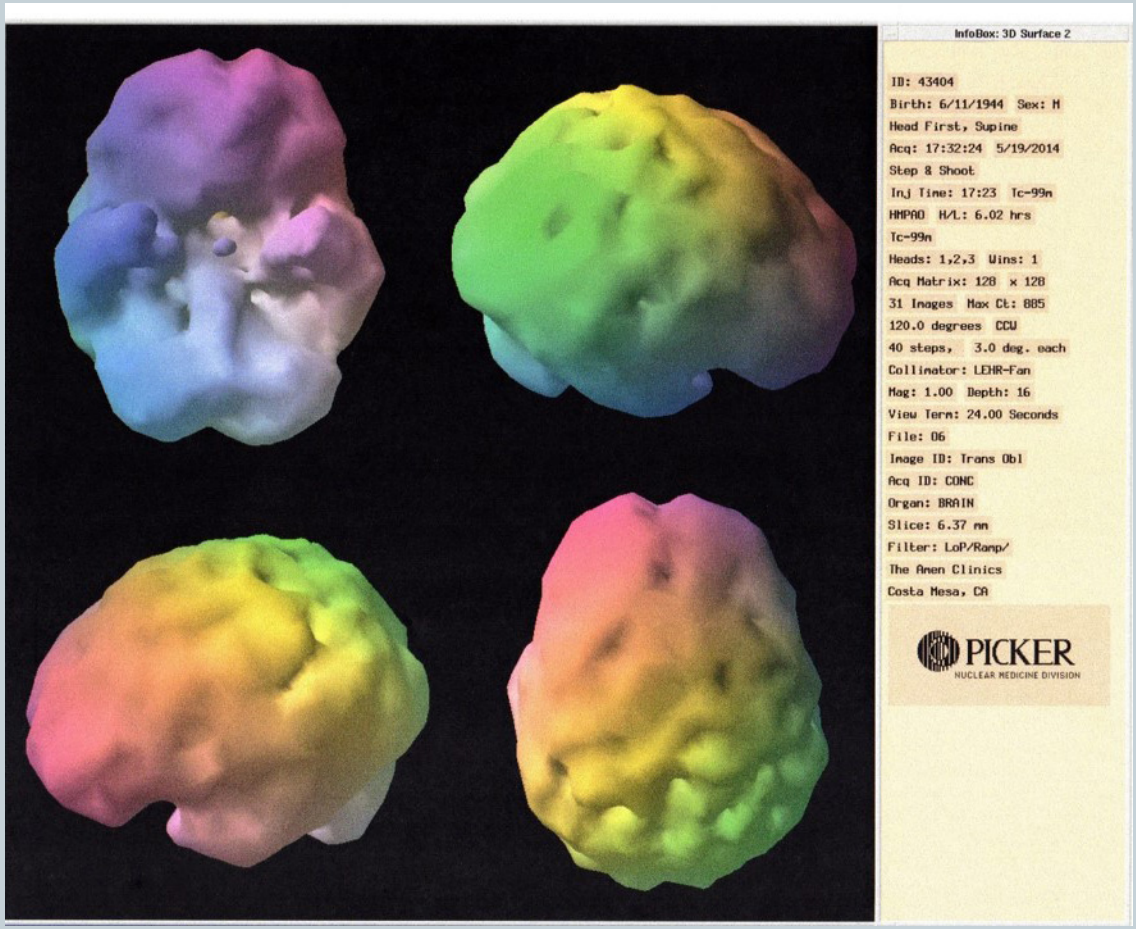
Patient C. R.

- Did ten days benzo formula, four days alcohol formula
- Had restoration of keen night vision after 5 days of treatment
- Body spasms, particularly around left orbit, much reduced and responsive to oral supplements
- Poor memory resolved
- Temperament much more even, enthusiasm restoring

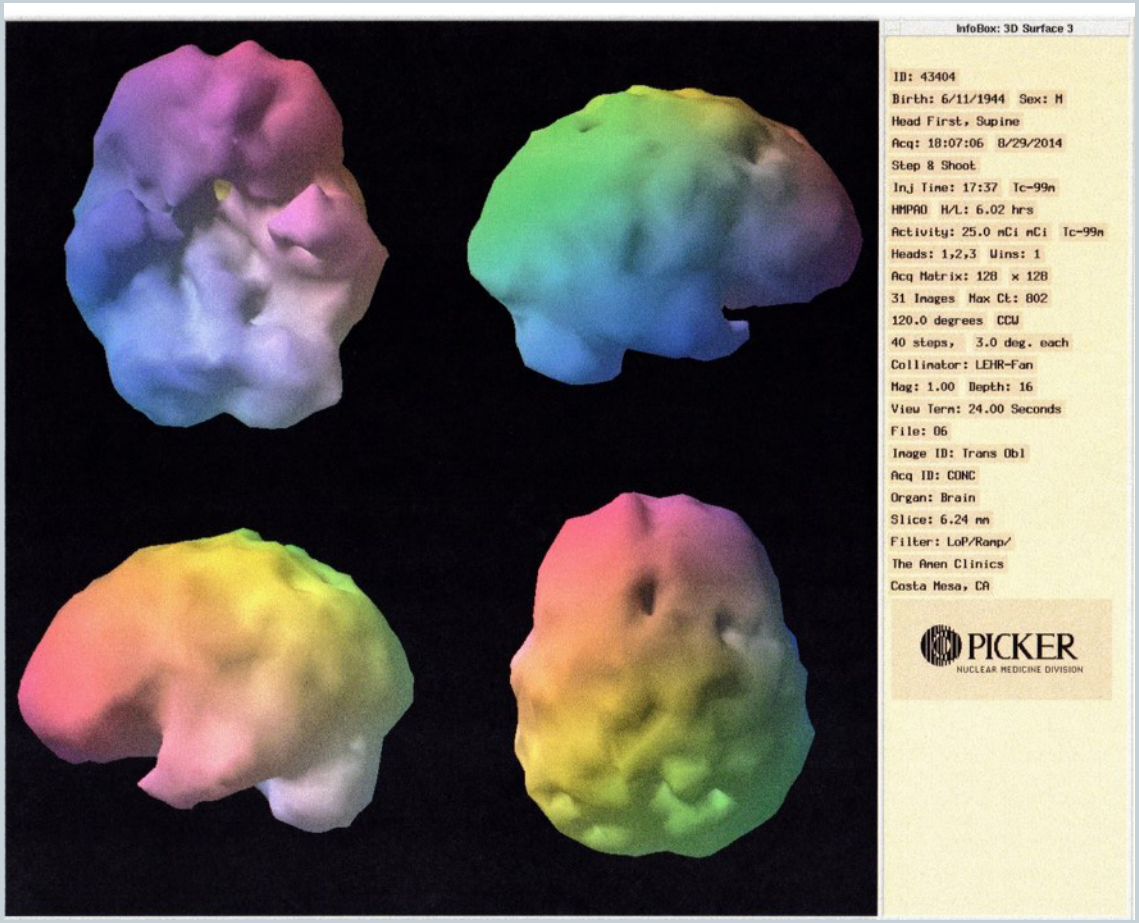
Patient J. C.

