Hardy™ nutritionals

Daily Essential Nutrients

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 and anxiety symptoms.

This clinical reference provides detailed information about **DEN** accumulated through extensive research with predecessor formulations of **DEN** and valuable feedback from healthcare professionals.

For your convenience, we've included Section 7, *Treatment Guidelines*, which is designed to simplify clinical use of **DEN** by putting information from other sections into clinical context.

Please feel free to call us with any questions or concerns you may have.

We look forward to working with you!

Sincerely,
The Hardy Nutritionals™ team
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1 Description

Daily Essential Nutrients (DEN) is a chelated micronutrient formula for oral administration. It consists of 17 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 yellowish-brown powder and is enclosed in a white opaque gelatin capsule. The capsules are made from an equal mixture of animal and plant gelatin.

Daily Essential Nutrients Capsules

Supplement Facts
Serving Size: 5 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 and menaquinone-7)	40 mcg	50%
Thiamin (as thiamin mononitrate)	20 mg	1333%
Riboflavin	6 mg	353%
Niacin (as niacinamide)	30 mg	150%
Vitamin B6 (as pyridoxine hydrochloride)	23.3 mg	1167%
Folic acid (50% as L-methylfolate calcium)	500 mcg	125%
Vitamin B12 (as methylcobalamin)	300 mcg	5000%
Biotin	360 mcg	120%
Pantothenic acid (as d-calcium pantothenate)	10 mg	100%
Calcium (as chelate)	440 mg	44%
Iron (as chelate)	4.6 mg	25%
Phosphorus (as chelate)	280 mg	28%
Iodine (from Pacific kelp)	68 mcg	45%
Magnesium (as chelate)	200 mg	50%
Zinc (as chelate)	16 mg	107%
Selenium (as chelate)	68 mcg	97%
Copper (as chelate)	2.4 mg	120%
Manganese (as chelate)	3.2 mg	160%
Chromium (as chelate)	208 mcg	173%
Molybdenum (as chelate)	48 mcg	64%
Potassium (as chelate)	80 mg	2%
Proprietary blend	852.9 mg	†
Choline bitartrate, alpha-lipoic acid, shilajit, inositol, acetylcarnitine (as acetyl-L-carnitine hydrochloride), grape seed extract, ginkgo biloba leaf extract, methionine (as L-methionine hydrochloride), cysteine (as N-acetyl-L-cysteine), germanium sesquioxide, boron (as chelate), vanadium (as chelate), lithium orotate (as chelate), nickel (as chelate).		
* Percent Daily Values (DV) are based on a 2,000 calorie diet.		
† Daily Value not established.		

Other ingredients: Gelatin, cellulose, glycine, citric acid, magnesium stearate, silicon dioxide.

2 Clinical Pharmacology

2.1 Clinical trials

According to a recent article in *BMC Psychiatry*, the predecessor formulations of **Daily Essential Nutrients (DEN)** are the most-studied in the world for mental health treatment.[1] There are currently 20 published articles on these formulations in medical journals, all but 2 of which are peer-reviewed. The study designs employed in the published articles range from case reports to case studies with years of historical information and two database analyses (see *Appendix A*).

Consistent research results have been found across scientists at more than a dozen independent institutions in several countries. None of the researchers have had financial ties to these formulations.

Significant research is continuing with the **DEN** formulation.

2.2 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[2–8] and regulation[9–16] of neurotransmitters in the brain.

In addition, genetic polymorphisms (variations) can often result in increased requirements for nutrients in enzyme pathways, and higher nutrient intakes have been shown to ameliorate the effects of many of these genetic conditions.[17–19]

2.3 Pharmacodynamics

In humans, **DEN** pharmacodynamics are presumed to be a complex interaction of individual nutrient pharmacodynamics, many of which have been studied extensively.[20–25]

In animal studies, accelerated structural and functional recovery of neurons were observed following experimentally-induced brain lesions when animals were supplemented with the chelated mineral blend of **DEN**.[26] Similar structural, chemical, and functional neuronal deficits exist in mood and cognitive regulation in humans[27–29] which would presumably respond in a similar way to **DEN** therapy.

2.4 Absorption and metabolism

2.4.1 Systemic bioavailability

As yet, there are no publications regarding nutrient bioavailability of **DEN** after a single oral dose.

