Hardy® nutritionals

CLINICAL REFERENCE

for Healthcare Professionals

Dear Healthcare Professional,

Thank you for your interest in *Hardy Nutritionals® Daily Essential Nutrients (DEN)* – a unique technology-enhanced vitamin-mineral formulation for the treatment of mood, anxiety, and behavioral symptoms.

This clinical reference provides detailed information about *DEN* and select nutritional adjuncts. This information was accumulated through extensive research and valuable feedback from healthcare professionals and patients.

For your convenience, we've included Section 2 *Treatment Guidelines*, which consolidates information from other sections into clinical context.

For the most up-to-date version of this document, please see our website.

We welcome any feedback, questions or concerns you may have. Please feel free to call us.

We appreciate working with you for your patients' health!

Sincerely,

The Hardy Nutritionals® Team
www.HardyNutritionals.com

Toll free: 1-855-955-1114
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Office Hours: Monday - Friday
9:00 AM - 5:00 PM (MST)

Table of Contents

About Hardy Nutritionals®

Hardy Nutritionals® was founded in October 2011 by David L. Hardy. David founded the company after spending nearly 15 years co-developing a specialized micronutrient formulation (EMPowerplus†), known at that time among nutrition researchers as the world's most studied micronutrient formula for mental health.[9]

David L. Hardy, Founder
Hardy Nutritionals® (1950-2016)

The first micronutrient formula version was developed over several years by David L. Hardy and Anthony F. Stephan, and eventually subsequent formulations were manufactured and distributed from the U.S. to many countries throughout the world.

Their formulations were based in large part on David's agricultural knowledge and 20 years of experience in livestock production as an animal feed formulator. Animal supplements have been developed empirically over generations of animal husbandry where improvements in health translate into large financial gains.

"I just really want to thank David Hardy for his work in this field. Over the last 20 years, his products have revolutionized mental health care and I think represent the single biggest change in the advancement of the treatment of mood disorders since the introduction of Lithium in the early 1950s."

Scott Shannon, MD, ABIHM. Founder, Wholeness Center*

Their first formula greatly improved two of Anthony's children who were suffering from serious mental health disorders. Both children were able to remain stable by taking the micronutrients and over time no longer had a need for psychiatric medications. Word spread quickly about the dramatic response of these children to the micronutrients, and soon others began to measure similar results.

The original formula required 32 capsules per day to deliver the clinical dose of vitamins and minerals. Over the years, a number of changes were made to the formula as research and use of the product expanded. In 2004, technological advances and a formula change reduced the daily dose from 32 to 18 capsules. In 2007, with minor changes to ingredients, the formula was fit into 15 capsules per day. Some of these changes were enabled by new proprietary mineral-delivery technologies which were refined over the years. The result of these changes was a more effective and tolerable formulation which continued to deliver consistent results. In 2007, there were 18 medical journal publications on these versions of the formula.

As the formula was evolving and was used by more and more individuals around the world, two of David's own children were diagnosed with serious mental illnesses. This gave David the same kind of personal experience with close family members suffering from mental illness that Anthony had faced just a few years earlier. Many important insights into the best use of micronutrients and other supportive products were developed by David as he struggled to help his own children regain wellness during this time. Today both of David's children, who were once very ill, serve in their communities, have their own children, and live normal lives without the debilitating symptoms of mental illness and without the aid of medications.

When David founded Hardy Nutritionals® in 2011, after a planned separation of business interests with Anthony, he made small changes to the core micronutrient formula and re-named it *Hardy Nutritionals® Daily Essential Nutrients* (*DEN*). These important changes significantly improved tolerability and reduced nutrient-medication interactions. In 2013, the Hardy Nutritionals® science team produced a new version of *DEN*, which retained both the nutrient guarantees and the efficacy supported by published research in only 12 capsules per day. Other nutritional products, either for general health or for use as therapeutic adjuncts to *DEN*, round out the Hardy Nutritionals® product line.

The team of scientists at Hardy Nutritionals® continually researches ways to improve the formulas. With additional research and experience, it is anticipated that formulation changes will continue as Hardy Nutritionals® remains at the forefront of nutritional health research.

"David Hardy's foresight and vision for the future of health care was critical in establishing the beginnings of a new movement in medical treatment, health promotion, and wellness. He was a visionary thinker who was also a careful observer of detail, a thoughtful synthesizer of disparate lines of research, and a courageous leader who helped force open the way for the medical community to think beyond its dogmas into a new world of possibilities. As we mark his passing, we know that he will not be here to see the fruition of his ideas, but he laid enough groundwork that we can know now that his ideas will ultimately prevail and profoundly alter the direction of medicine and the quality of human life."

*Charles W. Popper, M.D.**
Harvard Medical School

Clinical aspects and evidence relevant to DEN were reviewed in a recent publication of the American Psychiatric Association, *Complementary and Integrative Treatments in Psychiatric Practice*.[1]

†Refers to pre-2013 versions of EMPowerplus, which were co-formulated by David L. Hardy and Anthony F. Stephan.
** The views expressed are the opinion of the quoted indiviual. They have no financial or other ties to Hardy Nutritionals.*

1 Description

Hardy Nutritionals® Daily Essential Nutrients (*DEN*) is a micronutrient formula for oral administration. It consists of 16 minerals, 13 vitamins, 4 amino acids, and 4 antioxidants/botanicals. All minerals are chelated with a proprietary, technology-enhanced process which combines specialized organic molecules with micronized minerals to maximize mineral absorption and delivery to cells.

DEN is a light brown, gluten-free, non-GMO powder enclosed in a white opaque vegetarian capsule and meets all FDA good manufacturing standards.

daily Essential Nutrients

TECHNOLOGY-ENHANCED NUTRITION

Supplement Facts

Serving Size: 4 Veggie Capsules
Servings Per Container: 90

Amount Per Serving		%DV
Vitamin A *(as retinyl palmitate)*	1920 IU	38%
Vitamin C *(as ascorbic acid)*	200 mg	333%
Vitamin D *(as cholecalciferol)*	1000 IU	250%
Vitamin E *(as d-alpha tocopheryl succinate)*	120 IU	400%
Vitamin K *(as phylloquinone & menaquinone-7)*	40 mcg	50%
Thiamin *(as thiamine mononitrate)*	20 mg	1333%
Riboflavin	6 mg	353%
Niacin *(as niacinamide)*	30 mg	150%
Vitamin B_6 *(as pyridoxine hydrochloride)*	23.3 mg	1167%
Folate *(as calcium L-5 methyltetrahydrofolate)*	267 mcg	67%
Vitamin B_{12} *(as adenosylcobalamin & methylcobalamin)*	300 mcg	5000%
Biotin	360 mcg	120%
Pantothenic acid *(as d-calcium pantothenate)*	10 mg	100%
Calcium *(as NutraTek™ chelation complex)*	440 mg	44%
Iron *(as NutraTek™ chelation complex)*	4.6 mg	25%
Phosphorus *(as NutraTek™ chelation complex)*	280 mg	28%
Iodine *(as NutraTek™ chelation complex)*	68 mcg	45%
Magnesium *(as NutraTek™ chelation complex)*	200 mg	50%
Zinc *(as NutraTek™ chelation complex)*	16 mg	107%
Selenium *(as NutraTek™ chelation complex)*	68 mcg	97%
Copper *(as NutraTek™ chelation complex)*	2.4 mg	120%
Manganese *(as NutraTek™ chelation complex)*	3.2 mg	160%
Chromium *(as NutraTek™ chelation complex)*	208 mcg	173%
Molybdenum *(as NutraTek™ chelation complex)*	48 mcg	64%
Potassium *(as NutraTek™ chelation complex)*	80 mg	2%
Proprietary blend	596 mg	†

Choline bitartrate, alpha-lipoic acid, mineral wax, inositol, acetyl-L-carnitine, grape seed extract, ginkgo biloba leaf extract, N-acetyl-L-cysteine, L-methionine, *trace minerals as NutraTek™ chelation complex:* lithium orotate, boron, vanadium, nickel.

† Daily Value (%DV) not established.

Rev. 18-02

Other ingredients: Vegetarian capsule (hypromellose), microcrystalline cellulose, magnesium stearate, silicon dioxide, titanium dioxide.

"I have reached the conclusion…[that] the treatment of mental disease by the provision of the optimum molecular environment for the mind, especially the optimum concentrations of substances normally present in the body, may be found to be of great value and may turn out to be the best method of treatment for many patients."[2] *- Linus Pauling*

2 Treatment Guidelines

2.1 Critical treatment considerations

Unless contraindications (see 7.2 *Contraindications*) or precautions (see 6.2 *Precautions*) direct otherwise, *Hardy Nutritionals® Daily Essential Nutrients* (*DEN*) can generally be administered to patients as outlined in this section. Individual patient characteristics may require adaptations according to clinical judgment. Important clinical considerations include:

- Assess gastrointestinal health[3] (see 2.6 *Managing gastrointestinal issues,* 8.5 *Gastrointestinal problems,* and *Appendix B*)

  Researchers at John Radcliffe Hospital in Oxford, England, observed that 90% of the patients who repeatedly sought treatment for digestive tract symptoms (more than 12 visits in the previous 12 months) had at least one current psychiatric diagnosis; 48% had at least two.[4,5]

- Assess medication use[3] (see 2.3 *Potentiation of psychiatric medications,* 2.4 *Clinical response – CNS drug use,* 8.1 *Psychiatric medications,* and 8.2 *Non-psychiatric medications*)

  The online Merck Professional Manual indicates that drug interactions are changes in a drug's effects due to recent or concurrent use of another drug or drugs (drug-drug interactions), ingestion of food (drug-nutrient interactions), or ingestion of dietary supplements (dietary supplement-drug interactions).[6] For the purposes of this text we use the term drug-nutrient interactions.

2.1.1 Instructions for *DEN* use

Generally, *DEN* can be titrated up to an appropriate therapeutic dose (see 4.0 *Indications & Dosage*) within 4 days as directed on the label (see *Figure 1*):

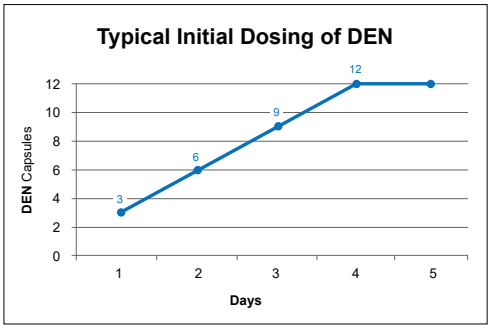

Figure 1: Typical initial dosing for DEN

Very sensitive patients may benefit from starting with 1 capsule per day and increase to therapeutic levels as they are comfortable. Patients who have difficulty falling asleep should take the evening dose of *DEN* as early as is practical (see 8.7.3 *Sleep*).

Suggested Use: "Consistently take 4 capsules 3 times daily, or a level recommended by your health professional. If desired, start with 1 capsule 3 times daily and increase gradually. Take with food."

Taking *DEN* with food further helps to avoid uncommon gastrointestinal side effects (see 5.1 *Side effects*). Children should take *DEN* under adult supervision (see 6.2 *Precautions*).

2.2 Clinical response – medication-naïve

"Broad-spectrum micronutrient treatments are straightforward for psychiatric patients who are drug-naïve as well as for individuals who are seeking benefits for normal brain functioning, assuming they are not using other CNS-active drugs. Micronutrient use is usually not complicated for patients who have been free of CNS drugs for several weeks or months, except if those medications have significant withdrawal symptoms."[1] (See *Figure 2*).

The average response time for an adult is approximately three weeks. Children and adolescents typically respond sooner. In open-label trials, approximately 80% of individuals responded to nutrients alone by 2 months without conventional psychiatric medication. For individuals with *no* recent medication use who are taking the recommended dose of *DEN*, it is possible to see benefits beginning as follows:[7]

- Mania - within 5 days
- Depression - within 4-8 weeks (longer if chronic or psychotic)
- Non-comorbid panic and anxiety may require adjuncts for best response (see 2.8 *Addressing residual symptoms*)

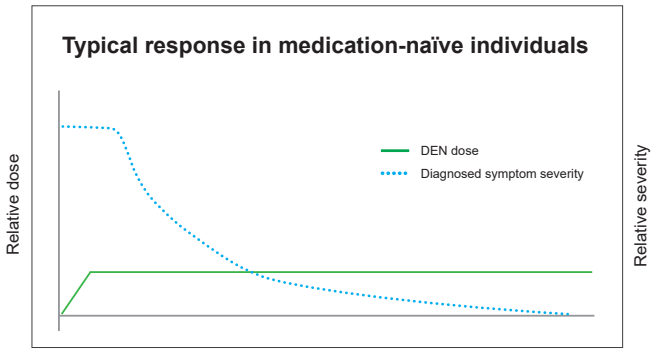

Figure 2: Typical response in medication-naive individuals

2.3 Potentiation of psychiatric medications

Drug interactions can be triggered by ingestion of food or by ingestion of dietary supplements.[6] In this document, we will refer to both of these interactions as drug-nutrient interactions.

