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## Do the Micronutrients Zinc and Magnesium Play a Role in Adult Depression?

Barbra Dickerman and Jianghong Liu, PhD

Department of Family and Community Health, School of Nursing, University of Pennsylvania, Philadelphia.

### Abstract

Depression is a widespread disorder that affects more than 120 million people worldwide. The unsatisfactory clinical efficacy and adverse effects of antidepressant medication have prompted the search for novel treatments. Micronutrient deficiencies may play a role in the development of depression, and recent research studies have explored the use of micronutrient supplementation as an adjunct to the pharmacotherapy of this psychiatric illness. This article provides a review of the empirical evidence linking zinc and magnesium deficiency and depression, discusses possible mechanisms of action in the psychopathology and therapy of depression, and explores the nursing and registered dietitian implications of these findings.

### Keywords

depression; magnesium; micronutrient; zinc

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Depression is a common psychiatric disorder that affects more than 120 million people worldwide.<sup>1</sup> It can accompany a variety of other medical conditions such as cancer,<sup>2</sup> psychiatric disorders,<sup>3</sup> and chronic pain.<sup>4</sup> Depression is currently the leading cause of disability, and it has been predicted that by 2020, depression will be the second leading contributor to the global burden of disease after ischemic heart disease.<sup>1</sup> While many cases of depression can be treated with antidepressant medications or psychotherapy, an estimated 60% of clinical depression cases are considered to be treatment-resistant depression (TRD), defined as the absence of remission from psychiatric medical and drug treatment.<sup>5</sup> This unsatisfactory clinical efficacy, further compounded by a variety of adverse effects associated with current antidepressant drugs, has made TRD a central focus of medical research and has prompted the search for novel treatments.<sup>6</sup>

Micronutrient deficiencies may play a role in the development of depression, and recent research studies have explored the use of micronutrient supplementation as an adjunct to the pharmacotherapy of this psychiatric illness. Micronutrients such as iron,<sup>7</sup> folate,<sup>8,9</sup> and vitamin B<sub>12</sub><sup>10</sup> have recently been associated with depression. Iron deficiency can be

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**Correspondence:** Barbra Dickerman, Department of Family and Community Health, School of Nursing, University of Pennsylvania, 418 Curie Blvd, Clare M. Fagin Hall, Philadelphia, PA 19104 (barbrad@nursing.upenn.edu).

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detrimental to the synthesis of neurotransmitters and has been correlated with postpartum depression.<sup>11</sup> There is a positive correlation between folate deficiency and the severity of depression,<sup>12</sup> and those who are deficient in folate are more likely to be unresponsive to antidepressant pharmacotherapy.<sup>13</sup> Moreover, the joint administration of folic acid and antidepressant drugs has been shown to enhance therapeutic effects.<sup>14</sup> While studies of the relationship between vitamin B<sub>12</sub> and depression have yielded mixed results, deficiency of this vitamin can influence neurotransmitter synthesis and thereby contribute to the development of depression. Among the studied micronutrients associated with depression, zinc and magnesium are 2 of the most commonly investigated and it has been suggested that they may act by a similar mechanism in the psychopathology and therapy of depression. Consequently, this article will focus on zinc and magnesium. The purpose of this article is to (1) review empirical evidence of the link between zinc and magnesium deficiency and depression, (2) discuss possible mechanisms of action, and (3) explore the clinical implications of such findings. The central aim of this article is to provide practical nursing and registered dietitian recommendations that can directly benefit the patient.

## ZINC

Zinc is an essential mineral that participates in a variety of biochemical processes related to brain growth and function.<sup>15</sup> Zinc is most highly concentrated in brain regions known to be important in depression and anxiety, such as the cerebral cortical regions, hippocampus, lateral septum, and most amygdaloid nuclei.<sup>6</sup> Here, most zinc is localized within the synaptic vesicles of specific neurons, where it is thought to regulate synaptic transmission or act as a neurotransmitter itself.<sup>16</sup> Zinc deficiency alters brain zinc homeostasis and can lead to disturbances in cognitive and behavioral function as well as emotional regulation.<sup>17</sup>

