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Nutrition 125 – Part 2

Drug-Vitamin-Herb Interactions

The B Vitamins

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Vitamin B1, Thiamin

Vitamin B1 (thiamine) is needed to form ATP, the major energy molecule used by the human body. Nerve cells also require thiamin in order to function properly.

Loop diuretics (particularly furosemide) may deplete vitamin B1. Supplementation with B1 may improve heart function in those with congestive heart failure who are taking loop diuretics. (Misumida et al., 2014) (Zenuk et al., 2003) (Seligmann et al., 1991)

Vitamin B2, Riboflavin

Vitamin B2 (riboflavin) helps convert carbohydrates into ATP, the energy molecule of the body. Vitamin B2 also activates vitamin B6. Vitamin B6 is needed for the production of corticosteroids, erythropoesis, gluconeogenesis, and thyroid enzyme regulation

Oral contraceptives may deplete the body of vitamin B2, particularly when taken long-term. (Palmery et al., 2013)

Vitamin B3, Niacin

Vitamin B3 (niacin) is an essential component of NAD and NADPH, two molecules that used to make energy from carbohydrates. Vitamin B3 is also a precursor of glucose tolerance factor.

Niacin may have some use in lipid control for secondary prevention as monotherapy, perhaps in patients intolerant to statins. (D'Andrea et al., 2019)

Niacin can lead to flushing. Niacin extended-release (NER) formulations have reduced flushing incidence, duration and severity relative to crystalline immediate-release niacin with similar lipid efficacy. Non-steroidal anti-inflammatory drugs (NSAIDs), notably aspirin given 30 min before NER at bedtime, further reduce flushing. (Kamanna et al., 2009)

The sustained-release form of niacin has been associated with severe liver damage. Niacin should be used with caution in those with liver or gallbladder disease. High doses of niacin (which is sometimes recommended to lower cholesterol levels) could increase the risk of muscle damage and kidney injury that are side effects of statin drugs. (McKenney et al., 1994)

Isoniazid appears to interfere with niacin production (from tryptophan) in the body, which can cause niacin deficiency (pellagra). (Bilgili et al., 2011) (Darvay et al., 1999)

Vitamin B6, Pyridoxine

Vitamin B6 (pyridoxine) is an essential cofactor for many reactions in the body, including: serotonin, melatonin, dopamine, fatty acids, homocysteine, and histamine.

High doses of Vitamin B6 should not be used with levodopa, since it can reduce therapeutic effect of levodopa alone in Parkinson's disease. (Hinz et al., 2014)

Oral contraceptives may adversely affect vitamin B6 status, although recent studies do not support this. Because vitamin B6 deficiency is relatively common, supplementation should be considered. (Palmery et al., 2013) (Lussana et al., 2003) (Bosse and Donald, 1979)

Penicillamine therapy can deplete vitamin B6, particularly in individuals with poor

nutritional status. Because vitamin B6 is commonly deficient in the diet, supplementation should be considered. (Tomono et al., 1973)

Hydralazine, Isonazid, and the MAO inhibitors phenelzine and isocarboxazid are structurally similar to vitamin B6. They are known to interfere with vitamin B6 by attaching to and disabling it in the body. Extra B6 is advisable. (Vidrio, 1990) (Pellock et al., 1985) (Malcolm et al., 1994)

Theophylline appears to impair the conversion of vitamin B6 into its active form, pyridoxal 5'-phosphate (P5P). Long-term theophylline treatment may deplete vitamin B6. (Weir et al., 1990)

Vitamin B12, Cobalamin

Vitamin B12 (cobalamin) is a cofactor for homocysteine metabolism, and is needed for DNA replication and normal nerve cell activity.

Oral contraceptives may decrease blood levels of vitamin B12, although some studies suggest that this may be a false reading. It is unclear whether vitamin B12 supplementation is needed with oral contraceptives. (Berenson and Rahman, 2012) (Lussana et al., 2003)

The antidiabetic agents metformin and phenformin have been shown to cause vitamin B12 malabsorption that persists after the drugs are stopped. Calcium has been shown to help correct the B12 malabsorption. (Ting et al., 2006) (Bauman et al., 2000)

Bile acid sequestrants have been reported to impair the absorption of many nutrients, including vitamin B12, although the effect may not be significant. (Teo et al., 1981)

Colchicine therapy may impair vitamin B12 absorption. (Gemici et al., 2013) (Palopoli and Waxman, 1987) (Webb et al., 1968)