Both clinicians and patients using *DEN* consistently report that the effects (including known side effects) of "virtually all CNS-active drugs"[1] are amplified by apparent drug-nutrient interactions (rough estimates range from 3-5 times). Notably, lithium may be more powerfully potentiated (from 10-100 fold), perhaps via unique mineral-mineral interactions. Therefore, side effects of psychiatric medications, including lithium, must be monitored carefully during *DEN* therapy and dosages adjusted accordingly (see 6.1 *Warnings*). As medication side effects increase, medication dosages should be gradually reduced (see *Figure 3*).

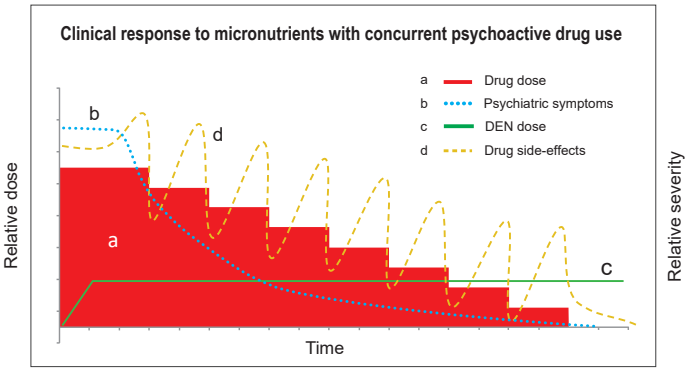

Figure 3. A graphical depiction of the clinical observations that [a] drug dose should be reduced over time as [b] psychiatric symptoms are increasingly well managed by [c] *DEN* dose. Micronutrient augmentation of drug effects is visualized by exacerbated [d] drug side-effects which are a consistent and accurate indicator of the need to reduce the relevant medication(s). Response times vary widely, but conducting patient evaluations at least every two weeks is prudent; weekly is ideal.

"In contrast [to drug-naïve or drug-free patients], cross tapering patients from ongoing psychiatric drug regimens to broad-spectrum micronutrients generally requires gradual and skillful management because of apparent interactions between broad-spectrum micronutrients and CNS-active drugs."[1]

This apparent potentiation of psychoactive medications generally emerges gradually over time. When pre-existing medication side effects increase in severity or additional drug side effects emerge, gradually reduce medication dosages (see 5.2 *Drug interactions*). Ideally, medication reductions should minimize patient discomfort by avoiding potentiated side effects (due to inadequate dose reduction), as well as symptom rebound or discontinuation effects (due to premature, overly rapid, or excessive dose reduction - see 8.1 *Psychiatric medication*). Figures 3 and 5 illustrate the importance of minimizing drug-related symptoms during the medication reduction process.

2.3.1 Managing withdrawal syndromes

Common symptoms of drug discontinuation (withdrawal) include:[7]

- Odd head feeling, headache, mental fog.
- Odd gastrointestinal feeling, nausea, GI upset, flu-like symptoms
- Light-headedness, dizziness, fatigue, malaise, myalgia
- Anxiety, irritability, insomnia, agitation, confusion, vertigo, hot and cold flashes, tremors, parathesias (pins and needles), "buzzing all over," generalized itching, "electric shock-like sensations," visual "jolts," sweating, pupil dilation, anorexia.

Hardy Nutritionals® Balanced Free-Form Aminos or protein powders, taken as needed, may temporarily ameliorate drug discontinuation symptoms. Amino acids in free form are essentially predigested and are rapidly absorbed, providing higher blood plasma concentrations compared to normal protein digestion[8,9] (see *Appendix C* for possible therapeutic mechanisms). Absorption of protein products will be expedited if taken between meals.

Due to the diversity of physiological functions performed by amino acids, a variety of possible mechanisms could contribute to their psychiatric effects. Amino acids are direct biochemical precursors to neurological pathways targeted by psychiatric medications. As such, amino acids may act as neurotransmitter mimetics, as substrates for increased endogenous production of neurotransmitters, or both. Amino acids may therefore help temporarily to ameliorate discontinuation syndromes after a drug dose reduction (see *Figure 4*).

As the fundamental building blocks for all enzymes and tissues, other potential mechanisms of amino acids include increased enzymatic activity and enhanced ability for cellular repair or replication. For instance, supplying amino acids to gastrointestinal epithelial cells, which are exposed to high levels of insult and subject to rapid turnover, can have very significant implications for the gut-brain axis. Glutamine, for example, is both required for proper intestinal barrier function,[10,11] and used for GABA production.[12]

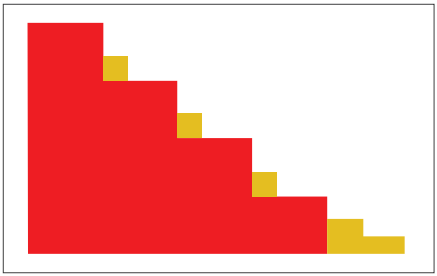

Figure 4. Dosing concept for free-form amino acids during drug discontinuation. Supplementing amino acids [yellow] as needed post reduction may be beneficial for drugs [red] which are neurotransmitter signaling agonists (eg. SSRIs).

A balanced complement of amino acids may be preferable to high doses of single amino acids (or amino acid metabolites), as stimulating only one neurotransmitter pathway at a time using a single amino acid can result in undesirably powerful dose-response sensitivity, especially when a drug is selectively acting on the same pathway simultaneously (see 8.4.4 *Amino acids*).

2.3.2 Managing post-withdrawal medication effects

Some patients report symptoms that appear to be medication side effects even after discontinuing all medications (see 8.6.3 *Prior psychiatric drug use*; 8.7 *Lifestyle factors*).

Some researchers and patients have reported that protein isolate or vitamin C can attenuate apparent post-withdrawal medication side-effects, tardive akathisia, or dyskinesia.

Oral doses of protein isolate (a concentrated protein source), taken as needed, may provide relief of mild to moderate medication effects and may last for several hours. (see *Appendix C*).

Oral doses of up to 3-5 grams of vitamin C at a time (or 1 gram of liposomal vitamin C), taken at least 30 minutes apart as needed, may provide relief of mild to moderate medication effects. Relief of severe medication-related symptoms have been reported to require up to 8-10 grams (about 2 grams of liposomal vitamin C). Relief may vary with the adequacy of the dose, but if benefit is to be had, it is usually recognizable within 30 minutes of ingestion and may last for several hours (see *Appendix D*).

There is some evidence that vitamin C bowel tolerance increases when it is in higher physiological demand, but there is potential for bloating and osmotic diarrhea at therapeutic doses. As the maximum dose tolerance varies between individuals

and may even vary from in the same individual based on physiological conditions, it is important to administer oral vitamin C on a case by case basis and only in the quantity and frequency necessary for symptom relief. Gastrointestinal side effects may be avoided by using liposomal or intravenous vitamin C.

2.4 Clinical response – CNS drug use

For some individuals taking *DEN* with CNS-active medication(s), benefits may be difficult to perceive until a significant portion of these medication(s) have been tapered.

We recommend that each patient and/or caregiver, together with the prescribing doctor when feasible, review the known side effects of the patient's medication(s) at least weekly while using *DEN* in order to detect any increases in the number or intensity of side effect as early as possible. These regular side effect assessments are critical to determine the ideal rate of medication tapering and thus allow the patient to enjoy optimal benefits from *DEN* treatment.

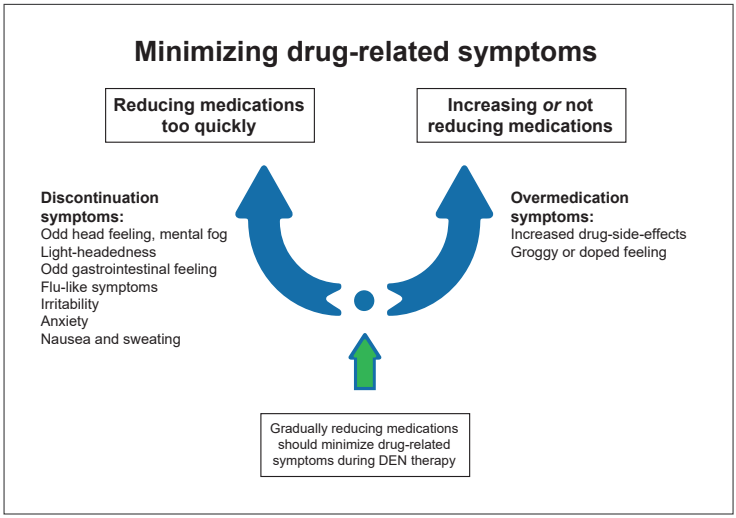

Figure 5. Drug discontinuation or overmedication effects can occur when reducing medication(s) too quickly or too slowly, respectively. Overmedication effects can be magnified as micronutrients are introduced. During treatment, careful attention to side-effects of medication(s) will be vital in order to taper medication(s) optimally.

2.4.1 Polypharmacy

Multiple psychiatric medications are often prescribed together to manage symptoms for which one medication alone may not be effective. Normally, these medications should be reduced at the same rate relative to each other, such that they are terminated simultaneously. This approach maintains, throughout discontinuation, the balance that the medications exert together on the central nervous system (e.g. an antipsychotic in combination with an antidepressant).

2.5 Other medications

All medications should be monitored by a physician during *DEN* therapy (see 6 *Warnings & Precautions* and *Appendix F*).

Medications for health conditions such as thyroid, insulin, and heart issues, high blood pressure, high cholesterol, and cancer need to be monitored closely as dosing for a wide variety of medication types may require adjustment during micronutrient therapy.

Common non-psychiatric medications that have been reported to interact with *DEN* are listed in 8.2 *Non-psychiatric medications*.

2.6 Managing gastrointestinal issues

Healthy gastrointestinal function is critical for optimal digestion and absorption of nutrients from foods and supplements. Various gastrointestinal issues, such as bowel disorders, constipation, diarrhea, parasite infection, and gut microflora imbalance (dysbiosis) can limit response to *DEN* therapy (see 8.5 *Gastrointestinal problems*).

If the symptom response to *DEN* is poor or atypical and cannot be explained by drug side effect potentiation, the individual may very likely benefit from a combination of pre- and probiotics such as *Hardy Nutritionals® Greens & Probiotics*. Nutrition-fueled "aggravation of pre-existing Candida (yeast) infections" has been documented with *DEN* use, but clinical experience has shown that these "can be adequately managed with antifungal medication, olive leaf extract, and probiotics."[3,13]

In using *Hardy Nutritionals® Olive Leaf Extract* or *Hardy Nutritionals® Greens & Probiotics*, patients and physicians should be aware of a possible Jarisch–Herxheimer reaction. This reaction is a self-limiting transient response traditionally associated with antimicrobial treatment of syphilis. It is thought to be triggered by the lysis of microbial cell membranes and the consequent release into the bloodstream of lipoproteins, resulting in a systemic inflammatory response. It manifests clinically with short-term constitutional symptoms such as fever, chills, headache and myalgias.[14] Similar symptoms have been observed with the use of *Olive Leaf Extract* and occasionally *Greens & Probiotics*.

Some individuals have reported that vitamin C attenuates the systemic symptoms of the Herxheimer effect. Oral doses of 2-5 grams of ascorbic acid at a time, taken as needed, may provide relief within 30 minutes. While there is some evidence that vitamin C bowel tolerance may increase when this nutrient is in higher physiological demand, potential osmotic effects of bloating or diarrhea can occur at these doses. Gastrointestinal side effects can be avoided by using liposomal vitamin C, which may be equally effective at a dose of 1 gram.

In addition to prebiotics and probiotics, amino acid supplementation, such as with *Hardy Nutritionals® Balanced Free-Form Aminos*, may significantly improve gut health during *DEN* therapy. Gastrointestinal epithelial cells are highly vulnerable to damage and subject to rapid turnover, making the protein-intensive activities of cellular repair and division extremely important to the gut-brain axis. Glutamine and arginine are two well-studied examples of amino acids which enhance intestinal barrier function.[15]

2.7 Other considerations for clinical management

2.7.1 Evaluation

Standard psychiatric evaluation with the patient and ruling out contraindications is best done *before* beginning *DEN* therapy (see 7.2 *Contraindications*, 6.2 *Precautions*, and 8 *Possible limiting factors*). During the transition from psychiatric or CNS-active medications to micronutrients, ongoing evaluation should occur weekly, if possible, in order to review potential treatment-limiting factors, assess drug side effect potentiation, and adjust medication dosing if necessary (see 2.3 *Potentiation of psychiatric medications* and 2.5 *Other medications*). For medication-free patients, bi-weekly ongoing evaluation may be adequate until symptoms are well-managed.

