

Continuing Education for Pharmacists

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Natural Products: Vitamins B-3, B-5, and B-6

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Goals. The goals of this lesson are to present information on the claims, mechanisms of action, typical dosages used and other items of interest on natural products and nutraceuticals alphabetically from vitamin B-3 to vitamin B-6, and to provide background information for assisting others on their proper selection and use.

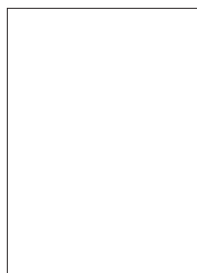
Objectives. At the conclusion of this lesson, successful participants should be able to:

1. exhibit knowledge of the claims, mechanisms of action, and typical dosages for natural products and nutraceuticals presented;
2. select from a list, the synonyms for these products;
3. describe popular uses of the products discussed; and
4. identify sources for information on natural products.

This lesson is part of a series that presents an overview of the common uses, proposed mechanisms of action, typical dosage regimens and



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other information of interest on natural products and nutraceuticals.

Vitamin B-3 (niacin), also known as niacinamide, anti-black tongue factor, antipellagra factor, nicotinamide, nicotinic acid and pellagra prevention factor, is present in many foods including cereal grains, eggs, fish, green vegetables, legumes, meat, milk, poultry, and yeast. In addition to utilizing preformed niacin, humans can also metabolize niacin from l-tryptophan contained in proteins in some of these foods.

Pellagra, the disorder resulting from niacin deficiency, was first recognized as a disease in the 18th century in Italy. Its name was derived from the Italian *pellagra* which denotes rough or irritated skin.

By 1912, scientists believed that a pellagra-preventive vitamin existed. In 1926, pellagra was induced in volunteers on a niacin-deficient diet and it was subsequently cured with yeast therapy. Soon thereafter, the chemical structure of vitamin B-3 was discovered.

Originally named nicotinic acid, vitamin B-3 was first synthesized as an oxidation product of nicotine. However, considerable confusion between the names nicotine and

nicotinic acid arose to the point that the name of the latter was simplified to niacin.

The term "niacin" specifically refers to nicotinic acid, but is also used to denote niacinamide/nicotinamide. Both niacin and niacinamide provide the nutritional benefits of vitamin B-3, but only niacin exerts vasodilatory and lipid-lowering activity.

Niacin (and its metabolites) is involved in a large number of biologic processes in humans, including: maintenance of genomic integrity (proper function of genes and chromosomes); production of energy; regulation of gene expression; and synthesis of fatty acids, cholesterol and steroids.

Pellagra is also called the "3 Ds" since it is characterized by dermatitis, diarrhea and dementia. Untreated, the condition leads to a fourth "D," death.

Gastrointestinal symptoms are often the first to appear. They include glossitis (inflammation of the tongue), stomatitis (inflammation of the mouth), loss of appetite and abdominal discomfort.

The dermatitis portion of pellagra is primarily located on sun-exposed skin on the arms, face, feet, and hands. Lesions progress from a red, itching rash to blisters with scales and fissures to thickened, lichenified (hard, flat, solid skin elevations that resemble leather), hyperpigmented skin.

Early mental symptoms of the deficiency include a feeling of weariness, apprehension, depression and loss of memory. These may be followed by disorientation, confusion, hysteria and sometimes, maniacal outbursts.

Table 1
Representative Sources for Information on Natural Products

American Botanical Council	www.herbalgram.org
Facts and Comparisons	www.factsandcomparisons.com
Food and Drug Administration	www.fda.gov (<i>click on Food</i>)
National Center for Complementary and Alternative Medicine of the National Institutes of Health	www.nccam.nih.gov
PDR for Herbal Remedies PDR for Nutritional Supplements	www.pdr.net
Pharmacist's Letter	www.naturaldatabase.com

While pellagra occurs relatively rarely in this country (due, in large part, to enriched flour and cereals), it can occur under certain conditions such as alcoholism, cirrhosis of the liver, malabsorption syndrome, and total parenteral nutrition lacking sufficient niacin.

