

## Lead Review Article

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### Nutrition and Depression: The Role of Folate

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*A relationship between folate and neuropsychiatric disorders has been inferred from clinical observation and from the enhanced understanding of the role of folate in critical brain metabolic pathways. Depressive symptoms are the most common neuropsychiatric manifestation of folate deficiency. Conversely, borderline low or deficient serum or red blood cell folate levels have been detected in 15-38% of adults diagnosed with depressive disorders. Recently, low folate levels have been linked to poorer antidepressant response to selective serotonin reuptake inhibitors. Factors contributing to low serum folate levels among depressed patients as well as the circumstances under which folate and its derivatives may have a role in antidepressant pharmacotherapy must be further clarified.*

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#### Introduction

Among common nutritional deficiencies with potential relevance to neuropsychiatric disorders, folate deficiency appears to be the most closely linked to depressive disorders. Evidence has been steadily mounting over the past several decades implicating folate in processes thought to underlie the regulation of mood and the mediation of antidepressant drug effects.<sup>1-3</sup> Of particular importance are associations between low serum or red blood cell (RBC) folate concentrations and depressive states in medical and psychiatric populations, relationships recently described

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between folate levels and response to antidepressant treatment, observations regarding the impact of folate supplementation on treatment outcome, and elucidation of key metabolic processes within the central nervous system (CNS) in which folate is involved.

#### Folate Deficiency and Depression

In 1962 Herbert<sup>4</sup> reported evidence supporting an association between folate deficiency and depressive symptoms. Herbert developed insomnia, irritability, fatigue, and forgetfulness after 4 months of having been on a folate-deficient diet. These symptoms abated following folate replacement. Among patients with folate deficiency severe enough to produce megaloblastic anemia, depressive symptoms have been described as the most common neuropsychiatric complication, followed by dementia and peripheral neuropathy.<sup>5</sup> In several patient cohorts, low to deficient serum or RBC folate concentrations, generally defined as plasma values  $\leq 2.5$  ng/mL or RBC values  $< 200$  ng/mL per day, were found in 15-38% of patients with depression.<sup>6-10</sup> Because anemia was rare among these patients with low folate and fewer than one-quarter had macrocytosis, folate deficiency would not have been detected in most of these individuals if laboratory hematologic indices had been used as a screen.<sup>7,9</sup>

Compared with folate, low serum B-12 concentrations ( $< 200$  pg/mL) were found less commonly (12-14%) among depressed patients,<sup>8,10</sup> did not appear to distinguish depressed from nondepressed patients,<sup>7</sup> and, when associated with macrocytic anemia, were accompanied by mood disturbance in 20% of a heterogeneous patient sample compared with an incidence of 56% among patients with folate deficiency.<sup>5</sup>

Compared with other psychiatric patients or normal controls, depressed patients have been consistently found to have lower serum or RBC folate concentrations,<sup>6,7,11</sup> and patients with very low folate levels generally have higher ratings for depression than do patients with normal folate.<sup>6,8,12</sup> Lower serum levels of the folate derivative 5-methyltetrahydrofolate have also been reported among depressed subjects compared with controls, and those levels were related to severity of depression before treatment.<sup>13</sup>

In a group of euthymic outpatients who were taking lithium (26 diagnosed with bipolar disorder and 81 with unipolar mood disorders), those with the highest plasma folate levels exhibited retrospectively over 2 years the lowest degree of "affective morbidity," a concept incorporating the severity and duration of mood disorder symptoms.<sup>12</sup> Additionally, a negative correlation has been reported between serum folate and duration of a current episode of depression in a sample of 44 depressed patients whose folate levels fell generally within the normal range.<sup>14</sup>

Taken together, these findings seem to indicate that folate deficiency is associated with the emergence and perhaps the severity of depressive illness in a subset of patients and that, within a normal range of concentrations, lower folate values may be linked to greater persistence of depressive symptoms. It should be noted, however, that these observations do not, of themselves, constitute proof of a causal association between folate and depression, nor do they clarify the direction of causality if such a relationship exists.

