Single-Micronutrient and Broad-Spectrum Micronutrient Approaches for Treating Mood Disorders in Youth and Adults

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KEYWORDS

• Vitamins • Minerals • Micronutrients • Children • Adolescents
• Psychopharmacology • Major depressive disorder • Bipolar disorder

KEY POINTS

- Vitamins and minerals are involved in virtually every biologic process, so micronutrient deficiencies have broad effects throughout the body and brain.
- Micronutrient insufficiencies affect most people, even in "well-fed" populations, especially patients with psychiatric disorders, including mood disorders in youth and adults.
- Folic acid, chromium, and perhaps zinc may be effective adjunctive treatments for depression in adults but are not powerful enough to be monotherapies.
- Broad-spectrum micronutrient treatments appear effective in early controlled trials as potent treatments of ADHD, aggressive and disordered conduct, and mood disorders in youth and adults.
- For bipolar depression and mania, the effectiveness of broad-spectrum micronutrients appears comparable to conventional medications, but with fewer adverse effects and possibly greater long-term stability.
- In healthy adults, broad-spectrum micronutrients may reduce posttraumatic symptoms, benefit memory, and increase mental energy and clarity.

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Abbreviations	
BDI	Beck Depression Inventory
CAARS	Conners Adult ADHD Rating Scales
CBCL	Child Behavior Checklist
CGI	Clinical Global Impression
CNS	Central nervous system
DHA	Docosahexaenoic acid
EAR	Estimated Average Requirement
EPA	Eicosapentaenoic acid
GAF	Global Assessment of Functioning
HAM-D	Hamilton Depression Rating Scale
MDD	Major depressive disorder
NHANES	National Health and Nutrition Examination Survey
OCD	Obsessive-Compulsive Disorder
POMS	Profile of Mood States
RCTs	Randomized controlled trials
RDAs	Recommended Daily Allowances
RDBPCTs	Randomized double-blind placebo-controlled trials
SAMe	S-adenosyl-methionine
SSRIs	Serotonin reuptake inhibitors

VITAMINS AND MINERALS IN HEALTH AND DISEASE

The technical term "micronutrients" refers to all vitamins and biologically active minerals required in trace and ultratrace amounts to sustain health. The term is often used more broadly to describe a variably defined group of dietary substances, including other bioactive nutrients required in "micro" amounts for a wide range of biologic processes (**Box 1**). In contrast, larger dietary quantities are needed of the macronutrients, which include carbohydrates, proteins, fats, and the macro-minerals (sodium, potassium, calcium, magnesium, chloride, phosphorus, and sulfur). For the purposes of this article, the term "micronutrients" will be used to signify vitamins and microminerals collectively.

Dietary intake of micronutrients must be maintained at nutritionally adequate levels to sustain biologic functionality and general health, both physical and mental.[1,2] At the level of global public health, iodine, iron, and vitamin A are usually considered the most common micronutrient deficiencies worldwide, especially in developing countries; but even in developed countries, deficiencies in iron, folate, and zinc are common. Children and pregnant mothers are considered particularly vulnerable to micronutrient deficiencies, and micronutrient deficiencies can have profound effects on physical growth and brain development.[3,4]

Micronutrient Functions in Biology

Micronutrients play a role in virtually every biologic, chemical, and physiologic process. Minerals and vitamins serve as cofactors in enzymatic reactions. Virtually all enzymes require some form of cofactor, and many enzymes require several cofactors. Vitamins may be a cofactor (biotin) or a component of a cofactor (folate in tetrahydrofolate). Minerals, in addition to functioning as cofactors, are also a structural part of some enzymes (iodine in thyroid hormone, magnesium and zinc in DNA polymerase) or may activate enzymes or other proteins (allosteric regulation). Enzymes are involved in neurotransmitter metabolism and drug biotransformation, potentially increasing or decreasing effects of pharmaceutical agents, among innumerable other

Box 1
Micronutrients

- Vitamins
  - Vitamin A: Retinol, retinal, retinoic acid, and other retinoids
  - Vitamin B complex
    - B1: Thiamine
    - B2: Riboflavin
    - B3: Niacin, nicotinic acid, niacinamide
    - B5: Pantothenic acid
    - B6: Pyridoxine, pyridoxal, pyridoxol, pyridoxamine
    - B7: Biotin
    - B9: Folic acid
    - B12: Cobalamins
  - Vitamin C: Ascorbic acid
  - Vitamin D: Calciferol, cholecalciferol, ergosterol, ergocalciferol
  - Vitamin E: Tocopherol, d-alpha tocopheryl, tocotrienols
  - Vitamin K: K1 (phytomenadione), K2 (menaquinones)
- Minerals
  - Trace and ultratrace minerals, including zinc, iron, iodine, copper, selenium, chromium, manganese, molybdenum, boron, silicon, nickel, vanadium; cobalt, fluorine, aluminum (arguably, lithium and strontium).
  - Macrominerals include sodium, potassium, calcium, magnesium, chloride, phosphorus, and sulfur.
- Other compounds sometimes considered micronutrients
  - Vitaminlike substances, including alpha-lipoic acid, coenzyme Q10 (ubiquinol, ubiquinone), L-carnitine, acetyl-L-carnitine, N-acetylcysteine, choline, inositol, phospholipids (phosphatidylcholine, phosphatidylserine)
  - Essential fatty acids
    - Alpha-linolenic acid, the omega-3 precursor for eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA)
    - Linoleic acid, the omega-6 precursor for gamma-linolenic acid and arachidonic acid
  - Amino acids, being constituents of protein, are technically macronutrients, but free amino acids are sometimes considered micronutrients.
  - Other organic acids, including citric acid, acetic acid, lactic acid, taurine (2-aminoethanesulfonic acid), para-aminobenzoic acid, and orotic acid.
  - Phytochemicals, including polyphenols (flavonoids) and carotenoids (alpha- and beta-carotene, lutein, lycopene, beta-cryptoxanthin, zeaxanthin).

roles. Transcription factors also require cofactors, and so micronutrients have an essential role in gene expression and epigenetic modification. With numerous and overlapping roles for vitamins and minerals, micronutrients are fundamental to biology (**Box 2**).

Box 2
A selection of (partially overlapping) mechanisms of micronutrient action

Modulation of enzyme activities (eg, cofactors "tune up" enzyme activity)

Regulation of the activity of transcription factors, so altering gene expression (eg, cofactors for transcription factors, changing DNA or histone methylation)

Transformation of receptors, transporters, ion channels, and pump mechanisms.

Alterations of membrane fluidity.

Varied effects on second and third messenger systems.

Modification of gastrointestinal absorption, the activity of vitamin-metabolizing enzymes, and the physiologic effects of other micronutrients.

Essential roles in neuron growth and brain development, neuronal repair, and the slowing of neuronal deterioration.

The nutrient requirements of an individual undergo continuous change, even though the establishment of Recommended Daily Allowances (RDAs) as fixed goals for nutrient intake may create the illusion that nutrient requirements are constant. The micronutrient status of an individual is governed by many factors that are related to both micronutrient utilization and micronutrient supply. Optimal dietary micronutrient intake is determined by these various factors. Some of these factors are relatively stable (genetics), some change over time and vary with development or physiologic state, and some are environmentally influenced (**Box 3**).

Physical activity and stress increase micronutrient utilization and needs. Micronutrient requirements are particularly high during pregnancy and early development, largely to optimize brain development.

Micronutrient bioavailability and absorption may be altered by changes in the intestinal flora. Gut flora help release micronutrients from partially metabolized food (digesting cellulose, releasing micronutrients from bound sites) and actively participate in vitamin synthesis and the conversion of minerals into more organically usable forms. Antibiotics, which diminish the gut flora, reduce micronutrient bioavailability and absorption. The nutrient supply is also reduced in advanced age, when senescent changes in the villae reduce intestinal absorption. Through these mechanisms, changes in the intestinal flora and aging gastrointestinal structures can affect brain function.[5]

Medical illnesses can alter micronutrient requirements in numerous ways. Intestinal and liver diseases affecting absorption degrade micronutrient supply. Hypermetabolic conditions (such as hyperthyroidism, infections, proliferative disorders) and conditions involving accelerated cell destruction (sickle cell anemia) increase nutrient requirements. Surgery and radiation treatment place a strain on micronutrient stores. Medications can modify nutrient intake, absorption, and bioavailability in complex ways.

Environmental factors influencing nutrient supply include the micronutrient content of local soil, which governs the nutritional value of foods grown from it; inhabitants may need increased oral supplementation in locales where the food supply comes from nutrient-poor soil. Sun exposure is critical for vitamin D synthesis, so indoor work, lack of outdoor recreation, illness, and bedridden status will reduce endogenous synthesis and increase dietary requirements. Cultural factors affecting nutrient supply include cuisine, cooking methods, and local food patterns[6]; for example, vegetarians are advised to take oral micronutrient supplementation. Inadequate food intake,

Box 3
Factors affecting dietary micronutrient requirements in an individual (most of which vary over time)

- Age
- Physical growth
- Physical activity
- Stress
- Pregnancy and lactation
- Geography (local micronutrient content of soil, sun exposure)
- Cuisine and cooking methods
- Food patterns (eg, Mediterranean, Western, vegetarianism, veganism, Norwegian, Chinese)
- Inadequate intake (poverty, dieting)
- Gastrointestinal flora (microbiome) alter micronutrient absorption
- Antibiotic usage
- Diseases
  - Reduced gastrointestinal absorption, including gastrointestinal disease.
  - Changes in metabolic requirements (eg, thyroid disease, infections, burns)
  - Chronic liver or kidney disease
  - Hematological conditions involving increased cell destruction (sickle cell anemia, hemolytic anemias)
  - Certain brain disorders or injuries may lead to increasing or decreasing requirements.
- Treatments of diseases
  - Long-term use of certain medications alters micronutrient absorption, serum levels, and effects
  - Surgery and radiation
- Tobacco, alcohol, recreational drugs, and candy
- Obesity
- Aging
- Genetics

whether due to poverty or dieting, will obviously alter the micronutrient status of an individual, and replenishment of depleted micronutrient stores requires more nutrient intake than normal health maintenance. Smoking, alcohol, and recreational drugs, as well as candy and processed foods with low nutrient density (ie, junk food) will increase utilization and reduce nutrient absorption.[7,8]

The micronutrient content of soil is an interesting factor. In developed countries, there is a dramatic depletion of many essential micronutrients in crops, largely caused by modern agricultural methods, which replenish soil with nitrogen and phosphorus, but generally fail to resupply the trace minerals and vitamins that are essential in the human diet. As a result, our soil has gradually become depleted of many essential nutrients, affecting the entire plant and animal food chain that comprises the bulk of human diets. In addition to overly selective soil replenishment and fertilization techniques, other factors contributing to reduced nutrient density in foods include

overgrazing, overirrigation, soil aging (organic decomposition, acidification, or alkalinity buildup), loss of organic acids in the humus that helpfully chelate nutrients and enhance nutrient uptake and erosion. Another factor is the use of herbicides, which often contain glyphosates that bind certain minerals and substantially reduce their bioavailability in the soil.[9,10]

The effect of modern agricultural methods has been identified as a factor contributing to the progressive and marked reduction in the nutritional content of the plants and animals that comprise human sustenance. For example, in England, the micronutrient contents of fruits and vegetables grown in the 1930s and in the 1980s were quantitatively compared.[11] Significant reductions were found over those 50 years in the micronutrient content of both vegetables (copper by 81%, sodium by 43%, magnesium by 35%, and calcium by 19%) and fruits (copper by 36%, iron by 32%, potassium by 20%, and magnesium by 11%). Only phosphorus, which is routinely replenished in modern farming techniques, showed no appreciable change over the 50 years. Similar types of changes have been observed in vegetables and fruits grown on soil in the United States.[12] Although doubts have been raised about these figures based on a variety of technical grounds, including cultivars (varietal changes) that reflect trade-offs between market demands (such as productivity) and nutrient content, it seems likely that the micromineral content of the human diet has reduced in agriculturally advanced countries.[13]

Perhaps the most important of all factors affecting micronutrient requirements in an individual is genetics (including epigenetics). An individual's genetic polymorphisms or haplotypes affect genetic differences in all aspects of physiologic functioning. This factor, called "biochemical individuality" in some nutritional circles, is critical, but just one of many factors governing the micronutrient requirements of an individual.

Micronutrient Mechanisms Leading to Disease and Dysfunction

A large variety of diseases and subclinical dysfunctions can result from an inadequate availability of micronutrients. Apart from the frank deficiency diseases, suboptimal micronutrient status can increase the severity of many disorders and, more subtly, contribute to subclinical syndromes related to physiologic underperformance. Diverse mechanisms underlie these conditions, but several specific mechanisms are worth highlighting (**Box 4**).

Bruce Ames, one of the leading authorities on micronutrient medicine, estimates that one-third of single-gene enzyme mutations result in an enzyme with a decreased binding affinity for its cofactor, leading to a slower enzymatic reaction speed (and a higher cofactor concentration required to drive the reaction). He describes about 50 human genetic disorders that are likely to be at least partially ameliorated merely by increasing the dose of an orally administrated vitamin cofactor.[15] In effect, the slightly deformed enzymes that characterize some genetic diseases can be made more functional by just increasing the cofactor supply. In this way, Ames suggests that a properly adjusted diet of micronutrients can in itself constitute effective treatment for a variety of genetic disorders.

Ames and colleagues[16] also provide evidence that micronutrient deficiencies can cause oxidative damage to nuclear DNA and to mitochondria, leading to metabolic changes, endothelial disruption, aggravated inflammatory processes, systemic diseases in various organs, neuronal decay, and accelerated aging.[17] These deteriorative processes can be slowed in rats by administration of alpha-lipoic acid and acetyl-L-carnitine.[18,19] Similarly, supplementation with a broad spectrum of micronutrients reduces the oxidative changes and DNA damage associated with chronic stress in

Box 4
Selected potential disease mechanisms related to micronutrient deficiencies

Inborn errors of metabolism: Genetic polymorphisms may cause reduced binding affinity (Km) of an enzyme for its micronutrient cofactor, leading to genetic disease.

Micronutrient deficiencies can increase oxidative damage to nuclear DNA (B12, folic acid, B6, C, E, iron, selenium, zinc), leading to numerous metabolic dysfunctions and increased risk for cancer.

Micronutrient deficiencies aggravate mitochondrial oxidative decay (iron, biotin), leading to inflammation-related diseases in multiple organ systems, neuronal deterioration, and accelerated aging.

Micronutrient deficiencies can lead to a temporary constriction of less essential biologic functions in order to preserve functions related to short-term survival (triage theory), but at the long-term cost of increased disease and aging.[14]

Adapted from Ames BN. Optimal micronutrients delay mitochondrial decay and age-associated diseases. Mech Ageing Dev 2010;131(7–8):473–9.

mice.[20] Ames[21,22] hypothesizes that physiologic functioning can be pervasively optimized by supplementation with a broad variety of micronutrients, a process he calls a "metabolic tune-up."

Need for a Full and Balanced Range of Micronutrients for Optimal Functioning

In considering the many biologic roles of micronutrients, it should be evident that optimal functioning requires fully adequate levels of all micronutrients, not just some or many. Given that depletion of specific micronutrients can result from a variety of physiologic stressors, it is especially critical that micronutrient supplies be well maintained during periods of stress. To that end, maintenance micronutrient stores in the body should be large enough to achieve and maintain adequate levels even during periods of stress.

With vitamins and minerals involved in virtually every biologic, chemical, and physiologic process, it should not be surprising that health effects of micronutrient inadequacies are abundant.

Micronutrient deficiencies in the general population

Most epidemiologic studies agree that most of the population in the developed world does not suffer from significant micronutrient deficiencies, if "deficiency" is defined as a severely compromised nutrient status. Nonetheless, there is substantive reason to believe that a broad array of specific micronutrient "insufficiencies" are common in the general population, even among the presumably well-fed.

According to data collected for the 2003 to 2006 National Health and Nutrition Examination Survey (NHANES), "10% or less" of the American population has nutritional deficiencies.[23,24] These data are largely based on biochemical indicators present in blood or urine, such as actual micronutrient concentrations or the activity of micronutrient-dependent enzymes. Wide age variations in specific micronutrient deficiencies are observed. For example, vitamin B12 deficiency is rare in children and adolescents (<1%) and more common in older adults (4%), whereas children are susceptible to iron deficiency (7%).[23] These estimates are based on a limited selection of biochemical indicators and so probably underestimate the true prevalence of deficiency.

Although the Centers for Disease Control and Prevention Executive Summary reports the deficiency prevalence as "10% or less," the NHANES data show a greater

than 10% deficiency prevalence of vitamin B6 alone (Fig. 1). An individual may have one or several specific deficiencies. These studies examine micronutrient deficiencies one by one, not collectively across the range of possible deficiencies. The various micronutrient deficiencies are not all concentrated in the same "10%" of the population. Instead, different specific deficiencies are scattered sporadically across a larger segment of the population. There have been few attempts to estimate the prevalence of individuals who have one or more of the many possible micronutrient deficiencies, but it is apparent from these data that more than 10% of the population must have at least one micronutrient deficiency.

An alternative to selected biochemical assays are attempts to estimate deficiency in a population based on "food memory" questionnaires or food diaries, but these and other methods of measuring nutrient intake to assess nutrient status are fraught with problems.[27] If this approach were pursued anyway, it might seem reasonable to ask what percentage of the population fails to meet the RDA for a micronutrient, as the RDA is often interpreted by the public as a nutritional goal for individual intake. However, the RDA is defined as the intake level required by 97% of the healthy population (it is not possible to set a requirement that is generally applicable to unhealthy individuals), so attempting to aim the average intake standard at the 97% level would overestimate the prevalence of deficiencies.[28]

Instead of using RDAs, the preferred approach is to use the Estimated Average Requirement (EAR), which is the average daily intake that meets the nutrient requirements of 50% of the healthy population. Using this statistic, one can compare *average* intake to *average* requirement, which is a more meaningful way to estimate nutritional adequacy (Fig. 2). Approached this way, a similar picture emerges: Large segments of the population are not meeting intake standards for a variety of micronutrients. A variety of micronutrients are found to be ingested below intake standards.

All of these types of approaches to estimating nutritional deficiency in the population have limitations. Nonetheless, in looking at these types of data across the

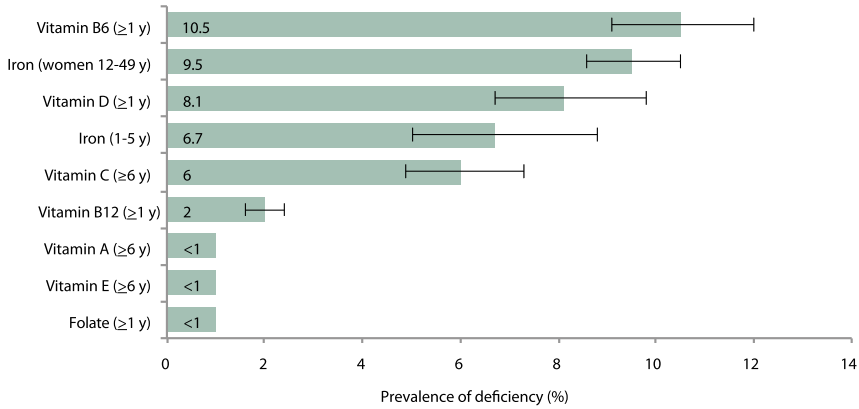

Fig. 1. Prevalence of single micronutrient deficiencies in the American population based on biochemical indicators of nutritional status. Prevalence estimates of nutritional deficiency based on data from the 2003–2006 NHANES in different age segments of the population. Error bars are 95% CIs. Similar profiles have been found in other databases in Canada[25] and England.[26] (*From* Centers for Disease Control and Prevention. Second national report on biochemical indicators of diet and nutrition in the US population. 2012 Executive Summary. Atlanta: Centers for Disease Control and Prevention; 2012. Available at: http://www.cdc.gov/nutritionreport/pdf/ExeSummary_Web_032612.pdf.)

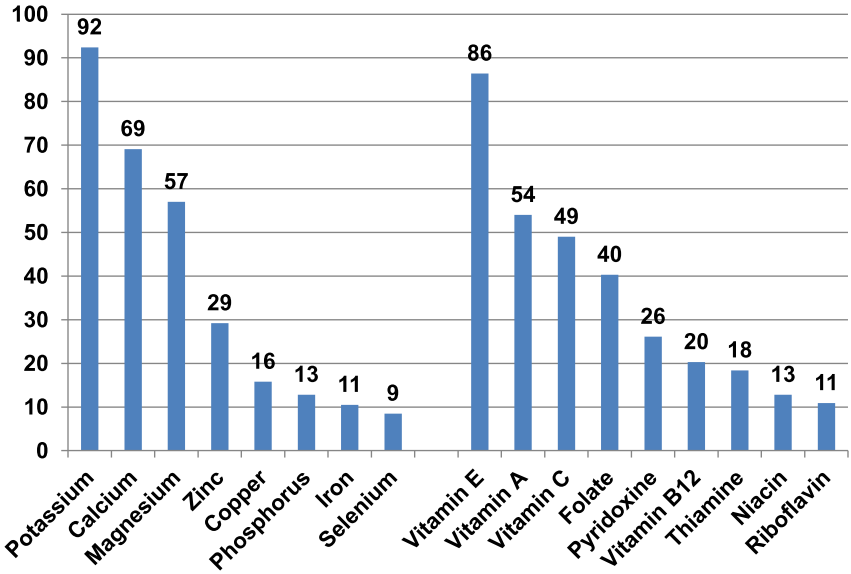

Fig. 2. Percentage of the US population that does ***not*** meet the estimated average requirements for specific nutrients. These figures do not include sources from vitamin supplements, so nutrient insufficiency may be overestimated. Also, not meeting the EAR (or the RDA) does not mean that an individual is nutrient insufficient. Food intake estimates are based on 1999–2004 data for the US population age 2 and older in "What We Eat in America," the dietary intake interview of NHANES. Food intake estimates are compared with EARs (or, if not available, Adequate Intakes), which is a component of the Dietary Reference Intake standards for nutritional recommendations set by the Institute of Medicine of the US National Academy of Sciences. (*Data from* United States Department of Agriculture (USDA), Agriculture Research Service (ARS). Community Nutrition Mapping Project. Available at: http://www.ars.usda.gov/Services/docs.htm?docid=15705. Accessed April 9, 2014. Data and figure assembled by Taron Fletcher.)

range of micronutrients, there is a consistent picture of gaps in nutrition in the general population, sporadic but not rare, varied and to some degree unpredictable, highly individual, and very hard to quantify. In view of the numerous nutritional insufficiencies in each individual micronutrient observed in parts of the population, it seems clear that a significant proportion of the population has suboptimal micronutrient status.[29] Despite their qualitative and quantitative vagueness, these data highlight the inadequacy of the common medical presumption that the American public has adequate micronutrient intake. To state the obvious, even a 10% prevalence of micronutrient deficiencies in a presumably well-fed or overfed nation is far from trivial and, based on NHANES data, this 10% figure appears to be a very significant underestimate. Even if these epidemiologic estimates do not and cannot describe them definitively, a priority goal for public health and a medical goal for individuals would be to address the sporadic micronutrient insufficiencies that these data imply.

Nutrient deficiencies and nutrient insufficiencies

The micronutrient intake standards, such as EAR and RDA, are generally established to help reduce the risk of deficiency states. Deficiency states were initially defined as the classic disorders associated with grossly inadequate nutrient intake (**Table 1**).

