Efficacy of Vitamin B_3 and Its Related Coenzymes for the Treatment of Bell's Palsy, Huntington's Disease, Migraine and Chronic Tension-Type Headaches, Multiple Sclerosis, Parkinson's Disease, and Tinnitus

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Abstract *This review summarizes the efficacy of vitamin B_3 and its related coenzymes for the treatment of Bell's palsy, Huntington's disease, migraine and chronic tension-type headaches, multiple sclerosis, Parkinson's disease, and tinnitus. This review includes a summary table of the doses and method of administration of vitamin B_3 and its related coenzymes that were used to treat these medical conditions effectively. The author encourages clinicians to consider the therapeutic benefits of vitamin B_3 and its related coenzymes and perform additional research to verify its multi-spectrum capabilities.*

Introduction

Vitamin B_3 refers to the vitamin whose deficiency causes the fatal disease called pellagra. Pellagra is a disease caused by a cellular deficiency of the nicotinamide coenzymes due to an inadequate dietary supply of tryptophan and vitamin B_3. Diarrhoea, dermatitis and dementia characterize this deficiency disease, which can result in death. The body can manufacture approximately 1 mg of niacin equivalents from 60 mg of tryptophan obtained mostly from dietary protein. This *in vivo* conversion makes it rather difficult to develop frank pellagra in affluent, industrialized countries, where food supply is seldom scarce unless there are mitigating factors like disease (anorexia nervosa, hypothyroidism, and alcoholism),[1-6] medication-induced nutrient depletion (the use of anticonvulsants),[7,8] or from a lack of food intake (homelessness).[9]

The two forms of vitamin B_3 are nicotinic acid (also called niacin, which is a widely available over-the-counter or prescription nutrient for treating certain hyperlipidaemias, usually in 500 mg tablets and prescribed in a dose of 1 g three times daily) and nicotinamide, (also called niacinamide), which is the amide of niacin and the direct biosynthetic precursor of coenzyme 1 (i.e., nicotinamide adenine dinucleotide/NAD and the reduced form of nicotinamide adenine dinucleotide/NADH). The two forms of the vitamin are rapidly inter-convertible in the body. Niacinamide, (being an amide), has a bitter taste. It is usually sold only in health

food stores since there is no specific indication for its use. Niacinamide does not normally induce skin flushing, but some people are rapid converters and will experience skin flushing. Niacin being an acid, tastes sour, and is an effective hypolipidaemic agent in high doses. Niacin causes transient skin flushing until tolerance develops, but niacinamide has no effect on blood lipids, and skin flushing occurs only rarely with it.

Niacin is the only therapeutic agent currently available that affects all components of the atherogenic lipid profile in a very favourable manner.[10] Specifically, it lowers triglycerides, raises high-density lipoprotein, decreases lipoprotein(a), and shifts low-density lipoprotein particles to a less atherogenic phenotype.[11,12] There is a prescription-only, extended-release form of niacin (i.e., Niaspan®), as well as several over-the-counter forms sold as no-flush. Unlike Niaspan®, which is potent in modifying the lipid profile, there is no data as to whether many of the over-the counter slow-release forms are actually effectively absorbed by the intestines. Furthermore, there are concerns that slow-release forms have a greater risk of liver toxicity.

While it is uncommon practice to use vitamin B_3 and its related coenzymes for medical reasons unless pellagra or hyperlipidaemia have been identified, orthomolecular practitioners have been using vitamin B_3 and its related coenzymes therapeutically for more than 50 years to treat numerous neuropsychiatric conditions. I am always searching for treatments that are safe and effective. Many times I have to manage medical conditions in which the likelihood of clinical success from standard medical treatments is not very good. Conditions that fall into this "difficult-to-treat" category include, but are not limited to, Bell's palsy, Huntington's disease, migraine and chronic tension-type headaches, multiple sclerosis, Parkinson's disease, and tinnitus. Because I have a keen interest in the clinical uses of vitamin B_3 and its related coenzymes, I reviewed numerous publications, many of which were decades old, to ascertain if this vitamin therapy could potentially help these medical conditions. This review is by no means exhaustive of the complete medical literature, since many good publications are in other languages or are difficult to obtain. Nonetheless, in my opinion, many orthomolecular clinicians will find this information helpful when managing these medical conditions.

1. Bell's Palsy

Bell's palsy (BP) is an idiopathic peripheral nerve palsy caused by inflammation of the facial nerve at the geniculate ganglion, leading to compression, and possible ischemia and demyelination.[13] It is diagnosed following an abrupt onset of impaired facial expression due to unilateral weakness of all facial nerve branches, causing the patient much distress.[14] The patient loses the ability to close or wink the eye or close the mouth, experiences numbness or pain around the ear, temple, mastoid or angle of the mandible, and notices an altered sense of taste, sound hypersensitivity, and decreased tearing.[15,16] While the aetiology is unknown, BP has a predilection for pregnant women, diabetic patients, patients having had a recent tooth extraction, and those with influenza, a cold, or some other respiratory illness.[17] It has an annual incidence of 20-25 cases per 100,000 of the population.[18-20] More than two-thirds of people with BP will achieve full spontaneous recovery regardless of treatment.[8] Medical treatment involves the use of oral corticosteroids (e.g., prednisone) either alone or in combination with antivirals (e.g., acyclovir or valacyclovir).[13,14]

Treatment with Vitamin B_3

The use of intramuscular (IM) and oral niacin (nicotinic acid) was successful in treating 74 cases of BP between 1947 and 1957.[21] In Kime's 1958 report, he provided niacin to 39 patients within 2 days of onset of facial nerve paralysis, and noted a return of facial motion within 7 days, and full recovery in 14 days. When niacin treatment was provided to 33 patients between days 3 and 13 (mostly, within 3-5 days of onset),

there was the beginning of facial movement 10 days post onset, and full recovery by three weeks. One patient was seen within a month of onset facial nerve paralysis, and had a full recovery after 18 days of treatment. Another patient was seen two months after the onset of facial nerve paralysis, and 21 days following treatment the patient had approximately 80% facial movement recovery. Thus, 73 patients completely recovered, while one patient had an 80% recovery.

