Folate in Depression: Efficacy, Safety, Differences in Formulations, and Clinical Issues

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Supplementation with folate may help reduce depressive symptoms. Folate, a naturally occurring B vitamin, is needed in the brain for the synthesis of norepinephrine, serotonin, and dopamine. Three forms of folate are commonly used: folic acid, 5-methyltetrahydrofolate (5-MTHF) (also known as methylfolate and L-methylfolate), and folinic acid. Some forms may be more bioavailable than others in patients with a genetic polymorphism and in those who take particular medications or use alcohol. Folic acid augmentation in depressed patients may reduce residual symptoms. The 5-MTHF formulation indicated efficacy as adjunctive therapy or monotherapy in reducing depressive symptoms in patients with normal and low folate levels, improving cognitive function and reducing depressive symptoms in elderly patients with dementia and folate deficiency, and reducing depressive and somatic symptoms in patients with depression and alcoholism. Adjunctive folinic acid reduced depressive symptoms in patients who were partially responsive or nonresponsive to a selective serotonin reuptake inhibitor. Evidence for the efficacy of folate in improving cognitive symptoms is equivocal, but most studies used folic acid. Although the studies reviewed have limitations and, historically, concerns have been raised about the role of folate in increasing cancer risk, masking B_{12} deficiency, and worsening depressive symptoms, folate is generally well tolerated, and 5-MTHF may be less likely to incur some of these risks. Several forms of folate appear to be safe and efficacious in some individuals with major depressive disorder, but more information is needed about dosage and populations most suited to folate therapy.

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Folate deficiency has been associated with the presence of depression,[1] may hinder response to antidepressants,[1,2] and may contribute to relapse of depression.[3] Low levels of folate, a B vitamin, have also been associated with poor cognitive function,[4] which is common among patients with depression.[5] Studies of several folate formulations have shown that some patients with depression may safely benefit from folate supplementation, although more information is needed about folate in major depressive disorder (MDD).

RATIONALE FOR FOLATE AUGMENTATION IN DEPRESSION

Antidepressant monotherapy tends to produce relatively low remission rates,[6] and residual symptoms are common even among people who have been treated to remission for depression.[7] However, remission rates can often be improved by using adjunctive medications that target specific symptoms of depression, such as insomnia.[8] The use of combination or augmentation therapies from the start of treatment may also accelerate antidepressant response through the synergy of different mechanisms of action.[9,10] Augmenting antidepressants with different forms of folate may provide beneficial effects for depressive symptoms. Dietary sources rich in folate (dihydrofolate) include leafy vegetables, legumes, and fruits, but cereals and breads are also fortified with a synthetic form of folate, folic acid (Table 1).[11]

Mechanism of Action of Folate in Depression

Three commercially available folate formulations, folic acid, 5-methyltetrahydrofolate (5-MTHF; also known as methylfolate and L-methylfolate), and folinic acid, can be used adjunctively with antidepressants and may have a role in improving MDD remission rates. Interconversion between the forms of folate takes place via the one-carbon cycle, which is a kind of biochemical pathway that leads to the methylation of compounds in our bodies and brains. Many important metabolic processes are regulated through this cycle, including the synthesis of the neurotransmitters norepinephrine, dopamine, and serotonin, which are known to be involved in depression. Disruptions in this mechanism may play a part in depression.

The forms of folate differ in their bioavailability (Figure 1). An active form of folate that can cross the blood-brain barrier and become available to the central nervous system is needed to synthesize dopamine, norepinephrine, and serotonin.[12–14] Folic acid requires a 4-step transformation

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For Clinical Use

- Consider folate supplementation from the start of treatment in patients with depression and low or normal folate levels.
- Folate appears to be well tolerated.
- Some forms of folate may be more effective than others in particular patient populations, but more rigorous study is needed.

in the intestines and liver to become L-methylfolate (see Figure 1), a biologically active form of folate that can cross the blood-brain barrier and activate the enzymes that synthesize dopamine, norepinephrine, and serotonin.[12]

The enzyme dihydrofolate reductase (DHFR) catalyzes the transformation of folic acid into dihydrofolate (see Figure 1). Patients who take lamotrigine and other medications that are inhibitors of DHFR may benefit from treatment with a form of folate that does not require DHFR (Table 2).[11] Folinic acid and 5-MTHF differ from folic acid in that they do not require DHFR for transformation into an active form of folate.

The enzyme methylenetetrahydrofolate reductase (MTHFR) is needed for the one-carbon metabolism of folic acid and folinic acid (see Figure 1); however, this enzyme is affected by the C677T polymorphism, a genetic variation that is common in individuals with depression[15] and can impair the transformation into L-methylfolate.[12] In patients with this genetic polymorphism, 5-MTHF may be more suitable than other forms of folate in reducing depressive symptoms because it does not need MTHFR to cross the blood-brain barrier.

