Vitamin D deficiency
Supplementation might help patients with depression, seasonal mood disturbances

In the United States, >50% of psychiatric inpatients have vitamin D deficiency—<30 nmol/L (<12 ng/mL). A growing body of literature has found associations between vitamin D deficiency and psychiatric illnesses, particularly depression. Several randomized controlled trials (RCTs) have demonstrated that vitamin D supplementation can benefit depression symptoms. In this article, we discuss the current literature on vitamin D and psychiatric illness, and provide practical information for clinicians on the use of vitamin D supplementation.

Biosynthesis of vitamin D
Biosynthesis of vitamin D begins with the sterol provitamin D3 molecule 7-dehydrocholesterol (Figure, page 20). When skin is exposed to sunlight, 7-dehydrocholesterol absorbs UV radiation and forms provitamin D3, which undergoes rapid transformation to vitamin D3.

Vitamin D3 is released from the plasma membrane and enters systemic circulation in a protein-bound form that has a serum half-life of 36 to 78 hours. Vitamin D3 can be taken up by adipocytes and stored in fat deposits, where it has a half-life of approximately 2 months.

Circulating vitamin D3 is metabolized in the liver by the enzyme vitamin D-25-hydroxylase to 25-hydroxyvitamin D (25[OH]D3), which has a serum half-life of approximately 15 days. Circulating 25(OH)D3 is not biologically active at the physiological level, and requires activation by conversion to 1,25-dihydroxyvitamin D (1,25[OH]2D3) in the kidneys by the enzyme 25(OH)D-1α-hydroxylase. Production of 1,25(OH)2D3 is regulated by serum phosphorus and parathyroid hormone levels and other factors.

Catabolism of 1,25(OH)2D3 is rapid, with a serum half-life of 3.5 to 21 hours. Vitamin D2 is structurally similar to vitamin D3 but occurs primarily in fungi, yeasts, and some invertebrates.

continued
Risk factors for deficiency
A patient’s vitamin D status is determined by measuring 25(OH)D (Box). Risk factors for vitamin D deficiency include conditions that affect cutaneous production (insufficient sunlight exposure), obesity, gastrointestinal disorders, aging, renal disorders, and medications (Table 1, page 22). The link between sunscreen use, either alone or in cosmetics, and vitamin D deficiency continues to be debated. While controlled studies have found that application of sunscreen with high sun protection factor can significantly reduce vitamin D production, studies in clinical populations have failed to confirm these findings. See this article at CurrentPsychiatry.com for a discussion of these risk factors and acute and long-term medical manifestations of deficiency.

Vitamin D’s role in the brain
Vitamin D’s role in psychiatric illnesses is suggested by region-specific expression of vitamin D receptors (VDR) in the cingulate cortex, thalamus, cerebellum, amygdala, and hippocampus. Most of these regions also express 1α-hydroxylase enzymes capable of metabolizing 25(OH)D to 1,25(OH)2D, which suggests that vitamin D may have an autocrine or paracrine function in brain.

Vitamin D regulates expression of tyrosine hydroxylase, the rate-limiting enzyme in the biosynthesis of dopamine, norepinephrine, and epinephrine. Vitamin D also promotes survival of monoaminergic neurons through upregulation of glial cell line-derived neurotrophic factor, which supports survival of midbrain dopaminergic neurons and confers resistance to...
neurotoxins that deplete dopaminergic neurons in Parkinson’s disease. Vitamin D also promotes neuronal survival by inhibiting oxidative pathways in the brain through inhibition of inducible nitric oxide synthase (reducing free radical formation) and upregulation of γ-glutamyl transpeptidase (increasing antioxidant production). Vitamin D may play a neuroprotective role through regulation of calcium channels. In vitro studies have shown that vitamin D downregulates expression of L-type calcium channels, conferring protection against excitatory neurotoxins in cultured neurons. Proteomic analysis of brain tissue in a rat model of developmental vitamin D revealed dysregulation of 36 brain proteins involved in many biologic pathways involved in calcium homeostasis, synaptic plasticity, and neurotransmission. Taken together, these findings suggest vitamin D has a neurosteroid-like role in the CNS.