A positive correlation between zinc deficiency and depression has been found in studies involving rats (as measured by forced swim and tail suspension tests of depression) and humans.<sup>18-20</sup> Moreover, serum zinc has been negatively correlated with the *severity* of depressive symptoms in both rats and humans.<sup>18,19</sup> In addition, researchers have found that serum zinc levels appear to be lower in patients who are resistant to antidepressant pharmacotherapy.<sup>19,21</sup> Intervention studies conducted in both rats and humans suggest that zinc supplementation may have an antidepressant effect, particularly in those previously unresponsive to antidepressant drug therapy, either independently or by enhancing the efficacy of antidepressant medications.<sup>19,20,22, 23</sup>

While the exact reason for the association between low serum zinc levels and depression remains unclear, several theories exist. First, since the correlational link between reduced serum zinc levels and depression does not prove that zinc deficiency is directly causing depression, it has been postulated that zinc deficiency is merely secondary to depression-related behavioral changes, such as reduced food intake.<sup>19</sup> However, several studies have found no relationship between serum zinc and food intake or anorexia in depressed subjects.<sup>19,21</sup> This finding suggests that reduced serum zinc levels are not simply a reflection of decreased food intake and may therefore be contributing to the actual development of depression.<sup>19</sup>

A second possible explanation deals with the elevated stress level and cortisol production that often accompany depression. It has been hypothesized that the stress-associated hormones, epinephrine and glucocorticoids, may increase the synthesis of zinc-binding metallothionein, resulting in cellular sequestration of zinc and reduced serum zinc levels.<sup>19</sup>

Finally, a third explanation is rooted in the theory that the activation of the immune system and consequent production of cytokines may trigger the development of depression.<sup>24</sup> Since the activation of the immune system requires zinc, this process can also contribute to cellular zinc sequestration and reduced serum zinc levels.

Data suggest that zinc intake has declined over time because of dietary and lifestyle patterns associated with both poor intake and/or increased loss via the gastrointestinal tract or kidneys.<sup>25</sup> Poor dietary intake is one of the most likely contributors to zinc deficiency. In addition to the great increase in the incidence of depression over the past century, people have consumed progressively more processed foods with lower amounts of bioavailable zinc.<sup>5</sup> The amount of zinc in these processed foods is substantially reduced by the chemical sequestration of metals and refinement of grains in processed foods and the removal of minerals from drinking water processed via distillation or reverse osmosis.<sup>5</sup> In fact, white bread has 77.4% less zinc than whole wheat bread.<sup>26</sup>

Factors that inhibit the absorption of zinc in the small intestine can further compound dietary inadequacy of these micronutrients in modern diets. Common zinc inhibitors include phytates, oxalates, fiber, polyphenols, and, to a certain extent, calcium. Phytates, which have been singled out as one of the more potent dietary inhibitors of zinc bioavailability, are present in legumes, nuts, and seeds.<sup>27</sup> Phytates bind with zinc and thereby inhibit the uptake of this micronutrient. Fortunately, some food-processing techniques exist that may help to reduce phytate content and thereby increase zinc bioavailability, such as fermentation (which releases endogenous phytases) and sprouting beans and oats.<sup>28</sup> Zinc absorption is improved when leavened products are used rather than unleavened ones.<sup>29</sup> In addition to phytates, calcium can also inhibit zinc absorption. This fact is particularly relevant to postmenopausal women who take calcium supplements to decrease their risk of osteoporosis and, in doing so, inadvertently prevent optimal zinc absorption.

Certain factors exist that, by promoting the excretion of zinc, inhibit efficient recycling of these valuable micronutrients. Factors promoting the excretion of zinc include diuretics, alcohol, cytotoxic drugs, and diabetes mellitus.<sup>30</sup>

### **Antidepressant action of zinc**

The hypothesis that zinc deficiency contributes to the development of depression is supported by research illustrating zinc's antidepressant effects in rats<sup>19,20,31</sup> and humans.<sup>22</sup> In animal studies, zinc has exhibited antidepressant-like effects in tests<sup>19,20,32</sup> (the forced swim test and tail suspension test) and models<sup>31</sup> (chronic mild stress [CMS] model) of depression. Research shows that zinc deficiency can induce anhedonia, behavioral despair, and anxiety-like behaviors in rats.<sup>19,20</sup> Fluoxetine administration has been shown to decrease anxiety and behavioral despair in rats fed zinc adequate and zinc-supplemented diets, with no effect on the behavioral despair of zinc-deficient rats.<sup>19</sup> These findings suggest that zinc