STUDIES OF FOLATE IN DEPRESSION

Folic Acid

Two randomized, controlled studies[16,17] have examined folic acid as augmentation therapy for depression. In a study[16] of lithium and folate, 75 patients (53 with unipolar depression, 17 with bipolar depression, and 4 with schizoaffective disorder) who were being treated with lithium received 200 µg/d of folate or placebo for 1 year. Patients whose plasma folate was 13 ng/mL or above at endpoint had a >40% reduction in Affective Morbidity Index scores over the 1-year trial period. Among patients with unipolar depression who received folate, a small but significant reduction in scores on the Beck Depression Inventory (BDI) occurred during the trial ($P < .02$), whereas those receiving placebo experienced a small increase in BDI scores. Augmentation with folate produced no significant changes in side effect scores. This study suggests that folate may reduce residual symptoms of depression, particularly in individuals with low folate levels.

In the second study,[17] 127 patients with first-episode depression were given 20 mg/d of the selective serotonin reuptake inhibitor (SSRI) fluoxetine and were randomly assigned to receive augmentation with either 500 µg/d of folic acid or placebo for 10 weeks. Fewer patients taking folic acid experienced side effects compared with those taking placebo (12.9% vs 29.7%, respectively). As shown in Figure 2, a significantly greater percentage of women who received folic acid, compared with those who received placebo, responded ($P < .005$). In men, folic acid did not separate from placebo as an augmenting agent. The 500-µg/d dose may have been insufficient for men, or perhaps 5-MTHF would have been a more appropriate supplement than folic acid since the MTHFR C677T polymorphism tends to be overrepresented ($P = .03$) among patients with depression,[15] impeding bioavailability.

Methyltetrahydrofolate

Five studies have examined 5-MTHF augmentation or monotherapy in depression; 3 were randomized, controlled trials,[18–20] and 2 were open studies.[21,22] Godfrey and colleagues[18] studied 123 patients with major depression or schizophrenia in a double-blind, placebo-controlled trial, and 41 of the patients (33%) were found to have a definite or borderline folate deficiency. These patients received either 15 mg/d of methylfolate or placebo in addition to standard psychotropic medications for 6 months. Among patients with depression (n = 24), Hamilton Depression Rating Scale (HDRS) scores were somewhat reduced in those who received methylfolate, while scores increased in those who received placebo, and this difference was apparent at both 3 months and 6 months, although changes were not significant.

A double-blind study[19] compared 50 mg/d of methylfolate monotherapy with 150 mg/d of amitriptyline in 31 outpatients with moderate depression and mostly normal folate levels over 6 weeks, after a 2-week placebo run-in phase to eliminate placebo responders. Three patients withdrew because of common side effects of amitriptyline. Similar response rates were found between the groups, but, among those who took methylfolate, the responders showed increased folate levels compared with nonresponders.

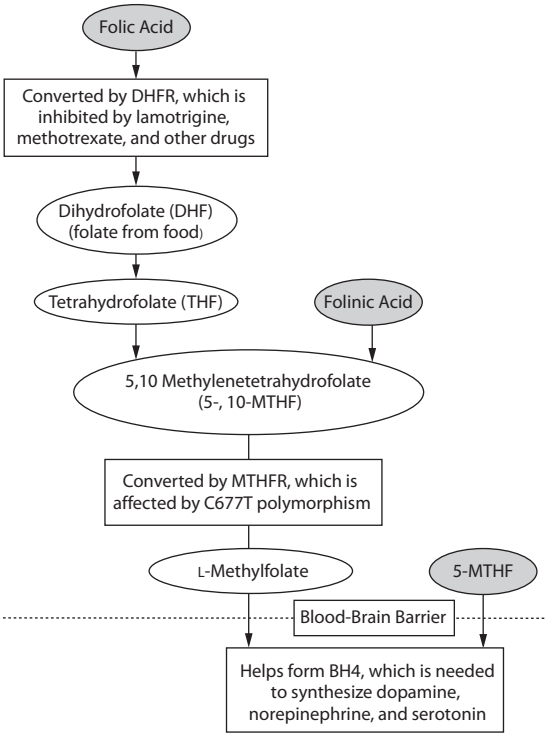
Monotherapy with 5-MTHF was compared with trazodone in a double-blind study[20] of elderly depressed patients with mild-to-moderate dementia and normal folate levels. Patients received a 2-week placebo run-in, and the 96 placebo nonresponders were then randomly assigned to 50 mg/d of 5-MTHF or 100 mg/d of trazodone for 8 weeks. No patients withdrew because of adverse events, but 1 patient

