# Nicotinamide-Adenine Dinucleotide (NADH) in Parkinson's Disease and Alzheimer's Disease

**Andrew Glasnapp, PharmD, FIACP**
*Professional Compounding Centers of America, Inc.*

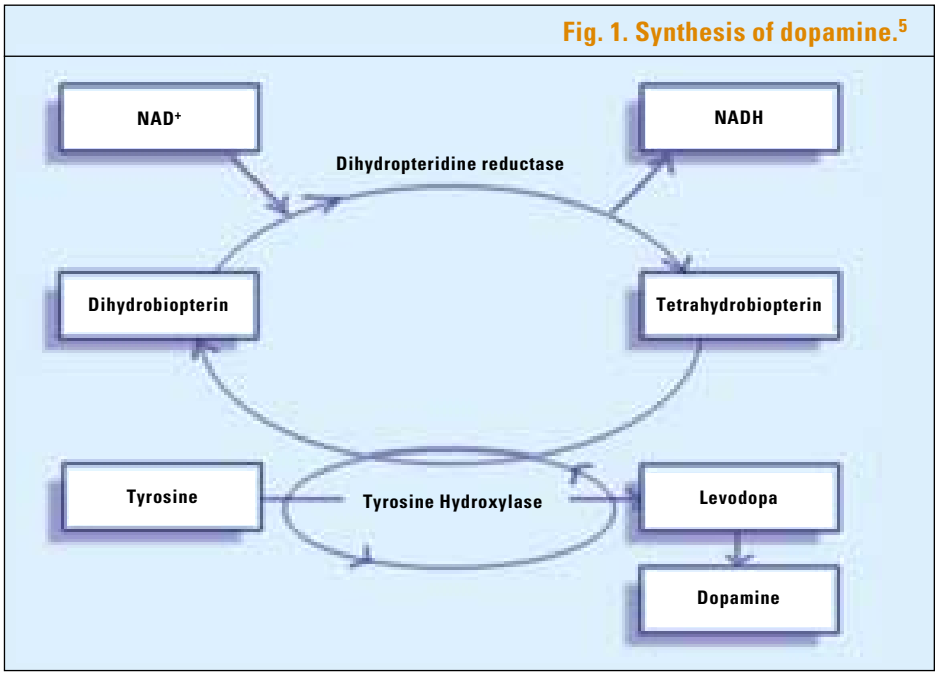
**Erin Schaefer**
*University of Houston College of Pharmacy Houston, TX*

**More than 2,000 individuals with Parkinson's disease have experienced positive results in trials supplementing with NADH.**

Nicotinamide-adenine dinucleotide (NADH), also known as Coenzyme I, is present in every living cell. It is currently being tested as a promising new therapy in the treatment of Parkinson's and Alzheimer's disease. In Parkinson's studies, 80% of patients have experienced an increase in motor function and/or mental status.[1] Results of Alzheimer's studies are even more dramatic, with 100% of patients improving their score on the Mini-Mental State Exam (MMSE).[2] Recent studies have used NADH, which is endogenous in the human body, at 7000 times below the dose considered safe.[3] Current estimates indicate that about 1% of the population over 65 years old suffers from Parkinson's disease and another 10% of the population over 65 years old is stricken with Alzheimer's disease. The implications are far-reaching for those who can be significantly helped by supplementation with this apparently safe and relatively inexpensive product.