- 70-y-o man with 30 yrs. + addiction to pornography, and only a few months of antidepressants in distant past
- Moderately depressed, obsessive thoughts
- Father was compulsive gambler

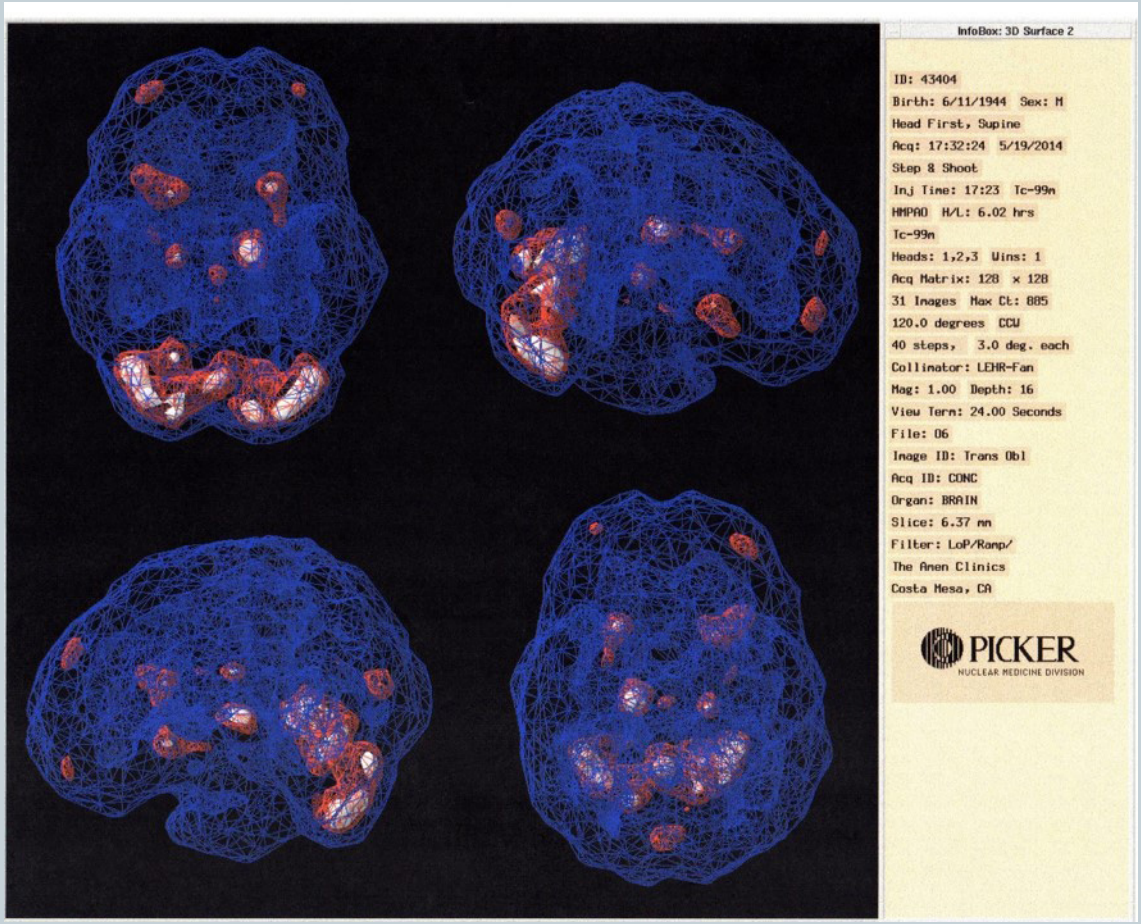
Patient J. C. – before treatment



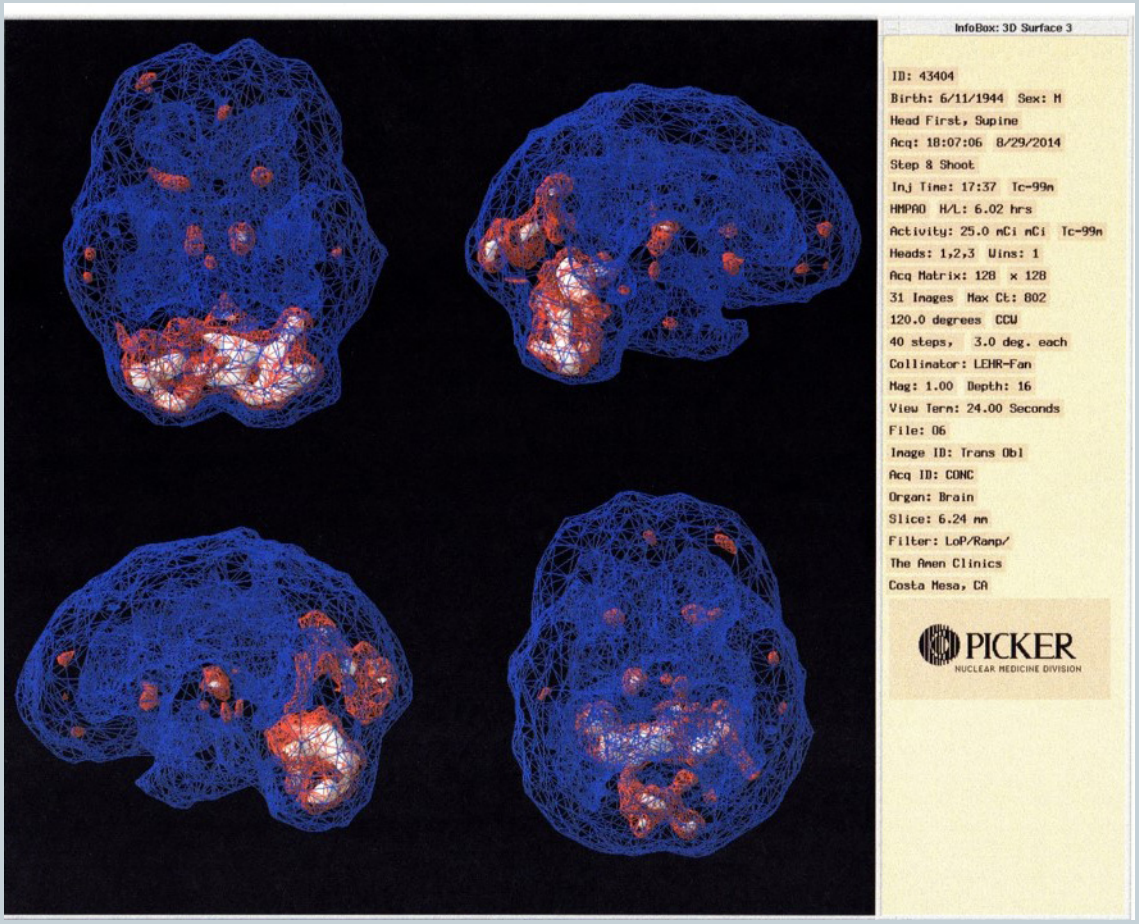
Patient J. C. – after treatment



Patient J. C. – before treatment



Patient J. C. – after treatment



Patient J. C.

- Did eight days of dopamine formula (covers compulsions like pornography and gambling)
- Stated, “When the drip is running, I don’t ruminate on thoughts.”
- Noted to become more social with other patients as the treatment progressed
- Felt a lasting mild to moderate improvement in mood, energy, sleep, and feeling less obsessive

Future of IV NAD

- Safety – Inherently safe at doses of 2 gms/day or less
- Generally give 800 to 1800 mg per day, over 3-8 hours
- Treatment for 7-16 days, depending on drug history
- Able to address benzodiazepine dependence
- Clearly the best current solution to the expanding problems of drug abuse (particularly heroin), prescription drug abuse, and post-acute withdrawal syndrome (PAWS)

References

- 1. Bürkle A (2005). "Poly(ADP-ribose). The most elaborate metabolite of $NAD^{+\cdot}$" *FEBS J*. **272** (18): 4576–89.
- 2. Smyth LM, Bobalova J, Mendoza MG, Lew C, Mutafova-Yambolieva VN (2004). "Release of beta-nicotinamide adenine dinucleotide upon stimulation of postganglionic nerve terminals in blood vessels and urinary bladder." *J Biol Chem*. **279** (47): 48893–903
- 3. Blander G, Guarente L (2004). "The Sir2 family of protein deacetylases." *Annu. Rev. Biochem*. **73**: 417–35
