

## NARRATIVE REVIEW

## THE ROLE OF NUTRITION IN MENTAL HEALTH

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**M**ental health conditions are a significant public health issue and a significant cause of human suffering. According to the National Institute of Mental Health, depression is the leading cause of disability in the United States for people aged 15 to 44 years and is the most common psychiatric condition worldwide, followed closely by generalized anxiety. Since the 1990s, the prescribing of antidepressant drugs has steadily increased in the United Kingdom, Canada, Australia, and the United States,<sup>1</sup> even though the clinical efficacy of these drugs has been called into question for almost a decade. In the published data, 94% of clinical trials demonstrated superiority of antidepressant drugs over placebo; however, in published and unpublished data, only 51% of trials are positive.<sup>2</sup> A 2010 meta-analysis published in *JAMA* concluded that "the magnitude of benefit of antidepressant medication compared with placebo increases with severity of depression symptoms and may be minimal or nonexistent, on average, in patients with mild or moderate symptoms."<sup>3</sup> This is not to say that there is no place for these drugs. The meta-analysis found substantial benefit for antidepressant medications in patients with very severe depression. There is, however, little question that the benefits of these medications have been overstated, leading clinicians to prescribe them for many patients who are unlikely to benefit from their use.

Anxiety disorders are extremely prevalent, with more than 18% of American adults experiencing them each year. Anxiety disorders often coexist with depression and/or substance abuse, and those living with anxiety disorders are three to five times more likely to visit a physician than those without them. Pharmacologic interventions include anti-anxiety and antidepressant therapies. Benzodiazepines can be associated with habituation and tolerance and so are typically used only in the short term. Antidepressants, interestingly enough, may be more effective for the relief of anxiety than for depression but can be associated with unwanted side effects.

Given the growing awareness of the human and economic costs to society, there is an urgent need to look for alternatives for addressing mental health issues. There are significant data supporting the role of mind-body therapies, including cognitive behavioral therapy, bibliotherapy, and a growing research base for mindfulness-based interventions.<sup>4,5</sup> There is no question that exercise and increasing physical activity have beneficial effects on mood,<sup>6</sup> as well as all the other well-known benefits (eg, maintaining body weight, reduced risk of heart disease). In addition to these interventions, data suggest that poor nutrition may be a modifiable risk factor for depression. To date, most research into the role of nutrition in depression has focused on the role of frank nutritional deficiencies and supplementation with single nutrients. While this has certainly contributed to our understanding of depression, we are only now beginning to evaluate the effects of dietary patterns on mental health.

## THE ROLE OF DIET IN MENTAL HEALTH

## Mediterranean Diet

The health benefits of traditional Mediterranean-style diets were first noted in observational studies in the 1950s that indicated that populations following these dietary patterns had lower rates of heart disease and cancer and longer life expectancy compared to other populations.<sup>7</sup> Newer data suggest that this eating pattern also may be good for our mental health. A study of 3486 British middle-aged individuals (mean age 55.6 years) found that a whole-foods diet comprised of fruits, vegetables, and fish gave protection against the onset of depressive symptoms, whereas a diet rich in processed meat, chocolates, sweet desserts, fried food, refined cereals, and high-fat dairy products increased vulnerability to depression.<sup>8</sup> This is consistent with another large longitudinal study of more than 10 000 healthy Spanish adults that found adherence to a Mediterranean dietary pattern was protective against major depressive disorder.<sup>9</sup>

The Mediterranean-style diet is characterized by an abundance of plant foods and includes vegetables, fresh and dried fruits, whole-grain cereals, nuts and legumes, and a moderate amount of wine.<sup>10</sup> These foods are rich in fiber, antioxidants, magnesium, zinc, and other micronutrients that are important for mental health. Meat is consumed sparingly with seafood being the primary protein source, followed by goat and sheep milk cheeses and yogurts. The omega-3 polyunsaturated fatty acids (PUFAs) that are abundant in seafood are relatively defi-

cient in many Western diets. There has been a dramatic increase in omega-6 PUFA vegetable oil intake at the expense of omega-3 PUFA from fish, wild game, and plants over the past century. While there is a substantial body of evidence that omega-3 fatty acids are essential for cardiovascular health, researchers are also discovering their importance for mental health. A study of 1190 men and women over 65 years of age living in Greece found that long-term fish intake was associated with both a lower incidence of depression and less severe depressive symptoms.<sup>11</sup>