Parkinson's disease is thought to occur because of a shortage of dopamine in the basal ganglia of the brain. In the *Journal of Neurochemistry*, McGeer and colleagues attribute this to diminished activity of tetrahydrobiopterin, the coenzyme for tyrosine hydroxylase.[4] Tyrosine hydroxylase is the enzyme capable of converting tyrosine into levodopa, which in turn becomes dopamine (see Fig. 1). Because tyrosine hydroxylase is diminished in Parkinson's patients, dopamine is diminished as well.[4] This dopamine shortage is currently treated by supplementing levodopa, but this is not ideal because the exogenous levodopa inhibits the body's own production of levodopa through a negative feedback loop.[6] This may be why tolerance often develops after time in many Parkinson's patients.[6] As the mechanism of dopamine synthesis became more clear, researchers began looking for a new agent that would not compromise the body's own production of chemicals such as levodopa and dopamine. They discovered that NADH plays an important role in activating tyrosine hydroxylase by increasing levels of tetrahydrobiopterin.[7] Further examination revealed that Parkinson's patients may have up to 50% less NADH activity compared with healthy individuals of the same age.[6] In fact, NADH supplementation increases serum levels of tyrosine hydroxylase by 75%.[1] This led to the obvious question of whether supplementation would be helpful in ameliorating the symptoms associated with dopamine depletion. Researchers at the Birkmayer Institute have found that dopamine synthesis in the brain of a rat increased by more than 40% after two weeks of intraperitoneal injections with NADH.[3] Further studies at Birkmayer show that NADH also increases within the cells following treatment, thereby increasing intracellular energy and theoretically allowing the cell to work more efficiently and to survive longer.[3]

Fig. 1. Synthesis of dopamine.[5]

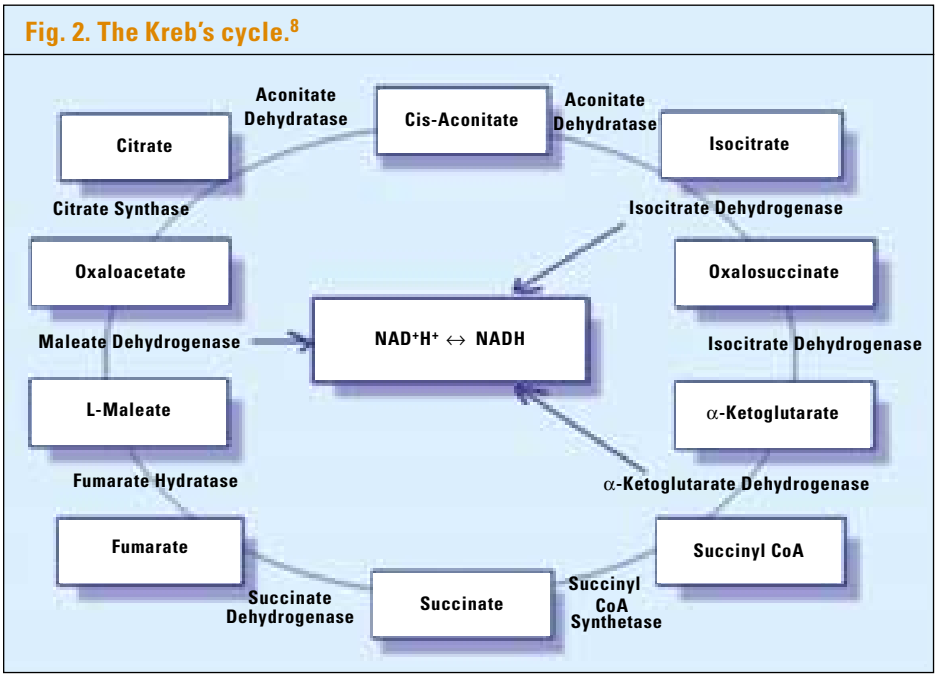



Nicotinamide-adenine dinucleotide is present in every living cell and is essential to cellular energy production. One mole of NADH produces three moles of ATP and 36 kilocalories.[2] Its most familiar role is in the Kreb's cycle, where it is formed at three different points (see Fig. 2). While NADH is available in the human diet, mostly in meats, it is not present in any great amount. One would have to eat four pounds of steak to consume 10 mg of NADH.[9]