All patients were started on 100-150 mg of IM niacin administered daily. After several treatments, the dose would be increased to 250 mg unless there was an adequate cutaneous flushing response from the lesser doses. The paralyzed side of the face exhibited an obvious pallor following initial niacin treatments. Following 3-4 IM injections (100-250 mg IM niacin), the paralyzed side began to improve, and eventually the cutaneous flush would be evenly distributed over the face. In addition to IM niacin injections, 59 patients were instructed to take 50 mg of niacin orally three times each day, whereas the remaining 15 patients were prescribed a combination of niacin and meclizine to be taken orally each day (doses were not specified). Seventy-three patients had a full recovery following this treatment approach, while one patient had an 80% response.

In another study, Farber treated BP by providing a compress to the affected side of the face containing 10 mL dimexide, 1% solution of niacin (5 mL), and normal saline (5 mL).[22] Sixty-five patients were administered 10-12 compresses over an unspecified treatment duration, and compared to a control group of BP patients given conventional medical treatment. The patients provided with the compress containing niacin had a statistically significant increase in full recoveries and a decrease in treatment duration compared to the control group.

Recall that BP has a very high natural remission rate, which means that any treatment, including niacin, will work for most people. Orthomolecular clinicians who want to prescribe niacin (or any other treatment) should inform their patients of this.

2. Huntington's Disease

Huntington's disease (HD) is an autosomal dominant, progressive neurodegenerative disorder, characterized by cognitive and psychiatric disturbances involving the basal ganglia and cerebral cortex, and worsening chorieform movements.[23] The psychiatric manifestations range from antisocial personality, psychosomatic disorder, delusional disorder, and affective disorder to schizophrenia.[24] Even though chorea is the foremost sign of HD, other motor abnormalities can be present, such as rigidity, bradykinesia, dystonia, cerebellar ataxia, and myoclonus.[24] While the precise mechanisms underlying neuronal death in HD are not fully known, leading theories of neurodegeneration include mitochondrial dysfunction and subsequent excitotoxic injury, oxidative stress, apoptosis, protein metabolism abnormalities, and transcriptional dysregulation.[25] The disease has a world-wide prevalence of 5-8 per 100,000 people, with no gender preponderance.[25] For unknown reasons, the penetrance of HD is highly variable with an onset late in life. The risk of developing it is 50% in the offspring of an affected person. Genetic testing is available to determine whether or not a person has the mutated gene. The diagnosis of HD is based on clinical signs and symptoms in an individual with a parent having definitive (i.e., proven) HD.[26] The prognosis is rather bleak with survival ranging from 10 and 17 years from the age of onset.[24]

Treatment with Vitamin B_3, Vitamin E, and other Nutrients

Decades ago, Dr. Abram Hoffer reported on a case of a patient with probable HD that benefited from nutritional treatment, primarily involving niacin.[27] The patient, Mrs. Annette B., had a mother with severe HD and thought that vitamin treatment might be helpful after witnessing her husband recover from schizophrenia with a combination of niacin, vitamin C, and vitamin B_6. While Annette did not undergo genetic testing for the disease, she reasoned that the nutritional treatment might prevent HD from manifesting in herself, her brother, and

perhaps her children. Through trial and error, she found that daily amounts of nutrients (i.e., 800 IU of vitamin E, 2500 mg of niacin, 1500 mg of vitamin C, one multiple vitamin/mineral, 500 mg of choline, and 500 mg of inositol) enabled her to return to work as an engineer without the debilitating fatigue that prevented her from working for the previous seven years. She also noticed that her fears and perceptual problems were ameliorated as a result of the nutritional treatments.

In a follow-up report about one year later, Hoffer reasoned that the HD gene carries an increased demand for vitamins (most notably, vitamins B_3 and E), and that the expression of the disease would be prevented as long as these vitamins were taken in optimal doses.[28] For children born to an affected parent, Hoffer recommended that they follow a similar vitamin program since it would keep the disease from manifesting in children who had inherited HD genes.

Hoffer's follow-up report included brief case histories of Annette and her three daughters. Annette continued to do well, having an absence of her previous debilitating fatigue and dysperceptions. Her modified nutritional programme consisted of 8,000 mg niacin daily, 1,500 mg of vitamin C daily, 800 IU of vitamin E daily, 700 mg of calcium daily, 300 mg of magnesium daily, a B-complex supplement daily, 200 mg of inositol every second day, and 425 mg of phosphatidylcholine daily. Her three daughters (none of whom received genetic testing) followed a similar program of nutrients, with the eldest daughter (age 22) on basically the same plan as her mother, whereas the two remaining girls (ages 21 and 13) followed a similar plan with lower daily doses. All three girls showed clear improvements in several neuropsychiatric manifestations (i.e., fatigue, facial twitching, and depression) from the nutritional treatments; therefore, it was assumed that they had inherited the disease from their mother.

Hoffer followed this family for at least 9 years and during this time Annette and her three girls remained well as long as they were consistent with the nutritional program.[29] In his report, Hoffer asserted that HD was the result of a double dependency of vitamins B_3 and E. He further asserted that the "gene or genes for HD activity in the body will be related to these vitamins," with vitamin B_3 controlling the psychiatric component and vitamin E controlling the neurological component, even though other nutrients have also proven useful, especially choline and inositol.