Though the Mediterranean diet is high in fat—roughly 35% of calories—it is primarily from the intake of olive oil, a monounsaturated fat. High intake of olive oil and low intake of other vegetable seed oils was inversely related to depressive symptoms in those over the age of 60 in the Greek cohort arm of the longitudinal European Prospective Investigation into Cancer and Nutrition (EPIC) study when followed for 6 to 13 years.<sup>12</sup>

Of course, the temptation is to try to find the “key” component of any approach that can explain the therapeutic benefit, but in the case of Mediterranean-style diets, it is likely that the sum of the parts is greater than the whole. The diet is low in refined and processed foods that have been stripped of their nutrients; rich in seafood, an excellent source of omega-3 fatty acids; packed full of antioxidants and fiber in the form of fruits, vegetables, and whole grains; high in monounsaturated fats; and low in omega-6 PUFA. This is the prototype for a wholesome diet.

#### Low Glycemic Index/Load Diet

The glycemic index and load are ways of measuring how foods affect blood sugar and insulin. Many highly refined foods and sweetened beverages have a high glycemic index, which means they are digested quickly and cause a brief spike in blood sugar and insulin followed by a decrease in blood sugar levels. This fluctuation in blood glucose has been shown in some studies, but not all, to have a negative effect on mood.<sup>13,14</sup> It is widely recognized that hypoglycemia can increase irritability and that missing breakfast has negative consequences on mood late in the morning, particularly in children.<sup>15</sup> A Tufts University study of 46 healthy overweight adults (body mass index 25-29.9 kg/m<sup>2</sup>) was undertaken to evaluate the effect of a high glycemic (HG)—and low glycemic (LG)—load diet on cognition and mood. Those on the HG diet experienced worsening of mood as assessed by Profile of Mood States for tension and depression at 6 months, whereas those on the LG diet experienced an improvement in these two parameters of mood.<sup>16</sup> In addition to the potential effect on mood, meta-analyses reveal that LG diets improve glycemic control in diabetes<sup>17</sup> and reduce the risk of heart disease.<sup>18</sup> Given what we know so far, a modified low-glycemic load, Mediterranean-style diet appears to be optimal for mood as well as for overall health.

#### Caffeine and Anxiety

In addition to skipping meals and an HG diet, one of the biggest causes of irritability and anxiety is caffeine. Americans consume on average two to three servings of caffeinated beverage

per day, primarily in the form of coffee and soda. This is equivalent to roughly 200 mg to 400 mg of caffeine. “Energy” drinks are growing in popularity and are loaded with caffeine, often from herbs such as guarana (*Paullina cupana*), yerba mate (*Ilex paraguariensis*), and kola nut (*Cola nitida*). People with anxiety disorders have reported increased anxiety from even small amounts of caffeine. A randomized, double-blind caffeine challenge study was conducted in 28 patients with panic disorder (PD), 25 patients with generalized social anxiety disorder (GSAD), 19 patients with performance social anxiety disorder (PSAD), and 26 control subjects.<sup>19</sup> None of the patients had taken any psychotropic medications in the 4 weeks preceding the test. On two occasions 7 days apart, 480 mg of caffeine and a caffeine-free solution were given to the participants, and anxiety scales were administered before and after each test. A panic attack was induced in 17 (60.7%) PD patients, 10 (52.6%) PSAD patients, and four (16.0%) GSAD patients. No one in the control group had a panic attack after ingesting caffeine, and none of the patients or controls had a panic attack after drinking the caffeine-free solution. This study supports what many clinicians and nutritionists have long known—that caffeine should be avoided or dramatically reduced in those with anxiety disorders.