Table 1
Selected examples of vitamin deficiency diseases

Vitamin A	Retinol	Night blindness, corneal and conjunctival changes
Vitamin B1	Thiamine	Beriberi (including irritability, emotional lability) Wernicke encephalopathy (short-term memory loss, disorientation, confabulation, hallucinations)
Vitamin B2	Riboflavin	Seborrheic dermatitis
Vitamin B3	Niacin	Pellagra (including mental confusion, dementia, depression, anxiety, agitation, aggression, hallucinations, paranoia)
Vitamin B5	Pantothenic acid	Peripheral nerve damage
Vitamin B6	Pyridoxine	Seizures, amino acid metabolism disorders
Vitamin B7	Biotin	Carbohydrate and fat metabolic disorders, dermatitis
Vitamin B9	Folate	Megaloblastic anemia
Vitamin B12	Cobalamins	Pernicious anemia (including depression, mania, hallucinations, paranoia) with spinal cord degeneration
Vitamin C	Ascorbic acid	Scurvy (including depression, irritability)
Vitamin D	Calciferol	Rickets, osteomalacia, osteoporosis
Vitamin E	Tocopherol	Neurologic and muscular disorders
Vitamin K	Phytomenadione Menaquinone	Hemorrhagic diseases —

These disorders are not subtle, and they tend to be associated with relatively extreme deficiencies of particular micronutrients. An individual might have "deficient" micronutrient levels even if they do not have signs of frank deficiency disorders. Failure to meet RDA or EAR intake levels does not imply that an individual has a deficiency, and adequacy of dietary micronutrient intake does not guarantee that an individual has adequate nutrient status, because of individual variations in micronutrient supply and utilization. As a result, deficiencies may be conceptualized in terms of overt disease states and functional underperformance, or, alternatively, in terms of inadequate nutritional levels regardless of symptom status.

Mild inadequacies, characterized by suboptimal status but not severe enough to cause overt disease, are called "insufficiencies." Insufficiency states tend to be less clinically obvious but are much more prevalent. Short of overt disease, micronutrient insufficiencies imply some degree, or at least a risk, of compromise in physiologic functioning.

Formal definitions of deficiency and insufficiency levels are described for many micronutrients, often expressed in terms of serum concentrations. For example, based on bone health, vitamin D deficiency has traditionally been defined as serum concentrations of 25-hydroxyvitamin D below 20 ng/mL (50 nmol/L), but the consensus now holds that levels below 30 ng/mL are indicative of vitamin D insufficiency for the many other functions of vitamin D beyond bone health.

In the NHANES, which surveyed 6275 American children and adolescents from 2001 to 2004, the prevalence of vitamin D deficiency (<15 ng/mL) was 9%, and the prevalence of 25-hydroxyvitamin D insufficiency (<30 ng/mL) was a remarkable 61%.[30] Such data demonstrate that epidemiologic studies of vitamin *insufficiency* are needed to better understand nutritional needs at the population level.

Large-scale data from the Canadian Community Health Survey 2.2 (n = 34,381) similarly suggest that children (1–13 years old) have a very low prevalence of nutritional adequacy. Fewer than 30% of children were found to have sufficient intake of most

micronutrients based on their dietary intake alone.[25] For the population 14 years or older, there was a similarly low level of nutritional adequacy, even when oral micronutrient supplementation was taken into account.

It should be clear that current data based on micronutrient *deficiencies* are likely to significantly underrepresent the extent of the problem and lead to policies that do not effectively serve the health needs of the public. Even conservative estimates of vitamin insufficiency implicate most of the population of both children and adults.

The intake amounts needed to obtain genuinely "optimal" functioning are above the cutoffs for vitamin insufficiency. There is no requirement that all areas of the body require similar amounts of a micronutrient, so optimal levels might vary depending on whether the target is hematological health, cardiac health, or brain health. In general, as more becomes known about nutritional effects on physiologic functioning, the standards of recommended micronutrient intake have tended to increase over time.

Still more subtle than nutrient insufficiencies are "relative insufficiencies," in which the biologically available amount of a nutrient might be adequate, but it is out of balance with respect to the availability of other micronutrients. Such imbalances in the ratios among micronutrients can have significant health consequences. A well-known example is the calcium-magnesium-phosphorus balance, in which excessive calcium leads to constipation and excessive magnesium leads to diarrhea. In another example, both chromium and vanadium can increase insulin sensitivity. The fact that chromium can counter insulin resistance does not mean that there is a chromium deficiency, because the problem might be due to low vanadium levels. These balances among micronutrients can be quite complex: the zinc-copper balance is strongly influenced by iron, magnesium, and manganese. A relative insufficiency may cause physiologic difficulty even if there is no absolute insufficiency of a micronutrient. Maintaining a proper balance among the various micronutrients can be critical to proper health.

The American problem in nutrition is minimal compared with the challenges in the developing world, where food shortages are endemic and food quality is too often abysmal. There remain enormous obstacles to dealing with the nutritional requirements and energy (calorie) needs of the world's population,[31] although some progress is being made in dealing with vitamin and mineral deficiencies on a worldwide basis.[32,33] Sufficient intakes of vitamin A, iodine, and iron have long been recognized as critical for immunologic and reproductive health, as well as physical growth and cognitive functioning, especially for children.[34]

Regardless of whether the health goal is to avoid deficiency diseases, to minimize insufficiency states, or to optimize functioning in part of (or the whole) body, the standard recommended intake levels are not assumed to be sufficient to replenish nutrient adequacy in the medically ill or in the seriously undernourished. Recommended dietary intake can vary by region, depending on the nutritional requirements and the nutritional resources of the local population. In geographic regions where low zinc levels in the soil might require local adjustment of copper intake standards, American RDA or EAR standards may not be helpful. In any case, the American population as a whole does not set a high standard for dietary competence.

General correlations between diet and mental health

Several epidemiologic reports have been extensively publicized for suggesting a link between depressive mood (not major depressive disorder) in adults and unhealthy "Western" dietary patterns (sugar-laden products, refined grains, red and processed meats, fatty and fried foods; low intake of fiber, fruits, and vegetables), but 2 recent

systematic reviews of these data (mostly in adults) found conflicting and inconclusive evidence of this link.[35,36] The only study examining bipolar disorder[37] in adults found some initial evidence that "Mediterranean" dietary patterns may be more favorable than Western or modern ("foodie") dietary patterns. Overall, the data in adults are limited and do not allow any clear conclusions.

Looking specifically at studies of youth, there appears to be a stronger correlation between diet and mental health, with more evidence of a link between poor diet and depressed mood. Several large independent studies have provided cross-sectional or prospective data supporting a link between an unhealthy diet in childhood[38] or adolescence[38–43] and lower general mental health scores. The 3 studies that collected data on internalizing (withdrawn/depressed) behaviors found correlations with poor diet quality.[38,39,42] Similarly, a study of 7114 adolescents (ages 10–14) found that depressive mood scores (Short Mood and Feelings Questionnaire) correlated with low diet-quality scores, with an adjusted odds ratio of 1.8 (1.5–2.1) for having depressive mood scores, when comparing the lowest and the highest quintiles for unhealthy diet scores.[44] One prospective study of 3757 children (ages 10–11) did not find diet quality correlating with internalizing disorders, but did find that increased variety in diet foods was associated with a lower prevalence of internalizing disorders,[45] so even this study could be viewed as positive evidence of a link.

The only clearly negative finding involved a different kind of experimental design. A prospective study of 23,020 mothers and their children found that higher intake levels of unhealthy foods (sugary drinks, salty snacks, refined cereals, processed meats) during pregnancy were not correlated with the presence of internalizing behaviors in the children at ages 1.5 to 5.0 years, although it did find a correlation with externalizing symptoms in early childhood.[38]

Overall, these studies provide reasonably consistent evidence of associations between diet quality and mental health in youth, with poor diets generally linked to an increased risk of internalizing disorders or depressive moods. These studies do not provide evidence addressing a possible connection to actual mood disorders in youth.

In fact, there are no studies of a mood-diet link in youths with mood disorders, but there is a study by Davison and Kaplan[46] that examined the relationship between dietary components and general functioning in 97 community adults with mood disorders. Scores for Global Assessment of Functioning were found to correlate with dietary intake of energy (calories), carbohydrates, fiber, total fat, linoleic acid, and certain micronutrients: magnesium ($r = 0.41$, $P<.001$); zinc ($r = 0.35$, $P<.001$); calcium, phosphorus, potassium, iron, B3, B5, B6, B9, and B12 (all $P<.05$). With each of the nutrients, there was a consistent pattern of increased nutrient intake correlating with better global functioning. However, depression and mania scores did not correlate with total daily intake of most micronutrients, except for iron and zinc. There was a correlation between decreased depression (Hamilton Depression Rating Scale [HAM-D]) scores and increased iron levels ($r = -0.22$, $P<.05$), and also a correlation between decreased mania (Young Mania Rating Scale [YMRS]) scores and increased levels of zinc ($r = -0.25$, $P<.05$). These findings are interesting but have not yet been subjected to replication in other samples.

Overall, the data linking general diet and mood seem suggestive but inconclusive in adults, even in adults with mood disorder. In contrast, the data in youth seem more suggestive, although there are no data on a link to mood disorders. Even if there is an association, it is unclear from these findings whether depressed mood is a cause or a result of a low-quality diet, although some prospective data

suggest that the dominant mechanism is poor diet leading to a depressive mood, at least in adolescents.[40] A more definitive answer to the question of causation could be provided by intervention studies showing nutrient-induced improvements in mood.

TREATMENT OF MOOD DISORDERS WITH SINGLE MICRONUTRIENTS

Kaplan and Shannon[47] conducted a review of the evidence linking specific micronutrients to mood symptoms in children and adults. Based on clinical trials, as well as biochemical correlational studies, significant mood effects in humans were identified for a large number of vitamins and minerals (**Box 5**), and beneficial therapeutic effects have been identified for a small number of single micronutrients.

The study of individual micronutrients for treating psychiatric disorders is an endeavor that goes back decades.[48] Overall, these studies have yielded relatively few consistent replicable findings.[49] Many reports on the efficacy of single micronutrients for treating mood in adults, conducted in healthy volunteers and in patients with mood disorders, have not stood up well on replication. Nonetheless, a small number of micronutrients have shown consistent evidence of some degree of antidepressant effectiveness in adults as single micronutrient treatments,

Box 5
Single micronutrients associated with mood alterations in adults

Vitamins
- Vitamin B1: Thiamine
- Vitamin B3: Niacin
- Vitamin B6: Pyridoxine
- Vitamin B7: Biotin
- Vitamin B9: Folate
- Vitamin B12: Cobalamin
- Vitamin C: Ascorbic acid
- Vitamin D: Cholecalciferol
- Vitamin E: D-alpha tocopheryl

Minerals
- Lithium
- Magnesium
- Calcium
- Iron
- Copper
- Zinc
- Chromium
- Selenium

Data from Kaplan BJ, Crawford SG, Field CJ, et al. Vitamins, minerals, and mood. Psychol Bull 2007;133(5):747–60.

including folic acid and vitamin D for major depressive disorder (MDD), vitamin B12 for MDD in the elderly, and, more speculatively, chromium for atypical depression with carbohydrate craving and selenium for prevention of postpartum depression.

This is a large and largely unsatisfying literature, involving a huge number of methodologically unsound studies, which will not be reviewed here. Instead, we will focus mainly on the relatively small number of randomized double-blind placebo-controlled trials (RDBPCTs), with emphasis on the few single-micronutrient treatments whose findings in adults offer some plausible hope that they may someday prove to have value in youth.

Folic Acid (Vitamin B9)

Folic acid is involved in many biologic processes. In its active forms, tetrahydrofolates participate in single-carbon transfers, methylation (including the rate-limiting step in DNA synthesis), cell replication, brain development, and red blood cell formation, among many others. It is a cofactor in the biosynthesis of S-adenosyl-methionine (SAMe) and choline, 2 small molecules that have well demonstrated effects on mood, as well as on the synthesis of serotonin, dopamine, and norepinephrine, which are neurotransmitters implicated in mood disorders.[50–53]

Folate deficiencies have been implicated in diverse disease states and abnormalities, including depression in adults. Low serum folate levels are associated with lower levels of serotonin and dopamine metabolites in cerebrospinal fluid. Clinically, lower folate levels are correlated with greater severity of depression, weaker response to serotonin reuptake inhibitors (SSRIs), more rapid relapse after effective treatment, and perhaps to weaker responses to lithium augmentation and to electroconvulsive therapy.[54] Some preliminary data suggest a specific association between low folate status and the melancholic symptoms of depression.[55,56]

The Complementary and Alternative Medicine Task Force of the American Psychiatric Association[57] found that the data on folic acid were inadequate to draw any conclusions regarding its value as a monotherapy, but concluded that folic acid was a "reasonable" adjunctive treatment for MDD in adults.

Four RDBPCTs have examined antidepressant-treated adults (ages 21–65) who received augmentation with either folic acid[58,59] or L-methylfolate[51,60] or instead received augmentation with placebo. An additional randomized controlled trial (RCT) of antidepressant augmentation compared higher and lower doses of folic acid.[61] In these studies, antidepressant treatment usually consisted of an SSRI, typically fluoxetine 20 mg daily. All 5 RCTs showed that folic acid or L-methylfolate augmentation of antidepressants was effective (in comparison with placebo or a lower dose), with an effect size of 0.35 to 0.4.[62,63] In addition to folic acid and L-methylfolate, an open-label trial suggests that folinic acid also may effectively augment SSRI treatment.[64] One study showed that L-methylfolate augmentation was effective after patients had not responded to 8 weeks of treatment with fluoxetine 20 mg,[51] and that this clinical response appeared linked to obesity and to specific genetic and biologic markers related to inflammation and folate metabolism.[62]

The only negative study on folic acid augmentation was a naturalistic RCT that examined a low dose of folic acid (in combination with vitamin B12) in 209 elderly subjects (ages 60–74), but this unblinded study was conducted on a community sample that was not systematically diagnosed, entry into the study was based on patients attesting that they were taking antidepressants, and details of the antidepressant treatments were not specified.[65] Although a naturalistic study of folic acid augmentation would be useful, this study does not provide strong evidence against the

treatment, especially in the face of 5 positive RDBPCTs. It might be noted, though, that 2 of the 5 RCTs were funded by pharmaceutical manufacturers.[51,58]

The available monotherapy studies of folic acid in MDD are methodologically limited. In fact, there are no RDBPCTs of folic acid monotherapy in MDD. In view of its relatively modest effect as an adjunctive therapy, folic acid seems unlikely to become a clinically relevant antidepressant monotherapy.

Several RCTs have examined the mood effects of folic acid in the general population. An RDBPCT of folic acid monotherapy, examining 211 women (ages 20–92) in a nonclinical sample, found positive effects after 35 days on cognition (including processing speed, recall, and recognition memory), but not on mood.[66] Three RCTs in the general population explored the effects of folic acid combined with other B vitamins, typically B12 and B6, and also found no beneficial effects on mood[67–69]; however, these samples consisted largely of elderly subjects, so it is unclear whether the B vitamin intervention did not have mood effects because the subjects were not depressed or because the sample was geriatric. In general, the effect of folic acid in nonpsychiatric and/or geriatric populations is unclear, but studies have generally been negative. However, one RDBPCT of 273 stroke survivors showed a reduced risk of developing MDD (18% vs 23%, adjusted hazard ratio 0.48) in subjects who were followed for a mean of 7 years after their stroke while taking folic acid combined with vitamins B12 and B6, although the effect did not reach significance in the intent-to-treat analysis.[70]

In youth, a cross-sectional study[71] conducted in 6517 community adolescents (ages 12–15) found that higher dietary folate intake was correlated with fewer depressive symptoms (adjusted odds ratio [OR] 0.6, $P<.002$). The same study found lower depression scores in youth correlated with low vitamin B6 (pyridoxine) intake (OR 0.73, $P<.02$) and (for girls only) low vitamin B2 (riboflavin) intake (OR 0.85, $P = .03$), but not with vitamin B12 (cobalamin) intake. No studies of folic acid are available in youth with depressive disorders, either as adjunctive treatment or as monotherapy.

Folic acid is generally well tolerated, but it is associated with a variety of adverse effects (**Box 6**). Central nervous system (CNS) reactions have included symptoms suggestive of depression[72] or mania,[73] although the mania has been questioned.[74] Rare allergic reactions[75–78] have been described with folic acid, even when used within moderate dose ranges. Folic acid treatment can lead to delayed recognition and treatment of vitamin B12 deficiency, because folic acid corrects the megaloblastic anemia that often heralds B12 deficiency (macrocytosis results from the inhibition of DNA synthesis caused by B12 or folate deficiency; B12 deficiency does not cause macrocytosis in the presence of adequate folate). There are also well-established nutrient-drug interactions involving folic acid with anticonvulsants, oral contraceptives, and alcohol.[79] Some epidemiologic data on folic acid raise the question of a possible increase in risk for cancer or cardiac events with chronic use,[80,81] a suggestive finding that underscores the need for safety testing, even for compounds as seemingly innocuous as folic acid.

Several versions of folic acid, L-methylfolate, and folinic acid are commercially available, but their clinical differences in treating depression are poorly defined. L-methylfolate is available by prescription at higher doses (7.5 or 15 mg) or over the counter at lower doses (0.8–1.0 mg). Although L-methylfolate was initially marketed for people who had difficulty in converting folate to its active form, some data suggest that methylfolate may help adults with depression who do not have the enzyme defect, consistent with the broader hypothesis that folic acid itself can contribute adjunctively to the treatment of MDD in adults.

Box 6
Clinical points on folic acid

Adverse Effects

Gastrointestinal effects, including nausea, anorexia, bloating, and flatulence.

Bitter or unpleasant taste.

Alterations in sleep (insomnia, vivid anxiety dreams), concentration, mood (depression and possibly mania), irritability, activity level, or mental clarity.

Seizures in patients receiving anticonvulsants, possibly due to lowered plasma anticonvulsant levels.

Question of increased risk of cancer and cardiac events.

Delayed recognition and treatment of vitamin B12 deficiency.

Allergic reactions, including erythema, rash, pruritis, urticaria, malaise, fever, and bronchospasm.

Nutrient-Drug Interactions

Folate absorption, blood levels, or effects are reduced by alcohol, nicotine (smoking), estrogens (oral contraceptives), nonsteroidal anti-inflammatory drugs (ibuprofen, naproxen, aspirin), H2 receptor antagonist antacids (ranitidine, famotidine), anticonvulsants (valproate, carbamazepine, lamotrigine, phenytoin, primidone), antibiotics (tetracycline), isotretinoin, metformin, diuretics (thiazides, furosemide), isoniazid.

Folic acid reduces levels or effects of anticonvulsants (phenytoin).

There is an RDBPCT describing folic acid as an effective augmentation agent for valproate treatment of acute mania in adults.[82] In an RDBPCT of 88 adults with mania treated with valproate, a 30% reduction in YMRS scores was apparent after 3 weeks of add-on folic acid (3 mg daily) compared with placebo augmentation ($P<.005$), with an effect size of 0.4. An early RDBPCT also suggests that folic acid (0.2 mg daily) may be effective for augmentation of lithium maintenance treatment in preventing relapse in adults with unipolar and bipolar depression, with the strength of the prophylactic effects correlating to plasma folate concentrations.[83] Neither of these studies has been replicated.

Overall, folic acid, L-methylfolate, and perhaps folinic acid appear to be modestly but clearly effective for augmentation of SSRI treatment of MDD in adults, with generally minimal adverse effects. It is unclear whether folic acid has value as a monotherapy of depression, whether its effectiveness for augmentation might be weaker in geriatric depression, and whether it alters mood in nonclinical samples. Based on findings in adults, folic acid appears to be the most likely of the single micronutrient treatments to have some potential role in treating depression in youth, albeit as an adjunctive option. However, there have been no trials of folic acid in youth with MDD.

Cobalamins (Vitamin B12)

The biologically active coenzyme forms of vitamin B12 are methylcobalamin (in intracellular fluids) and adenosylcobalamin (in mitochondria). Vitamin B12 is commercially available in oral supplements as cyanocobalamin, a synthetic but biologically inactive form, or in injectable depot form as hydroxocobalamin. Like folate, it participates in many biologic reactions, including methylation, DNA synthesis, hematopoiesis, and

numerous metabolic processes, including synthesis of SAMe, conversion of folate to its active form as tetrahydrofolic acid, and myelin formation.

Its value in treating depression appears to be mainly in elderly patients. Elderly people are more susceptible to B12 deficiency because of declining absorption associated with senescence (about 30% of people older than 60 have atrophic gastritis), but patients of any age with inflammatory bowel disease or other gastrointestinal absorption impairments can be at risk.

B12 supplementation may have a role in treating certain older patients, but it is unlikely to be relevant for treating depressive disorders in otherwise healthy youth. Arguably, screening for serum B12 (or methylmalonic acid) levels might be considered for youths with chronic malabsorption, but it is not relevant for typical cases of depression in children or adolescents. Youths with very severe B12 deficiency may present with depressive and psychotic symptoms in association with obvious neurologic symptoms; their mental symptoms respond to B12 injections within 1 to 2 weeks.[84,85]

Although there are several trials of B12 combined with folic acid (and sometimes other vitamins) in treating depression, the 2 trials in adults of vitamin B12 monotherapy[86,87] were negative. The only trial of B12 as augmentation to an antidepressant[88] showed a positive effect, but was methodologically weak.

There are no studies of vitamin B12 for treating major depression in youth, and it does not appear to be a promising area for research, except speculatively in youth with chronic gastrointestinal absorption impairments. Folic acid would be a better candidate for a trial for treating depressed youth.

Calciferols (Vitamin D)

Vitamin D has received much less attention than the B vitamins in psychiatry, and so this micronutrient is covered in more detail.

Vitamin D is traditionally viewed as crucial for calcium and phosphate absorption, calcium homeostasis, and bone health, including its role in preventing rickets (childhood osteomalacia), osteomalacia in adults, and osteoporosis. More current understanding recognizes vitamin D as a series of steroid hormones that are relevant in a broad range of physiologic processes. Low vitamin D status has been implicated in apoptosis, immunologic regulation (increased proinflammatory cytokines and inflammation), insulin resistance, aberrant cell proliferation and differentiation, and neuronal connectivity.[89–91]

Hypovitaminosis D has been implicated in the pathophysiology of hypertension; cardiovascular disease (eg, left ventricular hypertrophy); type 2 diabetes; infectious, inflammatory, and autoimmune disorders (including asthma); and certain cancers (colorectal and possibly breast, prostate, and pancreatic). During pregnancy, low levels are associated with preeclampsia, infections, premature birth, and low birth weight.[92] Early evidence suggests that vitamin D supplementation may exert a therapeutic influence in all of these conditions.[90,93,94]

Similar to other steroid hormones and to thyroid hormones, vitamin D isomers may be viewed as neurohormones that are essential to brain development and functioning. Vitamin D (calcitriol) receptors are distributed diffusely in the brain, including in the hypothalamus, basal ganglia, hippocampus, cerebellum, and thalamus.[95] In the CNS, hypovitaminosis D has been linked to Alzheimer disease and other forms of cognitive dysfunction, epilepsy, Parkinson disease, multiple sclerosis, and chronic pain, as well as depression, bipolar disorder, schizophrenia, and autism.

The 2 main forms of vitamin D are cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2). Vitamin D3 is synthesized in the skin after exposure to sunlight (ultraviolet

B radiation) or ingested in animal-derived foods. Vitamin D2 is obtained through the diet (eg, dairy, fish, plants). Both are converted to the biologically active form, called calcitriol or 1,25-dihydroxyvitamin D. The form that is most evident in circulation is 25-hydroxyvitamin D, and that is the form that is usually assayed to assess nutritional adequacy of vitamin D.