Nitrous oxide is well known to inactivate vitamin B12, possibly leading to a deficiency, particularly during long-term therapy. Those with low levels of vitamin B12, and those

that are seriously ill are at high risk of deficiency. (Kiasari et al., 2014) (Krajewski et al., 2007) (Safari et al., 2013)

Zidovudine (AZT) may deplete the body of zinc, copper and vitamin B12. (Paltiel et al., 1995)

H2 Antagonists and Proton Pump Inhibitors, by reducing stomach acid, can interfere with the binding of vitamin B12 to intrinsic factor, which is needed for its absorption. (Qorraj-Bytyqi et al., 2018) (Linder et al., 2017) (Hirschowitz et al., 2008) (Heidelbaugh, 2013)

The Fat-Soluble Vitamins (A, D, E and K)

Vitamin A, Retinol

Vitamin A (retinol) helps cells reproduce and differentiate. Vitamin A stimulates immunity and maintains healthy cell membranes. Vitamin A is also a precursor of rhodopsin, which is used for vision.

Isotretinoin (Accutane) all is a synthetic form of vitamin A. Vitamin A should not be combined with Isotretinoin, as they may increase each other's toxicity. There is, however, no data supporting this. (Danby, 2003)

Valproic acid may interfere with the body's ability to safely handle vitamin A. Those taking valproic acid should use vitamin A with caution and consider switching to beta-carotene (the precursor of vitamin A). (Nau et al., 1995)

Bile acid sequestrants may impair the absorption of many nutrients, including vitamin A. The effect, however, may be insignificant. (Jacobson et al., 2007)

Vitamin D

Vitamin D maintains normal levels of calcium in the blood by increasing its absorption from food and reducing urinary secretion. Vitamin D also plays a role in immunity and blood cell formation.

Anticonvulsant drugs may interfere with the activity of vitamin D and speed up its breakdown. Consider vitamin D supplementation with anticonvulsant drugs, such as Carbamazepine, Phenonarbital, Phenytoin, Primidone, and Valproic Acid. (Lee et al., 2010) (Nettekoven et al., 2008)

Cimetidine may interfere with the body's handling of vitamin D. However, the effect may not be significant. (Odes et al., 1990)

High doses or long-term use of heparin may interfere with the proper handling of vitamin D by the body. Calcium and vitamin D may help prevent heparin-induced osteoporosis. (Deruelle and Coulon, 2007)

Isoniazid may interfere with the conversion of vitamin D into its active forms. Rifampin may interfere with the formation of an important form of vitamin D. (Chesdachai et al., 2016) (Self et al., 1999) (Sheng et al., 2015)

Vitamin D may help prevent corticosteroid-induced osteoporosis. (Homik et al., 2000) (Amin et al., 1999)

Vitamin E, Tocopherol

Vitamin E (tocopherol) is a powerful antioxidant that helps protect cell membranes and LDL cholesterol from oxidation. Vitamin E supplementation has been shown to significantly reduce the risk of heart disease.

Vitamin E thins the blood, which may cause excess bleeding when combined with anticoagulant drugs, such as Warfarin (Coumadin). Monitor PT and INR values regularly. Consumption of high-dose vitamin E supplements ($\geq$ 300 mg/d), however, may lead to interactions with the drugs aspirin, warfarin, tamoxifen and cyclosporine A that may alter their activities. For the majority of drugs, however, interactions with vitamin E, even at high doses, have not been observed and are thus unlikely. (Podszun and Frank, 2014) (Pastori et al., 2013) (Corrigan, 1982)

Vitamin E may improve blood sugar control, possibly causing hypoglycemia if taken with

antidiabetic drugs. Monitor glucose levels regularly. (Soleymani et al., 2019) (Choi and Ho, 2018)

Vitamin E may help prevent the toxic effects of amiodarone (Cordarone, an antiarrythmic drug) on the lungs. (Zaki and Eid, 2009) (Bolt et al., 2001) (Honegger et al., 1995)

Vitamin E may help prevent the heart toxicity and hair loss associated with doxorubicin (and other anthracyclines) therapy. (Fayez and Zaafan, 2018) (Kumral et al., 2016) (Berthiaume et al., 2005)

High-dose vitamin E may be helpful in the treatment and prevention of drug-induced tardive dyskinesia caused by antipsychotic agents. (Soares-Weiser et al., 2018)

Bile acid sequestrants may impair the absorption of many nutrients, including vitamin E. The effect, however, may be insignificant. (West and Lloyd, 1975)

Vitamin E may help prevent cisplatin-induced kidney toxicity and alleviate mucositis (inflammation of the membranes lining the inside of the mouth), a common complication of chemotherapy. (Abdel-Daim et al., 2019) (Darwish et al., 2017)