Experimental Research Pertaining to Vitamin B_3 and HD

Hoffer was likely the first clinician to speculate on a relationship between vitamin B_3, genes, and HD. Hoffer's views were not far from reality since more recent human and animal research has found niacinamide to correct biochemical defects that might slow the neurodegenerative process. Magnetic resonance imaging spectroscopy studies have confirmed that HD is characterized by defective oxidative phosphorylation, resulting in elevations in lactate levels within the basal ganglia and cerebral cortex among patients with HD.[30] In rodents and primates, niacinamide was found to attenuate the defect in oxidative phosphorylation by ameliorating striatal lesions produced by mitochondrial toxins *in vivo*.[30] The administration of niacinamide was also shown to reduce elevated lactate levels among patients with HD.[30]

In a mouse model of HD, treatment with niacinamide resulted in biochemical and clinical benefits.[31] Biochemically, niacinamide increased mRNA and protein levels of brain-derived neurotrophic factor. Niacinamide also increased the levels of peroxisome proliferator-activated receptor-gamma (PPAR-γ) coactivator 1-α, identified as the master regulator of mitochondrial biogenesis. Clinically, niacinamide improved the motor dysfunctions in mice as shown by various tests of motor function. The authors concluded that niacinamide (or similar drugs) might be therapeutic for the motor dysfunctions of HD.

3. Migraine and Chronic Tension-Type Headaches

Migraines and tension-type headaches impose an important burden upon society and the working public. According to the

National Headache Foundation, approximately 45 million Americans suffer from chronic, recurring headaches, and of these, 29.5 million suffer from migraine headaches annually.[32] The work force loses approximately $50 billion a year due to absenteeism and medical expenses caused by headaches, with more than 157 million work days lost each year to migraine sufferers alone.[32]

Even though advances have been made in the treatment of acute migraine headaches with triptan formulations, many patients discontinue their migraine interventions due to treatment dissatisfaction.[33] Among individuals seeking treatment for tension-type headaches, the frequency of such headaches is often daily or almost every day.[34] Unfortunately, chronic tension-type headaches are associated with analgesic abuse,[35] and are difficult to manage in a primary care setting due to frequent comorbid psychiatric or analgesic use problems.[36] Thus, it is imperative that other methods of treatment be researched and developed to increase patient satisfaction, therapeutic response, and compliance.

The pathophysiology of acute migraine headaches is complex and has been the subject of much debate. Nevertheless, symptoms have been purported to arise from activation of the trigeminovascular complex. Activation of this complex leads to intracranial vasoconstriction causing the migraine aura, followed by headache due to vasodilatation of the extracranial vessels and activation of the perivascular nociceptive nerves.[37] Like migraine headaches, the underlying pathophysiology of chronic tension-type headaches involves central mechanisms, such as the trigeminal system.[38] Chronic tension-type headaches are also associated with cerebrospinal pressure or intracranial venous pressure (or both).[39] Tension-type headaches are similar to migraine headaches, in that they seem to involve an escalating pathophysiological process.[40]

Treatment with Vitamin B_3

The oral and/or parenteral (i.e., IM or intravenous/IV) administration of niacin might be beneficial for both migraine headaches and chronic tension-type headaches. Studies dating back to the 1940s have reported therapeutic effects upon migraine and chronic tension-type headaches from the oral and/or intravenous administration of niacin (**Table 1**, p.74).[41]

The mechanism of action of niacin's reported therapeutic effects are unknown and purely speculative. When taken orally or parenterally, niacin causes cutaneous flushing that might abort the acute symptoms of migraine by counteracting vasoconstriction of the extracranial vessels. Niacin might also mitigate the acute phase of tension-type headaches through the same hypothesized mechanism of action. It is highly unlikely that niacin promotes vasodilatation of the intracranial vessels despite my advancing this hypothesis in previous publications.[41,49] The high affinity niacin receptor, GPR109a, is known to be present in intracranial glial cells (non-neuronal cells that form myelin and protect neurons) and neurons.[51] While these glial cells might be capable of secreting prostaglandins in response to niacin, it is unlikely that niacin benefits migraine and chronic tension-type headaches by inducing intracranial vasodilatation. Even though niacin can cause blood pressure to acutely drop in rare individuals, this only occurs when venous (and not arterial) dilatation is very pronounced. It should also be noted that in some individuals niacin can cause headaches.[52]

4. Multiple Sclerosis

Multiple sclerosis (MS) is an autoimmune disease, in which the autoimmune response is to an autoantigen comprising several myelin proteins.[53] This results in the activation of cytokines, as well as complement and additional inflammatory compounds that injure oligodendroglia cells, especially their membrane myelin. The hallmark of the disease is multicentric, multiphasic central nervous system (CNS) inflammation and demyelination.

It is not known why lesions typically involve the optic and periventricular white matter of the cerebellum, brain stem, basal ganglia, and spinal cord. Unlike the central

Table 1. Summary of articles reporting niacin's therapeutic effects upon migraine headaches, tension-type headaches and headaches of other aetiologic types

Reference	Condition	Method of niacin administration	Result
42	Migraine headaches	IM, IV, and oral niacin	17 of the 21 subjects had a positive response
43	Headaches of different aetiologic types	IV niacin	75 of the 100 subjects had complete relief
44	Migraine headaches	IV niacin	13 of the 15 subjects had a positive response
45	Tension headaches	IV niacin	13 of the 22 subjects had a positive response
46	Emotional or tension headaches	IV and oral niacin	All 5 cases were very responsive to both oral and IV niacin
47	Tension headaches accompanied with depression	IV and oral niacin	44 of 50 subjects had positive responses
48	Migraine headaches	Oral niacin	The 1 subject reported complete resolution
49	Migraine headaches	Oral niacin	In 2 of 2 subjects niacin aborted symptoms of acute migraine
50	Migraine headaches	Oral niacin	The 1 subject was migraine-free for the first month, followed by a marked reduction in headaches over the subsequent 2 months