Although vitamin D *deficiency* has been conventionally defined by 25-hydroxyvitamin D serum levels below 10 to 20 ng/mL and vitamin D *insufficiency* by levels below 30 ng/mL, more recent data suggest that higher blood levels are desirable. Insufficiency is now increasingly defined as physiologic abnormalities associated with levels below 35 to 40 ng/mL. Many specialists clinically advise a normal range of 50 to 80 ng/mL. Undesirable effects may emerge above 80 to 120 ng/mL.

Low vitamin D levels often result from inadequate dietary intake and lack of sunlight exposure (eg, northern latitudes), but they also have been associated with female gender, older age, obesity, dark skin tone, low milk consumption (less than once weekly), more than 4 hours daily of screen time (television, computer, or video), high altitudes, malabsorption, and nonuse of vitamin D supplementation.

As previously noted, in the NHANES of more than 6000 American children and adolescents in 2001 to 2004, the prevalence of vitamin D insufficiency was 61% and of vitamin D deficiency was 9%.[30] Only 4% had consumed a daily mean of 400 IU, where the RDA is 600 IU. Among these youth, vitamin D deficiency was associated with more diabetes (OR 1.9), hypertension (OR 2.5), low high-density lipoprotein (OR 3.0), elevated C-reactive protein (OR 0.7), low serum calcium (OR 0.09), and increased parathyroid hormone levels (OR 3.6) compared with youths with 25-hydroxyvitamin D levels 30 ng/mL or higher.

Several clinical studies suggest a wide range of potential influences of vitamin D in the CNS. In a study of 308 girls who were followed from a gestational age of 18 weeks until age 20 years, the mothers' vitamin D levels at 18 weeks of pregnancy were found to be a significant predictor of the children's risk of eating disorders during adolescence.[96] Other data suggest a relationship between prenatal vitamin D status and language impairment at ages 5 and 10 years, although these may be specific deficits that do not apply to all aspects of CNS functioning.[97]

Correlations between vitamin D levels and depression in adults

Two recent reviews and meta-analyses examined large cross-sectional and prospective cohort studies assessing the link between serum 25-hydroxyvitamin D levels and the risk for depression in adults. In one meta-analysis,[98] lower vitamin D levels were found in adults with depression than in controls (Standardized Mean Difference = 0.60, 95% Confidence Interval [CI] 0.23–0.97). The cross-sectional studies showed an increased odds ratio of 1.31 for depression in the lowest compared with the highest vitamin D quartiles (95% CI 1.0–1.71), and the cohort studies showed an increased hazard ratio for depression of 2.21 (95% CI 1.40–3.49). The other analysis found low 25-hydroxyvitamin D levels to be significantly associated with depression in only 5 of the 11 case-control studies (n>43,000) and in 2 of the 5 prospective cohort studies (n>12,000, mostly elderly), but the overall data supported a small but significant reduction in risk for depression (OR 0.92–0.96) for each 10 ng/mg increase in serum 25-dihydroxyvitamin D levels.[99] Subsequently, 5 additional cross-sectional studies have examined this association. Four of the 5 studies showed a statistically significant correlation of lower vitamin D levels with increased depression.[100–104] The fifth study showed only a statistical trend.[105]

Despite the differences across studies, the overall findings point to a correlation between depression and low vitamin D status. Several instructive reasons may explain the variability in the data:

1. A cross-sectional study of 12,594 adults found that patients with a prior history of depression were at greater risk of depression associated with a low vitamin D level, whereas patients with no history of depression showed no correlation of vitamin D levels and current depression.[106] This suggests that the association of hypovitaminosis D with depression may be stronger in patients with repeated depressive episodes, a factor that other cross-sectional studies did not examine.
2. Two studies found that the depression/hypovitaminosis D correlation is strongest during low vitamin D months (eg, winter in North America) and that the association persisted only weakly during the high vitamin D months.[107,108]
3. A cross-sectional study in adults found that the risk of depression only began to reduce once the serum 25-hydroxyvitamin D levels were higher than 42 ng/mL,[109] suggesting that the standard cutoff for vitamin D insufficiency at 30 ng/mL might need to be revised for studies of depression, consistent with recent claims that optimal serum vitamin D levels are 50 to 80 ng/mL.

Correlations between vitamin D levels and depression in youth

Several cross-sectional studies in youth have been published and, as in adults, the findings are conflicting. A study of 945 young adults at age 20 years[110] found a 10% increase in serum 25-hydroxyvitamin D concentrations was associated with a 9% reduction in depression ($P<.001$) in males but not in females. Two smaller studies also found correlations of vitamin D status in youth with mood[111] or well-being scores.[112] In contrast, 4 cross-sectional studies in adolescents and young adults did not find such a correlation,[113–116] including a rigorous study of 104 adolescents finding no significant elevation of vitamin D deficiency among 36 youths with major depression or among 52 youths with other mood disorders.[114]

A large prospective cohort study[117] assessed vitamin D status at a mean age of 9.8 years and then evaluated depressive symptoms (Mood and Feelings Questionnaire) in 2750 youths at ages 10.6 and 13.8 years. Higher concentrations of 25-hydroxyvitamin D at 9.8 years predicted fewer depressive symptoms at 13.8 years (adjusted risk ratio 0.90, 95% confidence interval [CI] 0.86–0.95), but not at age 10.6 years (risk ratio 0.98), suggesting that the association between vitamin D3 levels and depression may emerge during early adolescence, perhaps related to puberty.

Overall, the correlational studies showed associations between vitamin D levels and depression in 7 of the 16 adult studies and in 4 of the 8 youth studies, so no clear age effect emerges. Again, the conflicting findings are difficult to interpret but could reflect a genuine correlation that is diluted by uncontrolled factors, such as single versus repeated depressive episodes, geographic differences (less sunlight exposure in northern latitudes), sampling season (winter vs summer), and dietary intake levels.

Correlational findings do not speak to causality; even if there is an association, it is unclear whether hypovitaminosis D is a cause or result of depression. Another possibility is that low vitamin D is a marker of upstream illness; for example, if inflammatory processes were a cause of low circulating vitamin D levels, then a wide range of inflammation-related medical disorders might be associated with reduced vitamin D levels, and treatment with vitamin D might have little or no value in treating these disorders. This explanation has been proposed to explain why so many medical illnesses are associated with low vitamin D levels and why so little health benefit

has been seen in clinical trials in a variety of medical fields.[118] Nonetheless, clinical trials may be helpful in assessing whether hypovitaminosis D is a causal factor in depression as well as to determine whether vitamin D supplementation has antidepressant effects.

Treatment of depression with vitamin D

Ten RCTs in adults have examined whether vitamin D supplementation can treat depressive moods, although only a small number examined patients with psychiatric disorders. Four of the 10 RCTs in adults have yielded negative results,[119–122] but only 1 used acceptable depression measures, and it found no benefit in 230 adults who received either oral 40,000 IU weekly or placebo for 6 months.[121]

Six randomized placebo-controlled treatment studies in adults were positive, but 4 provided only weak evidence. A study found statistically significant improvement after 1 year of vitamin D treatment in 441 overweight adults, but the change was not clinically significant, mainly because the subjects started with only very mild depressive symptoms (mean baseline Beck Depression Inventory [BDI] 4–5).[123] A study of a single administration of high-dose vitamin D (intramuscular 300,000 IU) in 120 depressive adults (BDI>17) found improvement 3 months after injections compared with placebo, but standardized psychiatric diagnostic evaluations were not used and the study was not double-blind.[124] A study of seasonal affective disorder found improvement compared with bright-light therapy, but the study was small (n = 15).[125] Two used inadequate methodology.[126,127] The best data come from an RDBPCT examining 42 adults with formally diagnosed MDD being treated with fluoxetine 20 mg. Compared with placebo augmentation, augmentation with vitamin D3 1500 IU daily for 8 weeks produced significant improvements (HAM-D, BDI-21) starting at treatment week 4.[128]

Overall, there were 6 positive and 4 negative vitamin D studies in adults, and the most methodologically reliable studies were split with 1 positive and 1 negative result. Two recent systematic reviews found that the studies in adults were inconclusive.[129,130]

Only 1 treatment study of vitamin D has been conducted in youth with depression.[112] In this open-label case series, 48 adolescents (ages 10–19) with clinically diagnosed depression (without standardized evaluations) and low vitamin D levels (<25 ng/mL) were treated with vitamin D3 for 3 months (4000 IU daily for a month, then 2000 IU). Improvements were shown on self-rated depression scores on the Mood and Feelings Questionnaire-Short Version (14.7 $\pm$ 3.7 to 7.1 $\pm$ 5.3, P<.05) and on the World Health Organization Well-Being Scale-5 (25 $\pm$ 18 to 43 $\pm$ 25, P<.001), and an unvalidated scale showed improvements in daytime tiredness, insomnia, somatic complaints, irritability, and concentration. The study was conducted in Sweden, 74% of cases were initiated in November through April, with no dark-toned youth in the sample, and again all subjects had low vitamin D levels. Although this is an uncontrolled study in a population characterized by factors that increase the likelihood of response, its findings justify an RCT in youth.

Clinical recommendations

Current evidence does not support vitamin D supplementation in the treatment or prevention of depression in adults or youth, but additional studies are clearly warranted. Especially in view of its relatively low toxicity, clinicians may consider its use in vulnerable populations or individuals with known risk factors, and especially if vitamin D insufficiency is documented by blood testing.

Clinicians might consider a variety of risk factors. Given the role of sunlight exposure, the risk of low vitamin D levels increases with higher northern latitudes, more use of sunscreens, more indoor work, little outdoor recreation, darker skin tone, obesity, advanced age, chronic illness, or bedridden status. Seasonal changes render lower vitamin D levels during the autumn and winter months in the northern hemisphere,[131–133] so clinical supplementation may be most relevant in the cold weather months. Adolescents may be at generally higher risk of low vitamin D levels than children,[131] perhaps because of their reduced milk intake.

Hypovitaminosis D appears more marked in patients with more severe depressions. Some data suggest that hypovitaminosis D is more likely in patients with psychosis, both in youth[114] and adults,[134–137] and in suicidal patients.[108,133,138,139]

Future RCTs should evaluate the clinical risk factors in individuals with and without low vitamin D levels, examining both the general population and patients with mood (and other psychiatric) disorders, with attention to possible differences in supplementation effectiveness in winter versus summer.

Although the Institute of Medicine has suggested that most Americans across the nation do not need high-dose D supplements,[140] the NHANES finding of a 61% prevalence of 25-hydroxyvitamin D insufficiency (<30 ng/mL) in children and adolescents remains noteworthy.[30] Supplementation might be more relevant in northern states and perhaps especially in psychiatric populations. A chart review found that 75% of 544 psychiatric adult inpatients in Chicago had vitamin D insufficiency (<30 ng/mL), with a mean level of 22.[141] Similarly, the vast majority of patients in my psychiatric practice in New England have levels below 25 ng/mL. On the other hand, I rarely see vitamin D supplementation produce a clinically noticeable mood improvement. Supplementation can still be justified for general health reasons in patients with demonstrated vitamin D insufficiency.

Consonant with growing evidence that higher serum vitamin D levels are more helpful than traditionally believed, the Institute of Medicine has recently announced a sharp increase in the Dietary Reference Intakes for vitamin D: the RDA was raised from 200 IU to 600 IU daily (for individuals aged 1–70 years).[140] The maximum daily intake that can be safely used chronically without medical supervision (the Upper Level Intake) is 4000 IU daily for individuals aged 9 years and older (3000 IU daily for 4–8-year-olds). Generally, supplementation with vitamin D3 seems more effective than D2 in maintaining nutrient adequacy.[142]

Clinicians who offer vitamin D supplementation should be aware of its potential adverse effects, which are mostly related to hypercalcemia (with chronic use or acute intoxication), and nutrient-drug interactions (**Box 7**). However, the documentation regarding the proposed interactions is not uniformly strong.[143,144]

The wide range of medical disorders associated with hypovitaminosis D highlights that numerous physiologic mechanisms can be affected, underscoring the multiple roles that vitamin D plays in biology. Once thought to be “the bone vitamin,” the plethora of effects of vitamin D in body and brain emphasizes the complexity of the influence of micronutrients in health and disease.

Pyridoxine (Vitamin B6)

Like other micronutrients, pyridoxine is involved in a vast number of biologic processes. As a cofactor for decarboxylase enzymes, pyridoxine plays an essential role in the synthesis of neurotransmitters, including dopamine, norepinephrine, serotonin, and gamma-aminobutyric acid. Vitamin B6 also participates in the metabolism of nucleic acids, proteins, carbohydrates (gluconeogenesis), fats (myelin, phospholipids,

Box 7
Clinical points on vitamin D

Adverse effects: Mainly related to hypercalcemia (increased risk if given with calcium)

- Anorexia, nausea, vomiting, constipation, diarrhea, weight loss
- Muscle weakness or pain, bone pain
- Irritability, confusion, dizziness, headache, fatigue
- Diabetes insipidus (excessive thirst and urination, low urine specific gravity)
- Proteinuria, azotemia
- Nephrolithiasis (kidney stones)
- Hypercalcification of the bones, soft tissues, kidneys, and heart
- Hypertension
- Cardiac arrhythmias

Proposed nutrient-drug interactions

- Vitamin D can reduce the effects of statins, calcium channel blockers, and digoxin (but also increase the risk of digoxin-induced cardiac arrhythmias).
- Vitamin D levels or effects can be reduced by alcohol, cimetidine, magnesium-containing antacids, certain anticonvulsants (valproate, carbamazepine, phenytoin), corticosteroids, orlistat (Xenical for weight loss), ketoconazole, and heparin.
- Vitamin D levels or effects can be increased by statins and thiazide diuretics.

prostaglandins), steroids, collagen, heme, and homocysteine, among many other functions in the body and brain.

There are 3 RDBPCTs of pyridoxine monotherapy on mood in healthy adults. A 5-week trial in 211 healthy women (ages 20–92) found no effect on mood (Center for Epidemiological Studies-Depression Scale, Profile of Mood States Questionnaire [POMS]), relative to placebo, although some cognitive benefits were observed, mainly in memory performance tasks.[66] A 3-month trial in 76 healthy elderly (ages 70–77) community volunteers also showed no effects of pyridoxine on mood, but it was inadequately assessed through a list of mood adjectives[145]; again, some limited cognitive improvements were noted. A RDBPCT examined the effects of pyridoxine on the adverse effects of oral contraceptives in 124 women (ages 18–40); outcome assessment was not rigorous, and trial duration was only 4 weeks, but again no effect of pyridoxine relative to placebo was observed on mood or physical symptoms; cognition was not assessed.[146] So the 3 monotherapy trials in healthy adults were negative.

Perhaps the strongest available suggestion that pyridoxine may be relevant to mood is an RDBPCT of 129 young healthy adults who took a 9-ingredient multivitamin (at 10 times RDA levels) for 1 year, which found that the observed improvements in "agreeable" feelings (and, in women, "composure" and general well-being) were positively correlated with pyridoxine (and riboflavin) levels.[147] Perhaps an interaction of pyridoxine with other B vitamins might explain this finding in the absence of monotherapy effectiveness. On the other hand, a large cross-sectional study of 6517 community adolescents (ages 12–15) unexpectedly found lower depression scores with *low* dietary intake of pyridoxine (OR 0.73, $P<.02$).[71] This finding is difficult to interpret.

Pyridoxine monotherapy has been specifically examined for specific effects on premenstrual mood. Reviews[148] and meta-analyses[149,150] of the many early trials found mostly conflicting effects or weakly supported positive effects, and 3 of the 4 best studies on premenstrual symptoms found no effect on mood.[151–154] All of these studies were compromised by use of outcome instruments not validated for mood measurement, lack of standardized diagnostic assessments, small unpowered sample sizes, inadequately presented data or statistical analyses, and uneven management or control for concurrent use of oral contraceptives. Few of the studies included adolescents, and none examined age effects.

Early questionable claims of pyridoxine benefits for autism have been largely dismissed[155,156] and, in any case, mood effects were not evaluated in those studies.

To my knowledge, there are no adequate RCTs of pyridoxine monotherapy in adults or youth with mood disorders. The best available data are inconclusive but do not support effects on mood, although there is a signal of possible benefit for cognition. There are no strong grounds for prioritizing pyridoxine trials on mood at this time.

Other Single Micronutrients

Several other micronutrients have been examined for mood effects in randomized controlled trials in adults, mostly with conflicting effects (**Table 2**). None of them have been examined in child or adolescent samples.

Chromium

Chromium monotherapy has been examined in 3 RDBPCTs. Two of the studies were conducted in atypical depression; one was small,[158] but the other[157] was adequately powered (n = 113). No overall change on mood was observed, but a subgroup with carbohydrate craving showed improvement in both carbohydrate craving and mood.[157] An RDBPCT on binge-eating disorder found nonsignificant reductions in depression ratings, binge frequency, and body weight.[159]

Zinc

Zinc has been examined in 3 RDBPCTs as a potential augmentation (add-on) treatment. In 2 studies of unipolar MDD from the same group, the earlier study found zinc augmentation of antidepressant treatment to be effective.[162] The second study had a more nuanced finding[160]: that zinc augmentation of imipramine was not routinely beneficial, but did appear helpful for patients who were previously known to be treatment-resistant (**Fig. 3**). The benefit of zinc for treatment-resistant depression, but not for routine depression, suggests a zinc-related mechanism in antidepressant treatment resistance, possibly glutaminergic: Glutaminergic neurons are the only intraneuronal location of zinc, where it is involved in allosteric modulation of N-methyl-D-aspartate and other receptors.[175] In a related study, zinc levels were lower in MDD than in 25 healthy controls, and zinc levels increased during imipramine treatment with or without zinc supplementation.[161]

Zinc "augmentation" of multivitamin supplements was examined in 30 young healthy volunteers (mean age 19) in an RDBPCT.[163] Compared with youths receiving a multivitamin formulation without minerals, the addition of zinc produced small but significant ($P<.02$) reductions in scores for depression/dejection (23% vs 18% for multivitamins alone) and anger/hostility (29% vs 13% for multivitamins alone) on the POMS Questionnaire.

All 3 RDBPCTs showed zinc to be an effective augmentation agent for mood, with 2 studies in patients treated for MDD and 1 study in healthy subjects on multivitamins.

Table 2
Randomized double-blind placebo-controlled trials of other single micronutrients on mood (not including folic acid, vitamin D, and pyridoxine; see text)

Treatment	Concurrent Treatment	Design	Age (y)	Population	Outcome Measures	Outcome (Statistically Significant Changes Compared to Placebo)	Citation
Chromium	Monotherapy	RDBPCT 2 mo n = 113	Mean 46	Atypical depression outpatients	HAM-D, CGI-I	No overall improvement; but in subgroup with carbohydrate craving, mood and carbohydrate craving improved	157
Chromium	Monotherapy	RDBPCT 2 mo n = 15	Mean 46	Atypical depression	HAM-D, CGI-I	Nonsignificantly reduced depression, perhaps more in overeaters	158
Chromium	Monotherapy	RDBPCT 6 mo n = 24	Mean 36	Binge-eating disorder, overweight	QIDS-SR, EDE-Q	Nonsignificant reductions in depression, binge frequency, and weight	159
Zinc	Imipramine	RDBPCT 12 wk n = 60	18–55	DSM-IV MDE unipolar	CGI, BDI, HAM-D, and MADRS	Zinc add-on had no benefit in nonresistant patients, but reduced depression in previously treatment-resistant patients	160,161
Zinc	Tricyclic or SSRI	RDBPCT 12 wk n = 20	25–57	DSM-IV MDE unipolar	HAM-D, BDI	Zinc add-on reduced depression	162
Zinc	Multivitamins	RDBPCT 10 wk n = 30	Mean 19	Healthy volunteers	POMS, Cornell Medical Index	Zinc add-on reduced depression and anger	163

Thiamine	Monotherapy	RDBPCT 2 mo n = 120	Mean 20	Healthy students	POMS, GHQ	Better mood and trend toward more clear-headedness	[164]
Thiamine	Monotherapy	RDBPCT 6 wk n = 80	65–92	Healthy elderly in thiamine-deficient region (65% had baseline insufficiency)	Subjective assessment	More well-being, energy, and appetite	[165]
Selenium	Some subjects took folate or iron	RDBPCT 8 mo n = 166	16–35	Postpartum depression	EPDS	Prenatal (starting first trimester) treatment reduced symptoms of postpartum depression	[166]
Selenium	Monotherapy	RDBPCT 5 wk n = 50	14–74	Healthy volunteers	POMS	Improved mood Reduced anxiety More mood changes in subgroup with lower baseline selenium levels	[167,168]
Selenium	Monotherapy	RDB 4 mo n = 11 No placebo, but 2 doses of selenium were compared	20–45	Healthy volunteers	POMS-BI	No change in mood, but more change in patients with lower baseline selenium levels	[169]

(*continued on next page*)

Table 2
(*continued*)

Treatment	Concurrent Treatment	Design	Age (y)	Population	Outcome Measures	Outcome (Statistically Significant Changes Compared to Placebo)	Citation
Selenium	Monotherapy	R 14 wk n = 30 No placebo, but two doses of selenium were compared Blinding unstated	18–45	Healthy volunteers	POMS-BI	Better mood, more clear-headed with high-dose selenium	170
Selenium	Monotherapy	RDBPCT 6 mo n = 448	60–74	Volunteers	POMS-BI	No benefit	171
Selenium	Monotherapy	RDBPCT 12 mo n = 115	24–53	HIV-positive drug users 25% probable MDE	BDI, POMS, STAI	Increased vigor Reduced anxiety No change in mood	172
Magnesium	Monotherapy	RDBPCT 2 mo n = 32	24–39	PMS	Moos Questionnaire	Reduced mood changes	173
Magnesium	Monotherapy	RDBPCT 2 mo n = 38	18–50 (mostly 18–25)	PMS	Moos Questionnaire	No effect on mood	174
Magnesium	Monotherapy	RDBPCT 1 mo n = 44	Mean 32	PMS	Moos Questionnaire	No mood improvement (but reduced anxiety if combined with pyridoxine)	151

Abbreviations: BDI, Beck Depression Inventory; CGI, Clinical Global Impression; EDE-Q, Eating Disorder Examination-Questionnaire; EPDS, Edinburgh Postnatal Depression Scale; GHQ, General Health Questionnaire; HADRS, Hospital Anxiety and Depression Rating Scale; HAM-D, Hamilton Depression Rating Scale; MADRS, Montgomery-Asberg Depression Rating Scale; MDE, Major depressive episode; MMSE, Mini-Mental State Examination; Moos, Moos Menstrual Distress Questionnaire; PMS, Premenstrual syndrome; POMS, Profile of Moods State (BI, Bipolar); QIDS-SR, Quick Inventory of Depressive Symptomatology-Self Report; RDBPCT, Randomized double-blind placebo-controlled trial; STAI, State-Trait Anxiety Inventory.