Psychotic disorders
Several epidemiologic studies have linked low vitamin D levels to schizophrenia and other psychotic disorders. Researchers in Norway who used a structured clinical interview to identify psychosis consistently found low levels of 25(OH)D among immigrants and native Norwegians with psychotic symptoms. A study of 8,411 Swedish women found low vitamin D levels were associated with psychotic symptoms. The Finnish birth cohort study found that use of vitamin D supplementation during the first year of life reduced the incidence of schizophrenia. In another pilot study, researchers measured third-trimester serum 25(OH)D levels and found that low levels of maternal vitamin D may be associated with an increased risk of schizophrenia. These studies suggest that low prenatal vitamin D levels may adversely impact the developing brain, increasing the risk for adult-onset schizophrenia.

Cognitive dysfunction
Low vitamin D concentrations have been associated with impairments in cognitive functions such as memory and orientation, executive function impairments, and Alzheimer’s disease (AD). A large study conducted from 1998 to 2006 in Italy concluded that persons with severe vitamin D deficiency (<25 nmol/L) had a higher risk of substantial decline on Mini-Mental State Examination than those with sufficient levels (≥75 nmol/L). Other studies have linked low vitamin D levels to poor cognitive performance in depressed older adults. Low vitamin D levels in older women have been associated with risk of AD, but not with other dementias. Polymorphisms of VDR have been associated with depression and poor cognitive performance.

Depression
Epidemiologic studies evaluating vitamin D deficiency have had conflicting results. The Third National Health and Nutrition Examination Survey, which used a sample of 7,970 non-institutionalized U.S. residents measured vitamin D levels and found that low levels were associated with increased risk of depression. However, other studies have not found a significant association between vitamin D levels and depression.

Clinical Point
Epidemiologic studies have linked low vitamin D levels to schizophrenia and other psychotic disorders.

Measuring vitamin D levels
Although 1,25-dihydroxyvitamin D (1,25(OH)2D3) is the biologically active form of vitamin D, its circulating half-life is only 4 to 6 hours. Therefore, 25-hydroxyvitamin D (25(OH)D) is the principal vitamin D metabolite measured to determine vitamin D status. Vitamin D levels commonly are expressed as ng/mL or nmol/L; the conversion factor from ng/mL to nmol/L is 2.496. The Institute of Medicine has defined vitamin D deficiency as a serum 25(OH)D level of <30 nmol/L (<12 ng/mL). However, many experts define vitamin D insufficiency as a 25(OH)D level of 21 to 29 ng/ml, and deficiency as <20 ng/mL. The upper limit is more difficult to define, but symptoms of vitamin D intoxication appear with blood levels >150 to 200 ng/mL.

Source: For reference citations, see this article at CurrentPsychiatry.com
age 15 to 39, demonstrated that individuals with serum vitamin D ≤50 nmol/L are at a significantly higher risk of developing depression than those with vitamin D ≥75 nmol/L. A study of 1,282 adults age 65 to 95 in the Netherlands found that 25(OH)D levels were 14% lower in depressed patients compared with controls. However, a large epidemiologic study in China did not detect a relationship between vitamin D and depression in 3,262 men and women age 50 to 70. After researchers adjusted for geography, body mass index, physical activity, and smoking, 25(OH)D levels did not correlate significantly with the presence or severity of depression. In a case series, after 48 vitamin D-deficient depressed adolescents were given vitamin D₃ over 3 months, there was a significant improvement in well-being, depressive symptoms, irritability, and fatigue. Other small, cross-sectional studies have examined associations between vitamin D status and depression with divergent results, which may reflect differences in population and methodology.

Prospective interventional studies. Although direct causal relationships are difficult to establish, several prospective studies have tested the hypothesis that treating vitamin D deficiency can improve depressive symptoms.

In a double-blind, controlled trial, Jorde et al. randomized 441 individuals age 21 to 70 to vitamin D, 20,000 IU per week; vitamin D, 40,000 IU per week; or placebo for 1 year. Individuals with serum 25(OH)D levels <40 nmol/L scored significantly higher on depression rating scales than those with serum 25(OH)D levels ≥40 nmol/L at the end of the study. There was no significant improvement in depression ratings in the placebo group (Table 2). These results must be interpreted with care because depressive symptoms were secondary endpoints in this study.