- 4. Billington RA, Bruzzone S, De Flora A, Genazzani AA, Koch-Nolte F, Ziegler M, Zocchi E (2006). "Emerging functions of extracellular pyridine nucleotides." *Mol Med*. **12** (11–12): 324–7.

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- 5. Broom SL, Owen S, Norris P, Mestayer R, Grace C, Shen G, Hitt W (2008). “Amino acid-based nutritional supplementation facilitates abrupt cessation (“stopping cold turkey”) of substance use by addiction patients: Reduction of withdrawal symptoms with minimal abuse potential.” Presentation, Soc. for Neuroscience annual meeting, 19 Nov. 2008.
- 6. Humiston J (2014). “Treatment of Drug and Alcohol Dependence and Chronic Pain with Intravenous Amino Acids.” Meeting of the Int’l College of Integrative Medicine, Dearborn, Michigan, 25 Sept. 2014.

Fagron North America, IACP: Nominators

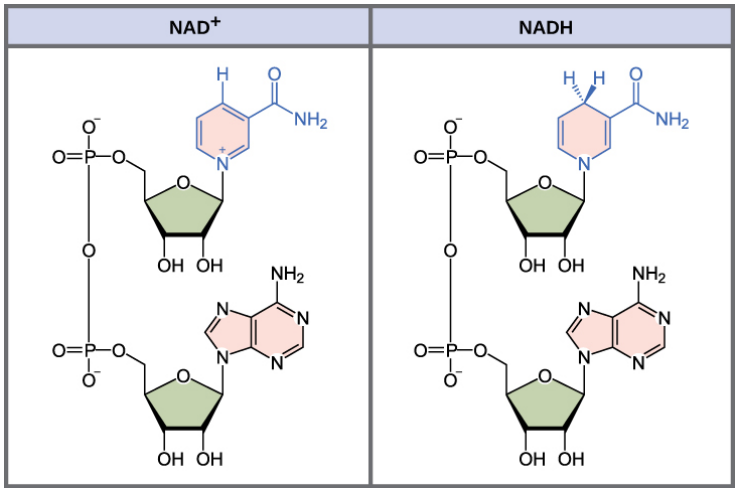
Pharmacy Compounding Advisory Committee review: Nicotinamide Adenine Dinucleotide Disodium Reduced (NADH)

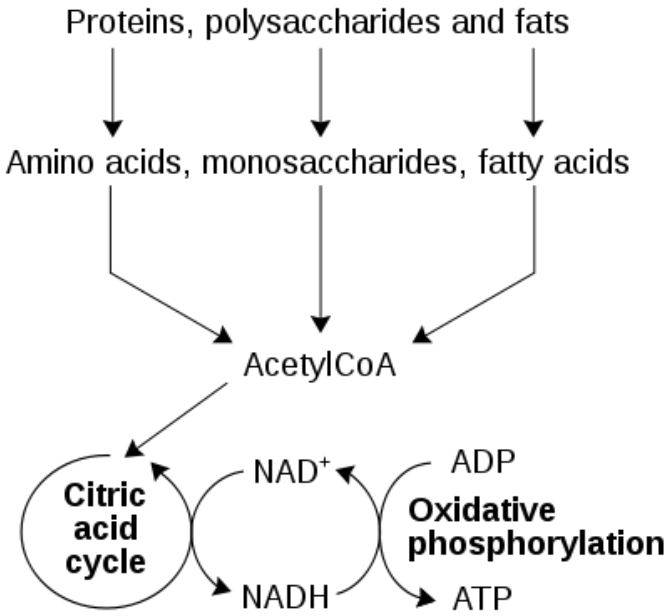
May 8-9th 2017

Tom Wynn RPh, Fagron NA

NADH - nicotinamide adenine dinucleotide reduced

- The reduced form of NAD+ a coenzyme found in all living cells
- Synthesized in the body from vitamin B3 (niacin, or nicotinamide)
- An important pyridine nucleotide that functions as an oxidative cofactor in eukaryotic cells
- Plays a key role in the production of energy through ATP generation





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Safety

“Safety of stabilized, orally absorbable, reduced nicotinamide adenine dinucleotide (NADH): a 26-week oral tablet administration of ENADA/NADH for chronic toxicity study in rats.