nervous system, the peripheral system is relatively spared in this disease. MS often presents with monocular visual impairment with pain (i.e., optic neuritis), paresthesias, weakness, and impaired coordination.[54] These symptoms are often accompanied by bladder urgency or retention, constipation, sexual dysfunction, fatigue, depression, diplopia, gait and limb ataxia, and Lhermitte's sign (i.e., electrical sensations down the spine on neck flexion).[54] Factors implicated in the etiopathology of MS involve several modifiable environmental-nutritional variables (i.e., poor dietary habits,

deficiency of omega-3 essential fatty acids and overconsumption of omega-6 essential fatty acids, deficiency of vitamin D, and deficiency of antioxidants in conjunction with increased oxidative stress).[55] Corticosteroids are provided during acute crises to shorten relapses even though they do not alter the long-term course of the disease, while disease-modifying treatments (i.e., beta-interferons, glatiramer, and mitoxantrone) are given to reduce exacerbations and possibly slow MS progression.

Treatment with Vitamin B_3 and Vitamin B_1 (thiamine chloride)

In 1940, Dr. Matthew T. Moore rationalized that niacin would be a safer therapy than the various forms of fever therapy used to treat MS.[56] At that time different fever therapies (i.e., malaria, typhoid vaccine, hot baths, diathermy, and other fever-inducing treatments) were used therapeutically to overcome vascular lesions (believed to be etiologic) "to promote hyperaemia and an increased flow of blood in nerve tissue." Since niacin produced marked cutaneous flushing of the skin, Moore thought it might also induce hyperaemia in the central nervous system, but would potentially be more effective and safer than fever therapy. Moore also used thiamine chloride, which he felt would augment the effects of niacin, because of its ability to facilitate oxidation within the nervous system.

Moore prescribed niacin to 5 patients with MS. All 5 patients had been previously given a variety of treatments (i.e., quinine bisulfate, germanin, high vitamin diets, hyperpyrexia, forced cerebral spinal fluid drainage, and histidine mono-hydrochloride) with little lasting benefit. Each patient was given IM niacin (60-120 mg) and IV niacin (60-160 mg) on alternate weekdays. Eventually, all patients were exclusively given IM niacin (80-140 mg) two to three times each week. When given IM niacin, Moore's patients were also administered 33 mg of IV thiamine chloride at the height of their cutaneous reactions from IM niacin. Then Moore combined niacin (120 mg) and thiamine chloride (33 mg) into one IM injection, which he also administered to the 5 patients. On the date of Moore's publication, all 5 patients had been treated with niacin in combination with thiamine chloride for a couple of years. All cases of MS were characterized by Moore as the chronic progressive type without remissions, which today would be classified as the primary progressive type in which there is gradual progression of the disease from its onset without remissions.

In all 5 cases the patients experienced improvements in bodily movements and in walking. In every case, when niacin-thiamine chloride treatment was stopped temporarily there was a return of previous "incapacitating spasticity and incoordination." When treatment was resumed, these symptoms ameliorated again within several days to 2 weeks. **Table 2** (p.76) describes the type of clinical responses that were observed by Moore.

Moore also assessed whether niacin could increase skin temperature and increase cerebral vasodilatation. In 2 patients (cases #1 and #4), he measured skin temperatures at various locations during the cutaneous flushing following IV and IM niacin respectively. In both cases there were marked (quantifiable) increases in skin temperature (via thermocouple readings) on the forehead, and right and left earlobes. There were lesser temperature increases at other sites on the face, upper thorax, and dorsal surfaces of the third finger for both patients. He also performed lumbar punctures on these 2 patients and recorded their cerebrospinal fluid pressures during the cutaneous flushing following IM injections of 168 mg niacin (case #1) and 120 mg niacin (case #4). In both cases, cerebrospinal fluid pressures increased during the time of active cutaneous flushing. Moore felt these results were "presumptive evidence of vasodilatation within the brain." To evaluate this hypothesis, Moore exposed the surfaces of a cat's brain to observe the large vessels of the cerebral cortex during active cutaneous flushing from IM niacin (48 mg) and observed an increased quality of the large vessels as a result of increased capillary filling. He took pictures and measured the pial

Table 2. Brief clinical descriptions of the therapeutic effects of niacin and thiamine chloride in Moore's MS patients

Case #1 (EN): "On September 8 therapy was discontinued for three weeks to see if any change occurred. The patient began to show return of the marked spasticity and was compelled to resort to use of the walker. He complained of difficulty in moving his body and in sitting and arising. When the nicotinic acid and vitamin B1 therapy was renewed he noted improvement within several days. Complete remission was not obtained, but he felt distinctly better able to walk and maneuver his body than previous to this form of medication."

Case #2 (EI): "Within two weeks after treatment was instituted she noticed improvement in walking and began to regain her ability to play the piano. The sensation of numbness of her lower limbs disappeared within six to eight weeks. On two occasions therapy was stopped for two weeks in order to determine if any change would occur. During one of these interludes, injections of sterile distilled water were substituted. During each two week interval there was a definite increase in spasticity of the four limbs, great difficulty in walking and increased incoordination and ataxia of the upper limbs. She insisted that a change for the worse had taken place. On returning to the use of nicotinic acid and thiamin chloride, she noticed appreciable lessening of spasticity, and at the time of writing she can play the piano fairly well and walk about the house, albeit in a spastic manner."

Case #3 (AI): "She stated that she no longer dragged her feet so much and was able to bend her legs at the knees and lift her feet from the ground. Later she noticed ease in moving her body and was elated about it. Changes in the objective neurologic signs were not noticed. This patient had invariably refused previous forms of treatment after a few months' trial when they failed to reward her with improvement, but she welcomed the injections of nicotinic acid and vitamin B1 and requested their continuance."