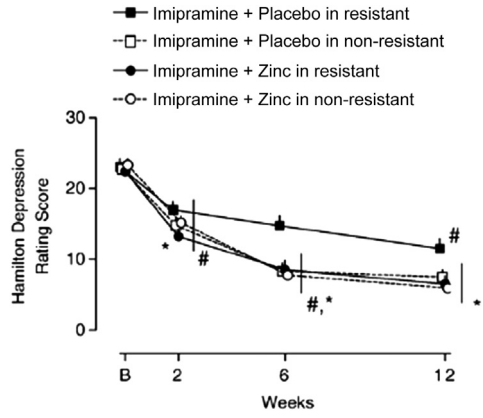

Fig. 3. Zinc augmentation helps treatment-resistant adults with unipolar depression treated with imipramine, but does not help nonresistant patients. Adults (ages 18–55) with previously documented treatment-resistant unipolar major depression or with nonresistant depression were examined in an RDBPCT of zinc augmentation of antidepressant treatment. All subjects were treated with imipramine and improved significantly at week 2 compared with baseline on the HAM-D. By week 6, the treatment-resistant patients augmented with zinc continued to improve, comparably to the nonresistant patients, whereas the treatment-resistant patients augmented with placebo did not improve relative to week 2. This pattern persisted at week 12. n = 9–16 patients in each treatment group. (*From* Siwek M, Dudek D, Paul IA, et al. Zinc supplementation augments efficacy of imipramine in treatment resistant patients: a double blind, placebo-controlled study. J Affect Disord 2009;118(1–3):187–95; with permission.)

The finding of a selective effect of zinc augmentation in treatment-resistant depression has not been replicated. Zinc has not been examined as a monotherapy for depression.

Thiamine

Two RDBPCTs have examined thiamine as a monotherapy in community samples. Benton and colleagues[164] examined 120 healthy students (mean age 20) in a 2-month trial of thiamine monotherapy and found mood improvement (POMS, $P<.05$) and a trend toward more clear-headedness, a cognitive indicator. A trial in 80 healthy elderly (ages 65–92) subjects living in a region with endemic thiamine deficiency (65% of the sample had baseline insufficiency) showed subjective improvements in appetite, energy, and sense of well-being at 6 weeks.[165]

Although not a monotherapy trial, an RDBPCT of B vitamins examined a combination of thiamine (vitamin B1), riboflavin (B2), and pyridoxine (B6) as an augmentation strategy for antidepressant treatment.[176] Among 16 elderly (mean age 75) psychiatric inpatients with MDD, 4 weeks of augmentation of nortriptyline treatment yielded a trend toward less depression and toward better cognition. The interpretation of this study is complicated because there was also a trend suggesting that the B complex increased the plasma antidepressant levels, so the small clinical improvements might have been pharmacokinetically mediated rather than being a direct effect of B vitamins on mood or cognition.

Again, thiamine monotherapy trials for treating mood disorders are not available in adults or youth, but there is one good RDBPCT suggesting thiamine alone (50 mg mononitrate daily) may be effective for improving mood in college students.

Selenium

Low dietary intake of selenium has been associated with a tripling of the likelihood of developing new-onset MDD in adults.[177]

Selenium monotherapy has been examined in 6 RCTs. Four studies assessed selenium effects in healthy volunteers spanning the adult age range, using the POMS to assess mood. Two studies were placebo controlled, and 2 studies compared 2 doses of selenium. Treatment outcomes were mixed, with 2 positive[167,168,170] and 2 negative findings,[169,171] including a negative study with 448 subjects.[171] Another RCT conducted in HIV-positive drug users (about 25% with probable MDD) showed improvements in energy and anxiety, but no mood change.[172] An additional RCT of elderly subjects in a nursing home (mean age 82) found that selenium, combined with folic acid and vitamin C, improved mood at 8 weeks.[178]

Despite these mixed treatment findings (3 positive, 3 negative), 2 of the monotherapy studies reported more mood improvement in patients with lower baseline selenium levels,[167,169] so there might speculatively be some value of selenium supplementation for depressed patients with demonstrated selenium insufficiency. Although depression may be a symptom of selenium deficiency,[179] there is little to guide clinicians regarding which depressed patients might benefit from selenium blood sampling.

An additional noteworthy RDBPCT examined selenium for prevention of postpartum depression among 166 first-trimester mothers (ages 16–35) who were treated with selenium starting in the first trimester and continuing for 2 months after delivery.[166] It is unclear whether additional prenatal nutrients were used by this sample in Iran, but an unstated number of the mothers took folic acid or iron. Two months postpartum, Edinburgh Postnatal Depression Scale scores were 18% lower in the selenium-treated than the placebo-treated mothers ($P<.05$). This finding is consistent with the longitudinal Alberta Pregnancy Outcomes and Nutrition study showing that prenatal selenium supplementation was correlated with a reduced risk of postpartum depressive symptoms (OR 0.76 for each 10 μg of daily intake, $P = .0019$).[180] Although not a randomized or placebo-controlled study, the long-term follow-up data on the Alberta children will be interesting, especially regarding their CNS development.

Age effects of selenium interventions have not been examined, and no monotherapy trials of selenium for MDD are currently available.

Magnesium

All 3 RDBPCTs on magnesium examined its effects on premenstrual mood, with 2 negative findings[151,174] and 1 positive finding.[173] The quality of these studies was generally weak, with all relying on the Moos Menstrual Distress Questionnaire. Similar to the findings on pyridoxine for premenstrual mood, it is difficult to draw any conclusions regarding its effectiveness, but there is little to encourage further monotherapy studies. No studies of MDD have been conducted.

As an aside, magnesium also has been examined as an adjunctive treatment of mania. Magnesium or placebo was added to ongoing verapamil (calcium channel blocker) treatment of 20 subjects (ages 22–30) in a 4-month randomized single-blind trial. Mean changes were not reported, but Brief Psychiatric Rating Scale scores were stated to have improved ($P<.02$) in the magnesium augmentation group but not in the placebo subjects.[181]

Implications of the Single-Micronutrient Intervention Studies

At present, none of these single-nutrient monotherapies have been examined in RDBPCTs for treating mood disorders in youth. Based on findings from RDBPCTs in adults, only a few treatments seem promising as potential treatments for depression in youth:

1. Folic acid as an adjunctive treatment for MDD appears to be the most promising of the single-micronutrient treatments for further study in youth. Despite the absence of controlled trials in youth, but based on current adult findings and its minimal adverse effects, it may be justifiable to run empiric trials of adjunctive folic acid in youth with MDD, minding its interactions with alcohol, oral contraceptives, and anticonvulsants.
2. Vitamin B12 appears primarily useful for geriatric depression, probably due to senescent B12 absorption. Vitamin B12 appears particularly unpromising in youth, except speculatively for depressed youths with chronic gastrointestinal diseases and impaired absorption.
3. Vitamin D shows mixed findings in adults, but might still be found to have value in youth. Clinical trials and research studies should be tuned to high-risk indicators which, based on current data, might include recurrent depressions, northern climes, low sunlight exposure (seasonal effects, indoor work, bedridden status), darker skin tone, chronic illness, or obesity. In certain populations with these risk factors, and perhaps in psychiatric populations in general, treatment seems sensible in cases with documented vitamin D insufficiency. Controlled data in youth are not available.
4. Chromium might have a niche for treating atypical depression with carbohydrate craving, but additional studies are needed.
5. Zinc might have a role in antidepressant augmentation, perhaps especially for treatment-resistant MDD, and maybe not in routine cases, but again more study is needed.
6. Thiamine might have value for improving mood, energy, and possibly cognition in healthy students, according to a single study.
7. Selenium may have a role as a prenatal treatment to prevent postpartum depression, based on a single RDBPCT and some longitudinal correlational data.
8. Current data would put a low priority on studies of monotherapy with pyridoxine (vitamin B6) and magnesium, at least for premenstrual dysphoria, and there is little in the data to encourage trials in MDD.

Although we have emphasized only the RDBPCTs, there is an enormous literature examining single-nutrient treatments in psychiatry. In general, perhaps what is most striking about these single-micronutrient studies are the few positive findings and the mostly minor clinical improvements. Few if any of these treatments would stand up to conventional psychiatric medications as monotherapy treatments of depression. At best, some might serve as relatively weak adjunctive treatments. For this vast literature, there is surprisingly little to show.

Historically, treatments of disease states are examined one drug at a time, following the traditional medical model of investigating the effect of changing a single variable. This model has largely guided the exploration of micronutrient treatments of disease states, such as depression, with the vast majority of studies examining one micronutrient at a time.

This approach makes sense for drugs, but it is suspect for nutrients: micronutrients typically act in concert physiologically rather than as single actors. For example, B vitamins are known to work as a “complex,” with different B vitamins working

interactively.[1,2] Similarly, many enzymes have multiple co-factors, so trying to correct the activity of those enzymes by adjusting just a single micronutrient does not make much sense. In fact, treating with a single micronutrient is often disruptive, because it throws off the balance among the interacting micronutrients,[182,183] potentially creating relative micronutrient insufficiencies.

In view of such micronutrient interactions, it is not surprising that this decades-old endeavor of studying individual micronutrients in treating psychiatric disorders has yielded relatively few positive replicable findings. A more nutritionally and scientifically sensible approach would be to examine the effects of micronutrients acting in concert.

The standard term for these approaches is "multiple micronutrient supplementation." Although there is no formal definition, the term is often used to refer to formulations that contain 3 or more micronutrients, for example, by the World Health Organization.[184] However, to denote supplementation with a much broader and more complete array of micronutrients, we will use the term "broad-spectrum micronutrient supplementation" to refer to interventions that involve at least 10 different micronutrients.

BROAD-SPECTRUM MICRONUTRIENT INTERVENTIONS

Broad-spectrum micronutrient strategies supply a wide range of vitamins and minerals, an approach that is likely to provide more pervasive and significant physiologic changes than supplying just one or a few micronutrients at a time. Sometimes seen as an implicit challenge to the conventional model used in medical pharmacology conceptualizing 1 drug having 1 effect (eg, the standard dose-response curve), a "nutritional pharmacology" approach views a multi-ingredient supplement consisting of a broad spectrum of micronutrients as a single, although complex, intervention. For medical researchers who have traditionally investigated single-entity drugs as medical treatments and who have viewed 2-component products with some leeriness, the nutritional pharmacology model is a very different way of thinking.

At present, a complete assessment of the micronutrient status of an individual is not technically feasible. Certain micronutrients can be straightforwardly assessed by clinical blood tests, but blood levels are not indicative of nutritional adequacy for most micronutrients.[2,27] Blood assays are rough measures useful to estimate comparative micronutrient insufficiencies at the population level, but they do not provide a clinically accurate characterization of the nutritional status of an individual patient. (It might be mentioned that numerous commercial groups claim to offer such comprehensive nutritional evaluations, but they are largely based on scientifically unvalidated methodology and often based on scientifically disproven methodology.)

Until the development of comprehensive nutrient assessment methods for all micronutrients that could guide individualized nutritional supplementation for each patient, we have the practical and sensible alternative of providing broad-spectrum micronutrient supplementation with the aim of correcting the full range of potential nutritional deficiencies and insufficiencies. ("Full range" assumes that we have already identified all of the vitamins and essential minerals, which may not be the case; that is an important justification for the consumption of natural foods.) This population-based approach to individual care (supplying all the nutrients that an individual might need on the assumption that we do not know which single micronutrients might actually be needed) may seem unreasonable in the traditional medical model of treatment, but it is very sensible in a nutritional pharmacology model and a public health model.

The nutritional rationale for exploring broad-spectrum micronutrient interventions in medicine is based on several considerations:

1. The involvement of vitamins and minerals in virtually all biologic processes;
2. The requirement for completeness in the complement of vitamins and minerals to support the full range of biologic processes;
3. The complex interactions among micronutrients, requiring an appropriate balance in the ratios among the micronutrients;
4. Epidemiologic evidence confirming widespread micronutrient deficiencies in the general population, including among "well-fed" individuals in wealthy societies;
5. The progressive generalized depletion of various micronutrients in modern over-farmed soil, leading to the reduced availability of many nutrients in our food supply[11,12];
6. The increasing overconsumption of fats and refined sugars in the modern Western diet, resulting in the common intake of foods with low nutrient value[6];
7. Biochemical individuality (genetically determined variations in micronutrient requirements among individuals);
8. Individual variations in micronutrient requirements over time; and
9. The inability of current clinical methods to identify the full range of potential micronutrient deficiencies in an individual.

When considering all of these factors, the study of single micronutrient interventions can seem simplistic and a bit naïve. At the least, studies that examine the effects of broad-spectrum micronutrient interventions, aimed at correcting a diversity of micronutrient deficiencies, insufficiencies, and relative insufficiencies in the general population, have plausibility, practicality, and heuristic value, as well as making basic clinical sense, at least until an effective comprehensive nutritional evaluation can be developed to assess the profile of micronutrient insufficiencies in individual patients.

Broad-spectrum micronutrient interventions have been examined and found surprisingly effective for altering mood, cognition, and behavior. A recent comprehensive review by Rucklidge and Kaplan[185] of the psychiatric effects of micronutrient treatments involving 4 or more ingredients described beneficial effects on mood, anxiety and stress, aggressive and antisocial misconduct, substance abuse and dependence, attention-deficit/hyperactivity disorder (ADHD), and autism.

Although this article is primarily concerned with mood disorders, it is instructive to survey the effects of broad-spectrum micronutrient treatments on conditions that frequently appear comorbidly with mood disorders, as well as conditions that appear in healthy adults.

Violent and Antisocial Behavior in Youth and Adults

Broad-spectrum micronutrient interventions have been found to reduce violent and antisocial behavior in children and adolescents. A randomized double-blind placebo-controlled trial was conducted on 80 public school children (ages 6–12) with aggressive behaviors or disordered conduct.[186] A micronutrient formula (13 vitamins, 10 minerals, supplying about 50% of RDA) was administered for 4 months and resulted in a striking 47% reduction is disciplined violent and nonviolent misconduct, including threats, fights, vandalism, defiance, disrespect, and obscenities. In a similar 13-week study on 62 young delinquents (ages 13–17) in a maximum security hospital, treatment with micronutrients (12 vitamins at 3 times the RDA levels, 11 minerals at RDA level) led to an 83% reduction in the micronutrient group, compared with a 55% reduction in the control group, in both violent and nonviolent offenses ($P<.005$).[187] In the second study, improvement was noted predominantly in subjects whose blood samples showed evidence of improved nutritional status following supplementation, with little clinical improvement in subjects whose nutritional status

remained unimproved by supplementation. These 2 RCTs demonstrated marked improvements in major conduct violations in American school children and delinquent adolescents following 3 to 4 months of broad-spectrum vitamin-mineral supplementation.

Two additional RDBPCTs conducted in young adults provide confirmation of these findings. In a very rigorous randomized multiply-blinded placebo-controlled study, Gesch and colleagues[188] examined the effects of nutritional supplementation with 13 vitamins and 12 minerals (all at or below RDA dosing), plus omega-3 and omega-6 fatty acids, on the disruptive behavior of 231 young prisoners (minimum age 18). The outcome measure was in-prison disciplinary offenses, consisting of violence or serious rule violations that required formal adjudication and were supported by "beyond reasonable doubt" evidence. Nutrient-supplemented prisoners committed a mean of 26% fewer offenses compared with the placebo group (95% CI 8.3%–44.3%, $P = .03$). Compared with baseline, nutritional supplementation (n = 90) for at least 2 weeks produced a mean 35% reduction in disciplinary offenses ($P = .001$), whereas placebo (n = 82) showed a nonsignificant 7% increase in offenses ($P > .1$). Both major and minor offenses showed a similar degree of improvement (**Table 3**). The period of supplementation was a mean of 142 days in both groups (range 2–9 months). No adverse responses to supplementation were reported. Compliance rates were high in both treatment groups, and the effectiveness of the placebo blinding was demonstrated. It is impressive that the improvements in antisocial behaviors were substantial (26%–36%), rapid (data based on prisoners who received nutrients for a minimum of 2 weeks), and observable across a range of severity of antisocial behaviors.

This rigorous study was replicated in detail by Zaalberg and colleagues[189] in 221 prisoners (mean age 21, range 18–25) who received nutritional supplementation that was virtually identical to Gesch and colleagues' formulation[188] (n = 115) or placebo (n = 106) for 1 to 3 months. Outcome findings based on incident reports were remarkably comparable to Gesch's, with a 34% decrease in staff-reported incidents of aggressive and rule-breaking behaviors (mainly alcohol or drug use), compared with

Table 3
Reduced frequency of major misconduct among incarcerated young adults who received nutrient intervention for at least 2 weeks

	Broad-Spectrum Micronutrients with Omega-3 Fatty Acids	Placebo
	n = 82	n = 90
Total infringements before intervention (offenses per 1000 person-days)	16.0	16.0
Total infringements after intervention	10.4	14.9
Percent reduction in total infringements	35%, $P<.001$	6.7%, NS
Percent reduction in serious incidents, including violence	37%, $P<.005$	10.1%, NS
Percent reduction in minor incidents, mainly antisocial behaviors	33%, $P<.025$	6.5%, NS
Mean treatment compliance rate	91%	90%

Abbreviation: NS, not significant.

Data from Gesch CB, Hammond SM, Hampson SE, et al. Influence of supplementary vitamins, minerals and essential fatty acids on the antisocial behaviour of young adult prisoners. Randomised, placebo-controlled trial. Br J Psychiatry 2002;181:22–8.

a 14% increase in the placebo group ($P = .017$). Interestingly, no significant differences between the groups were observed when less concrete measures of behavior were used, such as several validated rating scales reflecting self-reported and staff-reported impressions of hostility feelings, disruptive behaviors, and (loosely assessed) psychiatric symptoms. This underscores a potential weakness of traditional rating scales, which remain somewhat subjective, and the value of using more concrete measures like incident reports.

These 3 RDBPCTs on adolescent and young adult prisoners, reasonably sized and independently conducted, show that supplementation with 23 to 25 vitamins and minerals at RDA doses induced 25% to 35% reductions in aggressive behavior and nonviolent misconduct.[187–189] The findings of these 3 studies are comparable to the RDBPCT in 6-year olds to 12-year-olds in public schools showing a 47% reduction in aggressive behaviors or conduct disorder symptoms among 80 children who received a 23-ingredient formulation of vitamins and minerals, administered at about 50% of RDA levels for 4 months, without fatty acid supplementation.[186]

The addition of omega fatty acid supplementation in 2 of the RDBPCTs[188,189] is sensible from a nutritional and public health perspective, in that it maximizes the likelihood of eliciting a positive response to nutritional intervention, but it has the unfortunate effect (from the point of view of this article) of obscuring how much of the observed behavioral improvements could be attributed to vitamins and minerals rather than to fatty acids. However, the 2 other RDBPCTs conducted in children and adolescents[186,187] showed that comparable results were obtained without fatty acids, supporting the notion that vitamins and minerals alone (without essential fatty acids) can be effective. These 4 RDBPCTs constitute replicated demonstrations that broad-spectrum micronutrient treatment, with or without essential fatty acids, can have marked clinical effects on major misconduct and aggressive behavior.

As an aside, an oft-cited, although flawed, study conducted at the Pfeiffer Treatment Center Health Research Institute in Illinois examined 207 patients (mean age 12, range 3–55 years) with ADHD, conduct disorder, or oppositional defiant disorder.[190] The protocol included a battery of 90 biochemical assays, standardized protocols to identify "chemical imbalances" to be treated, and individualized modular therapies consisting of micronutrients and amino acids, among other compounds. The targeted chemical imbalances were described as malabsorption, glucose dysregulation, elevated copper-to-zinc ratio, overmethylation or undermethylation, "pyrrole disorder," and heavy metal excesses. A 92% reduction in physical assaults and an 88% reduction in destructive episodes was reported. The individually varied treatments, open-label design, lack of a comparison group, unvalidated biochemical assay interpretations, and the lack of standardized outcome instruments make it difficult to interpret the findings.

In short, the 4 positive randomized double-blind placebo-controlled studies, with no negative studies, provide strong support for broad-spectrum micronutrients as a treatment for violence and major misconduct. Especially in view of the minimal side effects, the 3 RDBPCTs in young incarcerated offenders are sufficient grounds to proceed now with implementation in correctional facilities. The RDBPCT on public school children in the community needs replication before clinical recommendations can be made, but this should be an extremely high research priority.

None of these studies attempted to identify the diagnoses of the subjects, and so their implications regarding treatment of mood disorders (or ADHD) are speculative. These studies also leave open questions about which of the many micronutrients are the most crucial (or, instead, whether supplying a broad spectrum of nutrients is crucial), whether the effects are mainly seen in individuals with poor diets or low

nutritional status, and whether higher micronutrient doses would be more effective than routine RDA dose levels.

ADHD

Open-label trials

Eight open-label studies on ADHD provide suggestive evidence that broad-spectrum micronutrient treatment may result in the improvement of both inattention and hyperactivity/impulsivity symptoms in youth[191–195] and adults.[196–198]

All but one of these studies[191] were conducted using a broad-spectrum micronutrient formulation, developed by David Hardy and Tony Stephan, consisting of relatively high but safe doses of about 36 ingredients, mainly vitamins, minerals, antioxidants, and a few amino acids. This type of formulation was originally developed as a nutritional intervention to reduce aggressive behavior among farm animals, but it was adapted for human use when it was observed to reduce symptoms of bipolar disorder. Several companies manufacture minor variations on this formulation (Daily Essentials Nutrients, manufactured by NutraTek Health Innovations, Raymond, Alberta, Canada; EMPowerPlus Advanced, manufactured by Truehope Nutritional Support, Raymond, Alberta, Canada; Equilib, manufactured by EvinceNaturals, Bountiful, Utah). These formulations contain more than 25 different vitamins and minerals. Most of the past research studies have used the EMPower version of the Hardy-Stephan formula. Possible differences among these minor variations of the formula have not been examined.

In a study of ADHD,[194] 11 youths (ages 8–15) with mood and behavior symptoms received open-label treatment with the Hardy-Stephan formula for 8 to 17 weeks and showed substantial improvement in Child Behavior CheckList (CBCL) scores for attention, as well as delinquent and aggressive behavior (all $P<.01$); 6 of the 11 children had ADHD, although their data were not analyzed separately because of sample size (**Fig. 4**).

A case series of 14 adults (ages 18–55) with ADHD and mood dysregulation reported that 8-week open-label treatment with the Hardy-Stephan formula led to significantly improved behavior and attention scores, as well as anxiety and quality of life ratings.[196] Hyperactivity/impulsivity and mood scores were normalized, but inattention ratings improved but remained within the clinically significant range (**Table 4**).

In a retrospective database analysis of 120 children (ages 7–18) with a parent-reported diagnosis of bipolar disorder, 24% of the subjects were also reported by the parents to have ADHD.[195] Open-label treatment with the Hardy-Stephan formula produced a 40% reduction in parent-reported ADHD symptoms, as well as a 43% reduction in parent-reported bipolar symptoms (**Fig. 5**). Also, the percentage of patients using conventional psychiatric medications declined from 79% to 38%, and the number of medications used decreased by 74%.