Food does not appear to affect 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.

2.4.2 Metabolism

The vitamins and minerals in **DEN** are presumed to be metabolized in the same fashion as those in foods and similar supplements.[20–24] The complexity of **DEN** metabolism may affect medication use (see 4.2 *Drug interactions*).

The effects 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.[1]

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

3 Indications & Dosage

3.1 Indications

Daily Essential Nutrients (DEN) is indicated for the treatment of mood and anxiety symptoms. The effect of predecessor formulations of **DEN** in the treatment of these symptoms has been documented in 20 case-control studies, within-subject crossover case studies, open-label case series, case reports and two database analyses.

Significant evidence exists to indicate that a wide range of mood and anxiety symptoms can result from inadequate intake of vitamins and minerals and/or poor nutrient status.[19]

3.2 Dosage

DEN should be administered throughout the day with food. The recommended therapeutic dose is 5 capsules 3 times per day. Both adults and children dosed in this range during clinical trials have demonstrated the most consistent and marked improvements.

Maintenance requires an adequate dose of **DEN** that prevents remission. Optimal maintenance dosage will vary with individual needs.

3.2.1 Biological safety data

Biological safety data from 144 children and adults were available from eight datasets of predecessor products with comparable therapeutic dosages. 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.[1]

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. In addition, 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.[1]

4 Side Effects & Drug Interactions

4.1 Side effects

Side-effect-free intake ranges for vitamins and minerals have been established by the United States Institute of Medicine and comparable authorities around the world based on a comprehensive review of relevant data in adults and children.[20–25]

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

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."[20]

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:[1]

4.1.1 Body as a Whole

Infrequent: headache

4.1.2 Digestive System

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

Infrequent: loose stools, nausea.

Rare: flatulence, diarrhea, stomach ache, vomiting.

4.2 Drug interactions

4.2.1 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.

4.2.2 Psychoactive drugs

Strong interactions with psychoactive drugs, including lithium, have been observed in clinical experience with earlier generations of **DEN**. On this issue, researchers have 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."[1]

The interaction of psychoactive medications with earlier generations of **DEN** was likely due to the presence of grapefruit furanocoumarins and other citrus bioflavonoid components which are known to impede hepatic clearance of many medications by inhibiting various cytochrome p450 enzymes, including CYP3A4, CYP1A2, CYP2C19, and CYP2C9.[30] This hepatic inhibition served to significantly amplify the effects of many psychiatric medications.

Based on initial clinical evaluations, **DEN** has shown many fewer interactions with most psychoactive medications than predecessor products. This improvement is believed to be a result of the absence of citrus bioflavonoids and furanocoumarins in the **DEN** formulation.

However, **DEN** appears to show interactions with lithium, likely because lithium is metabolized differently than other central nervous system (CNS)-active medications. Treatment guidelines for patients taking lithium are found in 7.2 *Psychiatric medications*.

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., glucocorticoids).

5 Warnings & Precautions

5.1 Warnings

All medication doses should be monitored by a physician while taking **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 certain symptoms (see 4.2 *Drug interactions*).

5.2 Precautions

5.2.1 Citrus bioflavonoids

Patients currently taking citrus bioflavonoid-containing formulations such as EMPowerplus™ should transition gradually (e.g. 1 capsule per day) to **DEN** in order to avoid medication withdrawal effects (see 4.2 *Drug interactions*).

5.2.2 Clinical worsening

Patients being treated for any indication should be observed closely by families and caregivers for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of therapy, or at times of **DEN** or medication dose changes (either increases or decreases). Such symptoms should be reported to the patient's prescriber or health professional, as medication dose changes may be required (see 8.1 *Psychiatric medication management*).

5.2.3 Iron

Although **DEN** contains a relatively low level of iron (less than 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/kilogram (27.2 mg of iron/pound) of body weight.

6 Overdose & Contraindications

6.1 Overdose

6.1.1 Human experience

No cases of overdose with **Daily Essential Nutrients (DEN)** or predecessor formulations have been documented.

6.1.2 Management of overdose

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

6.2 Contraindications

Treatment with **DEN** should not be introduced if the patient is diagnosed with a condition where specific nutritional factors are contraindicated: (e.g. Wilson’s disease) or if the patient has known hypersensitivity or allergy to any ingredients of **DEN**.