Vitamin K

Vitamin K directly counteracts the action of the anticoagulant drug Warfarin (Coumadin). (Ferland et al., 2019) (Luc et al., 2019)

Antibiotics can destroy “friendly” intestinal bacteria that produce vitamin K. Supplementation with vitamin K may be beneficial with antibiotics. (Aziz and Patil, 2015) (Bhat and Deshmukh, 2003)

Cephalosporins may interfere with vitamin K metabolism. Consider supplemental vitamin K with Cephalosporins. (Yılmaz et al., 2011) (Wong et al., 2006) (Rockoff et al., 1992)

Anticonvulsants speed up the normal breakdown of vitamin K into inactive byproducts,

which may cause a deficiency of active vitamin K. Consider supplemental vitamin K with anticonvulsants, such as Carbamazepine, Phenobarbital, Phenytoin, Primidone, and Valproic Acid. (Yamasmit et al., 2006) (Choulika et al., 2004)

Vitamin C, Folic Acid, and PABA

Vitamin C, Ascorbic Acid

Vitamin C (ascorbic acid) is a powerful antioxidant, and is needed to make collagen, the "glue" that strengthens muscles and blood vessels. Vitamin C also acts as a natural antihistamine and fights viruses.

Ascorbic acid may prevent acetaminophen-induced hepatotoxicity. (Abdulrazzaq et al., 2019) (Kurahashi et al., 2016)

Test tube studies suggest that high doses of vitamin C may reduce the blood-thinning effects of Heparin and Warfarin. (Sattar et al., 2013)

Animal studies suggest that antioxidants glutathione, and vitamin C may help prevent doxorubicin-related heart damage, increase survival time, or delay doxorubicin-related death. (Viswanatha Swamy et al., 2011) (Tavares et al., 1998)

Vitamin C may help protect against kidney damage during Cisplatin chemotherapy.

Vitamin C may help prevent the tolerance to nitroglycerin that develops over time. (Longchar and Prasad, 2015) (Maliakel et al., 2008) (Ajith et al., 2007)

Oral contraceptives appear to lower blood levels of vitamin C. (Kuo et al., 2002) (Naziroğlu et al., 2004) (Rivers, 1975) (Hudiburgh and Milner, 1979)

Folic Acid

Folic acid is involved in DNA synthesis and is important in pregnant woman to help prevent neural tube defects as the fetus develops. Folic acid (along with vitamin B6 and B12) also keeps homocysteine levels from rising.

Anticonvulsants deplete the body of folate. However, high levels of folic acid may increase breakdown of phenytoin, which may cause seizures in some individuals. The interaction between folate and anticonvulsants is complex. Folic acid has mixed interactions with anticonvulsants, such as Carbamazepine, Phenobarbital, Phenytoin, Primidone, and Valproic Acid. (Reynolds, 1973) (Dinç and Schulte, 2018)

Oral contraceptives may deplete folate. (Shere et al., 2015)

Antacids, H2 antagonists, and proton pump inhibitors reduce stomach acid, which lowers the absorption of folate, which may cause deficiency. (Russell et al., 1988)

Methotrexate prevents the conversion of folic acid to its active form. Folate supplements have been found to help Methotrexate work better and reduce its side effects. (Cline and Jorizzo, 2017)

Nitrous oxide inactivates vitamin B12, which may lead to a folate deficiency. (Weimann, 2003)

Triamterene (Dyreneum, a potassium-sparing diuretic) is structurally similar to folate and may cause a folate deficiency. A study, however, found that chronic diuretic therapy with moderate doses of triamterene is not associated with folate deficiency. (Mason et al., 1991) (Zimmerman et al., 1986)

Bile acid sequestrants impair the absorption of many nutrients, including folate. (West and Lloyd, 1975) (Hoppner and Lampi, 1991)

Trimethoprim (Trimpex or Proloprim, an antibacterial agent), Sulfamethoxazole (Gantanol) and the combination of both Trimethoprim-Sulfamethoxazole (Bactrim or Septra) interfere with folate metabolism in bacteria, and may also interfere with its metabolism in humans, which may cause folate deficiency. (Meidahl Petersen et al., 2016)

PABA, Para-Aminobenzoic Acid

Trimethoprim-Sulfamethoxazole (Bactrim or Septra) works by stopping the production of

folate from PABA by bacteria. Therefore, PABA supplements may decrease the effectiveness of TMP-SMZ. (Quinlivan et al., 2000)

Ephedra, St. John's Wort, Kava, Licorice, and Yohimbe

Ephedra (Ma Huang)

Ephedra is perhaps the most well known herb associated with adverse reactions. The active ingredients in ephedra, ephedrine and pseudoephedrine, are available in a number of over-the-counter and prescription products commonly used for weight loss or nasal decongestion. It is assumed that the side effects documented in these medications will also be found in the herb ephedra.