Table 1. Selected Food Sources of Folate and Folic Acid[a,b]

Food	Micrograms (μg)	Daily Value (%)
Breakfast cereals fortified with 100% of the DV, ¾ cup[c]	400	100
Beef liver, cooked, braised, 3 ounces	185	45
Cowpeas (blackeyes), immature, cooked, boiled, ½ cup	105	25
Breakfast cereals, fortified with 25% of the DV, ¾ cup[c]	100	25
Spinach, frozen, cooked, boiled, ½ cup	100	25
Great Northern beans, boiled, ½ cup	90	20
Asparagus, boiled, 4 spears	85	20
Rice, white, long-grain, parboiled, enriched, cooked, ½ cup[c]	65	15
Vegetarian baked beans, canned, 1 cup	60	15
Spinach, raw, 1 cup	60	15
Green peas, frozen, boiled, ½ cup	50	15
Broccoli, chopped, frozen, cooked, ½ cup	50	15
Egg noodles, cooked, enriched, ½ cup[c]	50	15
Broccoli, raw, 2 spears (each 5 inches long)	45	10
Avocado, raw, all varieties, sliced, ½ cup sliced	45	10
Peanuts, all types, dry roasted, 1 ounce	40	10
Lettuce, Romaine, shredded, ½ cup	40	10
Wheat germ, crude, 2 tablespoons	40	10
Tomato juice, canned, 6 ounces	35	10
Orange juice, chilled, includes concentrate, ¾ cup	35	10
Turnip greens, frozen, cooked, boiled, ½ cup	30	8
Orange, all commercial varieties, fresh, 1 small	30	8
Bread, white, 1 slice[c]	25	6
Bread, whole wheat, 1 slice[c]	25	6
Egg, whole, raw, fresh, 1 large	25	6
Cantaloupe, raw, ¼ medium	25	6
Papaya, raw, ½ cup cubes	25	6
Banana, raw, 1 medium	20	6

[a]Reprinted from the National Institutes of Health Office of Dietary Supplements.[11]
[b]The Daily Value (DV) for folate is 400 micrograms (μg). The Daily Value (%) listed in the table indicates the percentage of the Daily Value provided in one serving.
[c]Fortified with folic acid as part of the Folate Fortification Program.

Figure 1. Metabolic Steps Required for 3 Folate Formulations to Cross the Blood-Brain Barrier



Abbreviations: BH4 = tetrahydrobiopterin, DHFR = dihydrofolate reductase, MTHFR = methylenetetrahydrofolate reductase.

treated with trazodone reported vertigo and blurred vision; otherwise, the treatments were safe and well tolerated. Partial to complete response to antidepressant treatment was seen in a greater percentage of those who received 5-MTHF than in those who received trazodone (Figure 3).

In an open study,[21] 20 patients over 60 years old with depressive disorder received 50 mg/d of MTHF monotherapy for 6 weeks. Only 2 patients had low folate levels at baseline. Over the 6-week period, mean HDRS-21 scores decreased from 34.8 to 9.9 at endpoint. A statistically significant improvement was seen in HDRS scores from baseline at week 1 ($P < .01$) and became more robust over the 6 weeks ($P < .0001$). Overall, the response rate (≥ 50% decrease in HDRS score) for MTHF was 81%. In these individuals, MTHF showed efficacy and produced rapid improvement in depressive symptoms.

In another open study[22] of methylfolate monotherapy, 36 inpatients with depression and chronic alcoholism were followed for 4 weeks, during which they were treated with 30 mg tid methylfolate. Alcohol abuse can lower folate levels (see Table 2).[11] No adverse events were reported, and all 36 patients completed the study. Mean HRSD-21 scores fell from 35.27 at baseline to 18.83 at endpoint ($P < .01$) and were statistically significant versus baseline by week 2. Significant ($P < .01$) improvement in well-being and reduction in fatigue and pain from baseline to week 4, according to Visual Analog Scales, were also reported. Sleep improved but the changes were not statistically significant.