Case #4 (MP): "The first evidence of change was a subjective feeling of relaxation of the trunk and greater ease in moving his body. This occurred in June 1938, and in July he was able to uncross his legs voluntarily and to move them somewhat. His arms became less stiff, so that he could manipulate his wheel chair with increased facility. He managed to lift himself up in bed and to get in and out of bed, which previously was impossible. He invariably requested that the injections be continued after a brief interruption of treatment. The improvement has been limited thus far to a definite subjective feeling of lessening of rigidity and the objective finding of diminished spasticity of the lower limbs and trunk and improved coordination of the upper limbs. He is now able, for the first time in years, to stand while holding on to the bedstead."

Case #5 (JD): "By July 9 he was able to move his body freely and was able to sit up in bed and in an armchair. The marked rigidity of the legs had diminished greatly. He stopped treatment for two months, and during this time there was considerable regression, but not to his previous state. Treatment was resumed Sept. 10, 1938, with three injections weekly. He noticed improvement in a short time, with decrease in spasticity and cessation of the electric-like sensation in his spine, and for the first time he was able to use his hands in eating, smoking and dressing. He stated that with this form of treatment he had greater use of his limbs and body than at any time since he completed his first series of hyperpyrexia treatments, in the spring of 1935."

artery before and during active cutaneous flushing and observed an increase in blood vessel diameter and blood flow.

Moore's results are rather intriguing since there is controversial evidence showing chronic cerebrospinal venous insufficiency (CCSVI) in some MS patients.[57-59] CCSVI denotes a condition characterized by anomalies of the main extra-cranial cerebrospinal veins that interface with normal cerebrospinal outflow.[57] This hypothesis that MS is a vascular disease is challenging the long-held view that MS is an autoimmune disease. Treatment of CCSVI involves balloon dilatation of venous stenosis or stent implantation.[60] While Moore's report focused on cerebral vasodilatation, treatment with niacin and thiamine chloride might also affect venous blood flow by improving overall circulation, thus circumventing venous outflow abnormalities (if present). This is mere speculation since data on CCSVI is equivocal at best and far from proven.[60] In addition, there is no data (to my knowledge) that has examined niacin's ability to overcome venous insufficiency among healthy and diseased patients.

Experimental Research Pertaining to Vitamin B_3 and MS

There is an emerging amount of published literature examining the putative therapeutic properties of vitamin B_3 for the treatment of MS. An animal study showed that niacinamide prevented the degeneration of demyelinated axons and improved behavioural deficits in experimental autoimmune encephalomyelitis (EAE).[61] EAE is an inflammatory demyelinating disease of the central nervous system in rodents that resembles human MS. The protective mechanisms of niacinamide were related to a fusion protein named "Wallerian degeneration slow" (Wlds).

The history of Wlds and its relationship to nicotinamide adenine dinucleotide (NAD) was documented in a 2009 paper by Wang and He.[62] A little over two decades ago, the Wlds mouse strain was identified. The mouse has a mutation that results in the overproduction of a chimeric protein, Wlds, which contains a short fragment of the ubiquitin assembly protein (UFD2) fused to the full length NAD synthetic enzyme, nicotinamide mononucleotide adenylyltransferase-1 (Nmnat-1). Amazingly, the distal portions of transected axons from injured nerves remain alive and functional for about 3 to 4 weeks *in vivo* among mice having the Wlds strain. By comparison, normal neurons will degenerate within 24-26 hours following axotomy. Over expression of the Nmnat-1 protein in neuronal cultures alone provides neuroprotection, while UFD2 does not. In some ways, Nmat-1's neuroprotective effects are similar to the neuroprotective effects afforded to mice having the Wlds strain. Thus, NAD generated from either the over-expression of Nmat-1 (in neuronal cultures) or the overproduction of Nmat-1 among mice having the Wlds strain protects axons from demyelination.

A publication by Dr. W. Todd Penberthy explained the relationship between NAD precursors and the enzyme indoleamine 2,3 dioxygenase (IDO).[63] Endogenous biosynthesis of NAD arises from tryptophan. The rate-limiting reaction controlling this process is IDO. Interestingly, tryptophan is the least abundant amino acid in the body. Tryptophan is essential to life and its levels are tightly controlled by IDO activity in particular in the immune system, where IDO is highly induced inside professional antigen presenting cells (i.e., macrophages, microglial cells in the brain, B cells, and/or dendritic cells). Activation of IDO in these specific cells can lead to a depletion of extracellular tryptophan. This can leave collateral cells starving for tryptophan, the body's only source of endogenous NAD biosynthesis. This endogenous NAD precursor deficit is in part responsible for the myriad of pathological symptoms seen in MS. Thus, it makes therapeutic sense to circumvent the tryptophan NAD precursor deficit by administering niacin with the goal of rescuing neural cells.

Immune activation of IDO is the basic mechanism by which the immune system uses to starve T cells around the fetus to pre-

vent T cell auto-reactive rejection of the otherwise foreign new tissue.[63] MS pathogenesis arises due to auto-reactive T cells which our body failed to eliminate. The body tries to remove these T cells by activating IDO. However, hyper- or persistent activation of IDO leads to a decrease in plasma tryptophan levels, which itself leads to decreased endogenous NAD biosynthesis. Animal models of MS have repeatedly shown the importance of IDO in pathogenesis. On the one hand IDO is required to curb the T cells, but on the other hand the hyper-activation of IDO can lead to a deficit of NAD biosynthesis from tryptophan. In fact tryptophan levels are known to be exceptionally low in wide variety of autoimmune diseases. In summary, non-tryptophan NAD precursors such as niacin can alleviate many of the symptoms arising from the hyper-activation of IDO.