Kjærgaard et al. systematically examined vitamin D levels in a case-control study followed by a randomized controlled trial (RCT) of vitamin D supplementation. In the case-control phase, participants with low 25(OH)D levels at baseline were significantly more depressed than participants with high 25(OH)D levels. Participants with low 25(OH)D levels were randomized to placebo or 40,000 IU vitamin D₃ per week for 6 months. Low levels of vitamin D were strongly associated with depressive symptoms, but vitamin D supplementation did not have a significant effect on depressive symptom scores.

Seasonal affective disorder (SAD). Seasonal variation in vitamin D levels suggests that supplementation may help patients who have seasonal mood disturbances. In a randomized, double-blind study, 44 healthy individuals received vitamin D₃, 400 IU/d, 800 IU/d, or no vitamin D₃ for 5 days during late winter. Based on self-reports, vitamin D₃ significantly enhanced positive affect and there was some evidence it reduced negative affect. In a pilot study of 9 women with serum vitamin D levels <40 ng/ml, vitamin D supplementation during winter was associated with an average 10-point decline in Beck Depression Inventory-II scores. In a prospective RCT of 15 individuals with SAD, all patients who received vitamin D improved in all outcome measures.
dose showed some evidence of improved well-being compared with those taking the lower dose, although results were not significant for all comparisons. Two other trials did not observe any improvement in SAD symptoms with vitamin D treatment.41,42

Treating vitamin D deficiency
The Endocrine Society recently developed consensus guidelines for diagnosing and managing vitamin D deficiency.43 In addition, the Institute of Medicine of the National Academies recommends daily vitamin D supplementation to prevent deficiency:

- age <70: 400 IU/d
- age >70: 800 IU/d
- pregnant or lactating women: 600 IU/d
- upper limit: 4,000 IU/d.7

Higher doses may be used for patients deprived of sun exposure.8 A typical replacement regimen consists of oral ergocalciferol, 50,000 IU per week for 8 weeks.44 The optimal time for rechecking serum levels after repletion has not been clearly defined, but serum 25(OH)D levels should be measured again after therapy is completed. If values have not reached or exceeded 20 ng/mL, consider a second 8-week course of ergocalciferol (see the Box, page 21 for a discussion of measuring vitamin D levels). If serum 25(OH)D levels have not increased, the most likely cause is nonadherence or malabsorption.

Table 2
Effect of vitamin D supplementation on depressive symptoms in a controlled trial

<table>
<thead>
<tr>
<th>Vitamin D supplementation</th>
<th>Serum 25(OH)D levels at baseline</th>
<th>BDI total score, Median and range at end of study</th>
<th>After 1 year of vitamin D supplementation</th>
</tr>
</thead>
<tbody>
<tr>
<td>20,000 IU/week (&lt;40 nmol/L)</td>
<td>Significantly higher (more depressive traits), 6.0 (0 to 23)</td>
<td>Significantly improved BDI score</td>
<td></td>
</tr>
<tr>
<td>40,000 IU/week (≥40 nmol/L)</td>
<td>4.5 (0 to 28)</td>
<td>Significantly improved BDI score</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>-</td>
<td>No improvement in BDI score</td>
<td></td>
</tr>
</tbody>
</table>

25(OH)D: 25-hydroxyvitamin D; BDI: Beck Depression Inventory
Source: Reference 35

Table 3
Signs of vitamin D toxicity

<table>
<thead>
<tr>
<th>Headache</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metallic taste</td>
</tr>
<tr>
<td>Nephrocalcinosis or vascular calcinosis</td>
</tr>
<tr>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
</tbody>
</table>

Source: Reference 45

Contraindications and toxicity. Contraindications to vitamin D supplementation include granulomatous diseases, sarcoidosis, metastatic bone disease, and Williams syndrome.45 Table 3 lists signs of vitamin D toxicity. There is little risk of toxicity at dosages of up to 2,000 IU/d.46

References

Clinical Point
Seasonal variation in vitamin D levels suggests that supplementation may help patients who have seasonal mood disturbances.
50,000 IU per week regimen consists of A typical vitamin D supplementation might have a role in treating depression and SAD.