The most common and most disruptive interfering factors are medications and gut health (see 2.1 *Critical treatment considerations*). Additional patient characteristics that commonly influence the use of *DEN* and/or adjunct treatments include the following:

- Patient history (see 8.6 *Patient history*)
- Lifestyle factors (see 8.7 *Lifestyle factors*)
- Recreational drug use (see 8.3 *Recreational drugs*)
- Supplement use (see 8.4 *Supplements*)
- Other factors influencing nutritional requirements (see 8.8 *Physical health and life stage factors*)

2.7.2 Informed consent

We endorse the informed consent section of Chapter 6 in the 2017 APA publication *Complementary and Integrative Treatments in Psychiatric Practice*:

"Informed consent should be thorough and well-documented for any nonestablished treatment." In particular, "Documentation should specify reasons for using a nonestablished treatment, such as patient preference and potential for fewer adverse effects or better clinical response."[1]

It is often critical that clinical judgement overrule a protocol-based approach, especially when using micronutrient therapy in a medicated patient. "If transitioning a patient from psychiatric drugs, the medical record should explain the reason each time a psychiatric drug dose is lowered, such as adverse effects detected, withdrawal symptoms, or other specific clinical observations in the individual patient; *it is not sufficient to appeal to a general protocol*"[1] (emphasis added).

The authors recommend examples of explicit statements of informed consent for micronutrient therapy, such as:

1. This is not an established treatment.
2. Established treatments are available.
3. Limited randomized controlled trials are available to evaluate safety or efficacy.
4. If transitioning from psychiatric drugs, the following may be expected:
    a. Potentiated psychiatric drug side effects
    b. Potentiated, protracted, or delayed drug discontinuation symptoms (including anxiety)
    c. There may be a period of some symptom relapse and situational anxiety during the transition as drug doses are tapered down.

5. Adverse effects include potential worsening of Candida infections and speculatively of other pre-existing health problems known to be highly micronutrient-dependent (eg. while micronutrients are possibly protective against de novo cancer, pre-existing cancers may thrive with the additional nutrients, including folate).
6. Nutrient interactions with psychiatric and non-psychiatric medications can occur.
7. The prescriber should be contacted when starting any new drug, especially an antibiotic.
8. Reducing or preferably stopping recreational drugs, caffeine, alcohol, smoking, and any other psychoactive substances will enhance treatment effectiveness and safety. People who ingest large amounts of these substances (e.g., four cups of coffee daily, marijuana twice weekly) are likely to notice weaker therapeutic effects of micronutrients.[1]

2.7.3 Health Professional training

Clinical experience with medication-naïve patients helps immensely in recognizing the surprisingly abundant and complex interactions between *DEN* and CNS-active medications. "It is strongly advised that clinicians obtain training and/or supervision before attempting to transition patients taking conventional psychiatric medications to broad-spectrum micronutrients."[1]

In addition to this document, the following resources offer training in micronutrient therapy with specific applicability to *DEN*:

- Chapter 6 of the American Psychiatric Association-published clinical guide *Complementary and Integrative Treatments in Psychiatric Practice*[1]
- 'Nutrition and Mental Health', a course authored by micronutrient researchers (https://education.madinamerica.com/p/nutrition-mental-health)
- Practitioners experienced with clinical *DEN* use (https://www.hardynutritionals.com/health_professional_locator)
- The Hardy Nutritionals® science team (1-855-955-1114 • www.GetHardy.com)

2.7.4 *DEN* as a first-line treatment

Given that the transition from medications to micronutrients is significantly more difficult than *DEN* therapy in medication-naïve patients, the fact that long-term outcomes of medications are often suboptimal, and also the fact that most patients consider 'natural' alternatives to medications to be potentially safer (especially for children), many patients, parents, and practitioners prefer to use *DEN* as their first-line treatment for mood disorders.

In Chapter 6 of the American Psychiatric Association-published clinical guide *Complementary and Integrative Treatments in Psychiatric Practice*, the authors conclude, "Broad-spectrum micronutrients may be comparable in efficacy to conventional medications and appear safer, so first-line use is rational if the clinical presentation is not too acute. Furthermore, just as one might introduce exercise, sleep hygiene, and dietary measures in the initial phase of intervention for some individuals, broad-spectrum micronutrients might be considered in certain cases before conventional psychopharmacotherapy."

2.8 Addressing residual symptoms

DEN doses may need to be adjusted over time according to patient response and the presence of factors that limit the effectiveness of *DEN* therapy (see 8 *Possible Limiting Factors*). Adjunct treatments may also be useful.

2.8.1 Anxiety and stress

Physical symptoms of anxiety may include light-headedness, muscle tension, and 'butterflies' in the stomach, which may be accompanied by excessive worrying, poor concentration, and distractibility. Patients who continue to experience symptoms of physical anxiety or stress while taking a therapeutic dose of *DEN* may benefit from added inositol, such as *Hardy Nutritionals® Inositol Powder*, or L-theanine.[1]

Typical dose range of inositol with micronutrients is 1,000-4,000 mg as needed up to six times daily.
Typical dose range of L-theanine with micronutrients is 200-600 mg up to four times daily.

2.8.2 Mania

Patients who continue to exhibit rage, aggression, or racing thoughts while taking a therapeutic dose of *DEN* may benefit from added choline, such as *Hardy Nutritionals® Phosphatidylcholine*.

"Lithium may be used for residual symptoms of mania; however, when combined with micronutrient formulas, the lithium dose must not exceed 25 mg daily because of the risk of marked potentiation."[1] (See 2.3 *Potentiation of psychiatric medications*).

Typical dose range of choline with micronutrients is 50-100 mg up to four times daily.

2.8.3 Depression

Residual depression may respond to 5-hydroxytryptophan (5-HTP) or S-adenosylmethionine (SAMe)[1], although when taken alongside *DEN*, much lower doses may be necessary than when these same substances are used as monotherapies. Conceptually, one might think of *DEN* potentiating 5-HTP and SAMe similarly to the interactions observed between *DEN* and CNS-active medications or other psychoactive substances (see 8.4.3 *Psychoactive supplements* and 8.4.4 *Amino acids*).

Typical dose range of 5-HTP with micronutrients is 0.01-1 mg each morning.
Typical dose range of SAMe with micronutrients is 200-400 mg each morning.

3 Clinical Pharmacology

3.1 Clinical trials

A 2011 article in *BMC Psychiatry* concluded that the predecessor formulations of *Hardy Nutritionals® Daily Essential Nutrients (DEN)* were the only complex micronutrient formulas which had been studied extensively for mental health treatment.[16] More recently, *DEN* significantly improved attention, mood dysregulation, and global functioning in "the first fully-blinded, randomized, controlled trial of medication-free children with ADHD".[17] More than 30 medical journal articles have been published on these formulations, all but two of which are peer-reviewed. The study designs employed in the published articles include controlled trials, case reports, case studies with years of historical information, database analyses, randomized controlled trials, and double-blind randomized controlled trials (see *Appendix A*).

Consistent research results have been found independently by scientists at more than a dozen institutions in several countries. None of the researchers have had financial ties to these formulations or to Hardy Nutritionals®.

Important research using *DEN* is ongoing.

3.2 Mechanism of action

The exact mechanism by which *DEN* exerts its therapeutic effect is not entirely understood. It is presumed to be linked to the various roles of vitamins and minerals in the synthesis,[18-24] neurotrophicity, and regulation[25-32] of neurotransmitters in the brain (see *Appendix G*). Clinical observations of "pervasive upregulation of CNS functions" and "[potentiation of] virtually all CNS-active drugs"[1] suggest wide-ranging holistic effects.

Genetic polymorphisms (variations) can often result in increased requirements for nutrient cofactors in enzyme pathways, and higher nutrient intakes have been shown to ameliorate the effects of many of these genetic conditions.[33-35]

In animal studies, accelerated structural and functional recovery of neurons was observed following experimentally-induced brain lesions when animals were supplemented with a predecessor formula of *DEN*.[36] Similar structural, chemical, and functional neuronal deficits exist in mood and cognitive dysregulation in humans[37-39] which would presumably respond in a similar way to *DEN* therapy.

Strong evidence exists that the nutrient density of foods for human consumption has declined over the last century, and the percentage of people who ingest the recommended intake of many of the essential nutrients is dismally low in populations consuming a "western" diet. Well-documented correlations are also emerging between human disease and the use of nutrition-compromising practices in modern agriculture.

While causation may be difficult to prove for a mechanism that spans the entire food chain, the documented clinical efficacy of essential nutrient repletion is suggestive of pervasive and insidious micronutrient insufficiency in a variety of illnesses – probably biomagnified from the soil, to microbiota, to plants, to animals, and finally to humans. Considering that a nutritionally-compromised food supply is presented to the modern human through the potential additional filter of food processing, and

considering the prevalence of poor diet and lifestyle choices, environmental exposure to harmful chemicals, and even certain medical practices that may compromise nutrient absorption and utilization (such as overuse of oral antibiotics in early childhood), the theoretical basis for supplementation of essential nutrients becomes compelling.

3.3 Pharmacodynamics

In humans, *DEN* pharmacodynamics are presumed to be a complex interaction of individual nutrient pharmacodynamics, many of which have been studied extensively.[40-45]

3.4 Absorption and metabolism

3.4.1 Systemic bioavailability

As yet, there are no publications regarding nutrient bioavailability of *DEN* after a single oral dose. As per manufacturer specifications, complete dissolution occurs in less than 8 minutes after a *DEN* capsule is fully hydrated.

It is not known to what degree food affects the systemic bioavailability of *DEN*. Although food may decrease the rate of absorption, this effect does not appear to be clinically significant. Administering *DEN* with food is recommended.

3.4.2 Metabolism

The vitamins and minerals in *DEN* are presumed to be metabolized in the same way as those in foods and similar supplements.[40-45] The complexity of *DEN* metabolism may affect medication pharmacokinetics (see 5.2 *Drug interactions* and *Appendix G*).

The effect of age upon the metabolism of *DEN* has not been systematically investigated. No unusual age-associated pattern of adverse events has been observed in children, adolescents, or the elderly.[16]

It is not known how renal or liver impairment can affect the metabolism of *DEN*.

4 Indications & Dosage

4.1 Indications

Hardy Nutritionals® Daily Essential Nutrients (DEN) is indicated for the treatment of mood and behavioral symptoms. The effect of predecessor formulations of *DEN* in the treatment of mental, emotional, and cognitive dysregulation across a wide range of central nervous system-related diagnoses* has been documented in more than 20 case-control studies, within-subject crossover case studies, open-label case series, case reports, two database analyses, and randomized controlled trials (RCTs).

Significant evidence exists to indicate that a wide range of mood, anxiety, and behavioral symptoms can result from inadequate intake of vitamins and minerals and/or poor nutrient status.[28] Pervasive improvement across such a wide range of symptoms and disorders with *DEN* therapy suggests that micronutrients may be addressing physiological root causes of central nervous system aberrations, regardless of diagnostic differentiations (see also 3.2 *Mechanism of action*).

**The following is a non-exhaustive list of diagnoses or conditions confirmed to be present among the various populations in peer-reviewed positive outcome studies (in most cases it is not known which conditions, if any, were highest represented among treatment responders): attention deficit and hyperactivity disorder (ADHD), disruptive mood dysregulation disorder, various specific phobias, social anxiety disorder (SAD), generalized anxiety disorder (GAD), obsessive compulsive disorder (OCD), separation anxiety disorder, oppositional defiant disorder (ODD), conduct disorder, learning disabilities, enuresis, encopresis, tics, Asperger's, pervasive developmental disorders (PDD) including autism and autism spectrum disorders, bipolar disorder (including sub-types), depression and dysthymic disorders (including sub-types), panic disorders, Prader-Willi syndrome, psychoses, post-traumatic stress disorder (PTSD), insomnia, stress.*

4.2 Dosage

DEN should be administered throughout the day with food. The recommended therapeutic dose is 12 capsules per day in divided doses. Four capsules taken 3 times per day is preferable, though parents limited to dosing children before and after school may choose to administer doses of 6 capsules twice daily to good effect. Both adults and children older than 6 years of age dosed at or approximately at this level of nutrient intake during clinical trials have demonstrated the most consistent and marked improvements.

4.2.1 Initial and Maintenance Dosing

A person making a drastic diet change would expect significant gastrointestinal discomfort. To avoid similar discomfort and foster optimal tolerability, the therapeutic dose of *DEN* should be reached by gradual titration over the course of 4 days, or more, if needed (see 2.1.1 *Instructions for DEN use*, and 5.1.2 *Digestive system*).

Maintenance treatment consists of whatever *DEN* dose is efficacious in maintaining symptom remission. Optimal maintenance dosage will vary with individual needs.

4.2.2 Treatment Discontinuation

Discontinuation by patients usually results from:

1. The cost of uninsured treatment (most common)
2. Inability to tolerate the transition process, usually because of drug withdrawal effects (especially when use of abusable drugs is not disclosed to the prescriber)
3. Lack of benefit
4. Inability to swallow many pills

Techniques to facilitate pill swallowing may be helpful (Kaplan et al. 2010; see also video at *http://research4kids.ucalgary.ca/pillswallowing*).[1] Rucklidge et al. employed the techniques developed by Kaplan et al. in an attempt to help 38 otherwise eligible children meet the capsule swallowing capability inclusion criterion for a double-blind study and had a success rate of nearly 50% within 2 weeks (18 children).[17]

4.2.3 Dosing young children

For children ages 6 years and younger, doses lower than 12 capsules per day are usually adequate. The following are typical therapeutic dosages of DEN for children with diagnosable psychiatric conditions, based on published research and clinical experience:

- 1-3 years: Work up to 4 capsules/day (with food).
- 4-6 years: Work up to 8 capsules/day (with food).
- 7 years and older: Work up to 12 capsules/day (with food).