In another publication, Penberthy and coauthor Tsunoda, discussed how glial cells provide NAD to neurons during times of stress.[51] Neurons become "stressed" when there is hyperactivation of IDO, and degenerate as a result of being starved of extracellular sources of NAD. This might be one of the mechanisms which underlie chronic central nervous system inflammation in MS. Providing pharmacological doses of non-tryptophan NAD precursors like niacin and niacinamide might make neurons more resistant to axonal degeneration, which suggests that preserving NAD levels might be an important pharmacologic strategy in the therapeutic management of MS.

Penberthy also speculated that non-tryptophan NAD precursors might be more effective than glucocorticoids in the long-term treatment of MS.[64] Glucocorticoids provide life-saving but only temporary symptomatic relief (in part) through the induction of IDO and interleukin-10. Niacinamide treats and halts autoimmune-mediated demyelination in EAE by preserving levels of NAD. Niacin is likely more therapeutic since it produces higher NAD levels than niacinamide, while also activating GPR109a, followed by activation of PPAR-γ.

All of these publications demonstrate that NAD-mediated therapies protect against MS attacks. This includes pharmacologic approaches that utilize high doses of NAD precursors (e.g., niacinamide) or those that inhibit the pathological depletion of NAD (i.e., Poly [ADP-ribose] polymerase-1; PARP-1 inhibitors). PARP-1 mediates cell death, including death of astrocytes, by depleting intracellular NAD levels.[65] Astrocytes are glial cells that not only have the ability to augment immune mechanisms and prevent myelin repair, but they can also be protective and mitigate CNS inflammation while supporting oligodendrocyte and axonal regeneration.[66] NAD precursors, such as niacinamide, can prevent PARP-1-induced NAD depletion, and thus inhibit PARP-1-mediated astrocyte death.[67,68]

5. Parkinson's disease

Approximately 1% of individuals over the age of 60 will be diagnosed with idiopathic Parkinson's disease (PD). It is characterized by motor and non-motor symptoms that significantly worsen the health and quality of life of the patient and family members. The leading theory is that PD "is primarily an oxidative disease, driven by endogenous susceptibility and by the cumulative contributions of endogenous and exogenous (environmental) oxidant stressors."[69] Causes implicated in the pathogenesis of PD include environmental exposures to pesticides and herbicides, living near industrial plants, being exposed to chemicals having similar homologies to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), excessive oxidation, inadequate antioxidant mechanisms, increased lipid peroxidation, depressed levels of reduced glutathione, and increased iron within the substantia nigra.[70]

PD is described clinically by bradykinesia, resting tremor, cogwheel rigidity, and postural reflex impairment. Pathologically, there is the loss of pigmented neurons, most significantly in the substantia nigra, with associated Lewy body formation. The presence of Lewy bodies is, however, "characteristic, but not pathognomonic, of idiopathic PD."[70] The motor signs of PD do not manifest until

approximately 60% to 80% of dopaminergic neurons have been destroyed. A PD diagnosis is therefore made on clinical grounds and from response to levodopa, i.e., dopamine-replacement medication (e.g., levodopa/ carbidopa), dopaminergic agonist medication (e.g., pergolide, pramipexole, and rotigotine), or other medications that act on dopaminergic function (e.g., amantadine and rasagiline).

Treatment with the Reduced form of Nicotinamide Adenine Dinucleotide (NADH) and Vitamin B_3

NADH promotes the formation of tetrahydrobiopterin, which stimulates tyrosine hydroxylase and increases the endogenous production of dopamine in the brain.[71,72] Birkmayer et al administered NADH parenterally (i.e., IM or IV) to 34 patients with PD in an open-label trial.[73,74] All patients benefited from parenteral NADH administration, with 21 patients (61.7%) having a very good (better than 30%) improvement while the remaining 13 patients (38.3%) showed a moderate (up to 30%) improvement from their baseline disability scores. IV administration produced better results than the IM route. The dose of NADH that yielded the best therapeutic benefits was in the range of 25 to 50 mg per day. The clinical improvements in disability were concomitant with increases in urine levels of the dopamine metabolite, homovanillic acid (HVA). In addition, the daily "on phases" were increased from 2-9 hours following NADH administration.

In another open-label trial involving 161 patients with PD, Birkmayer administered NADH (25-50 mg) by IV administration every second day.[75] One hundred fifteen patients (71.4%) had a very good (better than 30%) improvement, while 28 patients (17.4%) had a moderate (up to 30%) improvement from their baseline disability scores. For the remaining 18 patients (11.2%), no improvements were observed following IV NADH. Like the previous study, the clinical improvements in disability were concomitant with increases in urine levels of HVA, which reflect endogenous L-3,4-dihydroxyphenylalanine (i.e., L-dopa) biosynthesis. Eight additional patients were treated with nicotinamide adenine dinucleotide phosphate (NADPH). Five patients from this small cohort showed a 35-55% improvement in their disability, while the remaining three patients had a 20-25% improvement. In these 8 patients, their disability improvements were concomitant with increases in urine levels of HVA.

In a further open-label trial involving 470 patients with PD, oral NADH was evaluated. Patients were given 5 mg of NADH orally every other day for 14 days. After two weeks of treatment, walking, pushing, posture, speech, as well as the ability to mimic another person's behavior or speech, improved.[76] This larger open-label trial involved 885 PD patients, with half (n=415) receiving NADH by IV route (12.5 mg), while the remaining patients (n=470) received oral NADH (5 mg).[77] Treatment was given every other day for 14 days. A beneficial clinical effect was noted to occur in about 80% of the patients, with 19.3% having a very good improvement in disability, while the remaining 58.8% having a moderate improvement in disability. The authors concluded that the improvement gained from the oral delivery of NADH was comparable to that of the IV delivery.