The safety of the stabilized, orally absorbable form of reduced nicotinamide adenine dinucleotide (NADH), known under the brand name ENADA, was **investigated over a period of 26 weeks**. **Eighty healthy rats (40 males and 40 females)** were divided into two groups. **One tablet ENADA/NADH 5 mg per day was administered orally** to one group while identical-looking white tablets not containing NADH (placebo) were given to the other group. **The following parameters were statistically analyzed: body weight, body weight gain, food consumption, hematology, clinical chemistry, organ weight and organ histology. Clinical signs and mortality were recorded. There were no deaths associated with the study drug and no treatment-related clinical signs.** No differences in body weight between the placebo and the ENADA-treated males were observed. In the second half of the treatment period (weeks 13-26) females treated with NADH gained significantly ($p < 0.05$) more body weight than the controls. Food consumption in the treated males was similar to that in controls. From approximately week 15, the treated females consumed up to 10% more food than the controls. No differences were observed between the control and the treated groups in terms of hematology or clinical chemistry parameters. There was no apparent treatment-related effect on urine analysis parameters or on either the absolute or the relative organ weight. Furthermore, no macroscopic evidence of specific target organ toxicity associated with the test drug was observed. Histological findings in the treated rats were generally similar to those in control rats. **A daily dose of 5 mg in a rat corresponds to a dose of 175 mg per day in a 70-kg human. This is 175 times the recommended daily dosage of 1 ENADA tablet per day. Hence ENADA/NADH 5 mg tablets can be generally regarded as safe.”**[1]

1. Birkmayer JG, Nadlinger K. Safety of stabilized, orally absorbable, reduced nicotinamide adenine dinucleotide (NADH): a 26-week oral tablet administration of ENADA/NADH for chronic toxicity study in rats. Drugs Exp Clin Res. 2002;28(5):185-92.

Safety

“On the safety of reduced nicotinamide adenine dinucleotide (NADH).

The objective of the study was **to determine both the toxicity of the stabilized orally absorbable form of nicotinamide adenine dinucleotide (NADH) and the maximum tolerated intravenous dose** (MTD) of betaNADH (the reduced form of NADH) in beagle dogs. The **administration of the stabilized orally absorbable form of NADH to beagle dogs at dose levels of 20, 100, and 150 mg/kg for 14 days elicited no signs of a toxicological effect.** A transitory change in stool formation was observed with the intermediate and high dose in males. There were also apparent increases in adrenal, heart, kidney, liver, brain, and thyroid weights, particularly in males, but none of these changes were considered to be toxicologically significant. In addition, four dogs (two of each sex) received intravenous infusions of 100 mg NADH/kg/day for 4 days, followed by 200 mg NADH/kg/day for 3 days, followed by 500 mg NADH/kg/day for 4 days, and 1000 mg NADH/kg/day on the final day. At the end of the MTD phase, the control animals that had received saline solution in the MTD phase were used to evaluate the potential toxicity of the established MTD. These animals received 500 mg NADH/kg/day for 14 days (fixed dose phase). **There were no deaths.** At dose levels between 100 and 1000 mg/kg/day, effects on the cardiovascular system and also some evidence of an effect on the central nervous system and on the adrenals were observed. **At doses of 500 mg/kg/day and above, food consumption and body weight were reduced.** On the basis of the observed changes, **the maximum intravenous dose of NADH tolerated by beagle dogs was considered to be 500 mg/kg/day. There were no gross histological findings indicative of toxicity in the organs of tissues examined. Based on these findings**, the stabilized orally absorbable form of **NADH can be regarded as safe.”**[1]

Birkmayer JG, Nadlinger KF, Hallström S. On the safety of reduced nicotinamide adenine dinucleotide (NADH). J Environ Pathol Toxicol Oncol. 2004;23(3):179-94.

Chronic Fatigue

“Therapeutic effects of oral NADH on the symptoms of patients with chronic fatigue syndrome.

The purpose of the study was to evaluate the efficacy of the reduced form of nicotinamide adenine dinucleotide (NADH) i.e., ENADA the stabilized oral absorbable form, in a randomized, double-blind, placebo-controlled crossover study **in patients with CFS**. Nicotinamide adenine dinucleotide is known to trigger energy production through ATP generation which may form the basis of its potential effects.”[1]

Clinical symptomology evaluated →

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. Ann Allergy Asthma Immunol. 1999 Feb;82(2):185-91.

Chronic Fatigue - Therapeutic effects of oral NADH on the symptoms of patients with chronic fatigue syndrome

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.

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.

Chronic Fatigue

ClinicalTrials.gov

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Text Size

Clinical Trial to Measure the Maximun HR After ReConnect ® Supplementation vs. Placebo in CFS. (ReConnect)

This study has been completed.

Sponsor:
Hospital Universitari Vall d'Hebron Research Institute

Collaborator:
VITAE NATURAL NUTRITION, S.L.

Information provided by (Responsible Party):
Hospital Universitari Vall d'Hebron Research Institute

ClinicalTrials.gov Identifier:
NCT02063126

First received: February 5, 2014
Last updated: February 18, 2015
Last verified: February 2015
History of Changes

Chronic Fatigue

“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]

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;22(8):679-685.

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

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;22(8):679-685.

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Chronic Fatigue

“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):826-34.

Chronic Fatigue - 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

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.**

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):826-34..

FDA Approved Therapies for Chronic Fatigue

- There are currently no FDA approved drug therapies for Chronic Fatigue
- Typically managed with psychological counseling, NSAIDs antidepressants, and stimulants[1,2]

1. Theoharides TC, Tsilioni I, Arbetman L, Panagiotidou S, Stewart JM, Gleason RM, Russell IJ. Fibromyalgia syndrome in need of effective treatments. J Pharmacol Exp Ther. 2015 Nov;355(2):255-63.
2. Theoharides TC, Asadi S, Weng Z, Zhang B. Serotonin-selective reuptake inhibitors and nonsteroidal anti-inflammatory drugs--important considerations of adverse interactions especially for the treatment of myalgic encephalomyelitis/chronic fatigue syndrome. J Clin Psychopharmacol. 2011 Aug;31(4):403-5.