Low levels of vitamin D are associated with depression, cognitive dysfunction, and seasonal affective disorder (SAD). Evidence also suggests a potential link between vitamin D deficiency and psychotic disorders. It is not clear whether vitamin D deficiency is a cause or effect of depression. Limited research suggests vitamin D supplementation might have a role in treating depression and SAD.


Clinical Point
Granulomatous diseases, sarcoidosis, and metastatic bone disease are contraindications to vitamin D supplementation.

To access our videos, go to http://gmeded.com/user/register
Use discount code: quadrant
Risk factors for vitamin D deficiency

Any factor that diminishes UV radiation penetration into the skin will affect cutaneous synthesis of vitamin D. For example, sunscreen with a sun protection factor of 15 can decrease vitamin D synthesis by 98%. Geography and its impact on yearly sunlight exposure is a well-known factor in vitamin D deficiency. Individuals who live below a latitude of approximately 35° North—approximately the southern border of Tennessee and through Albuquerque, NM—receive sufficient UV radiation exposure to ensure adequate vitamin D production throughout the year, but at higher latitudes, adequate vitamin D is not produced during winter months. Melanin affects UV radiation absorption in a manner that prevents vitamin D production, and increased skin pigmentation markedly reduces vitamin D synthesis. African Americans with very dark skin have significantly diminished cutaneous production of vitamin D.

Renal 1α-hydroxylase activity decreases with aging in parallel with age-related decreases in glomerular filtration. In addition, aging is associated with increased clearance of 1,25-dihydroxyvitamin D (1,25(OH)2D).

However, vitamin D absorption generally is adequate even at older ages. Studies have shown that obese individuals tend to have lower serum concentrations of vitamin D and 25-hydroxyvitamin D (25(OH)D) than those at a normal weight. Obese patients have been shown to have lower cutaneous production of vitamin D, and display lower bioavailability of orally administered vitamin D.

For patients with chronic renal insufficiency, creatinine clearance is positively correlated with serum 1,25(OH)2D levels. Any process that results in malabsorption of intestinal fat may impair vitamin D absorption. In patients with celiac disease, biliary obstruction, or chronic pancreatitis, absorption consistently is reduced. Individuals taking bile acid-binding medications, such as cholestyramine for hypercholesterolemia, also may have impaired vitamin D absorption. In addition, hepatobiliary disease is associated with low levels of 25(OH)D. Some drugs that alter hepatic metabolism are associated with vitamin D deficiency, including anticonvulsants or glucocorticoids, which can increase catabolism or vitamin D.

References
Vitamin D deficiency produces a range of clinical effects. One well-documented consequence of vitamin D deficiency is osteomalacia—bone demineralization—which produces characteristic bone deformity and growth retardation in children. In adults, osteomalacia may manifest as diffuse pain, bone discomfort, and muscle aches that may resemble fibromyalgia or arthritis. Because vitamin D receptors are present in skeletal muscle, deficiency also may lead to proximal muscle weakness; an increased risk of falls; global bone discomfort, often elicited with pressure over the sternum or tibia; and low back pain in older women.

Long-term effects. A large epidemiologic study found that adults with 25-hydroxyvitamin D (25(OH)D) levels <21 ng/mL had an increased risk of hypertension, diabetes, obesity, and dyslipidemia. Cardiovascular mortality was higher in individuals with 25(OH)D levels <10 ng/mL compared with those with >40 ng/mL. Adolescents in the National Health and Nutrition Examination Survey-III with serum 25(OH)D levels <15 ng/mL were more likely to have elevated blood glucose levels than those with >26 ng/mL. Other epidemiologic data have demonstrated associations of vitamin D deficiency with multiple sclerosis, seasonal allergies, asthma, and various infectious diseases.

Because vitamin D is known to promote cellular differentiation and inhibit cellular proliferation, its role in cancer has been studied extensively. A recent meta-analysis of case-control studies found that the odds of colon cancer were reduced by >40% for each 20 ng/mL increase in serum 25(OH)D levels. Another meta-analysis reported a lower risk of breast cancer among women in the highest quartile of 25(OH)D values compared with the lowest quartile.

References