deficiency can lead to the development of depression-like behaviors in rats as well as a decrease in the efficacy of antidepressant medication. Regarding CMS models of depression, Sowa-Ku ma et al<sup>31</sup> examined the effect of zinc treatment on rats and found that zinc hydroaspartate (10 mg/kg) had a rapid antidepressant-like effect on rats in CMS, as demonstrated by a quick reversal (within 1 week of treatment) of the CMS-induced reduction in consumed 1% sucrose solution. In addition, the joint administration of subeffective doses of zinc and antidepressants (imipramine or citalopram) has been shown to enhance antidepressant efficacy under conditions of chronic stress, highlighting the potential benefit of zinc supplementation in accelerating the effects of antidepressants.<sup>31</sup>

Human trials<sup>18,22</sup> designed to assess the efficacy of zinc supplementation as an adjunct to antidepressant therapy are consistent with the findings in rodents. Studies show a significant negative correlation between serum zinc levels and self-reported depression scores,<sup>18</sup> as well as a significant decrease in anger and depression psychological measures with 7 mg of daily zinc supplementation for 10 weeks.<sup>22</sup>

### **Possible mechanisms of zinc's antidepressant actions**

Given the data that demonstrate zinc's antidepressant-like effects in both animals and humans, it has been hypothesized that zinc either acts via similar mechanisms as antidepressants or augments the mechanisms of antidepressants. Agents that elevate the expression of hippocampal and cortical brain-derived neurotrophic factor (BDNF) are thought to be useful in treating depression.<sup>31</sup> Just as antidepressants work to increase BDNF expression, zinc treatment has similarly been shown to induce an increase in cortical, but not hippocampal, BDNF mRNA levels in rats.<sup>31</sup> Through their enhancement of BDNF activity, both zinc and antidepressants work to inhibit the function of *N*-methyl-D-aspartic acid (NMDA) receptors.<sup>20,31</sup> NMDA-receptor antagonists are known to increase brain concentrations of serotonin<sup>33</sup> and thereby potentially combat depression.<sup>34</sup> These possible mechanisms of zinc's antidepressant actions are summarized in Table 1.

Some research suggests that the antidepressant effects of zinc are mediated by the serotonergic system rather than the noradrenergic system.<sup>32</sup> This theory is supported by the data showing an additive effect of zinc when jointly administered with subeffective doses of selective serotonin reuptake inhibitors such as citalopram, fluoxetine, and imipramine but not when jointly administered with selective noradrenergic reuptake inhibitors such as reboxetine in the rat forced swim test.<sup>32</sup> However, this finding may be specific to the forced swim test, as other researchers have found that zinc has a synergistic effect with serotonergic, noradrenergic, as well as dopaminergic antidepressants in the mouse tail suspension test.<sup>35</sup>

### **Limitations and future research recommendations**

Recent studies on the effect of zinc on depression share several similar limitations. First, studies do not cross genders or a wide age range. Animal studies tend to focus on male rats,<sup>19,20,31</sup> while human studies focus on young women.<sup>18,22</sup> An expansion of the subject range to include both genders and a variety of age groups could help enhance the generalizability of the results. Second, several animal and human studies have analyzed only

a small sample size.<sup>20,22,31</sup> Increasing the sample size of future studies may enhance the internal validity of the results. Third, the exact role of zinc in the pathophysiology of depression is still under investigation. For example, it is unknown whether zinc deficiency is a causative factor in the development depression or whether it is secondary to depression-related behavioral changes (such as the decreased consumption of food).<sup>19</sup> While previous work has found no significant association between reduced serum zinc and food intake in depressed patients,<sup>21</sup> future researchers should consider this fact when designing their studies. In addition, while reduced serum zinc levels have been repeatedly linked to depression and zinc administration has been shown to have an antidepressant effect, the mechanisms by which zinc impacts depression are largely unknown. Fourth, the lack of a sensitive clinical measure of zinc status hampers any assessment of zinc deficiency. While most studies assess serum zinc levels, the use of this measure has been criticized since it is influenced by metabolic conditions unrelated to zinc status and it is insensitive to recent changes in dietary zinc.<sup>36</sup> It has been suggested that the measurement of both serum zinc and serum metallothionein levels could differentiate among the possible causes of low serum zinc levels, such as dietary zinc deficiency, stress, or infection.<sup>36</sup> The potential use of other zinc biomarkers such as zinc concentration in hair, cells, and zinc metalloenzymes has been explored,<sup>37</sup> but more research is needed to establish the validity and sensitivity of these new indicators. Fifth, and finally, few human studies have measured and addressed potential confounders of the zinc-depression interaction, such as socioeconomic status, ethnicity, access to healthcare, and physical activity.<sup>18,22</sup>