The most well-known study involving NADH supplementation took place at the Birkmayer Institute in Vienna, Austria, by J.G.D., and W. Birkmayer, C. Vrecko and D. Volc. In an open-label trial, 885 patients were given either 5-mg capsules orally every day, or 12.5 mg every other day, by intravenous (IV) infusion. For the IV preparation, 12.5 mg NADH was dis-

*Corresponding author: Andrew Glasnapp, PharmD, FIACP, Professional Compounding Centers of America, Inc., 9901 S. Wilcrest, Houston, TX 77099*

**Fig. 2. The Kreb's cycle.[8]**




solved in 100 mL 0.9% sodium chloride injection, buffered to a pH of 7.6 and filtered through a 0.22-µm filter and infused over 30 minutes. Treatment continued for 14 days. Parameters evaluated to assess improvement in motor function included posture, walking, pushing, speech and mimicking.[1]

The results are shown in Table 1.

Patients receiving oral formulations showed an average improvement of 19.8%, while the mean benefit by IV NADH was 20.6%.[1] These results were further corroborated by the fact that symptoms returned in the two- to- three-week period after NADH was discontinued.[1] It is important to note that all pharmacological therapies the patients were on prior to NADH supplementation were continued during this experiment.[1] An earlier study by J.G.D. Birkmayer and colleagues, however, detailed a study in which 40 Parkinson's patients were treated with 25 mg of NADH IV per day and one fifth of these patients were able to forego levodopa therapy and supplement NADH alone.[7] Other patients were able to reduce their levodopa doses.[7]

The implications for the use of NADH in Parkinson's disease are not limited to the alleviation of motor symptoms. Dementia, associated with both Parkinson's and Alzheimer's disease, is also thought to occur because of dopamine deficiencies, and these clinical studies are even more promising than the Birkmayer studies for Parkinson's disease. Reisberg and colleagues define dementia as a loss of memory, deterioration of intellectual functioning and impairment in the skills of daily living.[10] A study from the *Journal of Neurochemistry* reports that the metabolite of dopamine, homovanillic acid, was decreased in the cerebrospinal fluid of Alzheimer's patients with dementia.[11] Birkmayer supplies further evidence, revealing that dopamine concentrations were low in the caudatus nucleus and hypothalamus, as well as the globus pallidus, putamen, nucleus amygdala, substantia nigra and basal ganglia of patients suffering from dementia.[3] Naturally, NADH was considered a likely candidate to help reduce the effects of dementia and the studies are proving its value in this condition. An Alzheimer's disease study by Birkmayer assessed 17 subjects using the MiniMental State Exam (MMSE) (see Fig. 3). By this scale, scores range from 0 to 30. A patient scoring between 24 and 30 is considered normal, while a patient scoring below a 24 would be considered to be in some state of dementia.[12] The patients in Birkmayer's Alzheimer study were given 10 mg of NADH orally 30 minutes before breakfast. The results were quite significant. Before treatment, the average MMSE score of these patients was 15.82. After an average of ten weeks of treatment, the mean MMSE score rose to 24.18, an increase of 8.35 points. The minimum improvement was six points.[2] Amazingly, 100% of these patients experienced a meaningful increase in their mental status, as 53% of these patients returned to an acceptable range with a score greater than 24, and the average MMSE scores increased by 27.76%.[2]

Follow-up research from the Birkmayer study indicates that both dopamine and noradrenaline increased in the plasma of treated patients after NADH treatments.[9] Birkmayer also found that NADH ubiquinone reductase activity increased 240% after two weeks of treatment with NADH. This suggests yet another promising role for NADH, as this may result in an increase in the energy supply available to cells. This could certainly have positive implications for cell function.[2] When the hydrogen atoms of NADH are oxidized, energy is released. This process takes place within the mito-

**Table 1. Results of the Birkmayer Parkinson's Disease Study.[1]**

| Number of Patients | Percentage of Patients | Disability Improvement (%) |
|---|---|---|
| 42 | 4.7 | 50 |
| 54 | 6.1 | 40 |
| 75 | 8.4 | 30 |
| 147 | 16.6 | 20 |
| 374 | 42.2 | 10 |
| 193 | 21.8 | 0 |