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. Woźniacka 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

Woźniacka 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

- Topical NADH can effectively protect the cell and its membrane from destruction by free radicals[1]
- Reduced erythema and papules
- At a concentration of 1% NADH in ointment was effective in the treatment of rosacea and contact dermatitis[1]
- No adverse effects were observed[1]

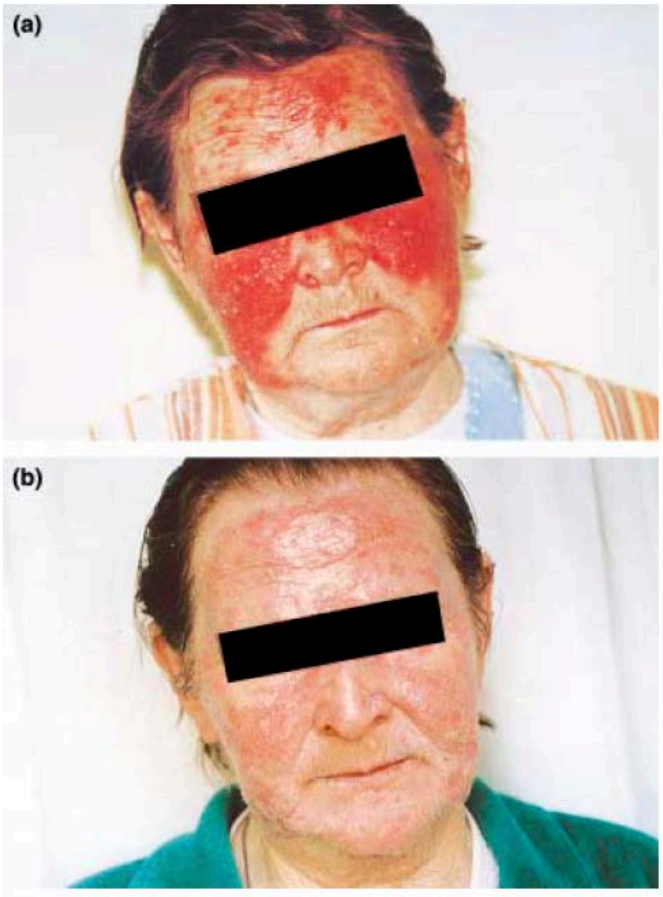


Figure 1 Treatment of rosacea with NADH ointment in a 61-year-old-woman. (a) Before treatment. (b) After 14 days of treatment.

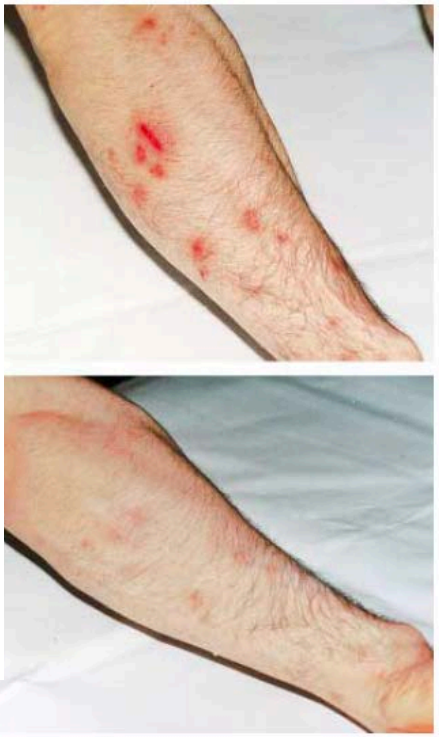


Figure 2 Treatment of contact dermatitis with NADH ointment in a 40-year-old man. (a) Before treatment. (b) After 14 days of treatment.

1. Woźniacka 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..

FDA Approved Therapies for Rosacea

- Oral antibiotics
- Topical metronidazole gel 1% gel (effective in 37% of respondents in 10-week clinical study)[1]
- Azelaic acid gel 15% (61% effective for clearance of papules and lesions but not evaluated for erythema)[2]
- Mirvaso (brimonidine) topical gel 0.33% (~30% successful - indicated for nontransient erythema only)[3]

1.Product Information: FINACEA(R) topical gel, azelaic acid topical gel. Intendis, Pine Brook, NJ, 2005.
2. Product Information: MIRVASO(R) topical gel, brimonidine topical gel. GALDERMA LABORATORIES, L.P. (per FDA), Ft Worth, TX, 2013.
3. Product Information: Noritate(R), metronidazole. Dermik Laboratories, Collegeville, PA, USA, 1999.

Conclusion

- Plays a key role in the production of energy through ATP generation[1]
- Exerts antioxidant properties[2]
- Animal studies suggest that NADH can be recognized as safe[3,4]
- In human trials reviewed, oral and topical NADH was well tolerated with no study related adverse event reported[1,2,5,6]
- All reviewed trials support efficacy [1,2,5,6]

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.
2. Woźniacka 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.
3. Birkmayer JG, Nadlinger K. Safety of stabilized, orally absorbable, reduced nicotinamide adenine dinucleotide (NADH): a 26-week oral tablet administration of ENADA/NADH for chronic toxicity study in rats. Drugs Exp Clin Res. 2002;28(5):185-92.4. J Environ Pathol Toxicol Oncol. 2004;23(3):179-94.
Birkmayer JG, Nadlinger KF, Hallström S. On the safety of reduced nicotinamide adenine dinucleotide (NADH). J Environ Pathol Toxicol Oncol. 2004;23(3):179-94.
5. 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;22(8):679-685.
6. 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):826-34.

Fagron North America: Nominator

Pharmacy Compounding Advisory Committee review: Ubiquinol

May 8-9th 2017

Tom Wynn RPh, Fagron NA

Ubiquinol

- Reduced form of Co-enzyme Q-10
- Has greater bioavailability over coenzyme q-10

General information

- Found in oily fish, organ meats, peanuts, avocados, spinach and whole grains
- Low water solubility
- Found naturally in the body - most common form
- Involved in many biological processes pertaining to its ant-oxidative abilities including production of ATP

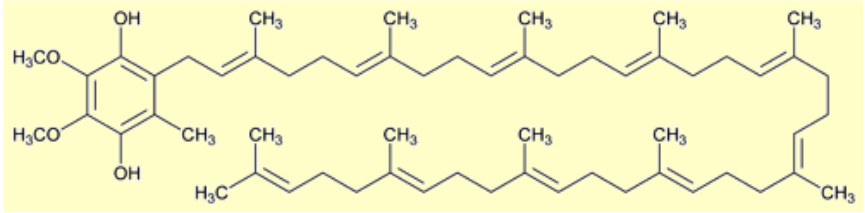
Kommuru, T. R., Ashraf, M., Khan, M. A., & Reddy, I. K. (1999). Stability and bioequiv- alence studies of two marketed formulations of coenzyme Q10 in beagle dogs. Chemical and Pharmaceutical Bulletin (Tokyo), 47(7), 1024–1028.