Most of the samples in these studies consisted of patients with presumptive ADHD and probable comorbid bipolar disorder. The morbidity makes it difficult to discern how much of the apparent micronutrient effect on ADHD symptoms might have been indirectly mediated by a micronutrient-induced reduction in bipolar symptoms (ie, without a direct micronutrient effect on ADHD itself). An additional study reportedly conducted on children with noncomorbid ADHD asserted the ADHD diagnosis without a standardized diagnostic evaluation (so comorbidity was not systematically assessed), and the treatment consisted of a complex chemical intervention including micronutrients as one component,[191] so it cannot help determine whether there is a direct micronutrient effect on ADHD. Perhaps more useful for this purpose was the subsample of 41 children from the database study whose parents reported their

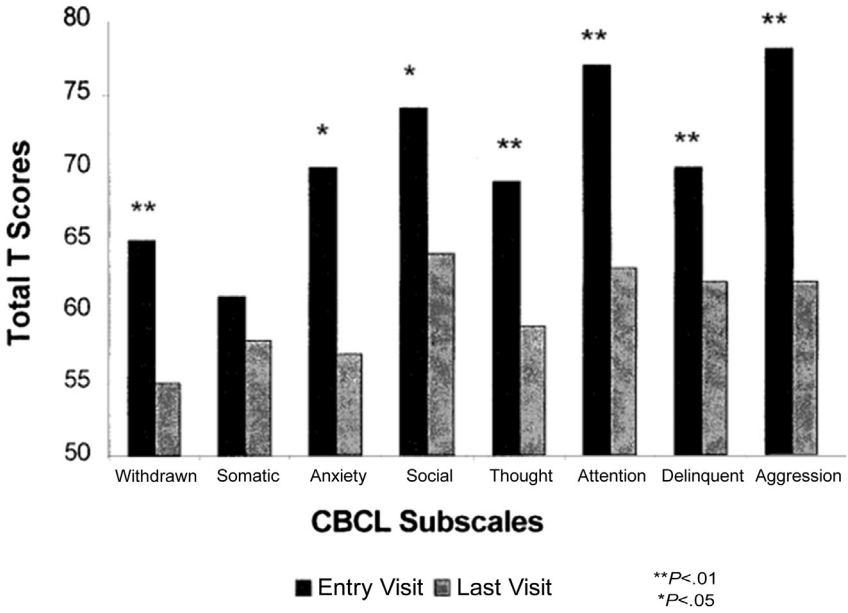

Fig. 4. Improvement on child behavior checklist scores in symptomatic youth during micronutrient treatment. Among 9 of 11 children with mixed mood and behavioral problems (mainly mood disorder and ADHD) who completed treatment with open-label EMPower for a mean of 14 weeks, Child Behavior Checklist scores improved significantly in all categories except somatic symptoms. (*From* Kaplan BJ, Fisher JE, Crawford SG, et al. Improved mood and behavior during treatment with a mineral-vitamin supplement: An open-label case series of children. J Child Adolesc Psychopharmacol 2004;14(1):115–22; with permission.)

diagnoses as ADHD without bipolar disorder.[195] In this subsample (in contrast to Fig. 5, which shows data from the entire sample predominated by ADHD-bipolar comorbidity), open-label treatment of ADHD (without bipolar disorder) for up to 6 months produced a 47% reduction in parent-reported ADHD symptoms from baseline to last observation (Cohen's d effect size [ES] 1.04). The response rates in this subsample of ADHD-only youths to micronutrient treatment are 63% to 76%, depending on the definition of clinical response (Table 5). These data suggest that micronutrient treatment can directly treat ADHD, but open-label data from a database that relies on parental reports of diagnosis and outcome leaves this question unsettled.

In most of the open-label reports examining the Hardy-Stephan formula as a broad-spectrum micronutrient treatment for ADHD, behavioral changes appeared stronger and sooner than attentional improvements, consistent with an indirectly mediated effect on attention or simply a weaker micronutrient effect on attention than behavior. For subjects who were using conventional psychiatric medications at baseline, the addition of micronutrient interventions appeared to reduce the dosage requirements for conventional medications or to allow their discontinuation in many cases.

Open-label reports are obviously limited by the lack of controls and blinding. Many reports lacked formally substantiated diagnoses, and the comorbidity obscured whether micronutrients directly reduced ADHD symptoms. In view of these limitations,

Table 4
EMPower treatment of 14 adults with "severe mood dysregulation" and ADHD: 8-week outcome of open-label treatment

Measure	Baseline Mean ± SD	8-wk Mean ± SD	*P*	ES
Mood				
MADRS (Depression)	22 ± 7.7	7.2 ± 3.4	<.001	1.96
DASS Depression	17 ± 9.3	7.1 ± 6.1	<.001	1.08
YMRS (Mania)	2.7 ± 3.7	0.7 ± 1.6	<.01	0.82
DASS Anxiety	12 ± 9.4	3.6 ± 2.6	<.01	0.88
CAARS Emotional Lability				
Self-Report[a]	68 ± 11	60 ± 11	<.001	1.29
Observer Report[a]	67 ± 11	56 ± 12	<.001	1.45
ADHD				
CAARS Self-Report				
DSM Inattention[a]	80 ± 8.9	70 ± 13	<.001	0.98
DSM Hyper/Imp[a]	67 ± 11	56 ± 13	<.001	1.88
DSM Combined[a]	78 ± 8.4	65 ± 13	<.001	1.58
CAARS Observer-Report				
DSM Inattention[a]	71 ± 8.4	65 ± 10	<.01	0.66
DSM Hyper/Imp[a]	65 ± 10	57 ± 12	<.01	0.70
DSM Combined[a]	70 ± 8.1	63 ± 11	<.01	0.70
GAF	54 ± 6.3	70 ± 6.5	<.001	2.44

[a] T scores.
P based on paired *t* tests (2-tailed).
Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CAARS, Conners Adult ADHD Rating Scale; CGI-S, Clinical Global Impression-Severity; DASS, Depression, Anxiety, and Stress Scale; DSM, Diagnostic and Statistical Manual of Mental Disorders; ES, Cohen's d effect size; GAF, Global Assessment of Functioning; Hyper/Imp, Hyperactivity/Impulsivity; MADRS, Montgomery-Asberg Depression Rating Scale; YMRS, Young Mania Rating Scale.
Data from Rucklidge J, Taylor M, Whitehead K. Effect of micronutrients on behavior and mood in adults with ADHD: evidence from an 8-week open label trial with natural extension. J Atten Disord 2011;15(1):79–91.

the numerous open-label studies are only suggestive of a possible effect of micronutrients on ADHD.

Controlled trials on ADHD

There are 2 controlled studies of broad-spectrum micronutrients in treating ADHD or ADHD-like symptoms, 1 in children and 1 in adults. In the child RDBPCT,[199] broad-spectrum micronutrients at low doses (Multivitamins and Minerals for Kids; Blackmore, Warriewood, Australia) were administered in conjunction with omega-3 fatty acids to 132 children (ages 7–12) with ADHD-like symptoms, but not necessarily ADHD. Diagnostic interviews were not conducted, and the sample consisted of subjects who scored 2 SDs above the mean on the Conners ADHD Index. The children were randomized to 1 of 3 treatment arms: broad-spectrum micronutrients (at or below RDA levels) plus omega-3 fatty acids EPA 660 mg and DHA 175 mg (n = 41); omega-3 fatty acids alone (n = 36); or placebo (n = 27). The effects of micronutrients alone were not examined in this study. Randomized double-blind

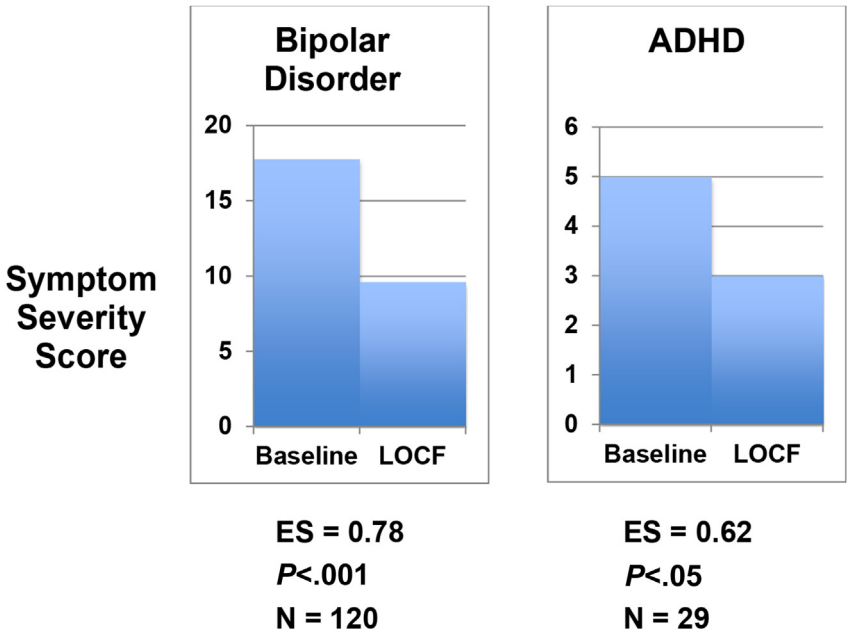

Fig. 5. Open-label EMPower treatment of youths with parent-reported bipolar disorder and ADHD comorbidity. Analysis of a database of open-label EMPower treatments of youths (ages 7–18) whose parents provided reports of clinical diagnoses of comorbid bipolar disorder and ADHD. Parents also provided daily symptom reports for 3 to 6 months using a Likert (0–3) scoring system for DSM-IV symptom clusters. Bipolar symptom severity scores range from 0 to 48. ADHD symptom severity scores range from 0 to 9. Mean ± SD. ES, Cohen's d effect size; LOCF, last observation carried forward. (*Data from* Rucklidge JJ, Gately D, Kaplan BJ. Database analysis of children and adolescents with bipolar disorder consuming a micronutrient formula. BMC Psychiatry 2010;10:74.)

Table 5
Response rates of youths treated with open-label EMPower: percentage of youths in database analysis showing improvement from baseline to last observation

	Bipolar (%)	ADHD (%)	Bipolar Disorder and Comorbid ADHD (%)
	n = 91	n = 41	n = 29
Response Criterion ≥30% Reduction in Symptom Severity			
Bipolar symptoms	68	—	55
ADHD symptoms	—	76	55
Response Criterion ≥50% Reduction in Symptom Severity			
Bipolar symptoms	45	—	48
ADHD symptoms	—	63	45

Response rates are expressed as the percentage of youths responding to treatment, based on 2 different definitions of response. Treatment reports were based on 3 to 6 months of treatment. Data from youths with comorbid bipolar disorder and ADHD are reported separately from youths with 1 primary diagnosis. Diagnoses and outcomes are based on parent report.

Abbreviation: ADHD, attention-deficit/hyperactivity disorder.

Data from Rucklidge JJ, Gately D, Kaplan BJ. Database analysis of children and adolescents with bipolar disorder consuming a micronutrient formula. BMC Psychiatry 2010;10:74.

treatments were administered for 15 weeks (104 completers), and there was a subsequent 15-week open-label extension. Both treatment groups did better than placebo on parent ratings of attention (ES 0.52–0.61) and behavior (ES 0.17–0.45), but teacher ratings showed no effects. The addition of broad-spectrum micronutrients did not improve on effect of omega-3 fatty acids alone, but the micronutrient doses were low in comparison with the previously mentioned studies on EMPower treatment, and the omega-3 fatty acid doses were low as well, so this study probably did not assess the full potential of the micronutrients or the fatty acids. The design also did not allow assessment of whether the effects of micronutrients would be improved by the addition of omega-3 fatty acids. In addition, despite the improvement in attentional measures, detailed neuropsychological testing showed few other areas of cognitive improvement.[200] The absence of significant effects on the teacher ratings, the lack of ADHD diagnoses, the low doses, and the lack of a micronutrients-only arm limit the value of these findings. This study does not provide information on the effectiveness of vitamin-mineral supplementation itself in treating ADHD in youth.

The best available study of micronutrient effects on ADHD was Rucklidge and colleagues' RDBPCT[201,202] conducted on 80 medication-free adults (age≥16) with formally diagnosed ADHD. Psychiatric comorbidity was intentionally retained in the sample to enhance generalizability. Subjects were randomized to receive the Hardy-Stephan formula (n = 42) or placebo (n = 38) for 8 weeks, without omega-3 fatty acids (**Table 6**). Dropout rate was 7.5%, and adherence rate was 95%. Compared with placebo, intent-to-treat analysis showed significant improvement on self-rated and observer-rated scores for hyperactivity/impulsivity (ES 0.46–0.67) and inattention (ES 0.33–0.62) on the Conners Adult ADHD Rating Scales (CAARS). Although changes were not significant on clinician-rated CAARS scores (ES 0.2), clinicians did report significant improvements on both Clinical Global Impression (CGI) for General Improvement and CGI for Improvement on ADHD symptoms (ES 0.53–0.57). At the end of 8 weeks, 64% of the micronutrient-treated and 37% of the controls

Table 6
Randomized double-blind placebo-controlled trial of the Hardy-Stephan formula in adults with ADHD

	Micronutrient-Treated, n = 42		Controls, n = 38			
	Baseline	8 wk	Baseline	8 wk	Treated vs Controls	Effect Size
CAARS DSM-IV ADHD Symptom Total						
Self-Report	80	67	75	70	*P* = .009	0.61
Observer	70	61	70	67	*P* = .026	0.59
Clinician	73	65	69	64	NS	0.23
MADRS	17	12	14	12	*P* = .078	0.41
GAF	59	64	62	64	*P* = .045	0.46

ADHD scores were reduced in self-report and observer (eg, a relative) reports, but not in clinician reports on CAARS. Mood (MADRS) and global functioning (GAF) also improved at 8 weeks.

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CAARS, Conners Adult ADHD Rating Scale; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; GAF, Global Assessment of Functioning; MADRS, Montgomery-Asberg Depression Rating Scale.

Adapted from Rucklidge JJ, Frampton CM, Gorman B, et al. Vitamin-mineral treatment of attention-deficit hyperactivity disorder in adults: double-blind randomised placebo-controlled trial. Br J Psychiatry 2014;204:306–15.

showed 30% or more reduction on at least one CAARS subscale, and 48% versus 21% showed much or very much improvement on the CGI-Improvement-ADHD scale. Approximately one-third of the micronutrient group appeared fully remitted at 8 weeks, compared with approximately one-sixth of the control group (Julia Rucklidge, personal communication, 2014).

One potential problem with this RDBPCT is that the micronutrient sample at baseline had more women (48% vs 18%) and more anxiety disorders (52% vs 29%) than the controls. However, the observed clinical effects of micronutrients relative to controls were not changed when gender and anxiety disorder diagnoses were entered as covariates. The baseline prevalence of mood disorders was comparable in both groups (past episodes 57%–60%, current episodes 21%–24%).

A 1-year follow-up study to this RDBPCT was conducted on 90% of the original sample.[203] After the 8-week RDBPCT, 51% of subjects stopped all medications, 24% switched to conventional psychiatric medications, and 19% continued on micronutrients. Participants who continued on micronutrients at the end of the study fared better than those who switched to conventional medications or to other natural treatments. Subjects who stayed on micronutrients throughout the follow-up year maintained their improvements or improved further, whereas subjects who discontinued micronutrients lost much of the treatment gains they had made while taking micronutrients. Even participants who switched to conventional psychiatric medications scored less well on ADHD and on depressive symptoms at 1-year follow-up than the micronutrient continuers. At 1 year, treatment response criteria ($\geq$30% improvement from baseline on clinician CAARS) were met by 64% who stayed on the Hardy-Stephan formula, 35% on conventional medications, and 20% who discontinued treatment ($P = .009$). Remission criteria (within normal nonclinical range on the clinician CAARS) were met by 64% on the Hardy-Stephan formula, 29% on conventional medications, and 28% of those who stopped treatment ($P = .039$). The subjects who discontinued micronutrients primarily cited treatment cost as the reason, but some cited treatment inconvenience (15 pills daily) or nonresponse. The fact that those who discontinued micronutrients cited cost as the primary factor makes it unlikely that micronutrient nonresponders were overrepresented among the switchers. Interestingly, side effects were minimal and were not a significant factor contributing to treatment discontinuation.

The effect size of micronutrients on ADHD (ES 0.2–0.67) in this RDBPCT compares favorably to effects of omega-3 fatty acids (ES 0.2–0.3)[4] and of diets excluding artificial food colorings (ES 0.2–0.4),[204,205] but is lower than for psychostimulants (ES 0.6–0.8).[206] Despite some complications in this study, this RDBPCT gives strong evidence of a micronutrient effect on ADHD, at least in adults in a community sample with mixed comorbidity. Given its promising degree of effectiveness in this trial, the favorable side-effect profile, the possible reduction in dosage requirements for concurrently administered conventional medications, and the numerous open-label trials suggesting clinical value, additional controlled trials of micronutrient treatment of ADHD are warranted in youth and adults.

Compared with psychostimulants, micronutrients offer some significant advantages in terms of side effects: no rebound hyperactivity, abuse potential, daily on-off effects, appetite suppression, height or weight loss, blood pressure or pulse changes, or psychotic reactions.

Mood Disorders

There are 17 currently available studies of broad-spectrum micronutrient treatments for major mood disorders in youth and adults, including 1 RDBPCT. Some of the

subjects had well-diagnosed bipolar disorder, and others had presumptive bipolar disorder by virtue of severe mood dysregulation, mood lability, and temper outbursts; some had major depression, and a few had dysthymia. Similar to the data available on ADHD, most of these reports are open-label studies, and most were conducted using the Hardy-Stephen formulation of broad-spectrum micronutrients (EMPower).

Open-label studies

In adults with bipolar disorder, several open-label case series[196,197,207–209] have suggested the effectiveness of broad-spectrum micronutrients for treating clinically diagnosed bipolar I or bipolar II disorder. In these reports, about 85% of the 40 adults (ages 18–68) showed improvement in mood and behavior over the course of 1 to 6 months of treatment, and most patients were treated successfully enough to be able to discontinue their previous conventional psychiatric medications entirely. For example, Kaplan and colleagues[207] noted reductions of 55% to 66% on depression (HAM-D) and mania (YMRS) scores in 11 adults over 6 months, with an effect size of about 0.80 for measures of depression and mania, and a reduction in the use of conventional medications of about 50%. Similarly, Rucklidge and colllegaues[196,197] described 14 adults with ADHD and severe mood dysregulation who were treated for 8 weeks with open-label EMPower, with 10 of 12 adults showing a 50% improvement in clinician-rated Montgomery-Asberg Depression Rating Scale (MADRS) scores. Mean MADRS scores reduced from 22 $\pm$ 7.7 to 7.2 $\pm$ 3.4 (P<.001; ES 1.96) and, although no subjects met criteria for mania, mean YRMS mania scores reduced from 2.7 $\pm$ 3.7 to 0.7 $\pm$ 1.6 (P<.01; ES 0.82).

In children and adolescents, several reports describe open-label treatments of presumptive bipolar disorder, mood lability and/or explosive rage. Some trials used multiple reversal designs (ABAB), meaning that treatment was applied, withdrawn, then reapplied. This approach allows open-label studies to provide evidence that the symptom change is actually linked to treatment rather than to incidental factors. The observation of several clinical changes (reversals) that are consistent and concurrent with dose changes increases the likelihood that the symptom change is, in fact, a result of the treatment.

Five reports used open-label ABAB designs in 6 youths. Kaplan and colleagues[193] described 2 children (ages 8 and 12) with mood lability and explosive rage whose symptom scores (Conners Parent Rating Scale, Child Behavior Checklist [CBCL]) improved with 3 weeks of broad-spectrum micronutrient treatment. In this naturalistic ABAB report, symptoms worsened when treatment was withdrawn, and improved again when treatment was reinstated. Both children then remained stable over 2 years of follow-up. In another report, a medication-naïve 10-year-old with clinically diagnosed *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) bipolar disorder and major temper tantrums showed complete remission within 5 days of starting treatment,[208] followed by multiple naturalistic reversals (ABABA-BAB) over 3 years, confirming treatment effectiveness. Rucklidge[210] described an 18-year-old with major depression and obsessive-compulsive disorder (OCD) who showed improved mood (BDI), anxiety (Beck Anxiety Inventory), and obsessive symptoms (Yale-Brown Obsessive Compulsive Scale [YBOCS]) after 8 weeks of broad-spectrum micronutrient treatment; effectiveness was confirmed by subsequent treatment discontinuation and reinstatement (ABAB). Rucklidge and Harrison[198] also described a 21-year-old with bipolar disorder, ADHD, social anxiety, and panic disorder who had significantly improved depression (MADRS), mania (YMRS), hyperactivity/impulsivity (CAARS), processing speed (Wechsler Adult Intelligence Scale, WAIS-III), and verbal memory (Wide Range Assessment of Memory and Learning

[WRAML-II]) scores, with full remission at 1-year follow-up (**Fig. 6**). A 20-year-old with major depression had MADRS scores drop from 30 to 3 after 6 weeks of broad-spectrum micronutrient treatment, with confirmation in open-label ABAB reversals.[192]

Several additional open-label reports, although not using an ABAB design, suggest possible effectiveness of micronutrient treatment for treating mood disorders in 34 children and adolescents.[194,208,211–214] Frazier and colleagues[212] reported on 10 children (ages 6–12) with *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR) bipolar disorder, 7 of whom completed a 6-month trial. The 3 dropouts had difficulty in swallowing the pills or adhering to the difficult regimen (5 pills, 3 times daily). Intent-to-treat analysis showed a statistically significant 45% decrease in YMRS mania scores ($P<.01$) and an almost-significant 37% reduction in depression scores ($P<.06$) from baseline to 6 months of treatment. For completers, statistically significant reductions were observed in both mania (58%) and depression (71%) scores.[213] Adverse effects consisted of transient mild dyspepsia and initial insomnia. Kaplan and colleagues[194] reported on 4 children (ages 8–15) with mood and behavioral problems whose YMRS scores reduced over 8 weeks of treatment ($P<.05$). One report described clinically significant improvement in 10 of 12 youths (9 adolescents, 3 preadolescents) with clinically diagnosed bipolar disorder,[208] with almost all able to completely discontinue their previous psychiatric medications. Two other reports describe complete resolution of psychotic symptoms and significant reductions in obsessive-compulsive symptoms associated with mood disorders in a 12-year-old[211] and an 11-year-old.[214]

In a retrospective database analysis on 358 adults with self-reported bipolar disorder,[215] mean symptom severity of self-reported symptoms of bipolar disorder reduced by 41% after 3 months and by 45% reduction at 6 months of treatment (ES 0.76, $P>.001$). At 6 months, 53% of patients reported greater than 50% symptom reduction, and improvements were found to be dose-dependent. This study is limited by the unverified diagnoses, self-reported outcome data, and open-label treatment, among other issues. In the absence of controlled data, these open-label studies on adults

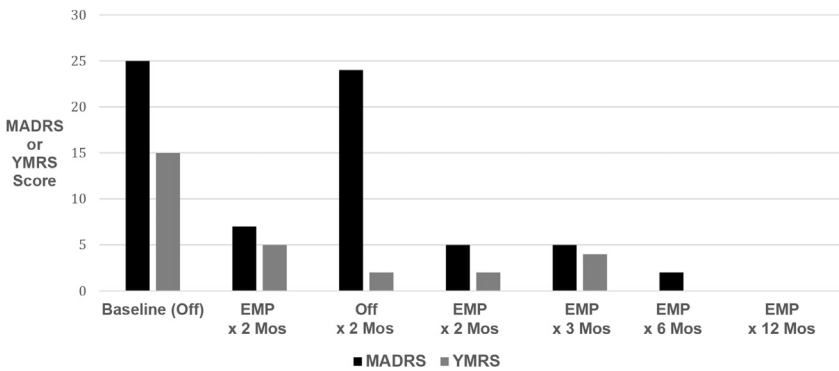

Fig. 6. Improvement in depression and mania scores in a 21-year-old with bipolar disorder and ADHD who was treated with open-label EMPower for one year. Starting medication-free at baseline, the patient was treated with EMPower for 2 months and then chose to discontinue treatment for 2 months. Follow-up data were available after 2, 3, 6, and 12 months of retreatment. MADRS and YMRS scores show treatment effects over time, including symptom-free status after 1 year. (*Data from* Rucklidge JJ, Harrison R. Successful treatment of bipolar disorder II and ADHD with a micronutrient formula: a case study. CNS Spectr 2010;15(5):289–95.)

with presumptive bipolar disorder suggest a clinically significant effect with a substantial effect size and apparent dose-dependent improvements in both depression and mania measures.