### **Folate and the Prediction of Antidepressant Response**

A relationship between folate levels and treatment outcome among 101 depressed adults admitted to a clinical research unit was suggested by Reynolds and colleagues.<sup>8</sup> These investigators found that depressed inpatients with low serum folate levels at admission had higher ratings of depression and neuroticism at discharge following treatment with electroconvulsive therapy (ECT), antidepressants, or tryptophan than did patients with normal folate levels. Patients with low folate were also more severely depressed at admission than were those with normal folate levels. Interpretation of the difference observed in treatment outcome between patients with low and normal folate levels is therefore confounded by the differences in depressive severity at baseline between the two groups. Also, most patients in this study were on antidepressant regimens at the time of study admission such that baseline folate levels were, in effect, interim rather than pretreatment values potentially altered by ongoing treatment.

More recently, we have found that among 213 adult outpatients presenting with major depressive disorder (MDD), those with low serum folate levels before initiation of antidepressant treatment were less likely to respond to 8 weeks of treatment with the selective serotonin reuptake inhibitor (SSRI) fluoxetine (20 mg/day) than were patients with normal folate levels.<sup>10</sup> Assessment of treatment response was performed by clinical investigators blind to patients' folate status. This relationship with treatment outcome did not appear to be related to baseline differences in depression severity. Moreover, the relationship appeared to be specific for folate, since pretreatment serum B-12 or homocysteine levels did not correlate with

antidepressant response. In our study, the proportion of depressed individuals with low folate levels was larger in those with melancholic depression compared with nonmelancholic depressive subtypes (e.g., atypical depression). This finding supports the stronger association between folate deficiency and endogenous depression compared with its relationship to neurotic depression described by Carney and colleagues.<sup>7</sup>

The relationship between low folate levels and response to antidepressant treatment has been further supported by a study of RBC folate and response to sertraline and nortriptyline.<sup>15</sup> Among 22 patients with MDD who were over the age of 60 years and randomly assigned to receive either of the two antidepressants, there was a significant correlation between folate and antidepressant response in the sample overall and within the subgroup of patients receiving sertraline in particular. The correlation with treatment response did not reach significance for the patients receiving nortriptyline. Because the number of patients in each treatment group was small, it would be premature to suggest that low folate at baseline may be a predictor of a partial response or nonresponse to some kinds of treatment (SSRIs) but not others (tricyclic antidepressants). A similar caveat applies to a study of serum 5-methyltetrahydrofolate levels in depressed patients in whom there was no difference in pretreatment values between responders and nonresponders to a subsequent course of ETC.

Overall, recent evidence suggests that low serum and RBC folate levels may predict poorer response to some forms of antidepressant treatment. Further studies are needed to replicate this finding and to clarify the degree to which the association between low folate and outcome with the SSRIs can be generalized to other classes of medications and other treatment modalities including ECT, phototherapy, and psychotherapy.

### **Folate in the Treatment of Depression**

An association between low folate levels and depression has suggested a potential role for folate in the treatment of depressive disorders. In support of this hypothesis, mood improvement has been observed in folate-deficient patients with epilepsy or gastrointestinal disorders following folate replacement.<sup>16,17</sup> In a retrospective survey, psychiatric patients treated with folic acid spent less time in the hospital and exhibited mood improvement and better social functioning than did those with low folate levels who did not receive supplemental folate.<sup>18</sup>

In a double-blind, placebo-controlled trial involving patients with unipolar and bipolar mood disorders who were receiving lithium prophylaxis, administration of small daily doses of folic acid (200 µg) reduced the occurrence and duration of mood disorder symptoms.<sup>19</sup>

In a randomized, controlled trial of 24 depressed patients with RBC folate levels < 200 ng/mL, addition of the

folate derivative methyltetrahydrofolate (methylfolate) at a dose of 15 mg/day to ongoing treatment with standard agents (tricyclic antidepressants, monoamine oxidase inhibitors, or lithium) was associated with better clinical outcome at 3 and 6 months than was the addition of placebo.<sup>9</sup> Methylfolate was selected because it is actively transported into the CNS and concentrated in synaptic regions where it is involved in essential metabolic pathways.