#### THE ROLE OF MICRONUTRIENTS IN THE DIET

Sixty percent of cases of clinical depression are considered to be treatment-resistant, and it is likely that a significant number of these patients would benefit from a wholesome diet as outlined above, as well as supplementation with specific micronutrients. Clinicians should do a thorough nutritional assessment, order laboratory tests to assess nutrient deficiencies, and treat accordingly. Following are some of the key micronutrients that are associated with depression, specifically treatment-resistant depression.

#### B-vitamins

Folate and vitamins B<sub>6</sub> and B<sub>12</sub> are involved in a series of methylation reactions that produce monoamine neurotransmitters, phospholipids, and nucleotides. Vitamin B<sub>6</sub> in its active form, pyridoxal 5'-phosphate (PLP), plays a role in the control of plasma homocysteine concentration, which is a risk factor for vascular disease and cognitive decline in aging. Studies also have linked low levels of PLP with depression.<sup>20</sup> A community sample of 3752 men aged 70 years or older in the Health in Men Study found that the odds ratio of depression increased 4% with every unit increase of total homocysteine concentration.<sup>21</sup> Vitamin B<sub>12</sub> is a cofactor in the formation of S-adenosylmethionine (SAME), an intermediate in the production of neurotransmitters.<sup>22</sup> Vitamin B<sub>12</sub> deficiency is associated with memory loss, depression, and cognitive dysfunction and is not uncommon in elderly patients and those who have hypothyroidism or atrophic gastritis or take proton-pump inhibitors and biguanides.<sup>23,24</sup> Higher serum levels of vitamin B<sub>12</sub> may be associated with better treatment outcomes in antidepressant therapy.<sup>25</sup>

Individuals with low folate levels have a lower treatment response to selective serotonin reuptake inhibitor antidepressant

drugs,<sup>26</sup> and research shows that folic acid supplementation can enhance antidepressant therapy.<sup>27</sup> Folate deficiency may be more widespread than we believe, especially in countries that do not fortify their food. A study of 6784 individuals aged 30 to 60 years in Denmark found the overall prevalence of low serum folate was 31.4%.<sup>28</sup> Even in the United States, where foods are fortified with folate, the Third National Health and Nutrition Examination Survey (NHANES III) found that 40% of women had inadequate intake of folate from food sources.<sup>29</sup> African American women had the lowest dietary intake of calcium, vitamin D, folate, and vitamin B<sub>6</sub> across racial and ethnic groups. Foods rich in folate include spinach and other leafy vegetables, orange juice, legumes, and whole grains—all of which are conspicuously absent from many Western diets. According to the Centers for Disease Control and Prevention,<sup>30</sup> 32.6% of adults consume fruit two or more times per day, and only 27.2% eat vegetables three or more times per day—far short of the 7 to 9 servings per day that is currently recommended.

Certain individuals may be at greater risk for folate deficiency than others in spite of food intake. One meta-analysis found a direct association between polymorphisms in the 5,10-methylenetetrahydrofolate reductase (MTHFR) gene, particularly the MTHFR C677T variant, and depression, schizophrenia, and bipolar disorder, which points to the use of folate in both treatment and prevention in this population.<sup>31</sup> MTHFR polymorphisms should be suspected in patients presenting with low folate and high homocysteine levels. Clinicians should order a complete blood count (CBC) for all patients presenting with depressive symptoms. With both B<sub>12</sub> and folate deficiency, hemoglobin levels will be low and red blood cells will be abnormally large (macrocytic or megaloblastic).