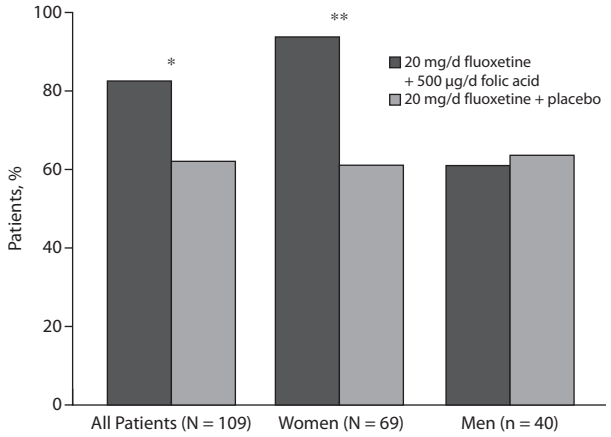
Folinic Acid

Folinic acid, or leucovorin, is an adjuvant chemotherapy agent. A group of 22 normofolatemic adults with MDD and partial or nonresponse to an SSRI after at least 4 weeks of treatment were treated with adjunctive folinic acid in an 8-week open, prospective trial.[23] Treatment with folinic acid (15–30 mg/d) was well tolerated. Among completers and the intent-to-treat group, mean HDRS-17 scores decreased significantly ($P < .01$) from baseline to endpoint (Figure 4). Among completers, 31% achieved response and 19% achieved remission.

FOLATE AUGMENTATION FOR COGNITION

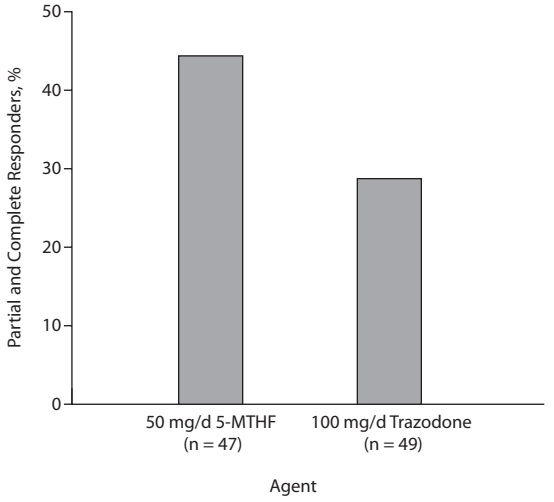
Folate has a potential role in depression treatment as an augmentation therapy to reduce cognitive symptoms. Difficulties with memory, concentration, or alertness are

Figure 2. Response to Fluoxetine With Folic Acid or Placebo Augmentation[a,b]



[a]Data from Coppen and Bailey.[17]
[b]Response was defined as a > 50% decrease in HDRS-17 scores at week 6 or week 10 of study.
*$P < .05$.
**$P < .005$.
Abbreviation: HDRS-17 = Hamilton Depression Rating Scale-17 item.

Figure 3. Partial and Complete Responders in 96 Normofolatemic Patients (aged > 65 years) With Mild-to-Moderate Dementia Treated With 5-MTHF or Trazodone for Depression for 8 Weeks[a,b]



[a]Data from Passeri et al.[20]
[b]Partial response was defined as a 25% to 50% reduction in HDRS scores and complete response was defined as a > 50% reduction in HDRS scores.
Abbreviations: 5-MTHF = 5-methyltetrahydrofolic acid, HDRS = Hamilton Depression Rating Scale.

common in people with MDD; more than 30% of patients who responded to antidepressants were found to have such difficulties.[5]

In elderly patients, poor cognitive function and dementia were found to be associated with low folate status.[4] Folate inadequacy in adults is associated with high blood levels of the amino acid homocysteine, a marker that has been linked with risk of arterial disease, dementia, and Alzheimer's disease.[24] In theory, supplementation with folate should lower plasma homocysteine and improve cognition. The double-blind study[20] that compared 5-MTHF monotherapy with trazodone in elderly depressed patients with mild-to-moderate dementia and normal folate levels examined not only depressive symptoms but also cognitive functions. A higher proportion of patients treated with 5-MTHF demonstrated improvement of at least 10% in immediate recall than those treated with trazodone (53% vs 37%; $P < .05$); improvement in immediate recall was significantly improved in the 5-MTHF group at week 8 versus baseline ($P < .01$). Delayed recall was not changed.

However, a review[24] of 4 double-blind, randomized, placebo-controlled studies and a subsequent 2-year double-blind, randomized, placebo-controlled trial[25] of folate with or without vitamins B_{12} and B_6 in older patients who either were healthy or had dementia or mild-to-moderate cognitive impairment found that, although serum homocysteine concentrations were reduced, no benefits were apparent for any measures of cognition. Although evidence for the efficacy of folate in cognition is equivocal, the use of folic acid in most of these studies may be a confound. Another formulation of folate that can cross the blood-brain barrier might have shown greater benefit.