In the database analysis conducted on 120 youths (ages 7–18) with bipolar disorder, as reported by parents (not clinically verified by investigators), rage outbursts, or severe mood dysregulation, changes were quantitatively almost identical to findings in the adult database.[195] There was a 46% reduction in mean severity of bipolar symptoms at 6 months compared with baseline (ES 0.78), and 46% of the patients reported greater than 50% improvement in symptoms at 6 months (see **Fig. 5**). About 24% of this sample had ADHD (by parent report), and similar changes in bipolar symptoms were observed regardless of ADHD status. Similar to adult findings, the percentage of patients who needed to use conventional medications reduced from 79% to 38%, and mean doses reduced by 74%. Within the pediatric database, the observed improvements were found to be not age-dependent.

It is notable that the magnitude of outcome effects are so similar in the child and the adult databases, reinforcing the suggestion that the effect of broad-spectrum micronutrients on presumptive bipolar disorder is robust (ES 0.8) across the age spectrum.

Controlled studies of mood disorders

Beyond these open-label data, the one available RDBPCT provides better evidence for the effectiveness of broad-spectrum micronutrients for treating mood disorders.[201] As noted previously, in Rucklidge's RDBPCT on medication-free adults (ages>16) with ADHD, more than one-fifth of the patients had a current mood episode (21.4% in the micronutrient group, 23.7% in the control group), with mood disorder defined as dysthymia, MDD, or bipolar disorder, as assessed using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID-I). The 8-week treatment produced only a trend ($P = .078$) toward improvement in clinician-rated MADRS depression scores in the overall ADHD sample, in which most of the 80 subjects had little or no depression (see **Table 6**).

However, there was a clear antidepressant effect of broad-spectrum micronutrients in the subsample of 21 patients with moderate or severe depression. Using a baseline MADRS score of 20 or more, which is a common cutoff score to qualify for entry into conventional antidepressant drug RCTs, there was a significant difference in depression outcome scores between patients treated with micronutrients (n = 11) and placebo (n = 10), with a moderate effect size (ES 0.64, $P<.04$) (**Fig. 7**). This compares favorably to a typical effect size of 0.3 to 0.6 for antidepressants in conventional registration RCTs, although the ES varies with baseline severity, among many other factors.[216–218] Most contemporary RCTs on conventional antidepressants purposively exclude patients with mild episodes of major depression, because their high placebo response rate makes it more difficult to demonstrate treatment effectiveness. So, as usual for antidepressant treatments, the effectiveness of micronutrients in this RDBPCT appeared to be more readily demonstrable for more moderate and severe depressive episodes. In this context, the micronutrient effect size of 0.64 appears comparable to the effectiveness of standard pharmaceutical antidepressants.

Other predictors in the Rucklidge and colleagues'[202] RDBPCT of a stronger antidepressant response to micronutrient treatment included lower baseline levels of vitamin D and copper, but not lower levels of folate, vitamin B12, iron, or ferritin. These predictor findings involved numerous comparisons and secondary exploratory analyses, so they require replication before being accepted at face value. This RDBPCT, which was designed for other purposes, does not allow an assessment of the effects of micronutrients in patients with bipolar disorder versus MDD versus dysthymia.

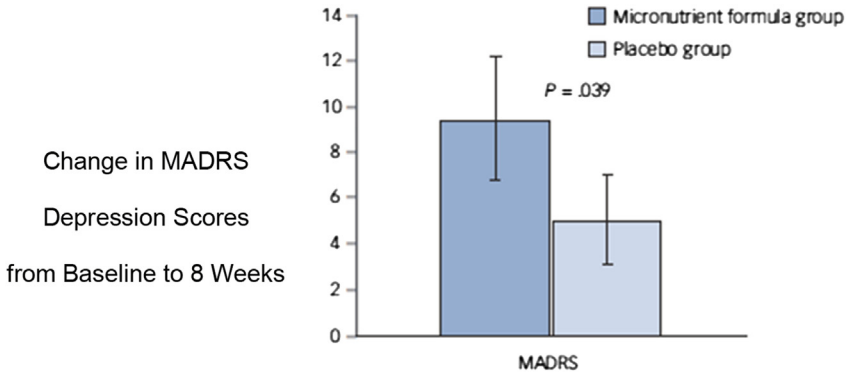

Fig. 7. Antidepressant effect of the Hardy-Stephan formula in a randomized double-blind placebo-controlled trial in adults with ADHD: effect size comparable to conventional antidepressant medications. In the RDBPCT of the Hardy-Stephan formula in adults, MADRS depression scores showed no significant change in the overall micronutrient-treated group compared with placebo (P = .078, ES 0.41, see Table 6). However, in this subsample of subjects with significant depression at baseline (MADRS$\geq$20), a clinically and statistically significant antidepressant effect of the Hardy-Stephan formula was demonstrated at 8 weeks (ES = 0.64). This subsample included 11 subjects treated with micronutrients and 10 subjects treated with placebo. (*From* Rucklidge JJ, Frampton CM, Gorman B, et al. Vitamin-mineral treatment of attention-deficit hyperactivity disorder in adults: double-blind randomised placebo-controlled trial. Br J Psychiatry 2014;204:306–15; with permission.)

Clinical caveats on the micronutrient treatment of mood disorders

Several observations, as yet undocumented in the literature, are commonly described by clinicians who are familiar with these micronutrient treatments. For example, once a patient with a mood disorder is stabilized on this treatment, the rate of symptom relapse is very low. Patients on micronutrients appear to have much fewer fluctuations in mood than patients on conventional medications, with fewer residual symptoms and fewer partial relapses into mild depressive or manic symptoms. This effect is apparent soon after stabilization, but it also increases over time. Whereas many patients treated with conventional medications require relatively frequent dose adjustments to manage the periodic variations in symptom control, physicians report a reduced frequency of necessary medication dose adjustments in patients receiving micronutrient treatment for mood disorders. (I would estimate that less than 1 yearly dose adjustment is required after a patient has been stabilized.) Some micronutrient-treated patients can be managed with much less than monthly medication check-ins. I have many patients who previously required close medication management on conventional drugs, but who now check in every 3 to 12 months with little symptomatology to report. Hospitalizations are rare. This "super stability" of micronutrient treatment relative to conventional psychiatric medication lowers the cost of medical care. Many of the open-label reports comment on this long-term stability, but it should be emphasized that these open clinical observations, although striking, are anecdotal opinion and have not been formally demonstrated in scientific studies.

One of the main disadvantages with this treatment is the dramatic interactions between micronutrients and psychiatric drugs. Drug-micronutrient interactions have been described with the Hardy-Stephan formula,[208] and several examples of effective micronutrient augmentation of psychiatric medications have been previously

discussed involving folic acid,[54,58,82] vitamin B12,[88] a thiamine/riboflavin/pyridoxine combination,[176] vitamin D,[128] zinc,[160,162,163] and magnesium.[181] These drug-nutrient interactions become a problem when a patient who is receiving conventional medications is started on broad-spectrum micronutrient treatment. When the Hardy-Stephan formula is added to a regimen of psychiatric medications, it appears as if the micronutrients potentiate the effects of the psychiatric drugs, potentially flooding the patient with adverse effects unless the doses of the drugs are concurrently lowered. The potentiation is about threefold to fivefold, so psychiatric drug doses need to be gradually and carefully lowered to about 20% to 30% of the original level (although patients actually do better once the psychiatric medications are discontinued entirely). If drug doses are lowered too quickly, psychiatric symptoms may emerge; and if lowered too slowly, side effects characteristic of the psychiatric drug increase. Obviously, lowering doses or discontinuing psychiatric medications requires physician caution and patient cooperation. These transitions from conventional medications to the Hardy-Stephan formula are complex, especially when further complicated by withdrawal syndromes (from benzodiazepine or SSRI treatment), because the micronutrients appear to potentiate the withdrawal reactions as well. This transition process is not at all similar to transitioning from one psychiatric medication to another. It requires careful supervision by a clinician who is knowledgeable and experienced in the use of this micronutrient treatment.

For this reason, it is advised that any clinician who first begins to use broad-spectrum micronutrient treatment (1) obtain consultation with a clinician experienced with this particular treatment, both before and during the addition of micronutrient treatment to a psychiatric drug regimen, and (2) start first with a medication-naive patient. Treating a medication-naïve patient is much simpler and more straightforward, because of the absence of the drug-nutrient interactions. This allows the clinician to begin to get some experience with micronutrient treatment before adding the complexity of drug-nutrient interactions.

This micronutrient potentiation, which has been documented in several of the open-label reports, applies to all virtually drugs active in the CNS, including nonpsychiatric medications.

Lithium is a special case: this mineral has extremely strong interactions with micronutrients. Instead of the 3-fold to 5-fold potentiation seen with most CNS-active drugs, broad-spectrum micronutrients produce a 100-fold potentiation of lithium. When adding lithium to a broad-spectrum micronutrient treatment, I usually begin with a dosage of 1 mg 4 times daily, and gradually increase to up to 5 mg 4 times daily if tolerated. Most patients are treated with 10 to 20 mg total daily, with typical lithium side effects emerging at higher doses. The standard dosage range for lithium is approximately 1000 to 2000 mg daily in youth,[219] so this represents a 100-fold potentiation. Administration of these low dosages entails use of either the liquid lithium elixir (diluted with water) or compounded pills. In cases in which micronutrients are helpful but residual manic symptoms persist, the addition of these “micro doses” of lithium can, in my opinion, be very helpful. No studies of lithium combined with micronutrient treatment are available.

In other cases in which micronutrients appear effective but additional fine-tuning is needed, it is possible to combine broad-spectrum micronutrient treatment with certain other “natural” treatments without incurring drug-nutrient interactions. Options for such adjunctive treatments include SAMe or 5-hydroxytryptophan for residual depression, choline (or lecithin) for residual mania (although adjunctive lithium, which does interact with micronutrients, is more effective), inositol or L-theanine for anxiety, and inositol or melatonin for sleep.[52,63,130,220–222] Omega-3 fatty acids can be considered

as well, although, based on anecdotal observation, it rarely seems to provide a significant benefit when added to the Hardy-Stephan formula.

Summary comment on mood disorders

The RDBPCT on adults with ADHD and the 16 open-label reports provide strong but early evidence that broad-spectrum micronutrient interventions can treat major symptoms of mood disorders, including depression and mania, in youth and adults. Virtually all of these studies conducted on youth and adults with mood disorders used the Hardy-Stephan formulation (eg, EMPower). In a recent systematic review, the Hardy-Stephan formulation was found to have substantial effect sizes for treating bipolar depression (Cohen d = 1.7) and bipolar mania (d = 0.83). By comparison, folic acid had a much lower effect size (d = 0.4) in bipolar depression.[63] Response rate (percentage of patients who improve significantly) appears to be about 80% for drug-naïve patients and about 50% for patients (as in the 2 database analyses) transitioning from previous psychiatric medications.

Particularly impressive in reviewing the reports on broad-spectrum micronutrient effects on mood disorders are (1) the virtual absence of significant adverse effects, (2) effectiveness for both manic and depressive symptoms, (3) the ability of most patients to discontinue their previous psychiatric medications entirely or at least reduce their doses, (4) the frequent reporting of remission rather than simple improvement of symptoms, (5) the low frequency of necessary medication dose adjustments, and (6) the anecdotal reports of long-term "super stability" in the treatment-responsive population, in which hospitalizations and even dose adjustments are rare.

Disadvantages of this treatment are significant. The lack of replicated RCTs assessing safety and efficacy remains a critical barrier at present. The cost of $150 monthly and the lack of insurance coverage puts these treatments out of consideration for many families, and cost (rather than adverse effects or ineffectiveness) is the most common reason for discontinuation by patients.[203] The treatment typically entails 8 to 15 pills daily for treating mood disorders, which is formidable for some patients, especially children. The drug-nutrient interactions are a challenge to patients when transitioning from conventional medications to the Hardy-Stephan formula (especially if withdrawal syndromes result from tapering of long-term treatments with benzodiazepines, SSRIs, or some antipsychotic agents) and to physicians (who need consultation or training when learning to conduct these transitions). Additional difficulties arise in the rare circumstance when a patient requires hospitalization, which is usually because of patient noncompliance or to unusually severe withdrawal syndromes from conventional medications. Most hospitals do not have these supplements in their formularies, and staff may decline to continue the treatments during hospitalization if they do not have access to a knowledgeable consultant.

The fact that there are so few reported negative open-label trials on broad-spectrum micronutrient treatment of mood disorders raises concern about publication bias. These concerns might be partially allayed by the 2 database analyses on several hundred youth and adults, which found that about half of patients show greater than 50% reduction in symptom scores. These estimates are based on a population in which 80% of patients were taking conventional medications at baseline, so this would underestimate the response rate that would be expected in a drug-naïve population. This substantial response rate in naturalistic data makes it unlikely that the highly favorable results in the open-label reports are due to publication bias alone.

It is evident that additional studies are needed before firm conclusions can be drawn. There are currently no RCTs examining broad-spectrum micronutrients in a

population of youths or adults recruited for major depression or bipolar disorder. New studies should first examine patients who are drug-naïve or who have not recently used conventional psychiatric drugs to avoid drug-nutrient interactions that arise during treatment transitions. For the same reasons, patients should be excluded from initial studies if they regularly use CNS-active substances, such as alcohol, recreational drugs, nicotine, or significant amounts of caffeine. Recruitment of such adults with mood disorders might be difficult in some locations, so assembling this type of sample might be easiest in a child population.[212,213]

Micronutrients for Other Psychiatric Conditions

Preliminary data suggest that broad-spectrum micronutrient treatment may have some potential for treating OCD, autism, substance use, and other psychiatric conditions.

OCD

Positive effects of broad-spectrum micronutrient treatments have been reported on OCD in children[193,194,210–212,214] and adults.[196,207] Two of the case reports included multiple reversal (ABAB) confirmation of the treatment effect.[193,210,223] All of these reports were conducted using the Hardy-Stephen micronutrient formulation (EMPower). Because 63% of patients with OCD have a mood disorder,[224] OCD symptoms may be expected to improve, even if only mediated through improved mood symptoms.

Autism

Two RCTs examining broad-spectrum micronutrient formulations have been conducted in youths with autism, but both are methodologically limited. In an initial pilot RCT of treatment with a 34-ingredient micronutrient product (manufactured by Yasoo Health, Jonesborough, TN), 20 youths (ages 3–8) were studied without the use of outcome measures. Parents described improvements in sleep and gastrointestinal symptoms, but no behavior, language, or social changes.[225] This Yasoo micronutrient formulation was then examined in an RDBPCT involving 141 subjects with clinically diagnosed autism, mostly children and adolescents.[226] No change was noted on 3 standardized outcome instruments, but the report stated (without presenting full statistical analysis) that the micronutrient group showed improvements compared with placebo on unvalidated Parental Global Impression-R scales ($P = .008$), including tantrum ($P = .009$), hyperactivity ($P = .03$), and receptive language ($P = .03$) scores. Neither the pilot nor the RDBPCT used standardized diagnostic assessments, and comorbidity was not reported.

A well-conducted study in a clinical setting, although open-label, provided more interpretable data. A naturalistic open-label study of the Hardy-Stephan formula examined children and young adults (ages 2–28) with autism and a variety of forms of comorbidity.[227] The study compared 44 patients whose families preferred nonpharmaceutical treatment, and who received the Hardy-Stephan formula, with 44 participants who were treated with conventional psychiatric medications. Over the course of treatment (mean 15 months, range 3 months to 10 years), both treatment groups improved, but the micronutrient group showed significantly more improvement in scores for Aberrant Behavior Checklist ($P>.0001$), self-injurious behaviors ($P = .005$), and CGI ($P<.003$) than patients receiving conventional psychiatric medications. Micronutrients also appeared to be more effective in reducing social withdrawal, improving spontaneity, and reducing anger.

The possible mediating role of micronutrient-induced mood changes could not be clarified in these designs.

Substance use

A recent ABAB case report suggests a possible benefit of micronutrients in reducing marijuana and cigarette use in a 20-year-old, presumably mediated by reduced symptoms of depression and ADHD.[192] Several early reports suggest possible effects of micronutrient interventions, often in combination with amino acids, in reducing craving and relapse rates for abuse of alcohol[228–233] and cocaine,[228,231,234] but inadequate methodology or incomplete data presentation limits their value.

Broad-Spectrum Micronutrient Interventions in Healthy Populations

Broad-spectrum micronutrient treatments have been examined in healthy adults and youth for their effects on cognition, normal mood, sense of well-being, and response to stress. These RCTs used heterogeneous protocols (ingredient profiles, high-dose vs low-dose strategies, treatment durations, and outcome measures), and the findings are inconsistent and not robust, but still offer some perhaps unexpected intervention options.

Cognition in healthy adults

An extremely large number of studies have investigated micronutrient effects on cognition in adults. A meta-analysis of 10 selected quality RCTs in 3200 adults (age>18) concluded that broad-spectrum micronutrient interventions induce a small but consistent improvement in immediate free recall memory (ES 0.32, $P<.01$).[235] Among the studies examined, a large RDBPCT in 4447 middle-aged adults (ages 45–60) treated with broad-spectrum micronutrients for several years showed a slowing of age-related declines in executive functions and verbal memory.[236]

Later in life, in elderly populations with or without medical illness or dementia, micronutrient trials lasting 3 to 12 months do not show consistent effects on cognition. The RCTs have found either positive effects on cognition,[237–239] benefits only in subgroups on post hoc analysis,[240–244] or no benefits.[245–249] Senescent gastrointestinal absorption of nutrients and the many non-nutritional factors that interfere with brain function in the elderly[250–253] may contribute to these weak findings.

Berocca (Bayer Corporation, Pittsburgh, PA), a commercial formulation containing 12 micronutrients (mostly B vitamins) at RDA levels, has been examined in healthy adults (ages 18–65) in a series of RDBPCTs that show small but consistent improvements on a limited number of cognitive measures.[254–257] There are also some RCTs showing positive cognitive effects of other Berocca products that included caffeine-containing guaraná, which may have contributed to the observed changes.[258,259] It should be noted that these studies were funded by the manufacturer, and manufacturer representatives were coauthors on most of the Berocca studies. The Berocca studies comprised 4 of the 10 articles in the meta-analysis and so may have weighted its findings.

Cognition in healthy youth

A literature review by Benton[260] reported that 10 of 13 controlled and uncontrolled intervention studies provided evidence that micronutrients, either singly or in broad-spectrum, improved cognition in healthy school-age children, with selective increases in nonverbal intelligence (performance IQ) scores of 2 to 4 IQ points, and not in verbal intelligence. The changes were observed in only a subgroup of children, presumably with poor dietary status. A more recent meta-analysis of RCTs focused on micronutrient formulations containing 3 or more ingredients,[261] included newer rigorous studies, and analyzed 12 studies in healthy children (ages 5–16). No significant effects were found on cognitive processing speed, working memory, long-term memory, or sustained attention, and the effect on nonverbal intelligence was found

to fall short of statistical significance (ES 0.14, $P = .083$). On the other hand, the 4 trials that examined academic performance collectively showed a cognitive benefit (ES 0.30, $P = .44$) in school-age children.[262–265]

It is not necessarily surprising that micronutrients could show a small or trending effect on nonverbal intelligence but no effect on verbal intelligence. Verbal intelligence can be viewed as more reliant on specific "crystallized" information, such as vocabulary and syntactic rules, and may depend more on education, environmental stimulation, interpersonal experience, and socioenvironmental influences. In contrast, nonverbal intelligence is more based on reasoning ability, problem-solving, reframing and set-shifting, and involves "fluid" or "organic" functioning that might be more reflective of biologic status. This division may be arbitrary to some extent, especially over time, as these types of intellectual functioning interact to promote individual development.[266]

An unexpected finding was raised by an RDBPCT of 81 healthy children (ages 8–14) using a commercial broad-spectrum micronutrient formulation (Pharmaton Kiddi, Boehringer Ingelheim GmbH, Ingelheim, Germany). It showed mixed effects on cognition, but included some improvements in selective attention that were apparent within 3 hours after the first dose administration.[267] The possibility that micronutrients might have rapid effects on cognition has not been well explored.

Surveying the cognitive effects of broad-spectrum micronutrients, healthy youths showed mild to moderate enhancement of academic performance (ES 0.44) and a trend toward a 2-point to 4-point improvement in performance IQ (ES 0.14). Adults showed some positive cognitive effects of micronutrients as well, including improved immediate free-recall memory (ES 0.32) and possibly a slowing of age-related declines in executive functioning and verbal memory. In the elderly, cognitive effects appeared mixed and inconclusive. These findings suggest that there are small but potentially clinically significant benefits of micronutrient interventions on cognition in youth and nonelderly adults.

Mood and well-being in healthy adults

Long and Benton[268] conducted a meta-analysis of RCTs examining mood and mood-related effects of broad-spectrum micronutrients in healthy adults. It found no overall effect on general mood in 8 RDBPCTs on 1292 healthy adults (ages 18–69) administered broad-spectrum micronutrients for 28 to 90 days. The 3 RDBPCTs examining subclinical depression in the general population also reported no effect (**Fig. 8**).[254,269,270]

Despite the absence of significant mood effects, the meta-analysis found that broad-spectrum micronutrients improved perceived stress (ES 0.35), anxiety (ES 0.32), fatigue (ES 0.27), mental fog (ES 0.23), and hostile mood (ES 0.23), all significantly ($P<.011$). Again, half of the 8 studies reviewed in the meta-analysis were manufacturer-sponsored reports on Berocca.[254–256,271] Two uncontrolled Berocca studies not included in the meta-analysis also found reductions in stress-related symptoms. The other four studies similarly showed positive effects on fatigue and mental clarity.[272–275]

Subsequent to the meta-analysis, an independent 4-month RDBPCT of a commercial formulation (Swisse Ultivite F1 Formula) in 138 healthy adults (ages 20–50) confirmed the meta-analysis findings of no change in mood measures, but some evidence of improved anxiety and physical fatigue scores,[276,277] including subjects' narrative reports describing an improved sense of well-being.[278]

As in the cognition studies, older adults ($\geq$50 years old) showed inconsistent results, with mood improvements in only 2[178,269] of 6 studies.[178,237,240,242,246,269]

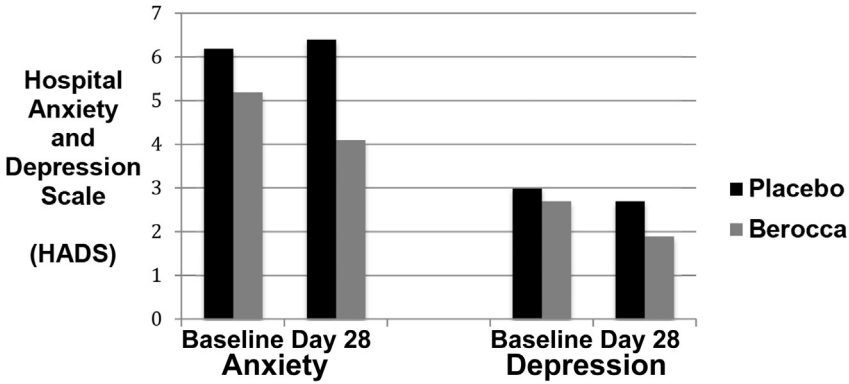

Fig. 8. Berocca, a commercial micronutrient supplement, reduced anxiety but not depression in healthy volunteers. A 4-week RDBPCT of Berocca in healthy male volunteers (ages 18–42, mean 25), with 40 subjects in each treatment group. The formulation of Berocca used in this study consisted several B vitamins, vitamin C, calcium, and magnesium, with no caffeine. At day 28, the effect on anxiety was significant ($P = .05$), but not on depression. (*Data from* Carroll D, Ring C, Suter M, et al. The effects of an oral multivitamin combination with calcium, magnesium, and zinc on psychological well-being in healthy young male volunteers: a double-blind placebo-controlled trial. Psychopharmacology (Berl) 2000;150(2):220–5.)