Ubiquinol

USP Dietary Supplement Monograph

Add the following:

■ **Ubiquinol**



USP Image 3D Image

$C_{59}H_{92}O_4$ 865.37

2-[(2*E*,6*E*,10*E*,14*E*,18*E*,22*E*,26*E*,30*E*,34*E*)-3,7,11,15,19,23,27,31,35,39-Decamethyltetraconta-2,6,10,14,18,22,26,30,34,38-decaenyl]-5,6-dimethoxy-3-methylbenzene-1,4-diol [992-78-9].

DEFINITION

Ubiquinol contains NLT 96.0% and NMT 102.0% of ubiquinol ($C_{59}H_{92}O_4$), calculated on the anhydrous basis.

IDENTIFICATION

- **A.** INFRARED ABSORPTION ⟨197K⟩
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

- **PROCEDURE**

Mobile phase: Acetonitrile and alcohol (50:50)

Ubiquinol and low density Lipoproteins

- LDL (low-density lipoprotein): A molecule that is a combination of lipid (fat) and protein. Lipoproteins are the form in which lipids are transported in the blood.

- (LDL) transports cholesterol from the liver to the tissues of the body. LDL cholesterol is therefore considered to be the bad cholesterol.

- This increase in cholesterol can lead to problems like atherosclerosis or plaques on the arteries. Which increases risk for stroke and heart attack

“Antioxidative activity of ubiquinol-10 at physiologic concentrations in human low density lipoprotein.

Ubiquinol-10 is a powerful lipid-soluble antioxidant found in cell membranes and lipoproteins in vivo. Its mechanism of action on lipid peroxidation has been determined in model and biological systems. Data concerning antioxidative activity of ubiquinol-10 in lipoproteins, however, are still controversial. The present work examines its role in the prevention of low density lipoprotein (LDL) oxidation, specifically its influence on a copper-mediated oxidative modification of human LDL in vitro. We found that ubiquinol-10 incorporated in LDL in subnormal concentrations (0.05-0.13 mol/mol LDL incorporated in comparison with 0.10-1.20 mol/mol LDL reported as normally in human LDL) slightly but not significantly decreased production of lipid peroxidation products (lipid peroxides, conjugated dienes, thiobarbituric acid-reactive substances) during the first hours of oxidation. The extent of apolipoprotein B modification (LDL fluorescence at 360/430 nm) was also decreased. Increasing the ubiquinol-10 concentration in LDL to 0.55-1.48 mol/mol LDL made it significantly more resistant to copper-mediated oxidation than native LDL. Adding the same amounts of either ubiquinone-10 or alpha-tocopherol to the LDL suspension had almost no effect on its oxidation. Ubiquinol-10 decreased alpha-tocopherol consumption during LDL oxidation and was consumed more rapidly than the latter. **These results demonstrate that LDL ubiquinol-10 content is an important factor influencing LDL susceptibility to oxidation by copper and suggest that it represents the first line of defense against oxidative modification in human LDL.”**[1]

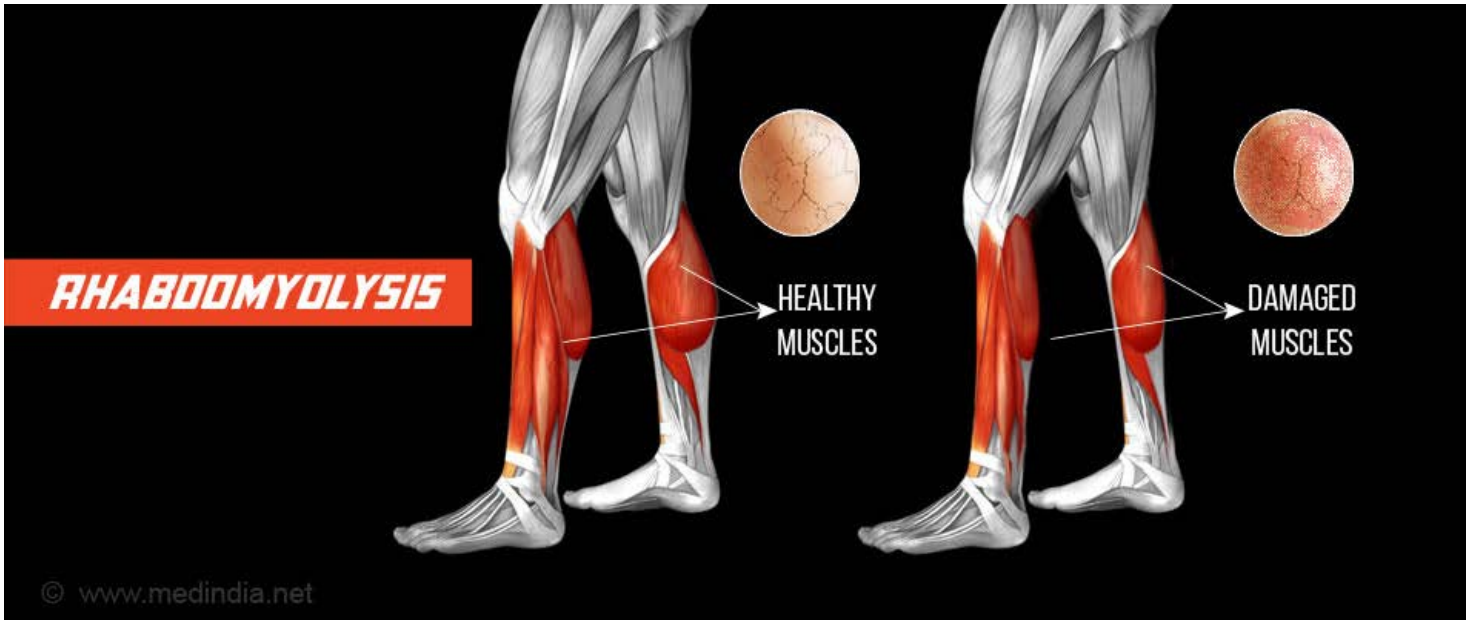
1. Kontush A, Hübner C, Finckh B, Kohlschütter A, Beisiegel U. Antioxidative activity of ubiquinol-10 at physiologic concentrations in human low density lipoprotein. Biochim Biophys Acta. 1995 Sep 14;1258(2):177-87.

“Ubiquinol rescues simvastatin-suppression of mitochondrial content, function and metabolism: implications for statin-induced rhabdomyolysis.