**Fig. 3[12] Mini-Mental State Examination (MMSE)**

Max Score 30
Normal 24-30

1. Can you tell me the date? Ask for year, season, date, day and month. Subtract one point for each item not given (max score 5).
2. Where are you? Ask for state, country, town, hospital, floor. Subtract one point for each item not given (max score 5).
3. Name three objects slowly and clearly and ask the patient to repeat them. Subtract one point for each item not named (max score 3).
4. Ask the patient to do serial sevens. Stop after five answers. OR Ask the patient to spell *world* backwards. Subtract one point for each wrong number or out of order letter (max score 5).
5. Ask the patient for the three words listed previously. Subtract one point for each item omitted (max score 3).
6. Show the patient a watch and ask for its name. Repeat with a pencil. Subtract one point for each item not named correctly (max score 2).
7. Ask the patient to repeat "No *ifs*, *ands*, or *buts*." Subtract one point if not repeated correctly (max score 1).
8. Offer the patient a piece of paper and ask them (sic) to take the paper in their (sic) right hand, fold it in half and put it on the floor. Subtract one point for each action not performed (max score 3).
9. Show the patient a piece of paper on which is printed "close your eyes" in large letters. Ask the patient to read it and do it. Subtract one point if the patient's eyes do not close (max score 1).
10. Ask the patient to write a sentence of his or her own. Subtract one point for missing subject, verb or sensible meaning (max score 1).
11. Ask the patient to copy a pair of intersecting pentagons onto a piece of paper. Subtract one point for fewer than ten angles or two intersecting lines (max score 1).

chondria of cells and is driven by NADH, but also involves NADH ubiquinone-reductase, Complex II, Complex III and Complex IV.[2] Therefore, one can rationally propose that, by increasing components necessary to make energy, one could, in fact, generate a higher energy level within the cell. Researchers are hopeful that supplementing a cell's energy level will help it work more efficiently and that it may even lengthen the life of the cell.[7] There is little clinical evidence to support this supposition, but trials are under way and related research appears promising. For instance, a recent study using NADH in chronic fatigue syndrome shows improvement in a variety of areas such as fatigue, postexertional malaise, muscle pain and sleep disturbances, and can be theoretically attributed to the aforementioned mechanism of action.[13] These new developments certainly have important applications in both Parkinson's and Alzheimer's diseases.

**Formula**

**NADH CAPSULES**

*Rx*

| | 5-mg Capsule | 10-mg Capsule |
|---|---|---|
| NADH | 500 mg | 1 g |
| Lactose | 20.96 g | 21.73 g |

1. Geometrically incorporate the NADH into the lactose until uniformly mixed.
2. Encapsulate into 100 No. 3 capsules.
3. Package and label.

The uses for NADH in Parkinson's and Alzheimer's disease appear endless as one explores the many roles of NADH throughout the cells of the human body. To this date, more than 2000 individuals with Parkinson's disease have experienced positive results in trials supplementing with NADH.[9] Toxicology studies at the Corning Hazelton laboratories in England have shown that the maximum safe dose of NADH is 500 mg/kg of body weight per day,[3] and the starting therapeutic dosage for humans in trials thus far has been around 15 mg per person per day. One can see there is little need for concern regarding side effects or toxicity.[3] In fact, no significant adverse events have been reported within the previously reviewed trials.[1,2,3]