Kuhn et al evaluated IV NADH. Fifteen patients with PD were given IV NADH (10 mg/day) for seven days in addition to standard treatment.[78] Symptoms of PD were evaluated at baseline (day 1) and following NADH treatment (day 8). As per the Unified Parkinson's Disease Rating Scale (version 3.0), there was a significant clinical improvement (p=0.025). The use of NADH also augmented the bioavailability of plasma levodopa. The authors concluded that NADH produces clinical benefits and might be a potent stimulator of endogenous levodopa biosynthesis.

Outside of studies evaluating NADH, J.M. Alisky documented symptomatic benefits from oral niacin in a 78-year-old man with PD.[79] The patient was taking levodopa/ carbidopa (37.5 mg/150 mg three times/ day), selegiline (5 mg twice/day), vitamin

E (400 IU/day), aspirin (81 mg/day), buproprion SR (150 mg/day), and niacin (500 mg/day). At a routine visit, his niacin dose was increased to 500 mg twice daily to lower triglyceride levels. Three-months later at a follow-up visit, the family noted improvements in the patient's ability to initiate many routine activities of daily living. Objectively, the patient could rise from a chair without any help, and could start walking with minimal latency. The patient's rigidity was markedly diminished as well. His niacin dose was again increased to 1,000 mg twice daily. Unfortunately, this resulted in nightmares, which had previously occurred when this patient was taking higher doses of levodopa/carbidopa. When he was put back on 500 mg of niacin, the nightmares stopped, but the patient could not tolerate the cutaneous reaction from niacin. As an alternative, the patient's doctor prescribed other lipid-modifying agents. While the cutaneous reaction and nightmares stopped, the previous bradykinesia and amotivation returned. The author commented on epidemiological data that has shown higher niacin intakes to be correlated with reductions in PD. He also commented on niacin's putative biochemical effects and noted that it might have increased neurotrophic factors, facilitated neurotransmission within the basal ganglia, corrected for a deficiency of the vitamin brought on by carbidopa (i.e., it inhibits kynurenine hydroxylase in the liver), or acted synergistically with the other therapeutic agents the patient was taking. He went on to discuss how randomized controlled trials might not be an effective way in which to study niacin since there might be some genetic anomaly of metabolism that possibly accounts for niacin's benefits among only a few individuals with PD.

Despite this promising case report, Fukushima hypothesized that niacin might be implicated in the cause of PD.[80] His report cites indirect evidence from several epidemiological surveys that have shown a relationship between niacin deficiency and protection from PD. Some of the cited examples include: (1) the low prevalence of PD in Africa and China despite pellagra being rather common; (2) the fact that isoniazid reduces symptoms of PD, but also induces pellagra as a possible side effect; and (3) that PD patients consume less-than-average alcohol compared to heavy drinkers that are at greater risk of developing pellagra. Then the author discusses how niacin would increase NAD and niacinamide levels, leading to the methylation of niacinamide to 1-methylniacinamide (MNA) in the brain. This might potentially be harmful as superoxides formed by MNA, via complex 1 of the electron transport chain, can destroy complex 1 subunits and directly or indirectly damage mitochondrial DNA. Furthermore, this mitochondrial damage might be accelerated by hereditary or environmental factors resulting in neuronal death.

While there is some evidence that niacin deficiency among people living in countries whose main energy source is maize is associated with lower mortality rates from PD and perhaps even less PD,[81] the studies and reports demonstrating benefits from NADH and niacin (as substrate for NAD and NADH) appear to contradict Fukushima's hypothesis. To assess niacin in isolation without paying attention to oxidative stress and depleted host antioxidant reserves undermines the high probability that niacin is therapeutic, especially when augmented with a complement of antioxidants. In the substantia nigra, dopaminergic neurons are highly susceptible to oxidative stress resulting from dopamine metabolism and auto-oxidation.[82] When these processes are combined with increased iron, decreased total glutathione levels and mitochondrial complex I inhibition-induced reactive oxygen species production, cell death ensues because the antioxidant capacities in that region of the brain are overwhelmed.[77] Thus, striatal oxidative stress and neurodegeneration are related to both auto-oxidation of dopamine resulting in highly toxic dopamine metabolites[83-85] and overwhelmed antioxidant mechanisms.[73] To remedy this, it would make sense to increase host antioxidant capacities with multiple neuroprotective agents to preserve dopaminergic neu-

rons and prevent their auto-oxidation.[86] To dismiss niacin on the grounds that it might lead to mitochondrial dysfunction and neuronal death excludes the more likely possibility that niacin in conjunction with an ample complement of antioxidants (e.g., coenzyme Q_{10} and R-lipoic acid) would be therapeutic to patients with PD precisely because niacin would prevent dopamine auto-oxidation while therapeutic antioxidants would limit oxidative damage to dopaminergic neurons. Hoffer noted clinical improvements in two patients with PD, resulting from therapeutic doses of niacin and a complement of antioxidants, including coenzyme Q_{10}. He attributed these clinical benefits to the prevention of dopamine autoxidation and increasing host antioxidant capacities.[87]

Experimental Research Pertaining to Vitamin B_3 and PD

An experimental study assessed niacinamide by examining its putative effects in a culture medium and in a Drosophila model of PD.[88] In the cell culture medium, niacinamide was shown to protect mitochondrial function, decrease oxidant generation, and prevent DNA damage and protein oxidation. In the Drosophila model of PD, niacinamide considerably improved climbing ability. The authors of this research concluded that supplemental niacinamide might prevent and reduce symptoms of PD by attenuating oxidative stress and improving mitochondrial and motor function.