7 Treatment Guidelines

7.1 Using Daily Essential Nutrients (DEN)

Unless contraindications (see 6.2 *Contraindications*) or precautions (see 5.2 *Precautions*) direct otherwise, **DEN** can generally be administered to patients as outlined in this section. Individual patient characteristics may require adaptations according to clinical judgment.

7.1.1 Initial dosing

Generally, **DEN** can be titrated up to an appropriate therapeutic dose (see 3 *Indications & Dosage*) within 5 days (see *Figure 1*).

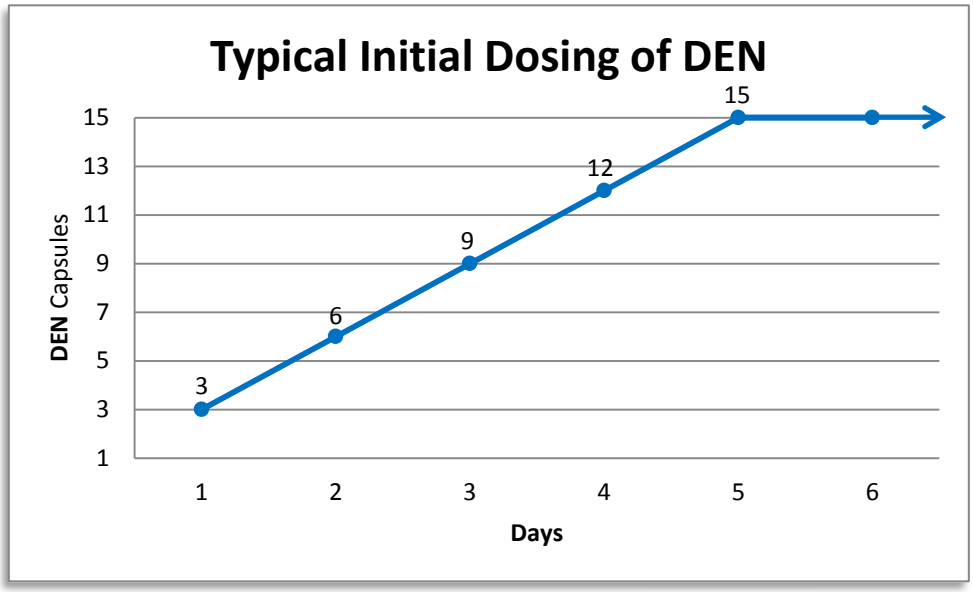

Figure 1 Typical initial dosing for **DEN**

7.1.2 Instructions for DEN use

Patients should take **DEN** as directed on the label to avoid potential gastrointestinal side effects (see 4.1 *Side effects*):

> "**Suggested Use:** Take with food. Start with 1 capsule 3 times daily. For optimal results, increase to 5 capsules 3 times daily or as recommended by a physician."

Children should take **DEN** under adult supervision (see 5.2 *Precautions*).

If a patient has difficulty falling asleep, he/she should take **DEN** prior to 6 pm (see 8.7.2 *Inadequate sleep*).

7.2 Psychiatric medications

Psychiatric medication doses, including lithium, should be monitored carefully during **DEN** therapy (see 5.1 *Warnings*).

If psychiatric medication side effects emerge, gradually reduce medication dosages (see 4.2 *Drug interactions*). Ideal psychiatric medication tapering minimizes patient symptoms by avoiding both adverse interaction and withdrawal effects (see 8.1 *Psychiatric medication management*). **Figure 2** illustrates the importance of minimizing drug-related symptoms during the psychiatric medication reduction process.

Hardy Nutritionals™ Free-Form Aminos or protein powders can help ameliorate drug-related symptoms until medication reductions are optimized, perhaps by binding to pharmacologically active drug metabolites and diminishing their pharmacologic effects. Absorption of protein products will be expedited if taken between meals.

7.2.1 Polypharmacy

Multiple psychiatric medications are often prescribed together to manage symptoms for which one medication alone may not be effective. These medications should be reduced at the same rate in order to maintain the balance that they exert together on the central nervous system.