### Iron

Iron deficiency is the leading nutritional deficiency in the world, especially affecting women and young children.<sup>33</sup> Low stores of iron in the brain may alter neurotransmitter synthesis and function,<sup>34</sup> and fatigue, apathy, and poor concentration are well-known symptoms of iron deficiency. A randomized, placebo-controlled trial in South Africa found that iron supplementation given from 10 weeks to 9 months postpartum improved depressive symptoms among anemic mothers.<sup>35</sup> Besides menorrhagia, the most common pathological causes of iron deficiency anemia are *Helicobacter pylori* infection, autoimmune gastritis, and celiac disease. Iron deficiency in children can increase lead absorption, putting them at increased risk for depression and learning problems. Clinicians should be aware of the relationship between iron deficiency and depression, screen for it, and treat it accordingly. In iron-deficiency anemia, a CBC will typically show low hemoglobin and hematocrit levels, as well as small, pale red blood cells.

### Zinc

Zinc is involved in numerous aspects of cellular metabolism, playing a role in immune function, DNA synthesis and cell divi-

### Vitamin B<sub>12</sub> Deficiency

A low level of B<sub>12</sub> is under 350 pg/mL, with levels less than 150 pg/mL indicating deficiency. If the level is less than 350 pg/mL, clinicians can check methylmalonic acid and homocysteine levels or begin empiric treatment. Vitamin B<sub>12</sub> is administered if MMA is elevated, and folate is administered if only homocysteine is elevated. Vitamin B<sub>12</sub> should be given if homocysteine elevation persists in spite of adequate folate replacement. Prospective studies provide evidence that oral cobalamin therapy (1000-2000 µg/d) is as effective as intramuscular vitamin B<sub>12</sub> for treating vitamin B<sub>12</sub> deficiency.<sup>32</sup>

sion.<sup>36</sup> Conservative estimates suggest that up to 25% of the world's population is at risk for zinc deficiency,<sup>37</sup> which is associated with symptoms including behavioral and sleep disturbances, increased sensitivity to allergies, and loss of sex drive. There is mounting evidence suggesting a relationship between low concentrations of zinc and mental health problems, especially in at-risk populations.<sup>38</sup> Evidence for the potential therapeutic use of zinc comes mainly from patient populations and may be effective when supplemented in combination with pharmacologic treatment.<sup>39</sup> A randomized, placebo-controlled trial reported that zinc supplementation significantly reduced depression scores and facilitated treatment outcomes in treatment-resistant patients taking imipramine.<sup>40</sup> Oysters, nuts, peas, meat products, eggs, whole-wheat grains, oats, and pumpkin seeds are rich sources of zinc. Assessing zinc deficiency is complex, and the optimal test method has not been established, though erythrocyte zinc levels appear to be more sensitive than plasma zinc levels.

### Magnesium

Magnesium is involved in more than 300 biochemical reactions in the body. It helps maintain normal muscle and nerve function, keeps heart rhythm steady, promotes normal blood pressure, supports a healthy immune system, keeps bones strong, and helps regulate blood sugar levels.<sup>36</sup> Symptoms of magnesium deficiency include agitation and anxiety, irritability, restless legs syndrome, sleep disorders, and possibly depression. Magnesium exhibits antidepressant-like activity in a variety of animal models,<sup>41</sup> and population data demonstrate a link between magnesium and mood. A study of 5708 individuals in western Norway noted an inverse association between magnesium intake and standardized depression scores.<sup>42</sup> Magnesium is involved in insulin secretion, binding, and activity, and deficiency can lead to insulin resistance.<sup>43</sup> A 2008 randomized clinical trial found that 450 mg per day of magnesium was as effective as 50 mg per day of imipramine for alleviating depression in patients with diabetes.<sup>44</sup> Magnesium is found in unrefined grains, nuts, and green vegetables. Red blood cell magnesium levels are more reliable than serum levels in assessing deficiency.

## Chromium

Chromium is a trace mineral involved in carbohydrate, fat, and protein metabolism and enhances the action of insulin.<sup>36</sup> It has been shown to have beneficial effects in diabetes and depression.<sup>45</sup> A double-blind placebo-controlled study suggested that chromium may be particularly beneficial in atypical depression<sup>46</sup>—depression that is associated with hypersomnia, excessive eating with weight gain, intense reaction or sensitivity to rejection, and a feeling of being weighed down or “leaden.” In addition to improving depressive symptoms, another study found that chromium reduced carbohydrate cravings and regulated appetite in obese/overweight adults with atypical depression.<sup>47</sup> The dose used in the adult studies was 600 µg chromium picolinate.