Another experimental study by Anderson et al assessed niacinamide's therapeutic effects against MPTP-induced substantia nigra neuron cell death and striatal dopamine depletion.[89] Adult mice (C57B1/6) received niacinamide prior to either acute exposure (i.e., 2 injections in 1 day) or prior to sub-acute (i.e., 2 injections daily for 5 days) of MPTP. In the acute exposure group, niacinamide resulted in a dose-dependent sparing of striatal dopamine levels and substantia nigra neurons. In the sub-acute group, only the highest dose of niacinamide resulted in sparing of striatal dopamine levels and substantia nigra neurons. Six weeks after MPTP exposure, there was notable sparing of striatal dopamine levels in both groups, yet neuroprotective effects were only apparent in the acute MPTP-treated mice. The authors concluded that supplemental niacinamide might yield broad neuroprotective effects.

6. Tinnitus

Tinnitus is an unwanted auditory noise of internal origin heard by the affected person and infrequently by others.[90] It affects 50 million US adults, and has its highest prevalence with increasing age peaking at 14.3% between 60 and 69 years of age.[91] Some people with tinnitus hear an occasional noise (e.g., ringing, hissing, buzzing, roaring, and clicking) in one or both ears, whereas other people can be so disturbed by hearing noises that they contemplate suicide.[90,92] There are many possible causes of tinnitus, including subjective tinnitus (e.g., otologic, ototoxic, neurotoxic, metabolic, and psychogenic) and objective tinnitus (e.g., vascular abnormalities).[93] Numerous (e.g., ginkgo biloba extract, trimetazidine, and betahistine) and emerging pharmacologic therapies (e.g., lidocaine, benzodiazepines, antidepressants, and anticonvulsants) have been prescribed to patients with tinnitus. It appears that no single treatment can help or cure all forms of tinnitus.[94]

Treatment with Vitamin B_3

In one study, 22 patients with tinnitus of multiple aetiologies were administered IV niacin followed by oral niacin.[95] Twenty-five milligrams of IV niacin was administered to each patient and the dose was increased by 5 mg daily until the patient received 100 mg. Once the IV dose reached 50-60 mg and 100 mg, audiological tests were conducted to assess the pitch and loudness of the tinnitus as compared to the tinnitus prior to niacin treatment. After reaching the maximum IV dose of 100 mg, all patients were given oral niacin (two tablets twice daily before meals), which amounted to a total daily intake of 400 mg. Each patient was examined clinically and audiologically before niacin

administration and also at one month intervals thereafter. The study commenced on September 1952, and the period of observation of the 22 patients was about 18 months. Of the 22 patients with tinnitus, 15 patients (68.2%) benefited from niacin treatment. The authors were surprised that niacin treatment helped such a diffuse symptom as tinnitus with its multiple aetiologies. They attributed these favourable results to the vasodilatory effect of niacin, which was thought to normalize blood flow in the labyrinth and osmotic pressures. They further speculated that the many different causes of tinnitus lead to secondary vascular problems, which is why niacin was able to help many of the tinnitus cases having multiple aetiologies. The types of tinnitus that responded the best to niacin treatment were of the cryptogenetic and menièriform varieties.

In a double-blind placebo-controlled trial, niacinamide or placebo was given to 48 patients with tinnitus.[96] There were no differences in treatment outcomes between niacinamide and placebo. It is surprising that the authors of this study thought niacinamide would help since the vasodilatory effects of niacin are likely responsible for its beneficial effects on tinnitus.

Treatment Guide

Based on the data presented in this article, I summarized the doses and methods of administration of vitamin B_3 and its coenzymes that have effectively treated the aforementioned medical conditions (**Table 3,** p.83).

Conclusion

A robust amount of medical literature appears to validate the therapeutic use of vitamin B_3 and its related coenzymes for the aforementioned medical conditions. While this vitamin treatment is not curative, using it therapeutically does offer patients a potentially effective, clinically-plausible intervention that is low-cost with little downside. The more I learn about vitamin B_3 and its related coenzymes, the more I am fascinated by its therapeutic potential as a broad-spectrum vitamin. Niacin continues to be the most essential orthomolecule that orthomolecular clinicians utilize in their clinical practices. More modern studies are warranted. Hopefully this review will encourage researchers and clinicians to perform additional studies and verify the benefits of vitamin B_3 and its related coenzymes.

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Competing Interests

The author declares that he has no competing interests.

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Table 3. Treatment summary of vitamin B_3 in select medical conditions

Medical Condition	Instructions
Bell's Palsy	100-250 mg of IM niacin once daily and 50 mg of niacin orally, taken three times daily, until resolution; for topical administration, a solution containing 10 ml dimexide, 5 ml of 1% niacin solution, and 5 ml of normal saline, applied to affected side once daily until resolution
Huntington's Disease	2500-8000 mg of niacin orally in divided doses daily; daily doses can be lowered in cases exhibiting prodromal signs and symptoms of the disease; niacin should be combined with vitamin E and other nutrients for optimal results
Migraine and Chronic Tension-Type Headaches	25-50 mg of IM niacin, or 100-200 mg of IV niacin administered as needed for the treatment of headaches of various aetiologic types; 300-500 mg of niacin can be chewed or swallowed at onset of migraine to facilitate headache amelioration; alternatively, 375 mg of sustained-release niacin can be taken twice daily for 1 month, and then reduced to once daily thereafter to reduce the frequency of migraine headaches
Multiple Sclerosis	IM niacin (60-140 mg) and IV niacin (60-160 mg) on alternate weekdays followed by regular (2-3 times/week) IM injections of a solution containing niacin (120 mg) and thiamine chloride (33.2 mg)
Parkinson's Disease	Parenteral NADH administered daily or every other day, either IM (25-50 mg) or IV (10-50 mg); as an alternative to parenteral administration, 5 mg NADH orally every second day; 500 mg of niacin twice daily, which should be combined with a complement of antioxidants (e.g. coenzyme Q10 and R-lipoid acid) for optimal results
Tinnitus	IV niacin, beginning with 25 mg daily and increasing to 100 mg, followed by 200 mg of oral niacin given twice daily before meals

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