Obviously, the above age ranges group children of widely varying size and metabolism, so the dosages presented here need not be viewed as strict minimums or maximums. One might better visualize a typical therapeutic dose across the age ranges presented by assigning the listed doses to 2 years, 5 years, and 7 years and interpolating between so as to create a smooth continuum of dosing recommendations for any age. As with any treatment, clinical observations should inform dosing recommendations by balancing symptom response with any emergence of side effects.

4.3 Safety

Nutrient intake from *DEN* is well within known safe intake ranges for most ingredients (see 5.1 *Side effects*), and conservative tolerable upper intake levels, extrapolated from primarily single-nutrient data,[40-45] are likely to over-estimate risk from a broad-spectrum formula such as *DEN*.

The following well-known inter-nutrient relationships illustrate the importance of balanced supplementation:

- either copper or zinc alone can induce a deficiency or the other
- supplemental vitamin B12 alone can mask a folate deficiency
- potassium without sodium will induce heart palpitations
- excessive calcium intake relative to magnesium can cause constipation, while excessive magnesium intake relative to calcium can cause diarrhea

"…single-nutrient or narrow-spectrum treatments might speculatively exert [their] deleterious effects by inducing imbalances and relative insufficiencies among micronutrients…Most adverse micronutrient effects have been associated with treatments involving three or fewer ingredients. The findings become more favorable with formulations of 10 or more micronutrients. This reinforces the principle that a full range of micronutrients is needed for optimal physiological functioning and for reducing potential drawbacks of narrow-spectrum approaches."[1]

Standard toxicology concepts were developed from the study of drugs. Although environmental chemicals may inform medication dosing strategies, they are wholly unfit for nutritional applications.

Most notable among the differences in nutrition and drug dosing paradigms is the fact that micronutrients are not foreign to the human organism; and therefore, the safest dose is not zero (i.e. the risk curve is u-shaped instead of linear or exponential when plotted against dose). In spite of food fortification programs in most jurisdictions around the world, the majority of people, even in developed nations, are likely to be more at risk due to *not* meeting recommended dietary intakes (RDI) than to be at risk due to over-intake.

Additionally, as noted above, instead of compounding risk with combined exposure, safety and dose tolerability increase when multiple micronutrients are ingested together.

Finally, physiological and metabolic demand seem to predict micronutrient dosing better than do standard toxicology models, which are based primarily on age or body weight. (For more discussion on this topic, see 8.8.4 *Developmental growth and puberty* and 8.8.5 *Physical and metabolic activity*).

4.4 Biological safety data

Biological safety data from 144 children and adults was available from eight datasets evaluating predecessor products with comparable therapeutic dosages to *DEN*. Blood was also analyzed from 93 children with ADHD taking *DEN* in a double-blind study published in 2017. In these reports, there was not a single reported occurrence of a clinically meaningful negative outcome/effect or an abnormal blood test that could be attributed to toxicity.[3,16] Testing included routine blood samples, heart rate, and blood pressure measurements.

One dataset included a full laboratory panel at baseline, completion, and at the end of open label extension. A smaller safety panel (hematology, potassium, calcium, alanine aminotransaminase, creatinine, and estimated glomerular filtration rate [eGFR]) was performed every two weeks during each study phase. For each dataset, no significant changes were noted, and all values remained within normal clinical reference ranges.[16]

After 10 weeks, data reveals only four significant differences between children taking *DEN* and children taking placebo: *DEN* users' data registered greatly increased serum vitamin B12 and folate along with decreased homocysteine and eosinophils. Copper status was among the many other measures found to be undifferentiated between the two groups.[17]

4.4.1 Interpreting clinical laboratory tests during *DEN* therapy

DEN contains sufficient supplemental biotin to interfere with many routine clinical laboratory analyses. “Biotin interference can occur in immunoassays that employ streptavidin-biotinylated antibodies when high biotin levels in blood samples, resulting from the use of oral biotin supplements, interfere with the streptavidin-biotin binding, thus distorting signal detection in these tests.”[46]

Falsely high or low results on clinical lab tests due to biotin interference have been well documented in scientific literature, but the problem often goes unsuspected – and therefore undetected – by health care professionals. “It is important for health-

care personnel to become more aware of immunoassay methods that are vulnerable to biotin interference and to consider biotin supplements as potential sources of falsely increased or decreased test results, especially in cases where a lab result does not correlate with the clinical scenario."[47]

Instructing patients to temporarily discontinue biotin supplementation to allow for biotin clearance before biological samples are collected for analysis will resolve this problem. "The take-home message, therefore, is that clinicians and researchers who order blood levels of vitamins such as Vitamin D, Vitamin B12, and folate, hormones such as thyroid hormones and thyroid-stimulating hormone, or other substances should also enquire about additional medications, including supplements, that the patient may be taking; should biotin supplementation be identified, this should be communicated to the laboratory that performs the tests. Should biotin interference be deemed likely, blood draw for the test should be deferred until after discontinuation of biotin for at least 3–7 days."[46,47]

Even when laboratory results have been confirmed trustworthy, it is worth noting that, for certain nutrients, serum levels outside of the normal reference ranges can be expected during *DEN* therapy. After all, reference ranges are most likely established using data from largely unsupplemented populations. Therefore, in the absence of a specific clinical concern, supranormal nutrient status due to supradietary intake is, by itself, no cause for alarm. For example, high vitamin B12 is considered relatively harmless if it is simply an artifact of supplementation and neither masks a folate deficiency nor presents with other known indicators of kidney malfunction. (Vitamin B12 is one of multiple B-vitamins with no evidence of toxicity and therefore no established UL.[41])

5 Side Effects & Drug Interactions

5.1 Side effects

Side-effect-free intake ranges for vitamins and minerals have been established by the United States Institute of Medicine and similar authorities around the world based on a comprehensive review of relevant data in adults and children.[40-45]

According to the intake ranges established by the Institute of Medicine, the most likely clinically relevant side-effect of therapeutic dosage of *Hardy Nutritionals® Daily Essential Nutrients (DEN)* is mild diarrhea and other mild gastrointestinal complaints in a small percentage of patients who are sensitive to therapeutic doses of magnesium.

Regarding this effect, the Institute of Medicine states, "Although a few studies have noted mild diarrhea and other mild gastrointestinal complaints in a small percentage of patients at levels of 360 to 380 mg (15.0 to 15.8 mmol) per day, it is noteworthy that many other individuals have not encountered such effects even when receiving substantially more than this [level] of supplementary magnesium."[40]

Undoubtedly the dietary context contributes to the individual variability in magnesium tolerance. *DEN* is more easily tolerated than supplemental magnesium alone at the same dose because the magnesium is in the context of other balancing minerals, including calcium, which is likely to have a constipating effect when supplemented alone.

The following treatment-emergent adverse events have been observed in patients with bipolar disorder, depression, ADHD, generalized anxiety disorder, mood lability and explosive rage, oppositional defiant disorder, Asperger syndrome, and Prader Willi syndrome:[16]

5.11 Body as a Whole

Infrequent: headache (usually transient), insomnia (usually transient)

5.12 Digestive System

Frequent: harmless change in urine color (a fluorescent yellow color due to riboflavin)

Infrequent: loose stools, nausea (both usually transient and easily managed by temporarily lowering the dose and then increasing it more gradually (see 2.1.1 *Instructions for **DEN** use*)), worsening of pre-existing Candida (yeast) infections (managed with reduced dose and adjunct antifungal therapy (see 2.6 *Managing gastrointestinal issues*))

Rare: flatulence, diarrhea, stomach ache, vomiting

5.13 Psychiatric

Rare: anxiety, agitation, insomnia, impulsivity, or depression (These may be indicative of gastrointestinal dysbiosis or unusual nutrient dependencies and may resolve with adjunct therapies. See 2.6 *Managing gastrointestinal issues* and 2.8 *Addressing residual symptoms*)

5.2 Drug interactions

5.2.1 Anticoagulant medications

DEN contains vitamin K, which promotes blood clotting function. Caution is advised when administering *DEN* to patients on warfarin-type anticoagulant therapy, as vitamin K may alter the hypoprothrombinemic response to anticoagulant drugs.

Periodic monitoring of prothrombin time is essential in determining the appropriate dosage of anticoagulant medications during *DEN* therapy. Dosage adjustments to anticoagulant medications may be required.

5.2.2 Psychoactive drugs

Strong interactions with psychoactive drugs, including lithium, have been observed in clinical experience with predecessor formulations of *DEN*. On this issue, researchers commented, "we recommend that, notwithstanding our findings of general safety of the formula when used in medication-free patients, use of multi-nutrient formulations as an adjunct should be monitored closely and with full attention to the possibility that optimum dosing of psychotropic agents may require significant adjustments."[16]

Because interactions of *DEN* with psychiatric medications have not been systematically evaluated, caution is warranted. Any agent with CNS activity has the potential to interact with *DEN* and complicate the management of micronutrient treatments. These include psychiatric medications, medical drugs with CNS actions (antihistamines, medications for 'colds', theophylline, etc.), recreational agents (alcohol, marijuana, heroin, etc.), other commonly used substances that are not necessarily thought of as recreational agents (caffeine, nicotine), and certain hormones (e.g. levothyroxine, glucocorticoids).[3]

5.2.2.1 Rapidly Emergent Interactions

Rapidly emergent medication interactions with *DEN* appear to occur mainly with medications whose absorption or excretion is directly affected by essential nutrients. For example, the absorption of many stimulants is enhanced by calcium and magnesium.[48]

Other relatively rapid medication interactions with DEN have been observed clinically in patients who metabolize the interacting medications slowly, or who are already experiencing a significant burden of medication side effects when they begin *DEN* therapy. Generally, these interactions manifest as a marked increase in known medication side effects.

5.2.2.2 Gradual Interactions

Gradually emergent medication interactions with *DEN* occur with a wide variety of medications. These gradual interactions generally manifest over a period of several weeks as an increase in the number and/or intensity of known medication side effects.

One partial explanation for these interactions is that over time, the vitamins and minerals in *DEN* boost key outputs of under-functioning biochemical pathways by serving as natural, essential cofactors to numerous enzymes (see *Appendix G*). As these key outputs become more optimized, the need for biochemical manipu-

lation by medications is reduced, and previously ideal medication dosages begin to result in overmedication effects. Gradual reductions in medication doses over time, as overmedication effects become apparent, can resolve these overmedication effects (see 2.3 *Potentiation of psychiatric medications*).

Another partial explanation for these gradual interactions is that some of the nutrients in *DEN*, including vitamin A, vitamin D, vitamin B6, niacinamide, zinc, copper, acetyl-L-carnitine, and ginkgo biloba, serve as substrates for cytochrome p450 (CYP) enzymes or cause CYP enzyme inhibition (see *Appendix F*).

DEN potentiates lithium much more powerfully than other psychoactive medications, presumably because lithium is metabolized differently than other central nervous system (CNS)-active medications. Treatment guidelines for patients taking lithium are found in 2.3 *Potentiation of psychiatric medications*.

6 Warnings & Precautions

6.1 Warnings

All patient medication doses should be monitored by a physician while taking *Hardy Nutritionals® Daily Essential Nutrients (DEN)*. Research indicates that psychoactive drugs may need to be gradually reduced or eliminated during nutrient therapy to avoid over-medication effects, with the recognition that abrupt medication discontinuation can be associated with adverse symptoms (see 5.2 *Drug interactions* and 2.3 *Potentiation of psychiatric medications*).

6.2 Precautions

6.2.1 Citrus bioflavonoids

Patients who are currently taking a citrus bioflavonoid-containing supplement and are currently taking or have recently taken psychoactive medication(s) should reduce the dose of citrus bioflavonoids gradually during DEN therapy in order to minimize medication withdrawal effects resulting from reductions in CYP enzyme-mediated drug potentiation caused by citrus bioflavonoids.

6.2.2 Clinical worsening

Patients being treated for any indication should be monitored closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of therapy and at times of dose changes (either increases or decreases) in *DEN* or medications. Patients and/or caregivers should promptly report any adverse symptoms to a health professional, as medication dose changes may be required (see 8.1 *Psychiatric medication,* 2.3 *Potentiation of psychiatric medications,* and 2.4 *Clinical response – CNS drug use*).

6.2.3 Iron

Although *DEN* contains a relatively low level of iron (about 1 mg per capsule), children should take *DEN* only under adult supervision. In cases documented by US Poison Control Centers, children who have died from iron supplements have taken more than 60 mg of iron/kg (27.2 mg of iron/lb) of body weight.

7 Overdose & Contraindications

7.1 Overdose

7.1.1 Human experience

No cases of overdose with *Hardy Nutritionals® Daily Essential Nutrients (DEN)* have been documented.

7.1.2 Management of overdose

Treatment should consist of general measures employed in the management of overdose with similar nutritional supplements.