## Vitamin D

Hypovitaminosis is prevalent, with estimates ranging from 25% to 54% of the general population being affected. Data suggest a possible association between vitamin D deficiency/insufficiency and basic and executive cognitive functions and possibly depression, bipolar disorder, and schizophrenia, though studies are mixed and have significant methodological shortcomings.<sup>48</sup> Interestingly, the main dietary source of vitamin D is fish. The well-established relationship between fish consumption and depression has been thought to be due to omega-3 fatty acids, but vitamin D may be another factor to consider. Given the importance of vitamin D for overall health, all patients should be screened periodically for deficiency using a 25(OH)D laboratory test. Optimal levels appear to be above 40 ng/mL.

## Omega-3 Fatty Acids

Omega-3 fatty acids are essential fatty acids that must be obtained in the diet. They are important structural components of the cellular membrane and play a crucial role in vision and nervous system function. Extensive research indicates that omega-3 fatty acids reduce inflammation and help prevent risk factors associated with chronic diseases such as heart disease and certain cancers.<sup>49</sup> The evidence also demonstrates an inverse relationship between omega-3 intake and depression. Three meta-analyses have examined the effectiveness of omega-3 fatty acids in depression.<sup>50-52</sup> All three reviews noted that the effectiveness of omega-3s is difficult to evaluate because of considerable heterogeneity in the studies, though Lin and Freeman both note that there is evidence that omega-3 fatty acid supplementation offers significant benefit for unipolar and bipolar depression when used as an adjunctive therapy.<sup>50,51</sup> When recommending fish oil supplementation, a good place to start is 1000 mg per day of eicosapentaenoic acid (EPA) and 300 mg to 500 mg docosahexaenoic acid (DHA). While numerous experts caution about the potential for high-dose fish oil supplements to increase the risk of bleeding, there is little evidence to support that doses of up to 4 g per day EPA+DHA pose a risk, even when taken in combination with aspirin and clopidogrel.<sup>53</sup>

## SUMMARY

A truly integrative approach to mental health includes a thorough assessment of dietary habits, level of exercise/physical activity, environmental exposures, medications, comorbid conditions, life stressors, level of social support, and family history. A complete physical exam and appropriate laboratory and imaging studies should be utilized to rule out underlying causes of depressed or anxious mood. Many patients will benefit from the use of specific dietary supplements, such as a multivitamin-mineral high in B-vitamins and omega-3 fatty acid. And no matter what the underlying cause of the mood disorder, patients should be counseled about the relationship between food and mood, for the evidence now substantiates what laypeople and medical professionals have long known intuitively: the way we eat affects the way we feel. The Western diet consumed in a growing number of countries is devoid of many of the key nutrients critical for the proper functioning of the central nervous system. When making dietary recommendations, clinicians should consider a low-glycemic, modified Mediterranean diet rich in fruits, vegetables, whole grains, and seafood (if not vegetarian) and low in processed, refined foods for optimizing mental health.

A future article on the topic of nutrition and mental health will address the role of nutraceuticals and herbal medicines in mental health.

### Possible Laboratory Evaluation

Complete blood count  
Methymalonic acid  
Homocysteine  
Fasting glucose  
Electrolytes  
Thyroid function  
25(OH)D

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## Do any of these patient symptoms sound familiar?



### Weight gain?

Many women experience weight gains in conjunction with hormone imbalances

### Fatigue?

Many women get fatigued and/or experience sleeplessness when they have a hormone imbalance

### Hot flashes?

80% of women experiencing these have a hormone imbalance

### Forgetfulness?

Many women experience short term memory lapses with hormone imbalances

### Irritable?

70% of women complaining of stress induced irritability have a hormone imbalance

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