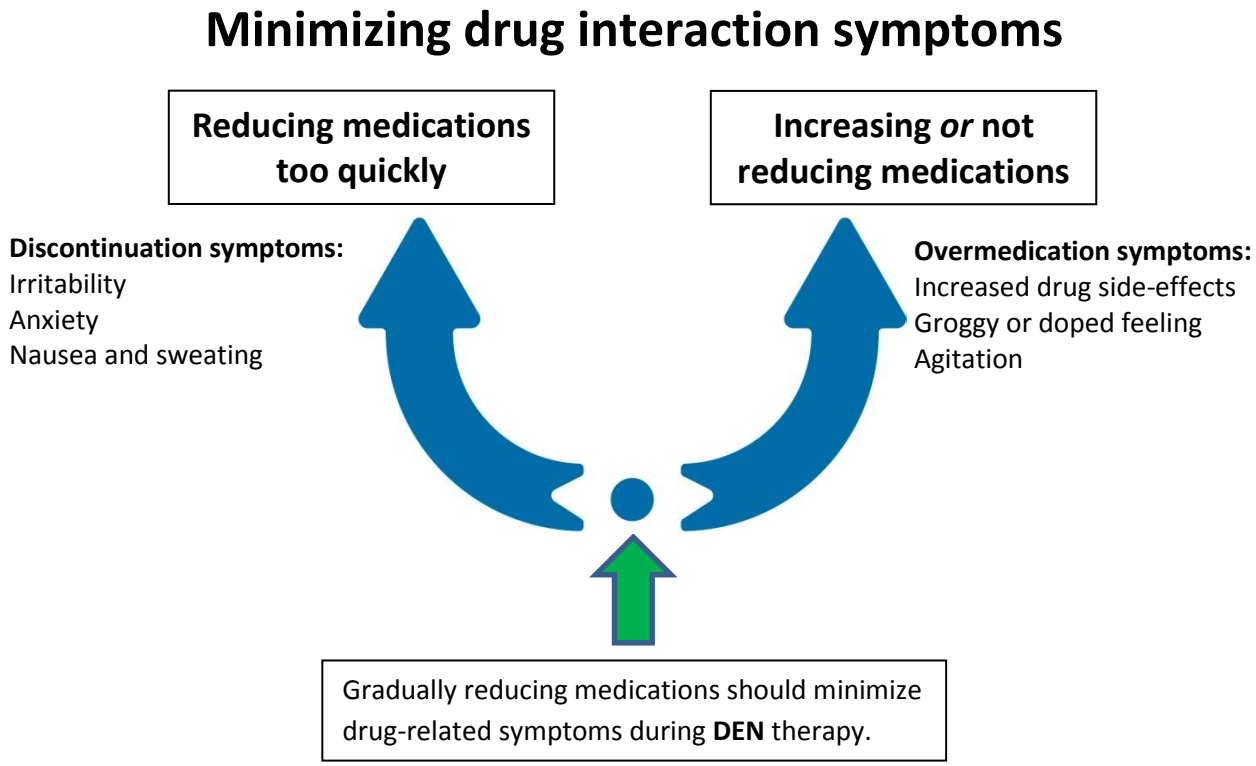

Figure 2 Psychotropic medication reduction guide

7.3 Other medications

All medication doses should be monitored by a physician during **DEN** therapy (see 5 *Warnings & Precautions*).

Medications for health conditions such as thyroid irregularities, insulin irregularities, heart issues, high blood pressure, high cholesterol, and cancer need to be monitored closely. Medication dosages may require adjustment.

Non-psychiatric medications that may limit a patient's response to **DEN** are listed in 8.2 *Non-psychiatric medications*.

7.4 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, and gut microflora imbalance can limit response to **DEN** therapy. For detailed recommendations, see 8.5 *Gastrointestinal problems*.

7.5 Other considerations

Additional patient characteristics that can 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*).

7.6 Addressing residual symptoms

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

7.6.1 Physical symptoms of 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 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**).

7.6.2 Racing or obsessive thoughts

Patients who exhibit rage, aggression, racing thoughts or obsessive thoughts while taking a therapeutic dose of **DEN** may benefit from added choline (such as **Hardy Nutritionals™ Choline Bitartrate**).

8 Possible Limiting Factors

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

8.1 Psychiatric medication management

Changing psychiatric medications inappropriately during **DEN** therapy can be a significant limiting factor. Improper medication dosages can affect neurotransmitter systems in various ways and 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**. We do not recommend abrupt discontinuation of any psychiatric medications during **DEN** therapy.