7.2 Contraindications

Treatment with *DEN* should not be introduced if the patient is diagnosed with a condition where specific nutritional factors are contraindicated, or if the patient has known hypersensitivity or allergy to any ingredients of *DEN*.

7.2.1 Strict contraindications

- Wilson disease (risk of copper overload)
- Hemochromatosis and hemosiderosis (risk of iron overload)
- Trimethylaminuria (risk of choline overload)

7.2.2 Relative contraindications

- Inability to reduce recreational drug use, including high intake of caffeine, alcohol, and nicotine
- Recent use of medical drugs with withdrawal syndromes
- Legally or medically required treatment with CNS-active agents
- Treatment-resistant *Candida*/microflora imbalance
- Severe hyperlipidemia, or severe protein malnutrition (which are associated with increased susceptibility to vitamin A toxicity)
- Alcohol related liver or renal disease
- Confirmed malignant cancer of any type

8 Possible Limiting Factors

Since 1996, we have observed that various factors can significantly limit responses to nutrient therapy. Recognizing these factors and taking appropriate steps can make a significant difference to *Hardy Nutritionals® Daily Essential Nutrients (DEN)* treatment response.

8.1 Psychiatric medications

Changing psychiatric medications inappropriately during *DEN* therapy can be a significant limiting factor. Improper medication dosages can lead to fluctuations in brain chemistry that complicate symptom management.

8.1.1 Discontinuation

Gradually tapering off psychiatric medications generally provides the greatest stability for patients during treatment with *DEN*. Abrupt discontinuation of any psychiatric medication is not recommended (see 2.4 *Clinical response – CNS drug use)*.

Reducing psychiatric medications as needed when overmedication effects increase should prevent pronounced discontinuation symptoms as well as rebound (a significant return of the original symptoms). The rate at which medications are terminated and the duration of the pharmacological treatment are key factors that influence discontinuation symptoms. Discontinuation effects are typically more acute with drugs that have a relatively short half-life.

8.1.2 Increasing dose

Increasing psychiatric medication dosages while using *DEN* may increase the possibility of drug-nutrient interactions (see 5.2.2 *Psychoactive drugs*).

8.2 Non-psychiatric medications

Worsening of symptoms has been observed when various non-psychiatric medications have been used together with *DEN*. These effects have been most pronounced with the following medications:

8.2.1 Anesthetics

Anesthetics have potential interactions with *DEN* due to their potential psychiatric effects. Psychiatric medication status is an important consideration in the management of the patient about to undergo anesthesia and surgery.[49-51] For example, benzodiazepines are commonly administered for many surgical procedures to sedate and relax patients. Anesthetic use may be considered increasing or changing medications (see 8.1 *Psychiatric medications*).

Some unmedicated individuals taking *DEN* have reported withdrawal or post-withdrawal symptoms following surgery which have responded to standard post-withdrawal drug symptom alleviation measures (see 8.6.3 *Prior psychiatric drug use*).

8.2.2 Antacids

Antacids (such as Zantac, Prilosec, Tagamet, etc.) neutralize or inhibit the production of stomach acid which is necessary for digestion. Acidic denaturation is a major step in the process of extracting food-bound nutrients. Inhibiting this step of the digestive process can reduce the bioavailability of critical nutrients during the absorption phase.

Chronic antacid use may also induce dysbiosis of gut microbiota in the form of small intestinal bacterial overgrowth (SIBO), which can negatively affect the response to micronutrient therapy.

8.2.3 Antibiotics

Antibiotics have saved countless lives, but the dangers of overuse are becoming increasingly well-documented and widely recognized. For example, oral antibiotics may vastly impact beneficial gut microflora in addition to the pathogenic target species, resulting in reduced nutrient absorption (and for some vitamins, reduced synthesis), depression, anxiety, and other effects.[52,53]

"Oral antibiotic and antifungal treatments usually require an adjustment in micronutrient dosing. The intestinal microbiome is crucially involved in micronutrient absorption (and for some vitamins, synthesis), so antibiotics sharply reduce nutrient absorption and can lead to a return of psychiatric symptoms. This problem is avoided by increasing the micronutrient dose by 40%-50% during the antibiotic therapy plus 4 additional days. For chronic antibiotic treatment (e.g., acne), the micronutrient dose can be adjusted around the antibiotic dose."[1]

Worsening of psychiatric symptoms has not been observed with intravenous antibiotics, suggesting that this antibiotic effect occurs in the gastrointestinal tract.

Adding a probiotic-prebiotic combination such as *Hardy Nutritionals® Greens & Probiotics* during the course of antibiotic treatment (taken between antibiotic doses), plus at least one to two weeks after completion, is also recommended.

A natural antibiotic/anti-fungal agent may sometimes also be indicated during and shortly after the antibiotic treatment, especially if the individual has a history of fungal/microbial infections. Possibilities include olive leaf extract (such as *Hardy Nutritionals® Olive Leaf Extract*), caprylic acid, garlic capsules, and oil of oregano.

8.2.4 Antihistamines

Clinically significant increases in psychiatric symptoms have been observed when some individuals have used certain antihistamines and related drugs (e.g. Zyrtec, Benadryl, etc.) together with *DEN*.

8.2.5 Contraceptives

Hormone-containing contraceptives may worsen depression, alter mood, and/or increase nervousness and irritability. Cautious use is warranted.

8.2.6 Hormone replacement therapy (HRT), including thyroid hormones

HRT may worsen depression, alter mood, and/or increase nervousness and irritability. Cautious use is warranted.

Thyroid hormone therapy can cause strong interactions with *DEN*. Iodine, selenium, and other supportive nutrients boost endogenous thyroid function and peripheral thyroid hormone metabolism. This often necessitates a dose reduction of prescription thyroid hormone to avoid potentiated side effects. Levothyroxine absorption is also known to be enhanced by calcium, further magnifying the interaction.

As micronutrients are implicated in the conversion of thyroxine to its various forms as well as in its production, a full thyroid panel should be used to evaluate oral thyroid hormone dosing during *DEN* therapy, including all of the following tests: TSH, Free T3, Reverse T3, Total T3, Free T4, Thyroid antibodies, Sex hormone binding globulin. However, *DEN* supplementation should be discontinued temporarily as per lab protocols before biological samples are taken, or the lab test results may turn out to be misleading due to biotin interference (see 4.4.1 *Interpreting clinical laboratory tests during DEN therapy*).

8.2.7 Opioid Analgesics

Individuals taking opioid analgesics may experience an increase in opioid side effects while taking *DEN*, perhaps as a result of cytochrome p450 enzyme interaction effects (see 5.2.2 *Psychoactive drugs* and *Appendix F*).

8.3 Recreational drugs

Recreational substances (including, but not limited to caffeine, marijuana, alcohol and nicotine) cause psychotropic effects, and their interactions with *DEN* may cause mood and mind-altering effects.[1] Keep in mind that many individuals who are addicted to substances may try to conceal their addictive behaviors, and a patient's lack of progress or unexplained symptoms may be the result of consuming these substances. Specialized nutrient therapy has been used to successfully treat addictions.[54]

8.4 Supplements

8.4.1 Vitamins

Although taking extra vitamins while taking *DEN* is not usually necessary, adding individual vitamins for specific clinical purposes may be useful (see 2.8 *Addressing residual symptoms*). For example, where long-standing, specific vitamin deficiencies or genetic conditions predisposing individuals to higher vitamin needs exist, it may be necessary to add therapeutic amounts of specific vitamins in order to optimize clinical response to *DEN*.

8.4.2 Minerals

Although taking extra minerals while taking *DEN* is not usually necessary, adding individual minerals for specific clinical purposes may be useful (see 2.8 *Addressing residual symptoms*). Generally, we recommend that the minerals copper, zinc, calcium and magnesium should not be added to *DEN* therapy, as they can alter critical mineral balances of the *DEN* formulation and render it less effective. Additional iron may be added to *DEN* while still remaining well within recommended intake levels.

8.4.3 Psychoactive supplements

Any psychoactive supplement has the potential to interfere with *DEN* effects. These include (but are not limited to) St. John's wort, ginseng, kava kava, skullcap, valerian root, and certain modified amino acids such as S-adenosyl methionine (SAMe) and 5-hydroxytryptophan (5-HTP). If patients choose to use psychoactive supplements during *DEN* therapy, advise cautious dosing and monitor their responses carefully.

8.4.4 Amino acids

Caution is advised with the use of psychoactive amino acids and metabolites. These include, but are not limited to, S-adenosyl methionine (SAMe), 5-hydroxytrypto-

phan (5-HTP), phenyl-GABA, and N-acetyl cysteine. Typical dose-response relationships of amino acids and amino acid metabolites can be expected to become dramatically more sensitive in the context of *DEN* therapy, as *DEN* provides the micronutrients involved in the endogenous function of the implicated pathways. Extensive clinical experience has shown that a balanced combination of amino acids, such as *Hardy Nutritionals® Balanced Free-Form Aminos*, is better tolerated long-term than isolated amino acids which target only one neurotransmitter pathway.

8.4.5 Fatty acids

DEN provides all the vitamin and mineral cofactors required by elongation and desaturation enzymes in the endogenous production of beneficial long-chain fatty acids. As a result, individuals with adequate intake of essential fats may have less need for supplemental fatty acids. Nevertheless, while taking *DEN*, some individuals report enhanced mental clarity and focus from omega-3 supplements such as *Hardy Nutritionals® Essential Omegas*, especially in the beginning stages of *DEN* therapy.

8.5 Gastrointestinal problems

Impaired digestive health can reduce the absorption of essential vitamins and minerals. Bowel disorders are strongly correlated with psychiatric conditions.[4,5] If bowel dysfunction is an issue, whole foods and probiotics are often useful. Adequate hydration and a healthy diet with plenty of fiber from fruit and vegetables prevent many problems.

8.5.1 Bowel disorders

Irritation and inflammation of the intestinal lining is a common occurrence in chronic bowel disorders. These disorders may improve in time while using *DEN* but can significantly reduce the absorption of key nutritional elements until they are corrected. Restriction diets, probiotics, digestive enzymes, fatty acids, and various other supplements may be beneficial in restoring and maintaining more normal bowel function (see 2.6 *Managing gastrointestinal issues*).

8.5.2 Constipation

Constipation, regardless of its cause, can be a critical limiting factor of *DEN* treatment by severely reducing absorption of essential vitamins and minerals. Depending on the cause of constipation, different measures may be appropriate to rectify the problem according to clinical judgment.

Treatment experience with *DEN* has shown that a few simple measures can often help constipation. Adequate hydration is essential. Fiber-rich whole foods like prunes, raw fruits and vegetables often help. In addition, patients with constipation often benefit long-term from a probiotic-prebiotic combination such as *Hardy Nutritionals® Greens & Probiotics*, which can help restore intestinal microflora balance.

8.5.3 Diarrhea

Diarrhea, regardless of its cause, can severely limit the effectiveness of *DEN* treatment by preventing absorption of essential vitamins and minerals. Depending on the cause of diarrhea, different measures may be appropriate to rectify the problem according to clinical judgment.

Treatment experience with *DEN* has shown that certain foods like unripe bananas, peanut butter, and cheddar cheese often help rectify diarrhea related to initiating nutrient therapy. In addition, many patients with chronic diarrhea benefit long-term from a probiotic-prebiotic combination such as *Hardy Nutritionals® Greens & Probiotics*, which can help restore intestinal microflora balance.

8.5.4 Parasites

Parasites rob their hosts of nutrients and may even induce relative nutrient imbalances, creating unique requirements for select nutrients.

The fact that parasites significantly contribute to malnutrition worldwide is widely recognized, but this problem is rarely suspected in parts of the world with considerable access to clean water, hygienic living conditions, and sanitary food production. However, many vectors for parasite transmission, such as pets, biting insects, and even soil, are common to all areas of the world. At best, essential nutrients will return suboptimal outcomes when one or more parasites are present, and at worst, micronutrients may fuel the infection.

If the response to *DEN* is poor, screening for parasites is recommended as part of a thorough evaluation of all the potential treatment-limiting factors. Invariably, a dramatically improved response to *DEN* is seen after any interfering parasites are successfully treated.

8.5.5 Microflora imbalance (dysbiosis)

Factors such as antibiotic use, infections, environmental chemicals, and diet patterns may diminish the population of beneficial microorganisms naturally present in the human gastrointestinal ecosystem relative to the other species. Restorative measures should be taken to ensure optimal tolerability and bioavailability of micronutrient treatments.

A probiotic-prebiotic combination product, such as *Hardy Nutritionals® Greens & Probiotics*, may be beneficial in restoring healthy gut function in individuals with mild microflora imbalance.

If this is not sufficient and symptoms do not improve, then a natural antibiotic/antifungal agent, such as *Hardy Nutritionals® Olive Leaf Extract*, may be warranted. In particular, patients with a history of extensive or chronic antibiotic use are often highly susceptible to severe microflora imbalances (see *Appendix B*).