Statin medications diminish cholesterol biosynthesis and are commonly prescribed to reduce cardiovascular disease. Statins also reduce production of ubiquinol, a vital component of mitochondrial energy production; ubiquinol reduction may contribute to rhabdomyolysis. Human rhabdomyosarcoma cells were treated with either ethanol and dimethyl sulfoxide (DMSO) control, or simvastatin at 5 μM or 10 μM, or simvastatin at 5 μM with ubiquinol at 0.5 μM or 1.0 μM for 24 h or 48 h. PGC-1α RNA levels were determined using quantitative reverse transcriptase polymerase chain reaction (qRT-PCR). Mitochondrial content was determined using flow cytometry and immunocytochemistry. Metabolism was determined by quantification of extracellular acidification rate and oxygen consumption rate. Treatment of human rhabdomyosarcoma cells with simvastatin significantly reduced oxidative, total metabolism, and cellular ATP content in a time- and dose-dependent manner which was rescued by concurrent treatment with ubiquinol. Treatment with simvastatin significantly reduced mitochondrial content as well as cell viability which were both rescued by simultaneous treatment with ubiquinol. **This work demonstrates that the addition of ubiquinol to current statin treatment regimens may protect muscle cells from myopathies.”[1]**

1. Vaughan RA, Garcia-Smith R, Bisoffi M, Conn CA, Trujillo KA. Ubiquinol rescues simvastatin-suppression of mitochondrial content, function and metabolism: implications for statin-induced rhabdomyolysis. Eur J Pharmacol. 2013 Jul 5;711(1-3):1-9.

- Rhabdomyolysis-Breakdown of muscle tissue that is released into the blood stream
- Rhabdomyolysis percent of incident in 26, 375 individuals pooled
- Rhabdomyolysis 1.838624 (0.497649–6.79302) 0.3611 NA



Alberton M, Wu P, Druyts E, Briel M, Mills EJ. Adverse events associated with individual statin treatments for cardiovascular disease: An indirect comparison meta-analysis. *QJM*. 2012;105(2):145-157.

Ubiquinol stability

“Study on safety and bioavailability of ubiquinol (Kaneka QH) after single and 4-week multiple oral administration to healthy volunteers.

The safety and bioavailability of ubiquinol (the reduced form of coenzyme Q(10)), a naturally occurring lipid-soluble nutrient, were evaluated for the first time in single-blind, placebo-controlled studies with healthy subjects after administration of a single oral dose of 150 or 300 mg and after oral administration of 90, 150, or 300 mg for 4 weeks. No clinically relevant changes in results of standard laboratory tests, physical examination, vital signs, or ECG induced by ubiquinol were observed in any dosage groups. The C(max) and AUC(0-48 h) derived from the mean plasma ubiquinol concentration-time curves increased non-linearly with dose from 1.88 to 3.19 micro g/ml and from 74.61 to 91.76 micro g h/ml, respectively, after single administration. Trough concentrations had nearly plateaued at levels of 2.61 micro g/ml for 90 mg, 3.66 micro g/ml for 150 mg, and 6.53 micro g/ml for 300 mg at day 14, and increased non-linearly with dose in the 4-week study. In conclusion, following single or multiple-doses of ubiquinol in healthy volunteers, significant absorption of ubiquinol from the gastrointestinal tract was observed, and no safety concerns were noted on standard laboratory tests for safety or on assessment of adverse events for doses of up to 300 mg for up to 2 weeks after treatment completion.”[1]

Recently, however, our chemical research group established a method enabling manufacture of ubiquinol bulk as Kaneka QH™ from our ubiquinone bulk of Kaneka Q10™, as well as stable capsule products containing Kaneka QH™

1. Hosoe K, Kitano M, Kishida H, Kubo H, Fujii K, Kitahara M. Study on safety and bioavailability of ubiquinol (Kaneka QH) after single and 4-week multiple oral administration to healthy volunteers. Regul Toxicol Pharmacol. 2007 Feb;47(1):19-28.

EXPLANATORY NOTES OF
KANEKA QH™ Stabilized Powder

Manufacturer:	KANEKA CORPORATION
Address:	3-2-4 Nakanoshima, Kita-ku, Osaka 530-8288, Japan
Contact:	Functional Food Ingredients Division
Telephone number:	+81-6-6226-5403
Facsimile number:	+81-6-6226-5059

Product name: Type No.:	KANEKA QH™ Stabilized Powder P30
Product description:	KANEKA QH™ Stabilized Powder, which contains 30% KANEKA QH™ (ubiquinol), is powder improved stability in air.
Components: (The following are food additives.)	Ubiquinol (KANEKA QH™) Dextrin Gum Arabic L-ascorbic acid Lecithin (soybean-derived)
Legal interpretation:	All components are of GRAS status.
Applications:	For industrial use as a raw material for dietary supplement or food. (See Product precautions on page 3.)

Ubiquinol safety

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No significant safety concerns were revealed in the studies, and no serious adverse events were observed. Ubiquinol thus exhibited an acceptable safety profile as a dietary supplement up to multiple daily doses of 300mg for 4 weeks

1. Hosoe K, Kitano M, Kishida H, Kubo H, Fujii K, Kitahara M. Study on safety and bioavailability of ubiquinol (Kaneka QH) after single and 4-week multiple oral administration to healthy volunteers. Regul Toxicol Pharmacol. 2007 Feb;47(1):19-28.

Ubiquinol Safety

- **Tested using bacterial reverse mutation**-results of these assays demonstrate that ubiquinol (1)does not induce reverse mutations in Salmonella typhimurium and Escherichia coli at concentrations as high as 5000µg/plate[1]

- **Tested chromosomal Aberration**-found not to induce chromosomal aberration in cultured CHL/IU cells exposed to concentrations up to the limit of toxicity; and (3) is devoid of chromosome or mitotic apparatus-damaging activity in rat bone marrow when administered orally to rats at doses up to the standard limit of 2000 mg/kg/day[1]

1. Kitano M, Mizuhashi F, Kubo H, et al. Evaluation of the mutagenic and genotoxic potential of ubiquinol. *Int J Toxicol*2007;26(6):533 544. doi:10.1080/10915810701707460.

Ubiquinol Efficacy

“Ubiquinol-10 supplementation improves autonomic nervous function and cognitive function in chronic fatigue syndrome.