Some conditions increase niacin requirements, including diabetes, hyperthyroidism, cirrhosis of the liver, pregnancy and lactation. Niacin is required for lipid metabolism, tissue respiration and conversion of glycogen into glucose. It is incorporated into the co-enzymes nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP) that serve as hydrogen carrier molecules. These biochemical functions are of paramount importance for normal tissue integrity, particularly for the skin, the gastrointestinal tract and the nervous system.

Niacin (or niacinamide) is used for preventing vitamin B-3 deficiency and menstrual headache; treating pellagra, schizophrenia, drug-induced hallucinations, chronic brain syndrome, hyperkinesia, depression, motion sickness, alcoholism, acne; improving circulation; and promoting relaxation. The nicotinic acid form of niacin is also used for treating hyperlipidemia, peripheral vascular disease, vascular spasm, migraine headache, Meniere's syndrome and vertigo. Except for treating

hyperlipidemia, the scientific establishment does not believe there are sufficient well-controlled studies to prove niacin is therapeutically effective in treating many of these conditions.

Beneficial effects of niacin in treating hyperlipidemia have been proven. The National Cholesterol Education Program (NCEP) recommends niacin as second-line single-drug therapy or in combination with other cholesterol-lowering drugs when diet and single-drug therapy have been ineffective. Niacin reportedly reduces cholesterol as well as HMG-CoA reductase inhibitor statins and bile acid sequestrants in many clinical studies, but it causes a much higher incidence of annoying adverse effects and lower tolerance by patients.

The controlled-release, extended-release formulations that are taken in the evening and release much of the niacin dose during normal sleeping hours are claimed to reduce the level of annoying adverse effects and assist patient compliance.

Niacin, but not niacinamide, given in high doses (1 gram or more per day) decreases serum low-density lipoprotein cholesterol (LDL-C), increases high-density lipoprotein cholesterol (HDL-C) and decreases triglycerides. The exact mechanism for these actions has not been determined.

It is known that niacin does inhibit free fatty acid release from

adipose tissue; inhibits cyclic AMP accumulation, which controls the activity of triglyceride lipase and lipolysis; decreases the rate of synthesis of LDL-C and very low density lipoprotein cholesterol (VLDL-C) in the liver; and increases the rate of triglyceride removal from the blood due to increasing lipoprotein lipase activity.

Niacin produces vasodilation of cutaneous blood vessels of the face, neck, and chest, possibly due to activity on prostaglandins. Tolerance to these effects has been found to occur within two weeks.

There are no known adverse effects caused by niacin contained in foods or multiple vitamin products containing Recommended Dietary Allowance (RDA) amounts. The form of niacin most commonly used for these foods and commercial supplements is niacinamide.

Flushing, characterized by burning, tingling, and itching, along with redness of the face and arms, have been reported with doses as low as 30mg of the nicotinic acid form of niacin. Higher doses have been associated with increased intracranial pressure and headache.

Megadoses (more than 3 grams) of nicotinic acid have been reported to cause flatulence, bloating, heartburn, nausea, vomiting, diarrhea, sweating, chills, insomnia, hypotension, dizziness, fainting spells, arrhythmias, severe headache and blurred vision.

Most patients taking the doses of nicotinic acid used in treating hyperlipidemia reportedly will experience flushing and other skin sensations. The controlled release dosage forms reduce this occurrence in many patients. Another method for lessening these effects is to pretreat patients with aspirin, since the vasodilatory effects of niacin are linked to its release of prostaglandins. Slow titration of the nicotinic acid dosing is beneficial. Additionally, flushing tends to decrease as therapy continues in most patients.

The typical dose of niacin as a dietary supplement is 10 to 20mg

daily. The U.S. Recommended Dietary Allowance (RDA) for niacin used to calculate the percent of daily values on food and nutritional supplement labels is 20mg. The U.S. RDA based on age are listed in Table 2.

The usual dose for treating mild vitamin B-3 deficiency is 50 to 100mg daily. For pellagra, 300 to 500mg daily in divided doses is given to adults. The dose used in children is 100 to 300mg daily in divided doses.

When treating hyperlipidemia, typically patients are titrated from starting doses, beginning as low as 125mg of a controlled-release dosage form twice daily, upward to 1.5 to 3 grams per day to minimize adverse effects. Some patients reportedly must receive as much as 9 grams of niacin daily to achieve an adequate response.