Ephedrine and pseudoephedrine (Sudafed) are sympathomimetics and adrenergic agonists. Side effects of include increased heart rate, palpitations, anxiety, restlessness and nervous-ness.

Interactions can occur with monoamine oxidase inhibitors (MAOIs) or tricyclic antidepressants; blood pressure medications like clonidine and reserpine; theophylline; amphetamine-derivatives; or other preparations that contain ephedrine, pseudoephedrine, caffeine, or phenylpropanolamine as an active ingredient.

Ephedra has been under FDA review for several years, and has recently been banned for sale in the United States. Proponents argue that a review the scientific evidence shows that the herb ephedra is safe when taken as directed. (Holstege et al., 2005) (Zell-Kanter et al., 2015)

St John's Wort (Hypericum perforatum)

Hypericum perforatum (St. John's wort) is commonly used as an antidepressant. It is well tolerated by patients, and has an extremely low incidence of side effects.

Several reports have suggested that Hypericum may influence the cytochrome P450

enzyme system, in particular CYP3A4, which may thus affect the metabolism and efficacy of certain drugs. Several human studies, however, have shown that this is a weak effect at standard doses. (Soleymani et al., 2017)

Several drug interaction reports are cause for concern with HIV drugs, warfarin, digoxin. (Borrelli and Izzo, 2009)

Women taking anticonvulsants and oral contraceptives at the same time are at risk of failure of contraception and should be warned to avoid the use of Hypericum. (Berry-Bibee et al., 2016)

The use of Hypericum with selective serotonin re-uptake inhibitors (SSRIs) is controversial. The controversy began after it a report that “the mode of action for Hypericum extracts is thought to be similar to that of conventional serotonin re-uptake inhibitors.” The exact mechanism of action of Hypericum is unknown, although it does appear to exhibit activity on several neurotransmitters. The activities found, however, are considered to weak to account for the anti-depressant action. (Russo et al., 2014)

Kava Kava (Piper methysticum)

Kava Kava (Piper methysticum) is relaxing herb that is a mild sedative or tranquilizer. It is commonly used for anxiety and insomnia.

The drug interactions with kava kava are based on a few case reports. One case report of coma induced by a combination of kava and alprozolam (a benzodiazepine). There are four reported cases of extrapyramidal side effects (dopamine antagonism), which resulted in oral, lingual and trunk dyskinesia. There are a few case reports of hepatitis associated with kava or kavain ingestion, usually after prolonged exposure 1-2 months as the maximum recommended doses One case required live transplant due to severe hepatocellular necrosis and extensive portal and lobular infiltration of lymphocytes and eosinophils. Due to these reports of liver damage, Kava was banned in Germany, and most supplement companies have discontinued its use. (Bressler, 2005) (Anke and

Ramzan, 2004)

Licorice

Glycyrrhiza glabra (Licorice) contains glycyrrhizin - a derivative of glycyrrhetinic acid that is similar to hormones produced in the adrenal cortex, especially desoxycorticosterone (DOCA). Licorice supports the adrenal glands and was commonly prescribed for Addison's disease in the early 1900s. Real licorice is known to increase blood pressure. Most of the licorice candies are made from star anise, a spice unrelated to licorice. Deglycyrrhized licorice (DGL) is available for those with hypertension. (Nazari et al., 2017) (Isbrucker and Burdock, 2006)

Yohimbe (Pausinystalia yohimbe)

Yohimbe is marketed in a number of products for bodybuilding and "enhanced male performance."

Serious adverse effects, including renal failure, seizures and death, have been reported to FDA with products containing yohimbe and are currently under investigation.

The major identified alkaloid in yohimbe is yohimbine. Yohimbine blocks alpha-2 adrenergic receptors, and causes vasodilation, thereby lowering blood pressure. Yohimbine is also a prescription drug in the United States. Side effects are well recognized and may include central nervous system stimulation that causes anxiety attacks.

At high doses, yohimbine is a monoamine oxidase (MAO) inhibitor. MAO inhibitors can cause serious adverse effects when taken concomitantly with tyramine-containing foods (e.g., liver, cheeses, red wine) or with over-the-counter (OTC) products containing phenylpropanolamine, such as nasal decongestants and diet aids. Individuals taking yohimbe should be warned to rigorously avoid these foods and OTC products because of the increased likelihood of adverse effects.