In an open-label trial of 20 elderly patients with depressive disorders, of whom only two were frankly folate deficient, administration of methylfolate (50 mg/day) alone, rather than as an adjunct to standard antidepressants, was associated with an impressive 81% response rate over a 6-week period.<sup>20</sup>

Growing evidence suggests that folate may have a place as an adjunct to antidepressant pharmacotherapy and perhaps as a single agent in the treatment of depressed patients with borderline low or deficient folate levels. In a more speculative context, folates may have a place in the treatment of some depressed patients with serum or RBC folate concentrations in the normal range.

Because folate supplementation in some studies has made a positive contribution to the treatment outcome of psychiatric patients with conditions other than depression, including schizophrenia,<sup>9,18</sup> the question remains whether the potential benefits of folate and methylfolate reflect intrinsic antidepressant properties or are evidence of a more pervasive impact of folates on various aspects of neuropsychiatric function, among which the regulation of mood, sleep, appetite, drive, and concentration comprises an integral subset.

Although the relationship between low folate and depression is well supported, as is the importance of correcting folate deficiency in the treatment of depression, the potential neuropsychiatric morbidity associated with elevated folate levels among depressed patients remains unclear. Sleep alterations, malaise, irritability, and hyperactivity have been reported among healthy volunteers given high daily doses of folate (15 mg).<sup>21</sup> Additionally, lowered serotonin (5-hydroxytryptamine) levels in the brains of rats fed diets oversupplemented with folate, as well as in rats receiving folate-deficient diets, have been reported.<sup>22</sup> These observations suggest that a curvilinear relationship may exist between folate dosing and antidepressant benefit such that administration of folate or methylfolate in quantities above or below a putative therapeutic window would be unlikely to benefit depressed patients and may, indeed, contribute to depressive symptomatology.

### Folate and CNS Metabolism

The biochemical mechanisms through which folate exerts an influence on neuropsychiatric status are likely to involve the one-carbon cycle, a pathway essential to many transmethylation reactions within the CNS, including the

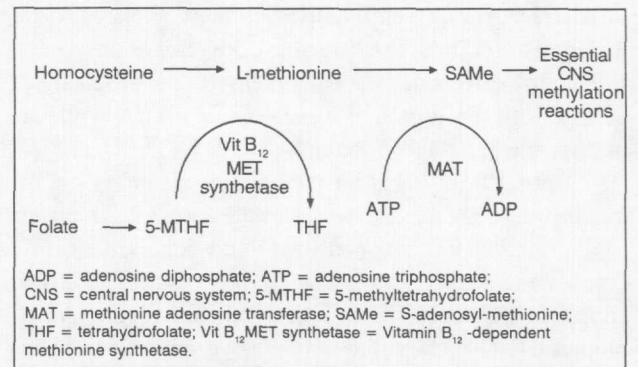


Figure 1. The role of folate in CNS metabolic pathways.

metabolism of neuroactive substances such as the monoamine neurotransmitters and melatonin, the formation of membrane phospholipids, and the synthesis, repair, and recombination of nucleic acids.<sup>1,23,24</sup> Folate plays an integral role in the one-carbon cycle (see Figure 1). It is first converted to 5-methyltetrahydrofolate (MTHF) and then combines with homocysteine, in a reaction catalyzed by vitamin B-12-dependent methionine synthetase, to produce L-methionine. Methionine produced through this cycle, and also furnished directly but in insufficient amounts as a dietary amino acid, is combined with adenosine triphosphate (ATP) in a reaction catalyzed by methionine adenosine transferase (MAT) to form S-adenosylmethionine (SAMe, or ademetionine). SAMe, in turn, is widely distributed throughout the CNS as an intermediary of more than 35 transmethylation reactions.<sup>24,25</sup>

In 1963, Smythies hypothesized a defect in the mechanism of the one-carbon cycle as an underlying factor in some psychotic and mood disorders.<sup>26</sup> Although the "transmethylation hypothesis" of schizophrenia as outlined by Smythies has not been well supported by subsequent research, evidence for a role of the one-carbon cycle in processes relevant to the expression of affective disorders continues to accrue. This includes the work of Tolbert and colleagues,<sup>27</sup> who observed that the RBCs of unipolar depressives had lower levels of activity of MAT compared with erythrocytes from controls. Following antidepressant treatment, moreover, a significant increase in the Vmax of the MAT activity of patients with major depression was observed.<sup>28</sup> Similarly, low cerebrospinal fluid levels of SAMe have been reported among a sample of depressed adults,<sup>29</sup> and parenteral doses of SAMe and some oral formulations of the compound have been associated with antidepressant efficacy greater than placebo and comparable to standard antidepressants, although, quite interestingly, with a more rapid onset.<sup>30</sup>