To prevent pronounced discontinuation symptoms as well as rebound (a significant return of the original symptoms), psychiatric medications should be reduced gradually. 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 4.2.2 *Psychoactive drugs*).

8.2 Non-psychiatric medications

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

8.2.1 Anesthetics

Anesthetics have potential interactions with psychiatric medications. Psychiatric medication status is an important consideration in the management of the patient about to undergo anesthesia and surgery.[31–33] For example, benzodiazepines are commonly administered for many surgical procedures to sedate and relax patients. This may be considered increasing or changing medications (see 8.1 *Psychiatric medication management*).

Some unmedicated individuals taking previous formulations of **DEN** have reported withdrawal or post-withdrawal symptoms following surgery which have responded to standard post-withdrawal drug symptom alleviation measures (see 8.6.2 *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 nutrients. Inhibiting this step of the digestive process can reduce the bioavailability of critical nutrients during the absorption phase.

8.2.3 Antibiotics

Antibiotics have saved countless lives. However, antibiotic use can cause collateral damage to the intestinal microbiome.[34] Oral antibiotics may vastly impact both good and pathogenic gut microflora, resulting in reduced nutrient absorption.

Individuals who take antibiotics during **DEN** therapy may experience a worsening of symptoms. This effect has not been observed with intravenous antibiotics, suggesting that the interaction occurs in the gastrointestinal system.

A temporary 50% increase in micronutrient dose for the duration of the antibiotic treatment generally compensates. Adding a probiotic-prebiotic combination (such as **Hardy Nutritionals™ Greens & Probiotics**) during the course of antibiotic treatment, plus one to two weeks after completion, is also recommended.

A natural antibiotic/anti-fungal agent is also recommended for the duration of 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

With predecessor formulations of **DEN**, we have observed clinically significant increases in psychiatric symptoms when some individuals used certain antihistamines and related drugs (e.g. Zyrtec, Benadryl, etc.).

8.2.5 Birth control

Observation with predecessor formulations of **DEN** showed that hormone-containing birth control medications may worsen depression, alter mood, and/or increase nervousness and irritability. Cautious use is warranted.

8.2.6 Hormone replacement therapy (HRT)

Observation with predecessor formulations of **DEN** showed that HRT may worsen depression, alter mood, and/or increase nervousness and irritability. Cautious use is warranted.

8.2.7 Opioid Analgesics

Opioid analgesics have been observed to interact with predecessor formulations of **DEN**, likely as a result of the inhibititory effects of citrus bioflavonoid ingredients that can inhibit various cytochrome p450 enzymes (see 4.2.2 *Psychoactive drugs*).

8.3 Recreational drugs

8.3.1 Street drugs

Street drugs can cause a definite psychotropic effect, and the potential interaction with **DEN** may cause mood and mind altering effects (see *Appendix A*, reference 1). Keep in mind that many individuals who are addicted to street drugs try to conceal their addictive behaviors, and a patient's lack of progress or unexplained symptoms may be the result of consuming street drugs. Specialized nutrient therapy has been used to successfully treat addictions.[35]

8.3.2 Alcohol

Alcohol abuse can significantly interfere with **DEN** therapy. Ideally, alcohol use should be minimized.

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. 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 therapeutic response to **DEN**.

8.4.2 Minerals

Additional iron may be added to **DEN** therapy without any issue. 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. Whole foods containing these minerals are not a problem.

8.4.3 Psychoactive supplements

Any psychoactive supplement has the potential to interfere with **DEN** effects. These include (but are not limited to) SAM-e, 5-Hydroxytryptophan (5-HTP), St. John's wort, ginseng, kava kava, skullcap, and valerian root. If patients choose to use psychoactive supplements during **DEN** therapy, advise cautious dosing and monitor their responses carefully.

8.5 Gastrointestinal problems

Diarrhea or constipation can reduce the absorption of essential vitamins and minerals. If either condition becomes 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, certain oils, fatty acids, and various other supplements may be beneficial in restoring and maintaining more normal bowel function.

8.5.2 Constipation

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

Treatment experience with predecessor products of **DEN** showed 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 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 can severely limit the effectiveness of **DEN** treatment by preventing absorption of essential vitamins and minerals. Causes of diarrhea are varied. Depending on the cause of diarrhea, different measures may be appropriate to rectify the problem according to clinical judgment.