Note: Antibiotic/antifungal agents may cause a die-off response, known as the Herxheimer reaction, which presents as flu-like symptoms and can arise any time from the first day to the first couple of weeks after beginning to take the product. If vomiting occurs, reduce the dosage or introduce an alternate antibiotic/antifungal agent (e.g. caprylic acid, garlic capsules, or oil of oregano). Changing antibiotic/anti-fungal products periodically may prevent organisms from adjusting to a single agent. If there is no Herxheimer reaction, complete the course at recommended levels.

8.6 Patient history

8.6.1 Antibiotic use

Oral antibiotic use can negatively impact beneficial intestinal microflora. If an individual has had a lengthy history of oral antibiotic use, particularly as a child, a probiotic-prebiotic combination, such as *Hardy Nutritionals® Greens & Probiotics,* which promotes a robust and diverse microbiome, is recommended. Normally, probiotics do not need to be taken on a continual basis for longer than a year. Once the probiotic has had its effect, it may only need to be taken periodically thereafter.

If symptoms do not improve with probiotic use, additional measures may be needed (see 8.5.4 *Parasites).*

8.6.2 Genetic factors

Excepting cases in which *DEN* is contraindicated (see 7.2 *Contraindications*), it is generally well-tolerated by individuals with genetic polymorphisms known to affect nutritional status and/or mood regulation (i.e. COMT, MTHFR, etc.). Some individuals with MTHFR polymorphisms report extreme dose sensitivity to methylfolate supplementation. Such individuals may benefit from supplemental niacin in addition to *DEN*, with dosing determined on a case by case basis (see *Appendix E*).

8.6.3 Prior psychiatric drug use

Post-withdrawal medication symptoms may be a result of the metabolism of drug residues stored in poorly perfused tissues, as they are often triggered by such things as physical exertion, weight loss, stress, prolonged exposure to sun or heat, and liver or bowel cleanses. To a lesser extent, post-withdrawal drug symptoms may also be triggered by massage, chiropractic, or acupuncture therapies (see 8.7 *Lifestyle factors*).

Residual medication-related symptoms can appear months, and in some cases, even years, after psychiatric medications have been discontinued.[56,57] Individuals often report that they feel medicated again despite having taken no medication recently.

Post-withdrawal symptoms are often mistaken for a return of psychiatric symptoms. Some post-withdrawal medication symptoms include insomnia, anxiety, depression, crying spells, agitation, and irritability.

Suggestions for treatment of post-withdrawal drug symptoms include avoiding or moderating 'trigger' activities and/or temporarily adding protein isolate to the patient's treatment regimen. Additional vitamin C (particularly liposomal vitamin C), taken on an as-needed basis, may also provide significant and rapid relief (see 2.3.2 *Managing post-withdrawal medication effects*).

8.6.4 Sensitivities

Sensitive individuals may require and/or tolerate lower doses of *DEN*. Sensitive individuals may be identified by their history or by low medication tolerance. They may become restless, agitated, irritable, or have some other anomalous response within hours or days of starting micronutrient products. Often, so-called sensitivities turn out to be attributable to nothing more than medication interactions, gastrointestinal microflora dysbiosis, or some other treatment-limiting factor identified in this document.

8.6.5 Special nutrient needs

Where long-standing specific vitamin or mineral deficiencies exist, including genetic conditions that predispose individuals to higher vitamin or mineral needs, it may be necessary to add therapeutic amounts of specific vitamins or minerals in order to optimize therapeutic response.

8.6.6 Electroconvulsive therapy (ECT)

A history of ECT may result in a slower response time and/or a reduced likelihood of complete response to micronutrient therapy.

8.6.7 Brain trauma & neurodegenerative disease

A history of brain trauma or the presence of advanced neurodegenerative disease may result in a slower response time and/or a reduced likelihood of complete response to micronutrient therapy.

8.7 Lifestyle factors

8.7.1 Heat

Acute heat loading is common in everyday situations such as physical exercise or work in a hot climate. Other forms of heat exposure can include hot tubs, steam baths, saunas, prolonged sunbathing, etc. Drug kinetics and dynamics may become altered as a result of physiological responses in persons exposed to heat.[58]

Possible increases in the rate of chemical reaction and drug metabolism may affect the activity of many drugs. Individuals who are not acclimatized to heat may be hypersensitive to these actions. A possible decrease in the glomerular filtration rate may decrease the clearance of drugs and metabolites, increasing drug activity and the probability of toxicity.[59,60]

Heat-intensive activities have been reported to induce an overmedicated feeling in those who have long since discontinued medications, perhaps due to metabolism of drug residues stored in poorly perfused tissues. For measures that may alleviate post-withdrawal drug symptoms, see 8.6.3 *Prior psychiatric drug use*.

8.7.2 Diet

DEN is designed to add vitamin and mineral density to an existing diet. Thus, it is still very important for patients to eat regular, well-balanced meals each day. There are many important nutritional factors that are best obtained from whole foods. Individuals taking *DEN* should avoid diet extremes and over-consumption of refined foods, especially if they are susceptible to gastrointestinal microflora imbalance (see *8.5.5 Microflora imbalance (dysbiosis)).*

8.7.3 Sleep

Adequate sleep is a significant factor in psychiatric health. Poor sleep quality and/or sleeplessness significantly exacerbate mania, psychosis, stress, and anxiety. While micronutrient therapy usually promotes more restful sleep, doses of *DEN* late in the day (after 6 pm) may contribute to wakefulness in some people.

In some cases, poor sleep may be a result of overmedication effects due to nutrient-medication interactions (see 5.2 *Drug interactions* and 8.6.3 *Prior psychiatric drug use*).

8.7.4 Hydration

Inadequate hydration can compromise gut health, psychiatric health, and overall health. Based on 'Adequate Intake' levels for daily water needs, as established by the US Institute of Medicine, adequate fluid intake ranges from about 5 cups (1.2 L) per day for children ages 4-8 to about 9 cups (2.2 L) per day for women and about 13 cups (3.0 L) for men, in addition to water obtained from foods. Pregnancy and lactation, as well as physical activity, climate and diet can increase individual water needs.[61] Adequate hydration is essential for moving nutrients into cells and flushing wastes out of the body.

8.7.5 Non-compliance

Inconsistent or “as needed” dosing of *DEN* is not recommended. Clinical results with micronutrient therapy are often achieved gradually over time, and regular, steady dosing is critical to achieve the best results. It may be helpful to think of *DEN* as food for a starving brain. Non-compliance may indicate that the individual may require additional education and/or assistance.

8.7.6 Physical activity

Healthy physical activity is rightfully encouraged by almost every source of health education. However, intense physical exercise has been reported to induce an over-medicated feeling in those who have long since discontinued medications, perhaps due to metabolism of drug residues stored in poorly perfused tissues. For measures that may alleviate post-withdrawal drug effects, see 8.6.3 *Prior psychiatric drug use*.

The effects of exercise on drug distribution are complex. Physical exercise, particularly when a person is not accustomed to it, may affect drug kinetics and dynamics. Exercise or physical work increases the rate and depth of respiration and increases muscular blood flow. Temporary reduction in blood flow to adipose and other inactive tissues may delay the distribution of some drugs that have been stored by these tissues. Lipids released for metabolic purposes may increase the distribution of drugs stored in adipose tissues. Renal plasma flow, urine excretion rate, and urine pH are reduced by exercise, causing an increase in the serum levels of drugs eliminated through the kidneys.[62,63]

8.7.7 Weight loss

Weight loss can trigger post-withdrawal drug effects, presumably by facilitating the release of medication residues stored in poorly perfused tissues (related to 8.7.6 *Physical activity,* above). For measures that may alleviate post-withdrawal drug symptoms, see 8.6.3 *Prior psychiatric drug use*.

8.8 Physical health and life stage factors

8.8.1 Menstrual cycle

Psychiatric symptoms may increase during menstruation. In part, this is likely due to changing hormone levels and increasing nutrient demands. Should additional symptoms become apparent during this time, it may be beneficial to increase *DEN* by at least one full dose of 4 capsules/day for about one week. In subsequent cycles, taking the additional *DEN* starting a few days prior to menstruation through to its completion may be preventative.

8.8.2 Physical illness

Additional *DEN* may be beneficial when a person becomes ill with a cold, flu, or other illness. Recurrent illness and infections are a sign of a weakened immune system. Increasing *DEN* by 4 capsules daily to support the immune system through the illness may lead to faster recovery.

8.8.3 Pregnancy and lactation

Nutritional requirements are significantly increased during pregnancy and lactation. The daily dose of *DEN* should be increased at least in relative proportion to daily caloric intake, particularly in individuals with psychiatric symptoms. An additional dose of 4 *DEN* capsules per day may be useful.

8.8.4 Developmental growth and puberty

Significant hormonal changes accompany puberty and growth spurts (adolescent or childhood), and the body's nutritional demands are often significantly increased during these times – a fact often evidenced by dramatic increases in appetite. To visualize the reality that metabolic demand for micronutrients is not strictly dependent on age or weight, consider that compared with an adult of average body weight, a teenager of equal weight may eat twice as much! Similarly, a small child may eat at least twice as much as an adult relative to body weight.

The onset of many psychiatric symptoms often corresponds with pubescence. For this reason, as well as to meet increased nutrient needs for growth and metabolism, additional *DEN* may be beneficial during this time.

8.8.5 Physical and metabolic activity

Physical activity significantly increases the need for essential nutrients in humans and in animals. For example, draft horses have significantly higher nutrient needs when working compared with when they are idle.[64] The same is true for human performance.[65]

9 Appendices

Appendix A

- Rucklidge JJ, Eggleston MJF, Johnstone JM, Darling K, Frampton CM. Vitamin-mineral treatment improves aggression and emotional regulation in children with ADHD: a fully blinded, randomized, placebo-controlled trial. *J Child Psychol Psychiatry*. 2018 Mar;59(3):232-246.
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Appendix B

While it does not always accurately predict the need for adjunct gastrointestinal health products, the following evaluation may be insightful. It can also be conveniently taken online at: https://www.hardynutritionals.com/microflora_questionnaire

Microflora Balance Questionnaire

Section A: History

Circle the score to the right of each question when a response is "yes", then total the circled numbers and write the total at the bottom of the section.

1. Have you taken tetracycline (Sumycin®, Panmycin®, Vibramycin®, Minocin®, etc.) or other antibiotics for acne for one month or longer? **25**
2. Have you, at any time in your life, taken other "broad spectrum" antibiotics for respiratory, urinary, or other infections for two months or longer, or for shorter periods four or more times in a one-year span?. **20**
3. Have you recently taken a broad spectrum antibiotic drug? **6**
4. Have you taken prednisone, Decadron® or other cortisone-type drugs by mouth or inhalation...
   - for more than two weeks? **15**
   - for two weeks or less?. **6**
5. If you have ever had thrush, athlete's foot, ringworm, jock itch, or other chronic fungus infections of the skin or nails, have such infections been...
   - severe or persistent? **20**
   - mild or moderate?. **10**
6. Do you crave sugar/ sweets? **10**
7. Do you crave breads? **10**
8. Do you crave alcoholic beverages? **10**

Section A: Total Score _____

Section B: Secondary Indicators

For each symptom that is present, enter the appropriate number in the Point Score column:

- *If a symptom is occasional or mild:* . . . . . 3 points
- *If a symptom is frequent or moderately severe:* . . . . . 6 points
- *If a symptom is severe and/or disabling:* . . . . . 9 points

Total the scores for this section and record them at the end of this section.

Fatigue or lethargy . . . . . ____

Feeling of being "drained" . . . . . ____

Drowsiness . . . . . ____

Feeling "foggy" or "spacey" . . . . . ____

Inability to make decisions. . . . . ____

Inability to concentrate . . . . . ____

Poor memory . . . . . ____

Frequent mood swings . . . . . ____

Attacks of anxiety or crying . . . . . ____

Headaches. . . . . ____

Abdominal pain . . . . . ____

Constipation. . . . . ____

Diarrhea . . . . . ____

Bloating, belching or intestinal gas . . . . . ____

Indigestion or heartburn . . . . . ____

Chronic rashes or itching . . . . . ____

Psoriasis or recurrent hives . . . . . ____

Rectal itching . . . . . ____

Section B: Total Score _____

Section C: Minor Indicators

For each symptom that is present, enter the appropriate number in the Point Score column:

- *If a symptom is occasional or mild:* . . . . . 1 points
- *If a symptom is frequent or moderately severe:* . . . . . 3 points
- *If a symptom is severe and/or disabling:* . . . . . 5 points

Total the scores for this section and record them at the end of this section.