Vitamin B-5 (pantothenic acid), also known as calcium pantothenate, dextranthenol, dextranthenolum, D-panthenol, D-pantothenol and D-pantothenyl alcohol, is widely distributed in plant and animal food sources. Its name was derived from the Greek *pantos* which means *everywhere*. Rich sources include organ meats such as liver, vegetables (especially broccoli, soybeans and lentils), cereal grains, legumes, egg yolks, cashews, peanuts, brown rice and milk. The intestinal flora of humans also synthesize pantothenic acid in small amounts. The dextrorotatory form of pantothenic acid provides the nutritional activity of vitamin B-5.

Rather than being commercially available as a single ingredient product, vitamin B-5 is most frequently marketed as a component of vitamin B complex formulations.

The activity of vitamin B-5 within the body mostly depends on its conjugated nucleotide form--coenzyme A (CoA). This coenzyme is found in nearly all human tissues and is one of the foremost coenzymes for tissue metabolism.

Table 2
Recommended Dietary Allowances (RDA) for Vitamins B-3, B-5, B-6*

Age	Vitamin B-3	RDA (Daily) Vitamin B-5	Vitamin B-6
infants			
0-6 months	2mg	1.7mg	0.1mg
7-12 months	4mg	1.8mg	0.3mg
children			
1-3 years	6mg	2mg	0.5mg
4-8 years	8mg	3mg	0.6mg
boys			
9-13 years	12mg	4mg	1mg
14-18 years	16mg	5mg	1.3mg
girls			
9-13 years	12mg	4mg	1mg
14-18 years	14mg	5mg	1.2mg
men			
19 years and older	16mg	5mg	1.7mg
women			
19 years and older	14mg	5mg	1.5mg
pregnancy	18mg	6mg	1.9mg
lactation	17mg	7mg	2mg

**Issued by the Food and Nutrition Board of the Institute of Medicine at the National Academy of Science.*

The other major biologically active form of pantothenic acid is acyl carrier protein (ACP). ACP functions as a coenzyme in the synthesis of new fatty acids (as compared to those that are a product of breakdown of lipid materials).

As a member of the B group of vitamins, vitamin B-5 is an essential nutrient for humans. It is involved in many biological reactions, including the catabolism of amino acids, acetylation reactions in gluconeogenesis, production of energy, and the synthesis of acetylcholine, cholesterol, heme, phospholipids and steroid hormones. It is also believed to be essential for the proper regulation of gene expression and signal transduction.

The presence of a "pellagra-like" dermatitis in chicks fed a restricted diet was first described in 1931. The existence of an antidermatitis factor in yeast given to chicks was recognized in 1939, and the actual compound was isolated the same year. Discovery of the chemical structure of vitamin B-5 and the synthesis of pantothenic acid occurred in 1940.

A clinical deficiency of vitamin B-5 in humans is rare, but it can be induced with a diet lacking the vitamin, which has been accomplished in human volunteers. Symptoms of vitamin B-5 deficiency include numbness in the toes and painful burning in the feet, headache, fatigue, insomnia, intestinal disturbances, impaired antibody and blood component production, and disrupted enzyme activity.

In addition to its use as a dietary supplement, pantothenic acid is also claimed to be useful for treating acne, alcoholism, allergies, alopecia, asthma, burning feet syndrome, carpal tunnel syndrome, colitis, conjunctivitis, convulsions, and cystitis. Further, it is used to treat dandruff, depression, diabetic neuropathy, enlarged prostate, glossitis, greying of hair, headache, hyperkinesia, hypoglycemia, immune system enhancement and insomnia. Pantothenic acid is also touted as being beneficial for treating leg cramps, multiple sclerosis, muscular dystrophy, neuralgia, osteoarthritis and rheumatoid arthritis, and

Parkinson's disease. In addition, it is used for peripheral neuritis, premenstrual syndrome, psychiatric disorders, shingles, skin disorders, stomatitis and vertigo, and providing reduced susceptibility to colds and flu. Topically, dexpantenol, the alcohol analog of pantothenic acid, has been used to treat itching and to promote healing of acne, dermatitis, diaper rash, eczema, insect bites, and poison ivy.