However, in contrast to the mixed results on mood and cognition, 2 studies in the elderly found positive micronutrient effects on measures of well-being and general functioning.[237,269]

In nongeriatric adults, 2 RDBPCTs again showed evidence of improved scores for feeling more "agreeable" ($P<.03$), and among women feeling more "composure" ($P<.01$).[147,279]

In youth, the only RDBPCT conducted on mood in children examined a commercial children's multivitamin/multimineral product (Pharmaton Kiddi) on 81 healthy children (8–14 years) in a 12-week study.[267] Mood data were collected via the Internet using only a visual analogue scale (faces) and a single number on a 7-point scale, so the findings are compromised by inadequate outcome measurement. The study found no effect on mood.

The meta-analysis found that micronutrient formulations with higher doses of B vitamins appeared to have more effect on actual mood ratings, especially if doses were well above RDA levels (5–10 times higher). This finding again challenges the validity of RDAs as reflecting optimal intake levels and instead suggests that supra-RDA levels may be needed to optimize brain function.

None of the studies conducted on cognition, mood, or well-being in healthy subjects have investigated the Hardy-Stephan formula. (It might be mentioned that none of the 28 reports on the Hardy-Stephan formula have been funded or coauthored by the manufacturers.)

Summing across these RCTs in healthy adults, broad-spectrum micronutrients appeared to have little effect on mood, but did improve sense of well-being, general energy, clear-headedness, and agreeable feelings and reduced anxiety and stress responses (ES 0.23–0.35). These statistically significant changes were not dramatic, but even these small changes should challenge some common preconceptions about nutrition and mental health. If judged by the standards of a therapeutic intervention for a medical disorder, this intervention might be viewed as worthwhile but not

particularly strong. If judged by the standards of an inexpensive and easy life enhancement, these same findings might be viewed as dramatic. Who wouldn't want a consistent, albeit small, improvement in mental energy and clarity of mind? Who wouldn't want a subtle "tune-up" for anxiety and stress management?

Mental energy, clear-headedness, and agreeable feelings can be conceptualized as aspects of mood that are not tapped by the common psychiatric instruments for measuring outcome in mood disorders. These features could be "sub-subclinical" signs of mood disorders, but it is also possible that they are aspects of mood overlooked by psychiatric measures. Antidepressants are usually thought to contribute little to "normal" people who are free of subclinical mood disorders. These micronutrient data in healthy subjects suggest that the sense of well-being and clear-headedness may be valuable to conceptualize and target for intervention as aspects of "mood" that might not be affected by antidepressants.

These RCTs seem to highlight a possible value of micronutrients for the general population of nonelderly healthy adults. Micronutrients, unlike conventional antidepressants, may be a rational option for enhancing a quality of well-being, emotional reserve, clear-headedness, and freedom from stress and mental fatigue, even if the effects are subtle. At present, comparable data are not available for healthy youths.

Response to stress

Micronutrient effects on mood, anxiety, and well-being have been examined in highly stressful life circumstances. Three settings in which broad-spectrum micronutrient interventions have been studied in RCTs are stressful urban living, military training, and the aftermath of earthquakes.

A study of 300 community adults living in "2 centers with high stress levels" in South Africa, Durban and Johannesburg, were administered Berocca Calmag (not available in the United States) or placebo under RDBPC conditions.[271] Both groups improved between baseline and day 30, but the micronutrient group improved significantly more than the controls in anxiety or stress levels, as measured by the Hamilton Anxiety Rating Scale, the Psychological General Well-Being Index, and an unvalidated stress instrument. This study is compromised by the vague description of the population and recruitment procedures, and by the manufacturer's direct involvement. It is unclear whether the micronutrient-induced changes are due to treating stress responses or to correcting endemic nutritional deficiencies in these populations; however, stressful life circumstances increase micronutrient utilization and turnover, so these are not necessarily separable effects. Regardless of the conceptualization of the mechanism, it is interesting to see a micronutrient-induced reduction in stress response in an endemically stressful region.

Military training also can be viewed as a major life stressor. An RDBPC crossover study examined the effects of just a single week of micronutrient supplementation in 240 men who were subjected to physical "overtraining" in rigorous endurance military training.[280] Findings included a reduction in psychological stress responses (probably including anger, tension, somatization), compared with placebo, as well as in pituitary, adrenal, and thyroid changes. The Chinese government has made the abstract of this report available, but the article itself is officially unavailable because of its secret contents, so no further information can be described. Potential military applications of micronutrient treatments are plentiful.

A third example of micronutrient effects on extreme stress is evident in the open-label reports and an unblinded RCT suggesting that broad-spectrum micronutrients, even used on a short-term basis, can prevent or reduce posttraumatic

stress symptoms following a natural disaster. An open-label study examined 33 adults with ADHD who had either been treated with the Hardy-Stephan formula or received no treatment for 2 weeks before a major earthquake.[281,282] The treatments were conducted in the context of research studies that were interrupted by the earthquake. These subjects were continued on open-label Hardy-Stephan formula or no treatment for 2 weeks after the earthquake and then assessed by using the Depression, Anxiety, and Stress Scale (DASS). Relative to baseline before the earthquake, the micronutrient-treated subjects at 2 weeks after the earthquake showed reductions in depression (ES 0.73, $P<.05$) as well as anxiety (ES 0.84, $P<.01$) and stress (ES 1.0, $P<.01$), with nonsignificant improvements in the untreated subjects. Two weeks after the earthquake, the micronutrient group showed lower anxiety and stress scores compared with controls (ES 0.69, $P<.05$). This study was conducted under extraordinary circumstances, involved nonrandom treatment assignments, an untreated control group, and differences in recruitment and treatment time, but nonetheless provides results suggesting that micronutrient treatment enhanced the resilience or recovery of adults with ADHD following a natural disaster.

A separate study was initiated as an RCT starting 2 to 3 months after a subsequent earthquake and conducted over a 4-week period while aftershocks were still occurring daily.[283] In this RCT, 91 healthy adults were randomized to 1 of 3 different micronutrient treatments: (1) EMPower administered at a moderate dose of 8 pills daily (the standard dose for treating mood disorders is 15 pills daily); (2) EMPower at a low dose of 4 pills daily; and (3) a once-daily dose of Berocca, which is the commercial RDA-level multivitamin/mineral formula that had been shown to have efficacy in reducing stress and anxiety (see **Fig. 8**),[254,255,271] with an effect size of 0.35.[268] A contrast group was separately recruited. All subjects had been selected for elevated baseline anxiety, depression, or stress scores. Although the study was randomized and different doses of micronutrients were compared with each other and with a separately recruited contrast group, this RCT was not blinded. One month later, all 3 micronutrient groups showed improvement ($P<.001$) on several scales (DASS; Impact of Event Scale; Perceived Stress Scale). The improvements in mood, anxiety, and energy were significant ($P<.03$) and appeared dose-dependent (**Fig. 9**). EMPower was more effective than Berocca in reducing intrusive thoughts ($P = .05$), and some other changes were significantly larger in the moderate-dose EMPower group than in the Berocca group. Over the 4-week trial, the prevalence of probable posttraumatic stress disorder (PTSD) reduced from 65% to 19% in the micronutrient groups, but increased from 44% to 48% in the control group ($P<.05$) (**Fig. 10**). In this postearthquake RCT, micronutrients appeared more effective than controls in diminishing anxiety, arousal, intrusive thoughts, and avoidance.

In a 1-year follow-up study to this RCT,[284] approximately 70% of the original subjects completed online questionnaires (Depression and Anxiety Stress Scale, Impact of Event Scale, CGI-I). Approximately 10% of the subjects still had PTSD symptoms at the 1-year point, but subjects treated with micronutrients soon after the earthquake had better DASS stress (ES 1.31), intrusions (ES 0.71), mood (ES 0.69), and energy (ES 0.71) scores, in comparison to controls after controlling for baseline values (**Table 7**). As in the ADHD RDBPCT, subjects who stayed on micronutrients for the entire year fared better than subjects who switched to conventional medications (**Fig. 11**).

These earthquake findings have potentially major implications, because they suggest that simple and inexpensive micronutrient supplementation may reduce acute

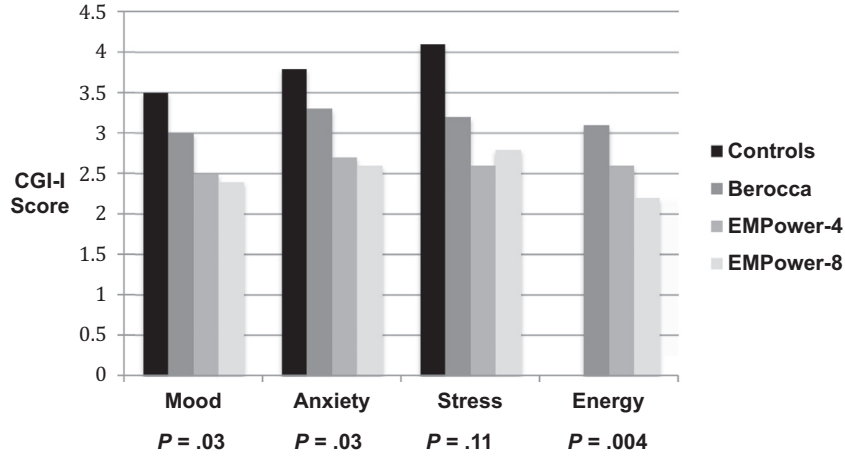

Fig. 9. Outcome after 4 weeks of micronutrient treatment following an earthquake. Two or 3 months after a catastrophic earthquake in New Zealand, 91 adults with elevated depression, anxiety, or stress scores were treated for 4 weeks with one of 3 micronutrient interventions: Berocca (1 pill daily), EMPower (4 pills daily), or EMPower (8 pills daily). A control group (n = 25) was separately assembled for comparison. All groups showed improvement in CGI scores for mood (DASS), anxiety (IES), and stress (Perceived Stress Scale) ratings. Clinical Global Impression-Improvement scores showed change from baseline to 4 weeks (1 = very much improved, 7 = very much worse, so lower score means better outcome). *P* values represent analysis of variance comparisons across treatments for each outcome measure. Comparison of combined micronutrient groups to controls was *P*<.001 for mood, anxiety, and stress (energy data for controls not available). (*Data from* Rucklidge JJ, Andridge R, Gorman B, et al. Shaken but unstirred? Effects of micronutrients on stress and trauma after an earthquake: RCT evidence comparing formulas and doses. Hum Psychopharmacol 2012;27(5):440–54.)

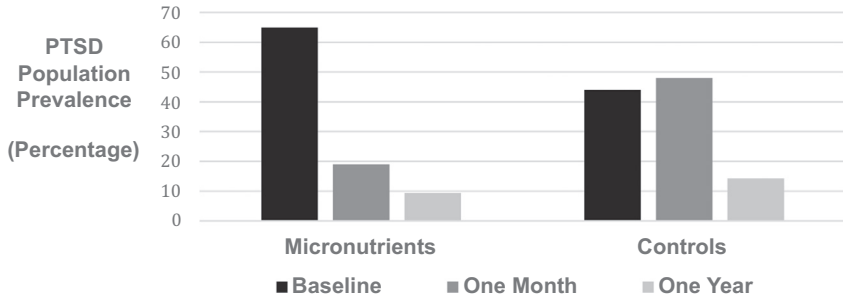

Fig. 10. Following a natural disaster, prevalence of probable PTSD was reduced after a 1-month RDBPC trial of EMPower, with follow-up at 1 year. Prevalence of probable PTSD was high in this population at baseline (2–3 months after earthquake). After a 1-month randomized double-blind placebo-controlled trial, probable PTSD was reduced in the micronutrient-treated subjects, but was unchanged in the separately recruited controls (comparison *P*<.05). After 1 year, part of the sample continued on micronutrients on an open-label basis, but by then, both groups had largely and equally improved. (*Data from* Rucklidge JJ, Andridge R, Gorman B, et al. Shaken but unstirred? Effects of micronutrients on stress and trauma after an earthquake: RCT evidence comparing formulas and doses. Hum Psychopharmacol 2012;27(5):440–54; and Rucklidge JJ, Blampied N, Gorman B, et al. Psychological functioning 1 year after a brief intervention using micronutrients to treat stress and anxiety related to the 2011 Christchurch earthquakes: A naturalistic follow-up. Hum Psychopharmacol 2014;29(3):230–43.)

Table 7
Earthquake victims treated for 1 month with the Hardy-Stephan formula in a randomized double-blind placebo-controlled trial showed better outcome 1 year later

	Micronutrient-Treated, n = 64			Control Group, n = 21			Effect Size for 4 vs 52 wk		
Months Treated	0	1	12	0	1	12	Treated	Controls	*P*
DASS									
Depression	16.0	8.2	7.2	12.0	8.5	8.1	0.13	0.10	NS
Anxiety	11.0	4.2	3.7	8.6	7.4	3.4	0.09	0.72	NS
Stress	22.0	11.0	3.7	17.0	15.0	9.9	0.80	1.12	<.001
Total	49.0	23.0	15.0	38.0	31.0	21.0	0.40	0.72	<.01
IES-R									
Avoidance	1.4	0.61	0.50	1.2	1.1	0.79	0.24	0.60	<.001
Arousal	2.1	1.2	0.82	1.6	1.8	1.1	0.39	0.62	<.001
Intrusion	1.9	1.1	0.76	1.7	1.5	1.1	0.44	0.77	NS
Total	39.0	21.0	15.0	33.0	32.0	22.0	0.44	0.74	<.001

Seventy percent of the original sample completed the 1-year followup evaluation, and all 3 randomized micronutrient-treated groups were merged for the 1-year follow-up data and compared with a separately recruited, nonrandomized control group.

All measures in both treatment groups showed improvement after 4 weeks and still more after 12 months (analysis of variance $P<.001$). Statistically significant improvements between 1 month and 1 year were observed for stress, avoidance, and arousal, but not for depression, anxiety, or intrusive thoughts. Given the large number of comparisons, change is considered significant only if $P<.01$.

Clinical Global Impression-Improvement (CGI-I) changes over time for mood, anxiety, and stress did not show statistically significant effects between treated and control groups.

Abbreviations: DASS, Depression, Anxiety, and Stress Scale; IES-R, Impact of Event Scale; NS, not significant.

Adapted from Rucklidge JJ, Blampied N, Gorman B, et al. Psychological functioning 1 year after a brief intervention using micronutrients to treat stress and anxiety related to the 2011 Christchurch earthquakes: A naturalistic follow-up. Hum Psychopharmacol 2014;29(3):230–43; with permission.

stress symptoms following natural disasters. These effects appear to be clinically significant, even with a brief 4-week intervention, similar to the improvement in anxiety and stress levels observed after a 4-week intervention in adults living in highly stressful urban centers in South Africa.[271] Although this earthquake study is limited by a lack of placebo controls, no blinding, and use of a nonrandomized control group, this RCT raises the possibility of an innovative and unique public health intervention for healthy populations following natural disasters.

Replicative studies are needed to assess micronutrients as an emergency intervention for treating and possibly preventing acute stress reactions in adults. Obviously, there are numerous potential applications for micronutrient interventions in response to major traumatic events in children and adolescents, but again, studies are needed.

Adverse Effects of Broad-Spectrum Micronutrient Interventions

The numerous open-label reports and controlled studies, both of the Hardy-Stephan formula and other broad-spectrum micronutrient formulations, have uniformly noted that broad-spectrum micronutrient treatments have a minimum of adverse effects in

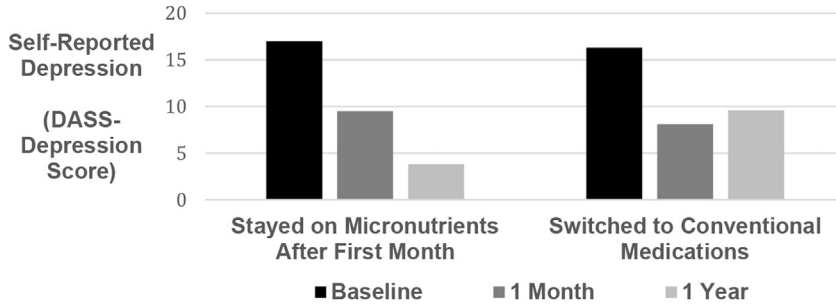

Fig. 11. After major stressor, staying on micronutrients for 1 year reduced depression scores more than switching to conventional medications. This is a reanalysis of the data, looking at outcomes (at 1 month and at 1 year) based on whether the subjects stayed on micronutrients for a full year or whether they switched to conventional medications after the 1-month RCT. Starting 2 to 3 months after the earthquake, all subjects in this subsample of the RDBPCT were treated with micronutrients for 1 month, and both groups responded about equally. After the first month, the 17 subjects who continued open-label micronutrients for 1 year had lower self-rated DASS depression scores than 12 subjects who switched to conventional medications after the first month ($P<.05$). The micronutrient continuers continued to improve between 1 month and 1 year, whereas the switchers did not. (*Data from* Rucklidge JJ, Blampied N, Gorman B, et al. Psychological functioning 1 year after a brief intervention using micronutrients to treat stress and anxiety related to the 2011 Christchurch earthquakes: A naturalistic follow-up. Hum Psychopharmacol 2014;29(3):230–43.)

children and adults. A naturalistic case-control study found markedly fewer adverse effects in 44 micronutrient-treated patients (ages 2–28) than in 44 medication-treated patients.[227] Two reports have given systematic descriptions of adverse effects in 151 children, adolescents, and adults,[213,285] including published and unpublished data.

The main adverse effects reported were mild nausea, dyspepsia, loose stools, initial insomnia, and headache (**Box 8**). In the ADHD RDBPCT, these symptoms appeared at similar frequency in the placebo-treated subjects, with no statistically significant differences between the 2 groups.[201] These adverse effects are typically mild and transient, and can be managed in the routine ways (taking capsules with food to reduce gastrointestinal symptoms, taking pills earlier to reduce insomnia, temporary dose reductions).

Anxiety, agitation, or impulsivity can appear if the broad-spectrum micronutrient dose is too high, but these exacerbations reliably resolve when the dose is lowered. Excessive dosing does not appear to trigger autonomous manic episodes. Another potential adverse effect is the aggravation of preexisting *Candida* (yeast) infections. In general, these infections can be adequately managed with antifungal medication, olive leaf extract, and probiotics.[286]

There was a report of a small asymptomatic increase in prolactin levels in micronutrient-treated patients (mean increased from 191 to 222 mIU/L, $P<.006$).[202] Two of 80 subjects had larger prolactin elevations, but no subject had levels rise beyond the normal range; it was unclear whether these changes were related to treatment. Two cases of mild blood sugar elevation also were described in that report, but they were judged not clinically significant, and again were not clearly related to treatment. No other changes have been observed in laboratory indices.

The systematic data and the numerous published descriptions document an absence of weight changes, sedation or fatigue, dry mouth, constipation, tremor,

Box 8
Clinical points on broad-spectrum micronutrient treatments

Adverse Effects

- Loose stools
- Nausea (rarely, vomiting)
- Dyspepsia
- Insomnia
- Headache
- "Neon" yellow urine (due to riboflavin excretion; not a medical problem)
- Flatulence
- Watery diarrhea
- Anxiety, agitation, or impulsivity if dose too high
- Aggravation of preexisting *Candida* (yeast) infections
- Slightly increased prolactin levels (reported in 1 study)[201]

Nutrient-drug interactions

- Critical: Interaction with virtually all psychiatric drugs and other medications with CNS effects, especially medications associated with discontinuation syndromes.
- Interaction with antibiotics (antibiotics reduce gastrointestinal absorption of nutrients, so micronutrient dosage needs to be increased during antibiotic treatment)

Strict contraindications

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

Relative contraindications

- Recreational drug dependence, including caffeine, alcohol, and nicotine
- Recent use of medical drugs with withdrawal syndromes
- Necessary medical treatment with CNS-active agents
- Treatment-resistant *Candida*
- Autoimmune thyroid disease or nodular goiter (iodine)
- High alcohol intake, hyperlipidemia, or severe protein malnutrition (which are associated with increased susceptibility to vitamin A toxicity)

sexual side effects, blood pressure or pulse changes, seizures, thyroid changes, motor side effects, dependency, or discontinuation effects.[194,196,207,227] Electrocardiographic data have not been reported in the literature, but I have observed no micronutrient-related electrocardiogram abnormalities in several hundred youths and adults.

It is evident that the adverse effects of the broad-spectrum micronutrient treatments are mild in comparison with the side effects of most conventional psychopharmacological treatments.

SUMMARY

The main findings on micronutrient treatments provide some encouraging data (Box 9, Tables 8 and 9). Several single-nutrient interventions show promise as effective augmentation agents for antidepressant treatments, but not as monotherapies. In contrast, broad-spectrum micronutrient interventions appear to have the potential to become a genuine monotherapy for mood disorders whose effects may be comparable to conventional antidepressant and mood-stabilizing agents.

Main findings on broad-spectrum micronutrient treatments are as follows:

- Three RDBPCTs support the treatment of violence and major misconduct in adolescent and young adult incarcerated offenders.
- One RDBPCT shows a reduction in aggressive and disordered conduct in school children.
- One RDBPCT in adults with ADHD shows moderate effect sizes for changes in hyperactivity/impulsivity (ES 0.46–0.67), inattention (ES 0.33–0.62), and CGI (ES 0.53–0.57), with a response rate of 64%.
- In youth with ADHD, the best estimate of response rate is 63% to 76%.
- Treatment of probable MDD (MADRS$\geq$20) in adults with comorbid ADHD has effect size comparable to antidepressants (ES 0.41) in the ADHD RCT.
- A sophisticated independent review gave higher estimates of the effect sizes for treating mood disorders: 1.7 for treating bipolar depression, and 0.83 for bipolar mania (Sarris 201).[63]
- Open-label data support possible effectiveness for OCD, autism, and substance abuse.
- Several RCTs suggest improved response to a diverse set of major stressors in healthy adults, including reduction in post-traumatic symptoms following a natural disaster.
- A meta-analysis finds improved academic performance in healthy school children (ES 0.44). (There is also a nonsignificant statistical trend suggesting a 2-point to 4-point improvement in performance IQ in healthy children.)
- A meta-analysis shows improved free-recall memory in healthy adults (ES 0.32), and a large multi-year RDBPCT showing a possible slowing of age-related decline in executive functioning and verbal memory.
- Subtle improvements in general energy, clear-headedness, and agreeable feelings in healthy adults (ES 0.2–0.3); no data in youth.