Irritability or jitteriness . . . . . ____

Dizziness/loss of balance . . . . . ____

Pressure above eyes or in ears…feeling of head swelling . . . . . ____

Tendency to bruise easily . . . . . ____

Food sensitivity or intolerance . . . . . ____

Dry mouth or throat . . . . . ____

Bad breath. . . . . ____

Foot, hair or body odor not relieved by washing. . . . . ____

Nasal congestion or post-nasal drip . . . . . ____

Nasal itching . . . . . ____

Sore throat . . . . . ____

Laryngitis, loss of voice . . . . . ____

Cough or recurrent bronchitis . . . . . ____

Burning or tearing of eyes . . . . . ____

Recurrent infections or fluid in ears . . . . . ____

Ear pain or deafness . . . . . ____

Numbness, burning or tingling . . . . . ____

Muscle aches . . . . . ____

Muscle weakness or paralysis . . . . . ____

Pain and/or swelling in joints . . . . . ____

Impotence . . . . . ____

Urinary frequency, urgency or incontinence . . . . . ____

Burning on urination . . . . . ____

Loss of sexual desire or feeling . . . . . ____

Section C: Total Score _____

Female-Specific History

Questions 1-3 circle the score, 4-7 use scoring points below:

- *If a symptom is occasional or mild:* . . . . . 3 points
- *If a symptom is frequent or moderately severe:* . . . . . 6 points
- *If a symptom is severe and/or disabling:* . . . . . 9 points

Total the scores for this section and record them at the end of this section.

1. Have you at any time in your life, been bothered by persistent vaginitis or other problems affecting your reproductive organs? **25**
2. Have you been pregnant…
   - 2 or more times? **5**
   - 1 time? **3**
3. Have you taken birth control pills for…
   - more than 2 years? **15**
   - 6 months to 2 years? **6**
4. Do you experience troublesome vaginal burning, itching or discharge? . . . . . ____
5. Do you experience endometriosis or infertility? . . . . . ____
6. Do you experience severe cramps and/or other menstrual irregularities? . . . . . ____
7. Do you experience premenstrual tension? . . . . . ____

Female-Specific History Score _____

Combined Score

Section A: _____ /116

Section B: _____ /162

Section C: _____ /120

Female-specific: _____ /81

Total Score: _____

Women	Men		Recommendation
0-90	0-78	Unlikely an issue	
90-229	78-196	Possibly present	Probiotic
229-479	196-398	Likely present	OLE + Probiotic

Microflora Balance Questionnaire for Children

Intended for children eight years and under
Source: Dr. William Crook

Points

1. During the two years before your child was born, were you bothered by recurrent vaginitis, menstrual irregularities, premenstrual tension, fatigue, headache, depression, digestive disorders or "feeling bad all over?" (30 points) ____

2. Was your child bothered by thrush (white coating on tongue or lips)? (Score 10 if mild, score 20 if severe) ____

3. Was your child bothered by frequent diaper rashes in infancy? (Score 10 if mild, score 20 if severe or persistent) ____

4. In infancy, was your child bothered by colic/irritability lasting over three months? (Score 10 if mild, score 20 if moderate to severe) ____

5. Are his/her symptoms worse on damp days or in damp or moldy places? (20 points) ____

6. Has your child had recurrent or persistent "athlete's foot" or chronic fungus infections on skin or nails? (30 points) ____

7. Has your child been bothered by recurrent hives, eczema or other skin problems? (10 points) ____

8. Has your child received:
   a. Four or more courses of antibiotic drugs during the past year? Or has he/she received continuous "prophylactic" courses of antibiotic drugs? (60 points) ____

   b. Eight or more courses of "broad spectrum" antibiotics (such as amoxicillin, Keflex, Septr, Bactrim or Ceclor) during the past three years? (40 points) ____

9. Has your child experienced recurrent ear problems? (20 points) ____

10. Has your child had tubes inserted in his/her ears? (10 points) ____

11. Has your child been labeled "hyperactive"? (Score 10 if mild, score 20 if moderate to severe) ____

12. Is your child bothered by learning problems (even though early development history was normal)? (10 points) ____

13. Does your child have a short attention span? (10 points) ____

14. Is your child persistently irritable, unhappy and hard to please? (10 points) ____

15. Has your child been bothered by persistent or recurrent digestive problems, including constipation, diarrhea, bloating, or excessive gas? (Score 10 if mild; score 20 if moderate; score 30 if severe) ____

16. Has your child been bothered by persistent nasal congestion, cough and/or wheezing? (10 points) ____

17. Is your child unusually tired or unhappy or depressed? (Score 10 if mild, score 20 if severe) ____

18. Has your child been bothered by recurrent headaches, abdominal pain, or muscle aches? (Score 10 if mild, score 20 if severe) ____

19. Does your child crave sweets? (10 points) ____

20. Does exposure to perfume, insecticides, gas or other chemicals provoke moderate to severe symptoms? (30 points) ____

21. Does tobacco smoke unusually bother him/her? (20 points) ____

22. Do you feel that your child isn't well, although diagnostic tests and studies haven't revealed the cause? (10 points) ____

Total the Score _____

0-50 unlikely a factor
60-100 possibly a factor
100-140 likely a factor

Appendix C

Possible Therapeutic Mechanisms of Supplemental Free-Form Amino Acids

- Affect drug distribution and binding
- Facilitate neurotransmitter synthesis and function in the brain
- Replete conditionally essential AAs depleted in stress conditions
- Facilitate repair of cellular infrastructure

Affect drug distribution and binding

Summary

Intake of amino acids leads to increased serum amino acids and proteins, which in turn lead to increased drug binding and reduced pharmacological effects.

Explanation

In the bloodstream, drugs are transported partly in solution as free (unbound) drug and partly as drug reversibly bound to blood components, including albumin, other serum proteins, free amino acids, and blood cells. Only unbound drug, which is available for passive diffusion to extravascular tissue, is thought to be responsible for drug concentration at the active site and, therefore, for the pharmacological effects. Dietary protein (including **Hardy Nutritionals™ Balanced Free Form Amino Acids**) stimulates albumin production and increases free amino acids in the serum, both of which interact with drugs in solution, increasing the bound drug fraction.

Beers MH, Editor. *Merck manual of diagnosis and therapy*. 17th Ed. Whitehouse Station N.J. 1999.

http://www.merckmanuals.com/professional/clinical-pharmacology/pharmacokinetics/overview-of-pharmacokinetics 2017 Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. Accessed 05 October 2017.

Supporting Evidence

"The protein component of the meal was sufficient to stimulate albumin synthesis in both the elderly (147 +/- 14 mg . kg body wt(-1) . d(-1)) and the young."

"Elderly subjects have lower rates of albumin synthesis than do young subjects during fasting, but they stimulate albumin synthesis proportionately in response to the oral ingestion of protein. The intakes of additional fat and carbohydrate do not stimulate albumin synthesis further."

Caso G, Feiner J, Mileva I, Bryan LJ, Kelly P, Autio K, Gelato MC, McNurlan MA. Response of albumin synthesis to oral nutrients in young and elderly subjects. *Am J Clin Nutr*. 2007 Feb;85(2):446-51.

"Recent research documents that albumin synthesis rate is influenced comparably in younger and older adults by dietary protein ingestion and changes in dietary protein quantity. This emphasizes the importance for all adults to consume an adequate amount of dietary protein."

Thalacker-Mercer AE, Campbell WW. Dietary protein intake affects albumin fractional synthesis rate in younger and older adults equally. *Nutr Rev*. 2008 Feb;66(2):91-5.

"When solutions of the amino acids are mixed with solutions of the drugs, characteristic changes in electronic spectra are observed … suggesting that intermolecular complexes are formed."

Samarskii V.A. Donor-acceptor interactions of pilocarpine and atropine with amino acids. *Pharm Chem J*. 1996 Feb; 30(2):72-73.

Facilitate neurotransmitter (NT) synthesis and function in the brain

Summary

Intake of amino acids leads to increased neurotransmitter synthesis, neurotransmitter activity, or signal sensitization.

Explanation

Neurotransmitter/Receptor	Amino Acid Precursor/Modulator
Serotonin, melatonin	L-Tryptophan
Dopamine, Norepinephrine, Epinephrine (catecholamines)	L-Tyrosine, L-Phenylalanine
Histamine	L-Histidine
Unaltered AAs which act as neurotransmitters	L-Glutamate, L-Aspartate, L-Cysteine, L-Homocysteine, Glycine, Taurine, L-Arginine
GABA	L-Glutamate, L-Glutamine
β-Alanine	L-Alanine
D-Serine	L-Serine
NMDA Receptor Agonists	L-Serine, Glycine, L-Glutamate, L-Aspartate, L-Arginine
Phenethylamine, N-methylphenethylamine	L-Phenylalanine
Tyramine, Octopamine, Synephrine	L-Tyrosine, L-Phenylalanine
Tryptamine, N-methyltryptamine	L-Tryptophan

Meyers S. Use of neurotransmitter precursors for treatment of depression. *Altern Med Rev.* 2000 Feb;5(1):64-71.

Supporting Evidence

"Aromatic amino acids in the brain function as precursors for the monoamine neurotransmitters serotonin (substrate tryptophan) and the catecholamines [dopamine, norepinephrine, epinephrine; substrate tyrosine (Tyr)]. Unlike almost all other neurotransmitter biosynthetic pathways, the rates of synthesis of serotonin and catecholamines in the brain are sensitive to local substrate concentrations, particularly in the ranges normally found in vivo. As a consequence, physiologic factors that influence brain pools of these amino acids, notably diet, influence their rates of conversion to neurotransmitter products, with functional consequences."

Fernstrom JD, Fernstrom MH. Tyrosine, phenylalanine, and catecholamine synthesis and function in the brain. *J Nutr*. 2007 Jun;137(6 Suppl 1):1539S-1547S; discussion 1548S.

Fernstrom JD. Effects on the diet on brain neurotransmitters. *Metabolism*. 1977 Feb;26(2):207-23.

Replete conditionally essential AAs depleted in stress conditions

Summary

Intake of amino acids decreases the likelihood of chronic or situational deficiency.

Explanation

By definition, the demand for essential and conditionally essential nutrients must be met through oral ingestion, as the body is either incapable of endogenous production or situationally incapable of adequate endogenous production.

Essential Amino Acids: Histidine, Isoleucine, Leucine, Lysine, Methionine, Phenylalanine, Threonine, Tryptophan, Valine

Conditionally Essential Amino Acids: Glutamine, Arginine

Supporting Evidence

"Glutamine and arginine are conditionally essential amino acids because depletion occurs in stressed conditions."

Moïse C, Pierre D. Combined infusion of glutamine and arginine: does it make sense? *Curr Opin Clin Nutr Metab Care*. 2009 Nov 9.

"amino acids, … are able to modulate inflammation and the associated oxidative stress, and maintain or improve immune function"

Xu J, Yunshi Z, Li R. Immunonutrition in surgical patients. *Curr Drug Targets*. 2009 Aug;10(8):771-7.

Fernstrom JD, Faller DV, Shabshelowitz H. Acute reduction of brain serotonin and 5-HIAA following food consumption: correlation with the ratio of serum tryptophan to the sum of competing amino acids. *J Neural Transm*. 1975;36(2):113-21.

"Under conditions of extreme physical exertion, trauma and severe infections, the rate of utilization of glutamine is more than its rate of synthesis, resulting in a significant decline in plasma glutamine concentration."

Rao R., Chaudhry K. (2015) Glutamine Protects GI Epithelial Tight Junctions. In: Rajendram R., Preedy V., Patel V. (eds) *Glutamine in Clinical Nutrition. Nutrition and Health.* Humana Press, New York, NY.

Facilitate repair of cellular infrastructure

Summary

Intake of amino acids leads to the repair and building of tissue.

Explanation

Multiple mood disorders are characterized by significant physical loss of neural tissue. Rebuilding lost nervous tissue mass and repairing damaged neurons increases energy & protein demands similarly to the healing of any other wound. Supplementing amino acids has been shown to accelerate tissue healing.

Supporting Evidence

"The undernourished category of malnutrition leads to loss of body cell mass, which, together with inflammation diminish host response and quality of life"

Soeters PB, Schols AM. Advances in understanding and assessing malnutrition. *Curr Opin Clin Nutr Metab Care.* 2009 Sep;12(5):487-94.

Consistent neuroimaging abnormalities include the presence of ventricular enlargement and white matter abnormalities in patients with BD.

Langan C, McDonald C. Neurobiological trait abnormalities in bipolar disorder. *Mol Psychiatry.* 2009 Sep;14(9):833-46.

Multiple deficits, including cell atrophy and loss, have been observed in limbic and cortical brain regions of patients with mood disorders.

Tanis KQ, Duman RS. Intracellular signaling pathways pave roads to recovery for mood disorders. *Ann Med*. 2007;39(7):531-44.

Nonetheless, there is enough evidence to suggest that white-matter abnormalities are reported with a greater frequency in BPD patients than in patients with UPD or schizophrenia.

Osuji IJ, Cullum CM. Cognition in bipolar disorder. *Psychiatr Clin North Am*. 2005 Jun;28(2):427-41.

…mood disorders are characterized by marked reductions in glial cell number and density in addition to subtle alterations in the density and size of cortical neurons in frontolimbic brain regions … that suggest cell atrophy, cell loss, or impairments in neuroplasticity and cellular resilience may underlie the neurobiology of major depressive disorder and bipolar manic-depressive disorder.

Rajkowska G. Cell pathology in mood disorders. *Semin Clin Neuropsychiatry*. 2002 Oct;7(4):281-92.

Nutrition profoundly influences the process of wound healing. Nutritional depletion exerts an inhibitory effect, and nutritional supplementation with such positive effectors as arginine can stimulate wound healing.