Several decades ago, dexpantenol was often administered by intramuscular or intravenous injection after major abdominal surgery to stimulate intestinal peristalsis to minimize paralytic ileus, for inadequate tone of intestinal smooth muscle causing abdominal distention, and to treat paralytic ileus.

As a dietary supplement, the typical dose of pantothenic acid is 5 to 10mg daily. The U.S. RDA based on age are listed in Table 2.

Vitamin B-6 is a collective term referring to a group of related chemicals: pyridoxal (an aldehyde), pyridoxine (an alcohol), pyridoxamine (an amine), and their phosphorylated derivatives. Discussion of vitamin B-6 generally refers only to pyridoxine, but all of these chemicals exert vitamin B-6 activity.

In humans, vitamin B-6 activity occurs principally in the form of the coenzyme pyridoxal 5-phosphate. It is involved in a wide range of biochemical reactions, including: the metabolism of amino acids and glycogen; synthesis of DNA and RNA; production of sphingolipids (building blocks of the myelin tissue in nerve fibers); and synthesis of the neurotransmitters dopamine, gamma-aminobutyric acid (GABA), norepinephrine and serotonin.

Vitamin B-6 reportedly is a coenzyme for over 100 enzymes in the body. These include many of the enzyme systems involved in amino acid metabolism such as decarboxylases and transaminases. It is also a cofactor for enzymes involved in the metabolism of homocysteine. High

serum levels of homocysteine are a risk factor for atherosclerosis. Vitamin B-6 deficiency has been linked to high plasma homocysteine levels, so there are advocates of the use of vitamin B-6 to reduce homocysteine levels and the incidence of atherosclerosis. At this point in time, there is insufficient clinical evidence to prove therapeutic benefits from this use.

Many foods contain vitamin B-6, including meat, fish, poultry, eggs, potatoes, noncitrus fruits, cereals and legumes. Bacteria in the intestinal flora can produce small amounts of vitamin B-6.

Vitamin B-6 deficiency exhibits itself as anemia, chapped lips progressing to lesions, inflammation of the mouth and tongue, seizures, seborrheic dermatitis, irritability, peripheral neuropathy, confusion and depression. Other than dietary deficiency of vitamin B-6, subclinical deficiencies of the vitamin can occur as a result of alcoholism, cancer, cirrhosis of the liver, heart failure, malabsorption syndromes, uremia; in the elderly; and during pregnancy.

There are drugs that reportedly deplete vitamin B-6, requiring supplementation concurrent with their therapy. These include estrogens, ethionamide, hydralazine, isoniazid, loop diuretics, penicillamine and theophylline. Vitamin B-6 supplementation is routinely given to patients receiving these drugs to prevent peripheral neuropathy, especially with isoniazid and oral contraceptives.

In addition to its use as a dietary supplement, vitamin B-6 is also claimed to be useful for treating alcoholism and alcohol over-indulgence, allergies and asthma, arthritis, carpal tunnel syndrome, depression associated with pregnancy or oral contraceptive use, diabetic neuropathy, dizziness and motion sickness.

It is also used to treat heart disease, hyperkinesis, hyperlipidemia, menopausal symptoms, muscle and night leg cramps,

morning sickness of pregnancy, premenstrual syndrome, prevention of cancer and kidney stones, radiation sickness, seizure disorders, stimulation of appetite, and tardive dyskinesia.

Proof of significant toxicity to vitamin B-6 is lacking, but with very high doses of pyridoxine, nausea, vomiting, abdominal pain, loss of appetite and breast soreness have been reported.

The typical dose of pyridoxine as a dietary supplement is 2mg daily, as well as the U.S. RDA used to calculate the percent of daily values on food and nutritional supplement labeling.

The usual dose for treating vitamin B-6 deficiency is 2.5 to 25mg daily for three weeks. For prevention of deficiency in women taking oral contraceptives, 25 to 30mg daily is recommended. For premenstrual syndrome, the usual daily dose is 50 to 100mg.

In patients taking isoniazid, the typical dose for prevention of vitamin B-6 depletion and the resulting peripheral neuropathy is 10 to 50mg daily. For nausea during pregnancy, 10 to 25mg every eight hours is recommended.