The aim of this study was to evaluate the benefit of oral ubiquinol-10 supplementation in CFS patients using an open-label study and a randomized, double-blinded, placebo-controlled (RCT) study. Twenty patients with CFS were randomly enrolled in an 8-week open-label oral ubiquinol-10 (150 mg ubiquinol-10/day) study. The patients and the attending physicians were not blinded to the supplementation. Forty-three patients with CFS were randomly assigned to receive either ubiquinol-10 (150 mg/day) or placebo every day for 12 weeks. The patients and the attending physicians were blinded to the supplementation, and a total of 31 patients (N = 17 in the ubiquinol group and 14 in the placebo group) completed the study. The beneficial effects of ubiquinol-10 were observed in the open-label study we conducted prior to the RCT. The RCT results suggest that supplementation with ubiquinol-10 for 12 weeks is effective for improving several CFS symptoms.”[1]

1. Fukuda S, Nojima J, Kajimoto O, Yamaguti K, Nakatomi Y, Kuratsune H, Watanabe Y. Ubiquinol-10 supplementation improves autonomic nervous function and cognitive function in chronic fatigue syndrome. Biofactors. 2016 Jul 8;42(4):431-40.

Ubiquinol efficacy

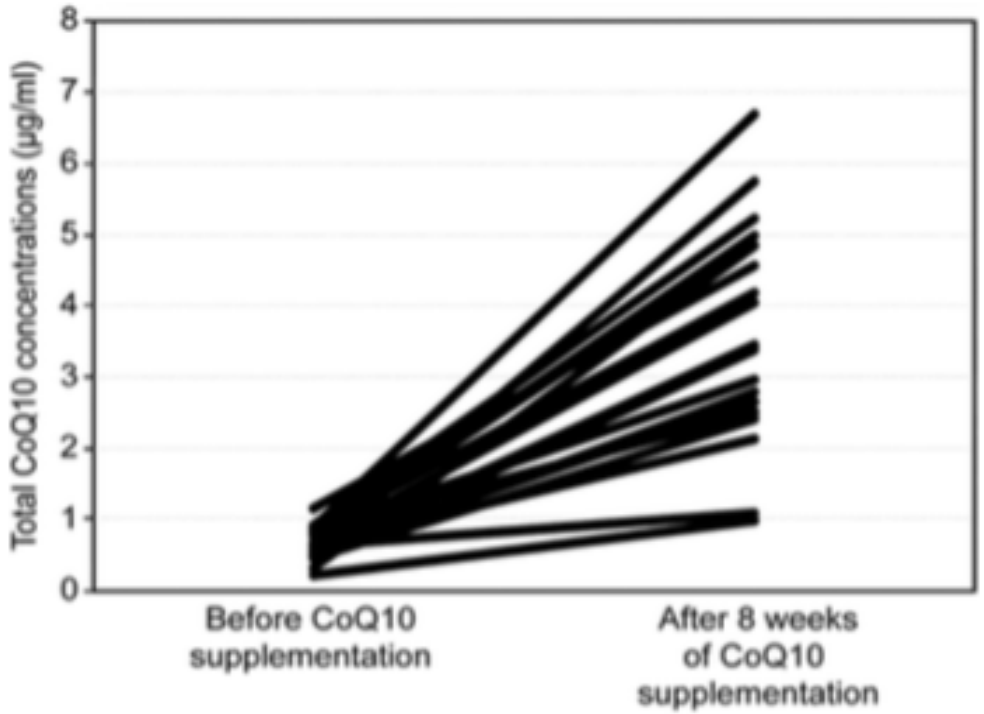

FIG 1 *Effects of an 8-week supplementation with ubiquinol on total coenzyme Q10 (CoQ10) concentrations.*

Ubiquinol efficacy

- Oxidative stress regarded as one of the major causes of renal dysfunction
- Ubiquinol normalized superoxide generation from kidney
- Supplementation may increase intrinsic antioxidant activity, thus suppressing redox- induced illnesses such as kidney injuries in salt-sensitive hypertension

Ishikawa A, Kawarazaki H, Ando K, Fujita M, Fujita T, Homma Y. Renal preservation effect of ubiquinol, the reduced form of coenzyme Q10. *Clin Exp Nephrol*. 2011;15(1):30-33. doi:10.1007/s10157-010-0350-8.

Ubiquinol Efficacy

- Ubiquinol plays various roles in the energy production of the muscles' cells.
- CoQ10 is an integral component of the mitochondrial oxidative phosphorylation system
- Oxidative phosphorylation harnesses energy from nutrients to produce ATP, the energy in each of our cells and all of our life processes

Alf D, Schmidt ME, Siebrecht SC. Ubiquinol supplementation enhances peak power production in trained athletes: a double-blind, placebo controlled study. *J Int Soc Sport Nutr*. 2013;10(1):24. doi:10.1186/1550-2783-10-24.

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Supplementation with ubiquinol-10 is effective for improving the HF (high frequency heart rate) power of the autonomic nervous system, nighttime awakenings and arithmetic task performance

1. Fukuda S, Nojima J, Kajimoto O, Yamaguti K, Nakatomi Y, Kuratsune H, Watanabe Y. Ubiquinol-10 supplementation improves autonomic nervous function and cognitive function in chronic fatigue syndrome. Biofactors. 2016 Jul 8;42(4):431-40.

Conclusion

- Ubiquinol is shown to have strong antioxidant properties[1]
- Can be stabilized[2]
- Has been shown in studies to be safe and non-genotoxic[3]
- Shows promise as an adjunct therapy in a variety of oxidative stress related chronic illnesses[4,5]

1. Kontush A, Hübner C, Finckh B, Kohlschütter A, Beisiegel U. Antioxidative activity of ubiquinol-10 at physiologic concentrations in human low density lipoprotein. Biochim Biophys Acta. 1995 Sep 14;1258(2):177-87.
2. Hosoe K, Kitano M, Kishida H, Kubo H, Fujii K, Kitahara M. Study on safety and bioavailability of ubiquinol (Kaneka QH) after single and 4-week multiple oral administration to healthy volunteers. Regul Toxicol Pharmacol. 2007 Feb;47(1):19-28.
3. Kitano M, Mizuhashi F, Kubo H, et al. Evaluation of the mutagenic and genotoxic potential of ubiquinol. *Int J Toxicol*. 2007;26(6):533 544. doi:10.1080/10915810701707460.
4. Ishikawa A, Kawarazaki H, Ando K, Fujita M, Fujita T, Homma Y. Renal preservation effect of ubiquinol, the reduced form of coenzyme Q10. *Clin Exp Nephrol*. 2011;15(1):30-33. doi:10.1007/s10157-010-0350-8.
5. Alf D, Schmidt ME, Siebrecht SC. Ubiquinol supplementation enhances peak power production in trained athletes: a double-blind, placebo controlled study. *J Int Soc Sport Nutr*. 2013;10(1):24. doi:10.1186/1550-2783-10-24.