Williams JZ, Barbul A. Nutrition and wound healing. *Surg Clin North Am*. 2003 Jun;83(3):571-96.

The use of glutamine and arginine supplements enhances wound healing and should be increased. Nutritional care is cost-effective.

Wallace E. Feeding the wound: nutrition and wound care. *Br J Nurs*. 1994 Jul 14-27;3(13):662-7.

“Arginine … is involved with protein synthesis … with cell signaling through the production of nitric oxide and cell proliferation through its metabolism to ornithine and the other polyamines. Because of these multiple functions, arginine is an essential substrate for wound healing processes. The requirement for this amino acid in tissue repair is highlighted.”

Witte MB, Barbul A. Arginine physiology and its implication for wound healing. *Wound Repair Regen*. 2003 Nov-Dec;11(6):419-23.

Appendix D

Vitamin C, also known as ascorbic acid, is a water-soluble vitamin. Unlike most mammals, humans cannot synthesize vitamin C. Therefore, we must obtain vitamin C through our diet.[1]

Vitamin C is the antiscorbutic or anti-scurvy vitamin. Although scurvy was first described during the Crusades and commonly plagued early explorers and voyagers, the specific relationship between scurvy, citrus foods, and ascorbic acid was not established until the 20th century. The antiscorbutic factor was isolated and named hexuronic acid in 1928 by Szent-Gyorgyi, who found it in adrenal tissue, orange, and cabbage. In 1932 both he and C. Glenn King demonstrated that hexuronic acid was vitamin C.[2]

Natural vs. Synthetic Vitamin C

Natural and synthetic L-ascorbic acid are chemically identical and there are no known differences in their biological activities or bioavailabilities.[3]

Effective Dosing

Dr. Robert Cathcart, in treating over 9000 patients with large doses of vitamin C, found effective doses to be proportionate to the stress or toxicity experienced which were in turn proportionate to the amount of oral ascorbic acid tolerated by the patient without producing diarrhea. This increased bowel tolerance phenomenon serves not only to indicate the amount which should be taken but indicates the unsuspected and astonishing magnitude of the potential use that the body has for ascorbate under stressful conditions. Cathcart named the process of determining optimum dose as titrating to bowel tolerance. "The patient tries to TITRATE between that amount which begins to make him feel better and that amount which almost but not quite causes diarrhea."[4]

Drug Withdrawal

Ascorbate, administered in high oral doses has been observed to relieve pain and reduce opioid use in cancer patients. In vitro studies have also shown that antioxidants, such as vitamin C, may, at high concentrations, inhibit endogenous opioid degrading enzymes and increase endorphin levels. The most recent study, conducted in 2000, has demonstrated that high oral doses (300 mg/kg bw/day [approximately 20 g/d]) of vitamin C were able to substantially reduce withdrawal symptoms in heroin abusers.[5] Libby and Stone (1977) successfully demonstrated the same effect twenty three years earlier.[6]

Mania and Psychosis

Dr. Abram Hoffer observed early in his career two cases of psychosis which resolved with vitamin C within three days on as little as 3g/day and as much as 1g/waking hour.[7] These individuals did have other medical conditions, but the change was clear and distinct. In 1963, Milner reported statistically significant improvement in the depressive, manic, and paranoid symptom-complexes, together with an improvement in overall personality functioning, was obtained using vitamin C.[8] Naylor et al. conducted a double-blind placebo controlled cross-over trial in 1981 which provided further evidence of vitamin C efficacy. Both manic and depressed patients showed that a single 3g dose significantly improved symptoms compared to placebo.[9]

Agitation and Stress

Individuals in stress, shock, surgery, trauma and critical illness have a drastic reduction of circulating plasma ascorbate; and 3g doses per day are required to restore normal ascorbate concentrations and improve outcome.[10,11]

Tardive Akathisia and Dyskinesia

Akathisia and dyskinesia are related disorders that frequently appear after long-term or high-dose use of antipsychotic drugs.[12] Tardive akathisia involves painful feelings of inner tension and anxiety and a compulsive drive to move the body. Tardive dyskinesia is characterized by repetitive, involuntary, purposeless movements. Hypersensitivity of certain dopamine receptors[12] and dopamine inhibition of certain mitochondrial enzymes[13] appear to play a role in the development and progression of these drug-induced disorders, as well as Parkinson's disease. Vitamin C is able to prevent the dopaminergic impairment of mitochondrial enzymes[14]; and in a small study, six patients experienced a reduction in tardive symptoms with a combination of vitamin E and C.[15]

Chemical Forms and pH

Sodium ascorbate can be obtained both as the pure crystalline powder and as 1g tablets. The crystalline powder is very soluble in liquids and has a slight salt taste. A level teaspoon weighs about 3g. A solution of sodium ascorbate has a pH of slightly over 7.[6]

Ascorbic acid can also be obtained as pure crystalline powder or as 1g tablets. While also quite soluble in water, it has a sour taste. A solution of ascorbic acid has a pH of about 3.[6]

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Appendix E

Dr. Benjamin Lynch found that a portion of his MTHFR patients developed anxiety, irritability, and other symptoms after taking methylfolate. He found that 50 to 100 mg of niacin ameliorated the effects.[1]

We also found that niacin (niacinamide) did, in fact, lessen anxiety and irritability when it developed in a small number of individuals who experienced these same symptoms after taking *Hardy Nutritionals® Daily Essential Nutrients (DEN)*. *DEN* contains methyfolate, methylcobalamin, and choline, which are all methyl donors. Several of these individuals had previously tested positive for MTHFR polymorphisms.

1. http://mthfr.net/methylfolate-side-effects/2012/03/01/ Accessed 13 April 2018.

Appendix F

Nutrient-CYP Action: Mechanism for drug-nutrient interactions

Nutrient	Action	Enzyme	Reference
Vitamin A (Retinol & RA)	Substrate	CES 1, CYP 1A1, 2B6, 2C19, UGT 287	1,2,3,4,5
	Inhibitor	CES 1, CYP 2C8	
	Inducer	CYP 1A1	
Vitamin C	Inducer	CYP 3A4	6
Vitamin D (Cholecalciferol)	Substrate	CYP 1A1, 2C19, 2J2, 2R1	1,3,4,7-19
	Inhibitor	CYP 1A1, 2B6, 2C19, 2C9, 2D6, 2J2, 3A4, 11A1, 27A1	
Vitamin E (Tocopherol)	Transporter	MRP 1	20
Thiamin	Inducer	CYP 4B1	21
Vitamin B3 (Niacinamide)	Inhibitor	CYP 2D6, 2E1, 3A4	3, 22
	Substrate	CYP 3A4	
Vitamin B6 (Pyridoxine)	Inhibitor	CYP 1A1	23
Biotin	Inducer	CYP 1B1	3
Zinc 2+	Inhibitor	CYP 3A4	24
Copper 2+	Inhibitor	CYP 1A1, 3A4	25
Ginkgo Biloba	Inhibitor	CYP 1A2, 3A4	26

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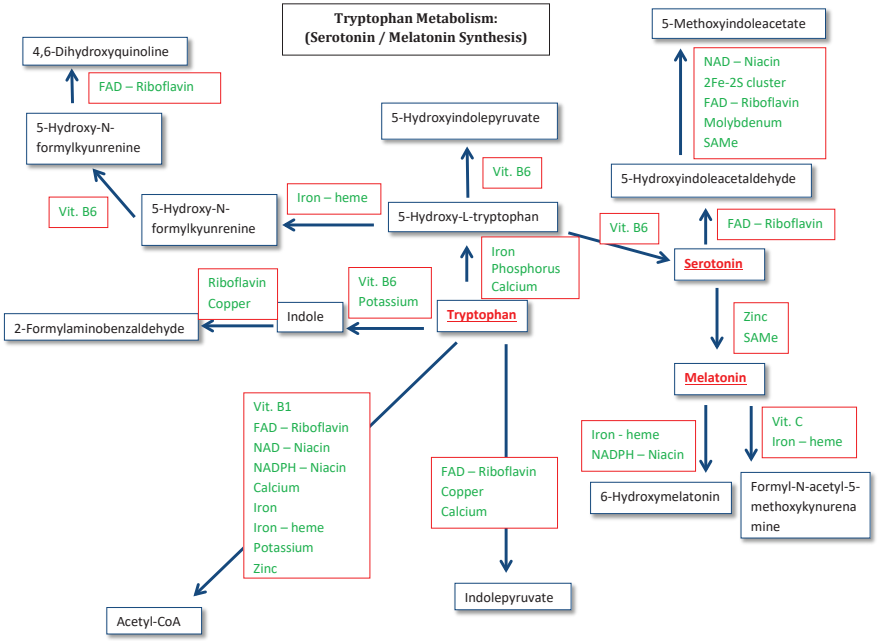
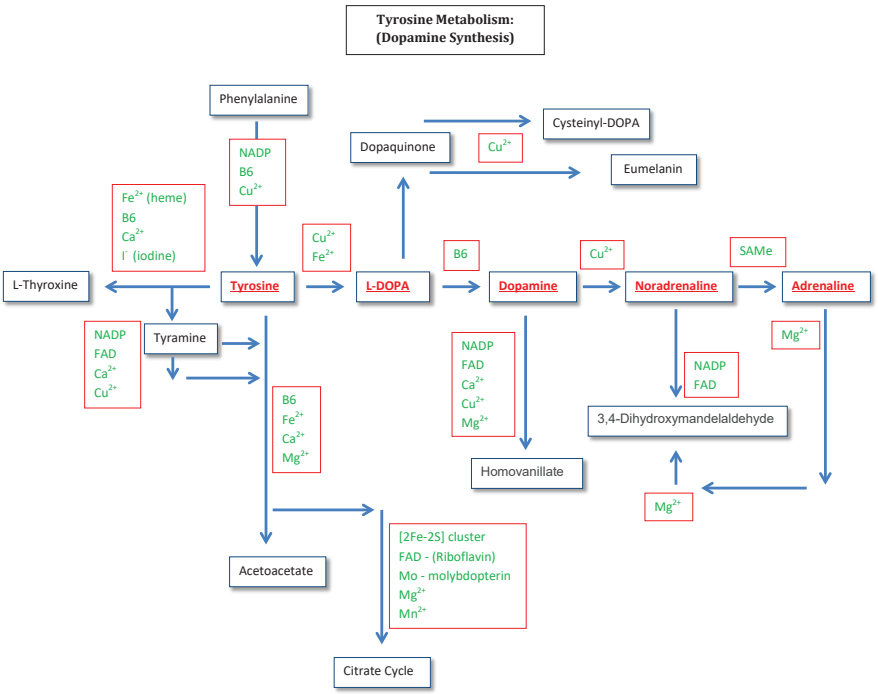
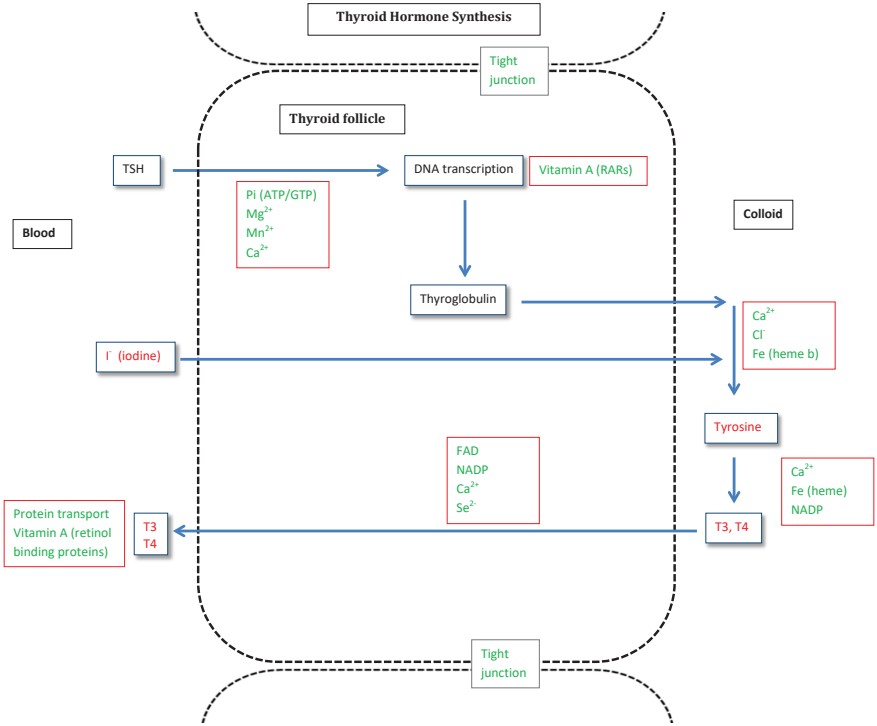
Appendix G

Neurotransmitter and Hormone Synthesis: Essential Nutrient Inputs







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KEGG PATHWAY Database – Map

http://www.genome.jp/kegg/pathway.html

The Universal Protein Resource (UniProt) Database

https://www.uniprot.org/

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