## MAGNESIUM

Like zinc, magnesium is an essential mineral required for a wide variety of physiological functions and biochemical reactions.<sup>38</sup> It is primarily an intracellular cation and is necessary for the action of more than 325 enzymes, most of which are involved in brain function.<sup>39</sup> For example, magnesium ions play a fundamental role in the electrical conduction of nerves by regulating the flow of calcium ions through neuronal calcium channels.<sup>40</sup> When levels of magnesium are adequate in the body, magnesium blocks calcium ion channels within the NMDA receptors of neurons. However, in states of magnesium deficiency, the channel is unblocked, resulting in an influx of calcium and sodium ions into the postsynaptic neuron and an efflux of potassium ions. This influx of calcium prompts the release of glutamate, further depolarizing the neurons. It has been suggested that this pattern of positive feedback may result in synaptic dysfunction that can be manifested as mood and behavioral disorders.<sup>40</sup> In addition, magnesium participates in all reactions that involve the anabolism and catabolism of ATP in energy metabolism.<sup>5</sup> In states of insufficient ATP, neurons are unable to maintain the function of their ion pumps, neuronal membranes will depolarize, and an excessive amount of calcium will move into cells, potentially resulting in severe neuronal dysfunction.<sup>5</sup> In terms of clinical manifestations, magnesium deficiency can result in serious neurological and psychological disruptions, with some of the most common clinical findings being personality changes (32.7%), depression (22.4%), and stupor (20.4%), among other conditions such as dementia, malaise, and sensory disturbances.<sup>30</sup>

Magnesium deficiency has been linked to depression in both mice<sup>38,41</sup> and humans.<sup>40,42,43</sup> While no significant association has been found between serum magnesium levels and the

severity of depression, it has been hypothesized that inadequate magnesium intake may be implicated in the development of TRD.<sup>5</sup> In fact, low levels of magnesium have been found in both the cerebral spinal fluid and brains of those with treatment-resistant and suicidal depression.<sup>42,44</sup> Both animal<sup>38,41,45,46</sup> and human<sup>40,47</sup> intervention studies have highlighted the antidepressant effect of magnesium supplementation.

Magnesium status is closely tied to the same factors (eg, poor intake and/or increased loss through the gastrointestinal tract or kidneys) discussed in the previous section. Regarding dietary intake, it has been reported that more than 60% of US adults consume insufficient amounts of magnesium with respect to the RDA (310 mg/d for women and 400 mg/d for man aged 19–30 y).<sup>48</sup> More information on RDAs<sup>27</sup> across gender, age groups, and subpopulations can be found in Table 1. Modern food preparation techniques that are applied to unprocessed foods may diminish their micronutrient content. For example, the boiling of vegetables results in a loss of 50% of their original magnesium content.<sup>49</sup> Several factors exist, such as calcium, that are known to inhibit magnesium absorption.<sup>50</sup> Studies show a reduction in dietary magnesium retention among individuals taking calcium supplements.<sup>49</sup> Other inhibitors of magnesium absorption include a high-fat diet, phosphoric acid, and oxalates. A diet high in fat can decrease the retention of magnesium by 50%, a statistic especially pertinent to those residing in America, where 40% to 45% of the typical caloric intake is in the form of fat.<sup>50</sup> Phosphoric acid, which is present in soft drinks, combines with magnesium, forming an insoluble precipitate that is not absorbed by the body. Oxalates, which are found in spinach and rhubarb, act in a similar way to bind magnesium and decrease its absorption. Factors promoting renal excretion of magnesium include diuretics; alcohol; high sodium, calcium, or sugar intake; coffee; and high blood levels of adrenaline, noradrenaline, or cortisol; chronic diarrhea, steatorrhea, or vomiting.<sup>51,49</sup>

Finally, it should be noted that depression is associated with decreased dietary intake,<sup>52,19</sup> gastric motility,<sup>53</sup> and micronutrient absorption.<sup>54</sup> These effects translate to decreased micronutrient bioavailability, which can further exacerbate a case of depression, regardless of whether the depression was initially rooted in a micronutrient deficiency or other cause.