Yohimbe should be avoided by individuals with hypotension (low blood pressure), diabetes, and heart, liver or kidney disease. Symptoms of over-dosage include weakness and nervous stimulation followed by paralysis, fatigue, stomach disorders, and ultimately death. (De Smet and Smeets, 1994)

Progesterone, Tyrosine & Phenylalanine, Oils

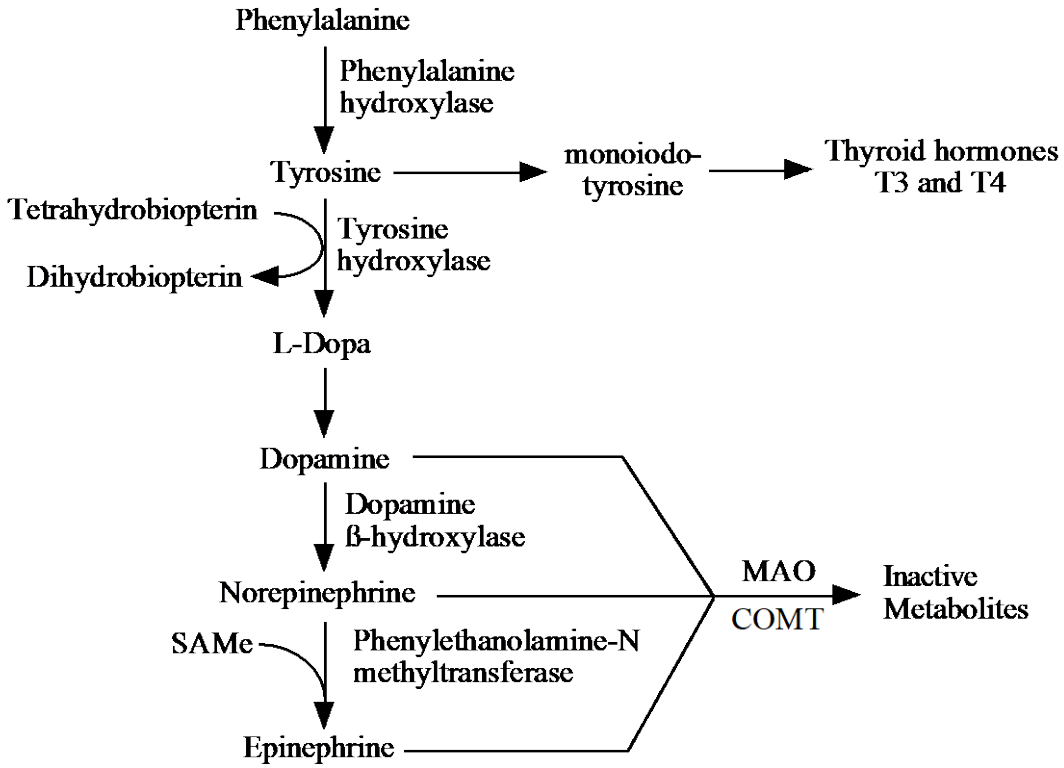
Progesterone

Progesterone creams have become very popular since Dr. Lee's published his books on *What Your Doctor May Not Tell You About Premenopause* and *What Your Doctor May Not Tell You About Menopause*. Dr. Lee believes that most women are estrogen dominant, instead of estrogen deficient. Progesterone creams are advertised as the natural choice for hot flashes and other menopausal symptoms. The problem is that without lab tests it is difficult (or impossible) to determine which hormones are deficient or in excess. A conservative approach would be to test estradiol and progesterone levels checked in women taking hormones, either natural or drug. (2001) (Stanczyk, 2014)

Tyrosine and Phenylalanine

Phenylalanine and tyrosine are precursors to epinephrine and norepinephrine. As such, they are mild adrenergic stimulants. Phenylalanine is an ingredient in Diet Coke. Caffeine in coffee and black tea has been shown to stimulate epinephrine release. Although these are mild effects, excessive consumption may cause over-stimulation, particularly with those taking MAO inhibitors. (Glatter et al., 2012)

Figure 1: Tyrosine Metabolism



Therapeutic Oils

Oils contain omega-3 and omega-6 essential fatty acids (EFAs). Therapeutic oils include fish oils, evening primrose oil, flaxseed and borage oil, and many others. Therapeutic oils are primarily used for their anti-inflammatory properties.

Therapeutic oils, especially fish oils, are natural blood thinners and should be used with caution by those prescribed anticoagulants, such as Coumadin. Regular monitoring of the PT and INR values is recommended. (Pryce et al., 2016) (Villani et al., 2013) (Buckley et al., 2004) (Bender et al., 1998)

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