We believe, upon review of the material, that this is a promising new therapy that is accessible to patients through compounding pharmacists. Though we would like to see more extensive testing in the future using randomized, double-blind clinical studies, especially regarding Alzheimer's patients, we are confident that NADH works based on the data discussed. It is inexpensive, safe and attainable, and we recommend that every patient with Parkinson's disease or Alzheimer's disease be allowed to initiate NADH therapy at 5 mg to 15 mg twice a day, titrated by measure of symptomatic improvement. Before treatment begins, Parkinson's disease patients should be evaluated by their physician to measure disability. Progress should be evaluated two weeks after NADH supplementation begins and a dose should not be changed more frequently than once every two weeks. The patient and pharmacist may evaluate when dosage increases are necessary based on alleviation of symptoms, while the patient's physician conducts more formal assessment of disability at regularly scheduled exams. Doses may be increased by 5 mg twice a day when necessary, unless side effects emerge. One would expect to see an abatement of symptoms within six weeks. Alzheimer's patients may be evaluated by their pharmacists through administration of the MMSE (see Fig. 3). Progress should be evaluated after six weeks of treatment and the MMSE should be repeated. Dosage increases of 5 mg twice a day may be added at these intervals unless side effects develop. Patients should experience an increase in MMSE scores by week 12 of therapy.

## References


1. Birkmayer JG, Volc D, Birkmayer W et al. Nicotinamide adenine dinucleotide (NADH) – A new therapeutic approach to Parkinson's disease. NADH – Life's Energy Source. Online. Internet. 28 Jul. 1999. Available: http://www.nadh.com/parknson/Prkns210.htm#Top
2. Birkmayer JG. Coenzyme nicotinamide adenine dinucleotide: New therapeutic approach for improving dementia of the Alzheimer type. NADH – Life's Energy Source. Online. Internet. 28 Jul. 1999. Available: http://www.nadh.com/alzhmrs/Alzhm210.htm#Top
3. Birkmayer JG. Coenzyme nicotinamide adenine dinucleotide: New therapeutic approach for improving dementia of the Alzheimer type. *Ann Clin Lab Sci* 1996;26:1-9.
4. McGeer EG, McGeer PL, Wada JA. Distribution of tyrosine hydroxylase in human and animal brain. *J Neurochem* 1971;18:1647-1658.
5. Birkmayer GD, Birkmayer W. Stimulation of endogenous L-dopa biosynthesis – A new principle for the therapy of Parkinson's disease. *Acta Neurol Scand* 1989;126:183-187.
6. Birkmayer JG, Volc D, Birkmayer W et al. Nicotinamide adenine dinucleotide (NADH) – A new therapeutic approach to Parkinson's disease. *Acta Neurol Scand* 1993;87:Suppl 146;32-35.
7. Birkmayer W, Birkmayer GD, Vrecko K et al. The clinical benefit of NADH as stimulator of endogenous l-dopa biosynthesis in Parkinsonian patients. *Adv in Neurol* 1999, Vol. 53. Online. July 28, 1999. Available: http://www.thorne.com/townsend/dec/nadhreaction.html
8. Bhagavan NV, ed. *Medical Biochemistry.* New York, Jones and Barrett. 1992, pp 254-255.
9. Birkmayer GD. The NADH reaction: European study documents effects of NADH on Alzheimer patients. *Adv in Neurol* 1999; 53. Online. Internet. July 28, 1999. Available: http://www.thorne.com/townsend/dec/nadhreaction.html
10. Reisberg B, Ferris SH, Kluger A et. al. Symptomatic changes in CNS aging and dementia of the Alzheimer type; Cross-sectional, temporal, and remediable concomitants. *Diagnosis and Treatment of Senile Dementia.* Berlin, Springer-Verlag 1989 pp 193-223.
11. Gottfries CG, Gottfries I, Roos BE. Homovanillic acid and 5-hydroxyindoleacetic acid in the cerebrospinal fluid of patients with senile dementia, presenile dementia and Parkinsonism. *J Neurochem* 1969;16:1341-1345.
12. Forlstein MF, Folstein SE, McHugh PR. Mini Mental State: A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975:196-198.
13. Forsythe LM, Preuss HG, MacDowell AL et al. Therapeutic effects of oral NADH on the symptoms of patients with chronic fatigue syndrome. *Ann Allergy Asthma Immunol* 1999;82:185-191.