### Antidepressant action of magnesium

Animal studies<sup>5,38,41</sup> have shed light on the effects of magnesium depletion on depression and anxiety and the effects of magnesium treatment on depression. Magnesium depletion has been shown to induce depression and anxiety-related behavior in mice and rats, with these symptoms reversed by the administration of common antidepressants and anxiolytic medications.<sup>5,41,45</sup> Compared to control mice fed a normal diet, mice receiving a low-magnesium diet (10% of daily requirement) for several weeks displayed increased depression- and anxiety-like behavior, as measured by the forced swim, light-dark, and open field tests.<sup>41</sup> This finding was validated by the fact that the behavioral changes that resulted from this magnesium depletion were reversed by the chronic oral administration of desipramine or *Hypericum* extract.<sup>41</sup> Magnesium deficiency has also been shown to result in depression- and anxiety-like behavior in rats.<sup>45</sup> The administration of magnesium salts alone and in conjunction with vitamin B<sub>6</sub> increased erythrocyte and plasma magnesium levels and had an antidepressant and anxiolytic effect.<sup>45</sup>

Magnesium treatment has also been shown to have positive effects on the behavior of animals stressed to exhibit depression-like behavior.<sup>5</sup> For example, immobility-induced stress in the forced swim test caused mice and rats to exhibit depressive symptoms, as reversed by magnesium treatment.<sup>38,46</sup> Moreover, low and ineffective doses of NMDA antagonists such as CGP 37849, L-701, 324, D-cycloserine, and MK-801 administered along with low and ineffective doses of magnesium resulted in a significant reduction of immobility time in the forced swim test.<sup>46</sup> The administration of magnesium also exerted an antidepressant and anxiolytic-like effect on rats subjected to the forced swim test and elevated plus-maze test.<sup>38</sup> When this experiment was performed on acute/chronic magnesium treatment schedules, researchers found that magnesium's efficacious effects remained even over time, with no tolerance developed by the mice.<sup>38</sup> This finding strongly suggests a potential antidepressant and anxiolytic activity of magnesium when applied to these disorders in humans.<sup>38</sup>

Human trials also indicate the importance of magnesium homeostasis in the psychopathology and therapy of affective disorders.<sup>5</sup> Studies report that highly depressed, drug-free patients have the highest erythrocyte magnesium values, suggesting a shift of intracellular magnesium to extracellular compartments and a translocation of magnesium from the brain to the blood.<sup>5</sup>

Case histories have been presented, showing rapid recovery (<7 days) from major depression using 125 to 300 mg of magnesium (as glycinate) with each meal and at bedtime, while restricting calcium, glutamates, and aspartates.<sup>40</sup> Clinical trials support the efficacy and safety of magnesium in the treatment of depression and show that magnesium chloride is as effective in the treatment of depressed, hypomagnesemic elderly as 50 mg of daily imipramine administration.<sup>47</sup>

### **Possible mechanisms of magnesium's antidepressant actions**

Recent research findings show how the action of magnesium ions is closely intertwined with the pathology of affective disorders, highlighting the therapeutic potential of magnesium supplementations in those with depression. Magnesium affects all elements of the limbic-hypothalamus-pituitary-adrenocortical axis.<sup>55</sup> This axis is closely related to emotional regulation and disturbances at this level may contribute to the development of depression and other mood disorders.