As would be predicted from the utilization of folate in one-carbon metabolism, reduction in brain levels of SAMe has been reported in rats maintained on a folate-deficient diet,<sup>31</sup> and lowered levels of SAMe have been reported in animal studies following treatment with the antifolate agent

methotrexate and in children with inborn errors of folate metabolism.<sup>24</sup> Thus, at least some of the important neuropsychiatric effects of folate and methylfolate are likely to be mediated through their direct impact on the synthesis of this principal methyl donor.

Among the myriad transmethylation reactions involving the one-carbon cycle, which of them are most relevant to the relationship between folate and depressive disorders remains a matter of speculation. Both folates and SAME appear to influence the rate of synthesis of tetrahydrobiopterin (BH4), the cofactor in the hydroxylation of phenylalanine and tryptophan.<sup>24,32,33</sup> Because this is the rate-limiting step in the biosynthesis of dopamine, norepinephrine, and serotonin—neurotransmitter systems that are thought to be involved in the pathophysiology and treatment of depressive disorders—alterations in the rate of synthesis of this important cofactor may be relevant to depression.<sup>34</sup>

In support of this hypothesis, BH4 synthesis in brain preparations from depressed patients has been reported to be lower than in preparations from controls,<sup>35</sup> and exogenous BH4 may have antidepressant properties.<sup>36,37</sup> Given the diversity of neural processes influenced by alterations in one-carbon metabolism—from gene transcription to membrane fluidity—these observations point to one of many potential mechanisms underlying the observed relationships between folate and depression, an intriguing area that requires further study.

### The Basis for Folate Deficiency in Depression

A wide variety of factors and conditions are associated with folate deficiency states, including drugs (particularly certain anticonvulsants, antibiotics, oral contraceptives, antifolate cancer chemotherapeutics), malabsorption syndromes, chronic diseases (including autoimmune disorders such as rheumatoid arthritis), inborn errors of folate metabolism such as 5,10-methylenetetrahydrofolate reductase deficiency, alcoholism, increased utilization states such as pregnancy, and dietary folate deficiency.<sup>1,38</sup> Does a primary folate deficiency produce depression and its symptoms, or does poor nutrition as a symptom of depression cause a decrease in folate levels?

Consistent with the latter hypothesis—that poor nutrition in depression leads to low folate levels—is the finding that when measured across depressive subtypes, low folate appears to predominate in melancholic depression; anorexia and weight loss are common features of this type.<sup>10</sup> Nevertheless, efforts to prove that low folate in depression is the result of poor diet have so far been inconclusive.<sup>8,11</sup> Mixed results may in part reflect the difficulty obtaining an accurate dietary record among depressed patients. They also may suggest a multifactorial etiology.

Abou-Saleh and Coppen<sup>38</sup> hypothesized that a combination of decreased appetite, decreased absorption, and

increased utilization for folate results in folate depletion and eventually produces a CNS effect. In addition, as appears to be true of depression itself, the etiology of folate deficiency in depressive disorders and the temporal relationship between low folate and depression are likely to reflect considerable heterogeneity across patient populations. Among alcohol-dependent and other medically ill populations, in particular, it is plausible to suggest that folate deficiency may be a predisposing factor to the development of depression. For other individuals with persistent depression, appetite loss or poor food selection may contribute to the secondary development of low folate levels, which then seem likely to exacerbate the depression and produce greater refractoriness to standard antidepressant therapies.

### Conclusion

Although theoretic models of folate-depression interrelationships are clearly in need of a more empiric foundation, growing evidence supports the routine evaluation of folate status among medically ill depressed patients and patients with chronic and/or treatment-refractory depression. In these settings, supplementation with folate or its derivative, methylfolate, may be found to play an important role in effective antidepressant treatment.

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