The main findings on single-micronutrient treatments provide some positive data as well:

- Folic acid is an effective, although not powerful, adjunctive treatment for MDD in adults (ES 0.4), but has not been evaluated in youth with MDD.
- Vitamin B12 appears useful in geriatric depression but is unlikely to be helpful for youth, except perhaps in depressed youth with chronic gastrointestinal malabsorption.
- Vitamin D might sometimes be useful in depressed patients with documented hypovitaminosis D, and several factors may help estimate level of risk in an individual.
- Chromium may prove to be useful for atypical depression with carbohydrate craving in adults, but has not been examined in youth.
- Zinc should be examined further for antidepressant augmentation, especially in treatment-resistant MDD.
- Thiamine needs further study for its potential to improve mood, energy, and cognition in psychiatrically healthy individuals.

Box 9
Explanation of modified US Preventive Services Task Force grading system used in Tables 8 and 9

Tables 8 and 9 use a modified form of the US Preventive Services Task Force (USPSTF) grading system for describing published evidence in the medical literature supporting a treatment intervention.

Each treatment is assigned a grade for "Quality of Evidence" and a grade for "Strength of Recommendations."

USPSTF Quality of Evidence grade is based on the strength of the published evidence:

- Good: Consistent effect in well-conducted studies in different populations.
- Fair: Data shows effects, but data are weak, limited, or indirect.
- Poor: Cannot determine effect due to data weakness.

USPSTF Strength of Recommendations grade provides a ranking of the clinical recommendations that can be drawn from data in the published studies:

- Insufficient Data
- Recommend Against: Fair evidence of ineffectiveness or harm.
- Neutral: Fair evidence for, but appears risky.
- Recommend: Fair evidence of benefit and of safety.
- Recommend Strongly: Good evidence of benefit and safety.

Adapted from U.S. Preventive Services Task Force Grade Definitions. May 2008. Available at: http://www.uspreventiveservicestaskforce.org/uspstf/grades.htm. Accessed February 26, 2014.

- Selenium may be useful as a prenatal measure to prevent postpartum depression, but more research is needed.

The fact that broad-spectrum micronutrient treatments are much more powerful than single-nutrient treatments is not surprising in view of the basics of nutrition. Indeed, one might question the general strategy of single-micronutrient interventions. The interactions among nutrients make their combined use much more potent (witness lithium), and the high rate of single nutrient insufficiencies in the population makes generalized supplementation sensible. In fact, the risks of creating micronutrient imbalances (relative insufficiencies) might serve as a warning against the introduction of just one or a few micronutrients, except in specific situations (eg, vitamin D for Northerners and for bedridden patients, iron for menstruating women).

The findings of widespread micronutrient deficiencies, even in presumably well-fed populations, should also serve as an alert that large sections of the general population might benefit from nutrient supplementation.[256] Judging by the early data, broad-spectrum micronutrient treatments seem to be helpful for several different psychiatric indications and in so-called "normal" people as well. This highlights the question of the specificity of broad-spectrum micronutrient treatments.

If broad-spectrum treatments are able to treat mood disorders and ADHD, as well as stress reactions in medical and nonmedical populations, could the effects of broad-spectrum micronutrient treatments operate through a promotion of general CNS functioning rather than through mechanisms specific to mood or mood disorders? A generalized improvement in CNS functioning would be consistent with Bruce Ames' concept[21,22] of a "metabolic tune-up," in which biologic functions are pervasively enhanced by broad-spectrum micronutrient supplementation.

Table 8
Evidence base in published medical literature for single-micronutrients and broad-spectrum micronutrients for treating major depression and bipolar disorder

	Major or Bipolar Depression		Bipolar Mania		
Micronutrients	**Youth**	**Adults**	**Youth**	**Adults**	**Evidence Base for Recommendation**
Folic acid adjunctive therapy					
Quality of evidence	No data	Good	No data	Poor	Multiple RCTs in adults
Clinical recommendation	Insufficient data	Recommend	Insufficient data	Insufficient data	
Vitamin B12 adjunctive therapy					
Quality of evidence	No data	Good in geriatrics Fair in adults	No data	No data	Multiple RCTs in geriatrics, 2 RCTs in adults
Clinical recommendation	Insufficient data	Recommend for geriatrics Recommend against in adults	Insufficient data	Insufficient data	
Vitamin D adjunctive therapy					
Quality of evidence	Poor	Fair	No data	No data	2 RCTs in adults
Clinical recommendation	Insufficient data	Neutral	Insufficient data	Insufficient data	One open-label in youth
Pyridoxine adjunctive therapy					
Quality of evidence	No data	Poor	No data	No data	4 RCTs in adults with premenstrual symptoms
Clinical recommendation	Insufficient data	Recommend against in adults	Insufficient data	Insufficient data	
Chromium monotherapy					
Quality of evidence	No data	Fair	No data	No data	2 RCTs in adults with atypical depression
Clinical recommendation	Insufficient data	Neutral	Insufficient data	Insufficient data	1 RCT in bulimia

Zinc adjunctive therapy					
Quality of evidence	No data	Fair	No data	No data	3 RCTs in adults
Clinical recommendation	Insufficient data	Neutral (to Recommend but weakly)	Insufficient data	Insufficient data	
Thiamine monotherapy					
Quality of evidence	No data	No data	No data	No data	2 RCTs in nonclinical volunteers were positive
Clinical recommendation	Insufficient data	Insufficient data	Insufficient data	Insufficient data	
Selenium monotherapy					
Quality of evidence	No data	Poor	No data	No data	1 RCT for preventing postpartum depression
Clinical recommendation	Insufficient data	Insufficient data	Insufficient data	Insufficient data	3 of 5 positive RCTs in nonclinical adults
Magnesium monotherapy					
Quality of evidence	No data	Fair	No data	No data	3 RCTs in adults with premenstrual symptoms
Clinical recommendation	Insufficient data	Recommend against	Insufficient data	Insufficient data	
Broad-spectrum micronutrient monotherapy					
Quality of evidence	Poor	Fair	Poor	Fair	1 RCT in adults with MDD, 4 RCTs in nonclinical stressed adults.
Clinical recommendation	Neutral	Neutral	Neutral	Neutral	

Abbreviations: MDD, major depressive disorder; RCT, randomized controlled trial.

Table 9
Author's personal opinion of single micronutrients and broad-spectrum micronutrients for treating mood disorders in youth and adults

Micronutrient	Treatment Evaluation	Author's Clinical Opinion
Folic acid	Good evidence as adjunctive treatment for major depression in adults; no data in youth.	Moderately useful in adults. Despite lack of data, reasonable to try in youth based on lack of risk.
Vitamin B12	Good evidence as adjunctive treatment for major depression in geriatrics, but not in other adults; no data in youth.	Unlikely to help youth, unless chronic gastrointestinal malabsorption.
Vitamin D	Little evidence to support use for major depression in adults, few data in youth.	May be useful in depressed youth and adults with documented low serum levels of vitamin D, but even in those cases, effects on mood appear small.
Pyridoxine	Mostly negative results as adjunctive treatment of premenstrual mood.	Overall, little evidence of benefit.
Chromium	Mixed results as monotherapy for atypical depression in adults, no data in youth.	Might be useful for subgroup of atypical depression with carbohydrate craving.
Zinc	Mostly positive effects as adjunctive treatment in 3 RCTs in adults, perhaps mainly in treatment-resistant depression.	Needs more data, but low risk of harm.
Thiamine	Few data on monotherapy for depression, but might brighten mood in nonclinical youth and adults.	Unclear implications for treating mental illness.
Selenium	One RCT suggests possible preventive intervention for postpartum depression; conflicting data on mood in nonclinical samples.	Unclear implications for treating mental illness.
Magnesium	Monotherapy mostly ineffective for premenstrual mood.	Little mood effect, but not examined in major depression.
Broad-spectrum micronutrients	In mostly open trials, appears effective as monotherapy for bipolar depression, unipolar depression, and mania in youth and adults; one RCT in adults with ADHD shows antidepressant benefit that is comparable in effect size to conventional medications.	May prove useful as monotherapy. Because of few adverse effects compared with standard treatment, can be considered for medication-free youth and adults with mood disorders, but drug-nutrient interactions make this unsuitable for currently medicated patients unless treated by clinician familiar with this approach.

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; RCT, randomized controlled trial.

Such a "metabolic tune-up" also could explain why broad-spectrum micronutrient treatments can amplify the effects of virtually all CNS-active drugs. Perhaps most psychiatric patients, or most people, are underresponding to their conventional medications because their biologic responses are not generally optimized. Tuning up the nutritional status of patients might speculatively improve their response to psychiatric medications, or to medications in general, by enhancing overall biological functioning.

Until there is more substantial evidence of the efficacy of these broad-spectrum micronutrient treatments, discussion of mechanisms in treating diseases remains entirely speculative. Once there is strong scientific evidence that these treatments are effective, then it will make sense to ask questions about mechanism: How do micronutrients alter disease processes? Are there particular nutrients that are essential, or is a broad-spectrum approach required? Is the same approach needed for all patients with a particular disorder, or does the optimal intervention depend on the nutritional requirements of the particular individual? Are nutritional insufficiencies even relevant, or are other individual factors more decisive? Until more clinical efficacy data are available, such questions are premature. The model of a metabolic tune-up is appealing, but it is not the only possible model. Nonetheless, at this time, Ames' notion of a broad-spectrum micronutrient "tune-up" of a broad range of physiological functions is sensible, supported by diverse biologic examples, and highly applicable to the seemingly wide-ranging effects of micronutrients on brain functioning.

The notion that broad-spectrum micronutrient supplementation might have broad-ranging effects on brain function and brain development is supported by a series of experiments conducted in rats. Celeste Halliwell and Bryan Kolb[287,288] have examined the effects of EMPower on recovery from early brain injury. Rats lesioned on postnatal day 3 in the frontal cortex show drastic permanent reductions in cortical thickness and functional performance, including decrements on tasks that involve motor skills and spatial learning and memory. When tested as adults, lesioned rats administered EMPower in their chow throughout their lives showed, relative to rats fed standard chow, increased brain weight, increased cortical thickness, and restoration of normal functioning on both behavioral tasks, as well as evidence of enhanced new dendritic growth and increased spine density (**Figs. 12** and **13**). Rats with perinatal posterior parietal lesions, when fed EMPower, showed generally similar anatomic recovery (including reversal of decreased brain size, atrophy of dendritic arborizations, and reduced spine density in pyramidal cells in the cortex), as well as restoration of cognitive and motor capacity.

These studies suggest a powerful neurotrophic effect of broad-spectrum micronutrients on rat brain structure, function, and development following early perinatal cortical lesions. The potential clinical implications of these findings for children with prenatal or perinatal brain injury (for example, in response to intrauterine drug or nicotine exposure, or to perinatal anoxia) or with neurodevelopmental disorders (for example, learning disorders or schizophrenia) have not been investigated.[289,290]

In addition to such broad-spectrum approaches, more targeted interventions also might have generalized neurotrophic effects on cerebral plasticity, dendrite growth, spine density, brain development, and brain function.[291,292] Halliwell and Kolb,[287,288] as well as Richard Wurtman,[293] have provided evidence that choline can have similar effects. Wurtman[293,294] has noted that increasing the dietary intake of choline, the omega-3 fatty acid DHA, and the nucleoside uridine can improve synaptogenesis during early development and in senescence.

In this review, we have glossed over a variety of technical details in the clinical studies. Optimally, intervention studies would control for subjects' oral micronutrient intake obtained through foods and supplements. We have not discussed proper

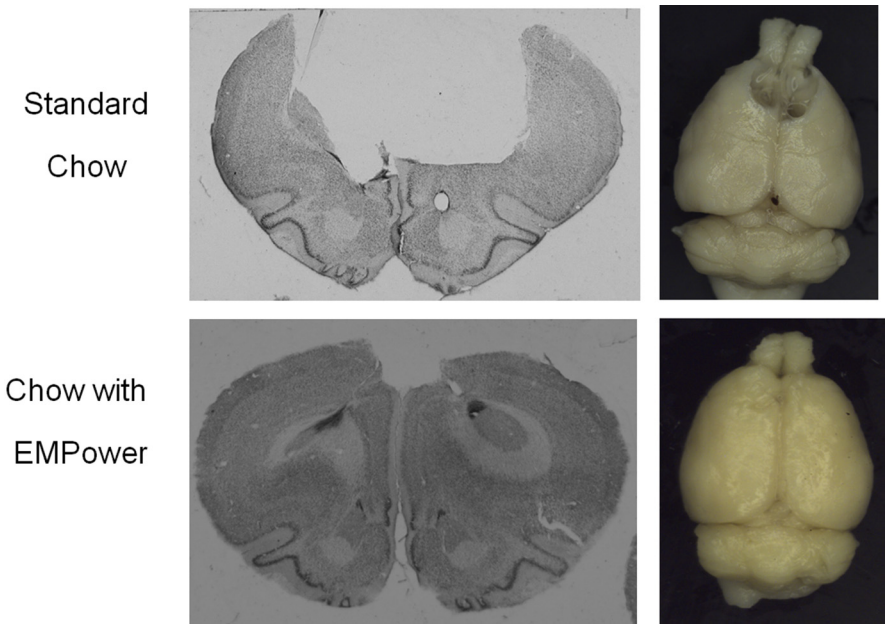

Fig. 12. Micronutrients enhance anatomic recovery after early cortical lesions in rats. Rats received aspiration lesions in the midline medial frontal cortex on postnatal day 3, and were then examined anatomically in adulthood. Animals receiving standard rat chow showed the expectable permanent damage resulting from early cortical lesions. Animals receiving EMPower in their rat chow showed significant restoration of brain tissue, although the cortical structures were not fully normal.[287] (*Courtesy of* Celeste Halliwell, PhD and Bryan Kolb, PhD, University of Lethbridge, Alberta, Canada.)

dose levels for the various micronutrient interventions or what goes into creating a well-balanced micronutrient supplement. We have not emphasized different responses in subgroups based on baseline micronutrient sufficiency status, or that data analyses could be stratified based on endogenous micronutrient deficiency markers. We have only glanced at the issue of micronutrient-micronutrient interactions. We have ignored the less popular minerals, such as molybdenum, which in deficiency can cause CNS symptoms ranging from fatigue to mental retardation[2] and which may be involved in the allosteric modulation of glutamate receptors.[295] Similar to pinning down mechanisms of micronutrient action, all of these questions will become more important once the basic principles and place of micronutrients in psychiatric care become better acknowledged.

One of the interesting findings embedded in this research is that therapeutic effects of broad-spectrum micronutrients have been reported with a diverse range of micronutrient formulations. It does not appear that any particular nutrients are required to produce improvements, although the effect sizes can vary, but a larger number of different micronutrients does appear to deliver more effectiveness. Most of the broad-spectrum micronutrient research on mood disorders and ADHD has been conducted using the Hardy-Stephan formulation (such as EMPower or Daily Essential Nutrients), so this broad-spectrum product containing vitamins, minerals, and antioxidants at relatively high doses has some data to support its use. There also has been a series of papers on Berocca, a formulation consisting mainly of several B vitamins, which appears effective for enhancing stress responses and perhaps a sense of

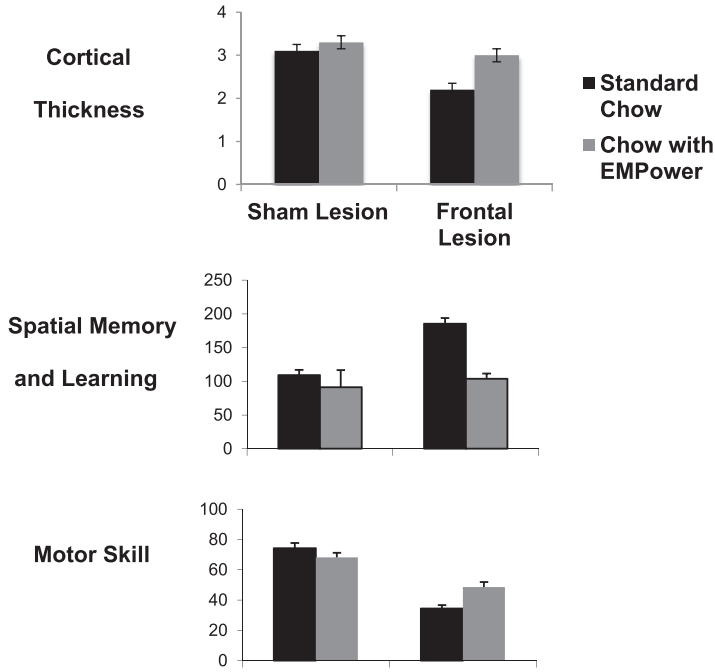

Fig. 13. Broad-spectrum micronutrients help restore structure and function in rats following early lesions of the frontal cortex. After receiving midline medial frontal lesions at postnatal day 3 (which cause permanent structural changes and chronic functional deficits), rats were fed either standard chow or chow fortified with EMPower throughout their lives, and then assessed as adults. In rats fed standard chow, cortical lesions produced a reduction in cortical thickness (measured in millimeters). The lesions also caused chronic deficits in spatial memory and learning, demonstrated on the Morris Water Navigation Task that requires rats to learn to swim to a safe zone (measured in the seconds it takes to reach the safe zone in several runs). In addition, the lesions produced decrements in motor skill performance, assessed by the Tray Reach Task that involves skilled forelimb movements, scored as percent success in obtaining food. The rats fed chow with broad-spectrum micronutrient showed a return to the normal range of cortical thickness and of performance on the spatial processing task, as well as a partial normalization on the motor skill task. Generally similar findings were observed following early lesions in the posterior parietal cortex. (*Adapted from* Halliwell C. Dietary choline and vitamin/mineral supplement for recovery from early cortical injury. Master of Science thesis, University of Lethbridge, Department of Psychology and Neuroscience; 2003.[287] Available at: https://www.uleth.ca/dspace/handle/10133/222; and Halliwell C, Kolb B. Diet can stimulate functional recovery and cerebral plasticity after perinatal cortical injury in rats. Soc Neuroscience Abstracts 2003;459:11.[288])

well-being. In a direct comparison, the Hardy-Stephan formula at 4 or 8 pills daily outperformed Berocca at 1 pill daily in enhancing stress responses in the post-earthquake RCT, but a head-to-head comparison using equivalent doses is not available. In general, it appears that stronger effects have been seen with formulations involving a more diverse range of micronutrients and higher doses, especially when aiming at optimal functioning. On the other hand, some studies have shown effectiveness at RDA levels, perhaps mostly in subgroups with low baseline nutritional status, when aiming at the correction of deficiencies.

Using high doses of micronutrients has the potential to induce vitamin or mineral toxicity. The Hardy-Stephan formulation has been well-researched for a vitamin-

mineral product (although not by Food and Drug Administration standards for novel medications). It conforms to governmental guidelines for safety, and it appears safe in clinical trials at recommended doses. Using higher doses of other formulations should be approached with caution, although other formulations may work as well.

What constitutes optimal dosing remains an open issue. As discussed earlier, the doses of micronutrients required to avoid frank classical deficiency diseases is almost certainly too low to optimize biologic functioning. Optimization of biologic functioning is a complex concept. Should optimal functioning be defined based on cardiovascular indicators, mood or cognitive parameters, stress responses (capacity for higher than routine demands), or longevity goals? It is clear that RDAs were never aimed at optimizing brain functioning.[260]

Although the term "anti-aging" suffers from tremendous baggage, the findings that micronutrients can reduce oxidative damage to nuclear and mitochondrial DNA, and reduce chronic inflammation, raises the possibility micronutrients might slow age-related deterioration in multiple organ systems. This possibility is underscored by recent findings that multivitamin use is associated with longer telomere length[296]: daily multivitamin users were found to have 5% longer telomeres (leukocyte DNA) than non-users ($P = .002$).

To be sure, micronutrients do not help everything. Various studies examining micronutrient interventions have produced disappointing findings regarding their effects on cardiovascular functioning, cancer prevention, and all-cause mortality.[297,298] These findings may be criticized on various technical grounds,[299,300] and it is clear that multivitamins may be helpful for subpopulations and for other health goals.[301] It is also possible that multivitamin use could have negative effects.[302–305] Single-nutrient or narrow-spectrum interventions also could have adverse effects, including the induction of relative deficiencies in other micronutrients, and there are reports of deleterious effects at routine doses of beta-carotene, vitamin A, B vitamins, or vitamin E.[80,81,306–311] Most of these reviews of adverse micronutrient effects have generally examined formulations with 3 or more ingredients, and it appears that the findings become more favorable with formulations containing 10 or more micronutrients.[312] The benefits, risks, and scope of micronutrient interventions will be decided empirically in the future.

In the meantime, psychiatrists have an opportunity to explore a new set of tools and principles for treatment and prevention. This is a new approach to mental health care, and one that youths and families embrace as de-stigmatizing. Micronutrient treatments are acceptable to many individuals who hesitate to use conventional psychiatric medications. Some parents seek the opportunity to use micronutrients to forestall or prevent the initial appearance of psychiatric illness by introducing these treatments early, including to patients' troubled younger siblings.

It is advisable for clinicians to be prepared to deal with overly enthusiastic families (and colleagues) whose excitement about a "natural" treatment might cloud their thinking or disrupt their balance in assessing risks. It also is sensible to be ready to deal with excessive skeptics, especially colleagues (and some patients), whose doubts about "natural" treatment might lead them to disregard evidence of effectiveness because micronutrients do not fit the prevailing models of disease and pharmaceutical treatment.

Some clinicians have raised the question of whether the low risks involved in micronutrient treatments, compared with conventional treatments, might justify their use as first-line treatments in some cases. Normally, there would be a simple response based on the absence of controlled trials showing the efficacy and safety of these treatments. However, for a treatment whose safety appears significantly better than the standard

of care, the answer could be more nuanced in some situations. In response to patient and family interest, I have chosen to offer broad-spectrum micronutrient treatments, despite the lack of RCTs, in cases in which (1) the symptoms are mild and nonacute, (2) there is low clinical risk in a temporary delay of established treatment, and (3) chart documentation outlines informed consent based on a discussion of the available established treatments, reasons for the patient and/or family preference to use a nonestablished treatment, an explicit statement of the lack of controlled trials regarding safety and efficacy, risks (including unknown risks), drug interactions with CNS-active medical drugs, and adverse effects (including aggravation of preexisting *Candida*). Needless to say, this option is restricted to families who are competent to make these judgments and who understand the financial burdens compared with insurance-covered conventional treatment.

Although emphasized previously, it is worth restating that clinicians are energetically advised to avoid using broad-spectrum micronutrient treatments for patients receiving psychopharmacotherapy without ongoing consultation with a specialist familiar with this treatment approach. Until a clinician is well informed about the techniques of managing nutrient-drug interactions and the pitfalls involved in transitioning a patient from psychiatric medications to micronutrient treatment, it is not sensible to attempt to reduce doses of prior psychiatric medications in a patient with active illness. Although treatment of drug-naïve patients is much more straightforward, clinicians are still advised to have an established connection to a consultant who can advise on technical details.

The hope generated by this line of inquiry is the possible development of a low-risk, low-stigma, health-promoting treatment for violence in prisons and conduct disorder in schools; a nonabusable treatment for ADHD that is more likely to enhance growth than to diminish it; a treatment for MDD and bipolar disorder with fewer side effects and seemingly greater long-term stability than current approaches; and the enhancement of stress response, cognition, and sense of well-being in healthy individuals. Obviously, additional research is needed. Interestingly, perhaps because of its low risks and adverse effects, broad-spectrum micronutrient intervention is one area of psychiatry in which treatment research to date has been generally well-balanced between studies in adults and youth.

The recent trends toward greater openness in general medicine to look at the role of nutrition and the health effects of micronutrients is commendable and exciting. Significant advances in the future may be attainable by a more focused consideration of the biology of micronutrients and their place in medical treatment, health promotion, and wellness.

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