Similar to zinc and antidepressant drugs, magnesium is an important modulator of NMDA-receptor activity and increased levels of magnesium are known to inhibit NMDA receptors.<sup>46</sup> In addition to being an NMDA antagonist, magnesium is also a  $\gamma$ -aminobutyric acid<sub>A</sub>-antagonist and an angiotensin II-antagonist, systems that have all been implicated in the pathophysiology of depression.<sup>55</sup> These potential mechanisms are outlined in Table 1. In addition, similar to zinc deficiency, decreased magnesium ion levels have been correlated with impaired protein and DNA synthesis and thereby decreased serotonin levels, implying that magnesium supplementation may be useful in the treatment of depression.<sup>56</sup>

## Limitations and future research recommendations

While many studies that address the relationship between magnesium deficiency and depression use serum magnesium as an indicator of magnesium status, it has been suggested that this practice may produce misleading results since 99% of magnesium is found intracellularly and serum magnesium therefore only reflects the remaining 1% of total-body magnesium.<sup>51</sup> Since there is only a weak relationship between brain and blood magnesium, it has been suggested that blood and cerebrospinal fluid tests be avoided.<sup>5</sup> Future trials should study larger populations in the form of either double-blind, placebo-controlled clinical trials or comparative trials in which the effects of magnesium administration are compared with the effects of an antidepressant. The magnesium compounds administered should be bioavailable, soluble, and ionizable, with an emphasis on the use of magnesium glycinate as opposed to magnesium glutamate and magnesium aspartate, which have been found to severely worsen depression.<sup>40</sup> Finally, since large, therapeutic doses of orally administered magnesium have been associated with adverse effects such as diarrhea,<sup>57</sup> nonoral means of increasing brain magnesium such as the use of IV drips, injections, or transdermal administration should therefore be investigated.

## Recommendations

While in recent years, research has suggested the role that zinc and magnesium may play in the psychopathology of depression, general clinicians rarely pay much consideration to these important micronutrients.<sup>30</sup> Nurses often have the most interaction with their patients and are therefore in an excellent position to conduct a preliminary screening of dietary intake when necessary. Patients should be referred to a registered dietician who can conduct a more comprehensive nutritional assessment and incorporate nutrition education into their care. Nurses, particularly those specializing in psychiatrics, are additionally in a pivotal position to screen for depression and report findings to the interdisciplinary care team in an attempt to draw connections between the patient's mental health and lifestyle factors (ie, dietary intake).

Low zinc and magnesium levels can sometimes be difficult to detect. The lack of a sensitive indicator of zinc status is an obstacle in assessing zinc status. Research also shows that there are not usually observable clinical signs or symptoms in patients with a low serum magnesium concentration of 1.8 to 1.6 mg/dL<sup>30</sup> and total body magnesium stores and serum magnesium levels are poorly correlated.<sup>58</sup> For instance, patients with alkalosis may have low serum magnesium levels without an accompanying total-body magnesium deficiency, while patients with acidosis may have normal serum magnesium levels despite being magnesium deficient.<sup>58</sup> Other researchers have reported that serum magnesium remains unchanged despite a period of prolonged fasting during which a 20% loss of total-body magnesium occurs.<sup>49</sup> Since serum magnesium levels can appear normal even in the presence of low intracellular stores, cases of hypomagnesemia often go unrecognized, as illustrated by a retrospective study in which Hashizume and Mori<sup>30</sup> reported that of the patients found to have hypomagnesemia (defined as having serum magnesium concentration < 1.5 mg/dL), this condition was only noted in the medical records of 50% of these individuals.<sup>30,58</sup> For these reasons, it is important for clinicians to consider the possibility of a patient having an insufficient zinc and magnesium status even when serum levels appear normal or in the



absence of symptomatic manifestations.<sup>30</sup> A clinician can cultivate a broader understanding of a patient's micronutrient status by obtaining dietary records in addition to looking for symptoms of deficiency and assessing serum zinc and magnesium levels. By assessing a patient's nutritional intake for a low intake of zinc and magnesium as well as the presence of factors that inhibit absorption or promote excretion, a clinician may be able to better gauge a patient's true zinc and magnesium status and work toward remedying a deficiency before it becomes symptomatic.

After assessing zinc and magnesium status, a clinician could provide nutritional education and describe the physiological importance of zinc and magnesium, the potential role that these micronutrients may play in depression, as well as ways in which the patient can obtain sufficient amounts of these micronutrients in their diet (Table 1).