Treatment experience with predecessor products of **DEN** showed that certain foods like unripe bananas, peanut butter, cheddar cheese often helped 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 Microflora imbalance

Gut microflora may become imbalanced due to factors such as antibiotic use, infections, and diet patterns. Restorative measures should be taken to ensure optimal absorption 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* for indicative questionnaire).

Note: Antibiotic/antifungal agents like **Hardy Nutritionals™ Olive Leaf Extract** may cause a die-off response, known as the Herxheimer reaction, which presents as flu-like symptoms and can arise anywhere from the first day to the first couple of weeks after beginning 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 product. If there is no Herxheimer reaction, complete the course at recommended levels.

8.6 Patient history

8.6.1 Antibiotic use

If an individual has had a lengthy history of oral antibiotic use, particularly as a child, a probiotic (such as **Hardy Nutritionals™ Greens & Probiotics**) is recommended. Normally, probiotics do not need to be taken on a continual basis. 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 *Microflora imbalance*).

8.6.2 Psychiatric drug use

Residual medication-related symptoms can appear for months and in some cases even years after psychiatric medications have been discontinued.[36,37] Post-withdrawal medication symptoms are often triggered by such things as physical exertion, weight loss, stress, prolonged sun exposure, and liver or bowel cleanses. To a lesser extent, post-withdrawal drug symptoms may also be triggered by massage, chiropractic, or acupuncture therapies.

Some symptoms of post-withdrawal include insomnia, anxiety, depression, crying jags, agitation, and irritability. Individuals often report they feel medicated again. Post-withdrawal symptoms can often be mistaken for a return of psychiatric symptoms.

Suggestions for treatment of post-withdrawal drug symptoms include avoiding or moderating 'trigger' activities and/or temporarily adding protein isolate or free-form amino acids (such as **Hardy Nutritionals™ Free-Form Aminos**) to the patient's treatment regimen.

8.6.3 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, or irritable within hours or several days of starting micronutrient products.

8.6.4 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.

8.7 Lifestyle factors

8.7.1 Inadequate 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 8.5.4 *Microflora imbalance*).

8.7.2 Inadequate sleep

Poor sleep quality and/or sleeplessness significantly exacerbates mania and psychosis issues. Adequate sleep is a significant factor in psychiatric health. Doses of **DEN** late in the day (after 6 pm) may contribute to wakefulness in some people.

8.7.3 Inadequate hydration

It is important to drink an adequate amount of water. Eight cups (approximately 2 quarts or 2 liters) of fluids per day are typically recommended. Water assists in moving nutrients into and flushing wastes out of the body.

8.7.4 Non-compliance

Inconsistent or "as needed" dosing of **DEN** is not recommended. The best results come from regular, steady dosing. 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.

8.7.5 Weight loss

Weight loss can trigger post-withdrawal drug symptoms, presumably by facilitating the release of sequestered medication residues from poorly perfused tissues. For measures that may alleviate post-withdrawal drug symptoms, see 8.6.2 *Psychiatric drug use*.

8.8 Physical health and life stage factors

8.8.1 Menstrual cycle

Psychiatric symptoms may increase during the menstrual cycle. This is likely due, in part, to changing hormone levels and increasing nutrient demands. Should symptoms become apparent during this time, **DEN** should be increased by at least one full dose of 5 capsules/day for about one week. In subsequent cycles, additional **DEN** taken a few days prior to menstruation 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 5 capsules daily to support the immune system through illness may lead to faster recovery.

8.8.3 Pregnancy and breastfeeding

Nutritional requirements are significantly increased during pregnancy and breastfeeding. The daily dose of **DEN** should be increased in relative proportion to daily caloric intake, particularly in individuals with psychiatric symptoms. An additional dose of 5 **DEN** capsules per day may be useful.

8.8.4 Puberty

Puberty is a time when hormones are changing and the body's nutritional demands may be changing as a result. The onset of many psychiatric symptoms often corresponds with this period of development. For these reasons, additional **DEN** may be beneficial during puberty.

9 Appendix A

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10 Appendix B

Microflora Imbalance 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 1 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 2 months or longer, or for shorter periods, 4 or more times in a 1 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 2 weeks?..... **15**
   - for 2 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 point**
-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 at the bottom 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

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