Special attention should be paid to the dietary intake of vegetarians, the elderly, and women, particularly those taking oral contraceptives. Vegetarians tend to consume more vegetables than their omnivorous counterparts and thereby consume more of the oxalates known to inhibit the absorption of zinc and magnesium. In addition, it is well-known that there is decreased nutrient absorption in the elderly. While the micronutrient absorption as a function of age has not received much attention, recent rat studies show that zinc absorption is considerably decreased while magnesium absorption is moderately decreased.<sup>59</sup> These decreases may be due to the functional and morphological changes that take place in the intestines with advancing age or due to the development of hypo- or achlorhydria, conditions common in the elderly and characterized by decreased or absent gastric secretions. Furthermore, postmenopausal women may be taking calcium supplements that may in turn inhibit the absorption of zinc and magnesium.<sup>49,50</sup> Finally, special consideration should be paid to pregnant women and women taking oral contraceptives, 2 conditions known to result in low magnesium.<sup>60</sup> This is especially important since it has been hypothesized that postpartum depression results from inadequate magnesium intake during pregnancy (due to loss of magnesium to the fetus, coupled with insufficient magnesium intake). Also, the low magnesium that results from the use of oral contraceptives is responsible for the gender difference in depression and suicide attempts, particularly in the 12% suicide rate of female psychiatrists in America.<sup>5</sup> Case reports suggest that postpartum depression is preventable with magnesium treatment.<sup>40</sup> Unfortunately, many of the vitamin and mineral supplements provided to pregnant women do not contain effective dosages of magnesium if they contain any magnesium at all.<sup>61</sup> Moreover, studies show inadequate magnesium intake among pregnant women.<sup>62</sup> It is therefore important for clinicians who treat pregnant women to assess their patients' micronutrient intake during prenatal visits and make dietary recommendations that will help the mother-to-be obtain adequate zinc and magnesium. Research supports the benefits of micronutrient (magnesium, folate, etc) supplementation in the diets of reproductive-age women.<sup>63,64</sup>

When making lifestyle assessments, it is important for clinicians to know that chronic stress intensifies the release of catecholamines and corticosteroids, driving down intracellular magnesium ions.<sup>65</sup> Chronic stress, whether physical (exertion, heat, cold, illness, trauma, noise) or emotional (pain, depression, anxiety), increases the need for magnesium.<sup>50</sup>

Magnesium supplementation is therefore recommended for patients living in conditions of chronic stress.<sup>66</sup>

## CONCLUSION

Recent studies have indicated the potential involvement of zinc and magnesium in the development and treatment of depression. Both animal and human studies have found significant correlations between serum zinc and serum magnesium concentrations and depressive symptoms. The results of such studies illustrate the antidepressant effects of zinc and magnesium administration, as indicated by decreased anxiety and behavioral despair in rats and decreased anger and depression in humans.

The fact that micronutrients such as zinc and magnesium are variables of interest in depressive disorders has important implications for psychiatric nurses and registered dietitians in particular. Given the significance of TRD and the potential benefit of zinc and magnesium administration in ameliorating this disease, such findings highlight the importance of addressing the zinc and magnesium status of depressed patients and considering the use of supplementation as an adjunct to antidepressant therapy. A nutritional modification could be a relatively easy, inexpensive way to benefit one's psychiatric health and overall well-being.

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**Table 1**

Mechanisms of Antidepressant Action, Food Sources, and RDA of Zinc and Magnesium

	<b>Potential Mechanisms of Antidepressant Action</b>	<b>Food Sources</b>	<b>RDA</b>
Zinc	NMDA antagonist  Elevate expression of hippocampal and cortical brain-derived neurotrophic factor	Oysters, beans, nuts, certain types of seafood (crab and lobster), whole grains, fortified breakfast cereals, dairy products	Men:  <i>Age 19+</i> : 11 mg/d  Women:  <i>Age 19+</i> : 8 mg/d  <i>Pregnant women</i> : 11 mg/d  <i>Lactating women</i> : 12 mg/d
Magnesium	NMDA antagonist  $\gamma$ -aminobutyric acid antagonist   Angiotensin II antagonist	Spinach, some legumes (beans and peas), nuts and seeds, whole, unrefined grains	Men:  <i>Age 19–30</i> 400 mg/d  <i>Age 31+</i> : 420 mg/d  Women:  <i>Age 19–30</i> 310 mg/d  <i>Age 31+</i> : 320 mg/d  <i>Pregnant women</i> 360–400 mg/d  <i>Lactating women</i> 310–360 mg/d

Abbreviation: NMDA, *N*-methyl-D-aspartic acid.

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