Limitations of Studies

Some of the studies discussed are limited by the use of a mixed diagnostic population, eg, those with depression, schizophrenia, and dementia. Findings may have been confounded because the focus of some studies was on depressive symptoms as opposed to MDD and subjects had concurrent diagnoses such as dementia. Studies frequently had small sample sizes or used uncommon assessment scales.

Many of the studies of folate and cognition used forms of folate that require multiple steps to cross the blood-brain barrier. Individuals with the polymorphism on the 677th coding of the MTHFR enzyme and those who take particular medications or consume alcohol might respond better to MTHF. The most active form of folate, 5-MTHF, has recently been approved in the United States as a prescription medical food for depressed patients with folate deficiency. Doses are usually 7.5 to 15 mg/d.

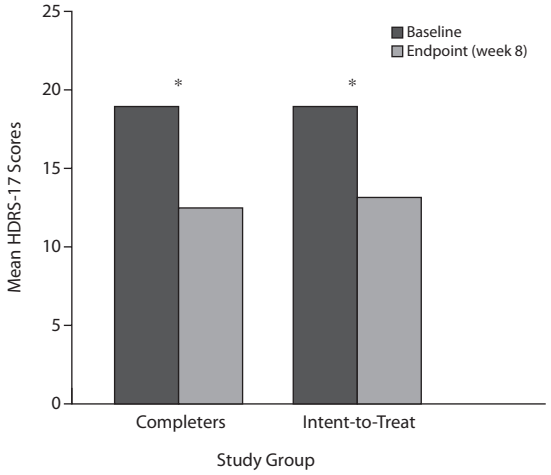
Measurement of peripheral folate levels may not necessarily reflect the amount of folate in the central nervous system (CNS). People with depression may have lower CNS folate level but still appear to have a normal folate level, if the peripheral folate was measured. In the future, normofolatemic people will likely constitute the majority of study populations because folate fortification is now mandatory in some foods in the industrialized world. Folic acid deficiency in itself is therefore likely to become increasingly rare, and researchers and clinicians will need to characterize

Table 2. Some Contributors to Folate Deficiency[a]

Medical Conditions
Pregnancy and lactation
Alcohol abuse
Malabsorption
Kidney dialysis
Liver disease
Certain anemias
Medications
Anticonvulsants
Metformin
Sulfasalazine
Triamterene
Methotrexate
Barbiturates
Other factors
Dietary insufficiency

[a]Adapted from the National Institutes of Health Office of Dietary Supplements.[11]

Figure 4. Mean Reduction in HDRS-17 Scores After 8 Weeks of Adjunctive Folinic Acid in 22 Normofolatemic Depressed Patients With Inadequate Response to an SSRI[a,b]



[a]Data from Alpert et al.[23]
[b]Folinic acid was administered at 15 mg/d for 2 weeks followed by 30 mg/d for 6 weeks.
*$P < .01$.
Abbreviations: HDRS-17 = Hamilton Depression Rating Scale-17 Item, SSRI = selective serotonin reuptake inhibitor.

factors that might be associated with a response to folate supplementation in individuals with normal folate levels.

Safety Considerations

The studies reviewed indicate that folate is generally well tolerated. Historically, the greatest concern with folate supplementation has been its ability to mask vitamin B_{12} deficiency. Inadequate B_{12} results in anemia identical to that caused by folate deficiency; however, inadequate B_{12} also causes irreversible damage to the central and peripheral nervous systems.[24] Folic acid supplementation corrects the anemia of B_{12} deficiency, delaying diagnosis but concealing the continuing lack of B_{12}, thus leaving the patient vulnerable to permanent nervous system damage. However, 5-MTHF is unable to synthesize DNA and is, therefore, not expected to mask B_{12} deficiency.[26]

Cancer risk has also been a concern with folate supplementation. A recent review[26] of the evidence concluded that those claims are not well supported. The benefits of folate supplementation probably outweigh the risks of cancer.[27] However, caution should be used in at-risk patients, such as those with a family history of colorectal cancer.[28]

Another concern is that folate doses > 800 µg/d can result in high levels of unmetabolized serum folic acid, reducing the amount of brain L-methylfolate and leading to decreased monoamines, an outcome that potentially increases the risk of or exacerbates depression. Again, the findings are mixed, but, in individuals in whom this is a concern, 5-MTHF may be less likely to incur these risks.[26–28]

CONCLUSION

Despite study limitations and some safety concerns, several folate forms appear to be well tolerated and efficacious for some individuals with MDD. Folate monotherapy may benefit certain depressed populations, and augmentation with folate may enhance antidepressant efficacy from the start of treatment or convert partial and nonresponders into responders or even into remitters. Folate has historically been used in subjects with low plasma or red blood cell folate levels, but studies suggest that some individuals with normal folate levels may also benefit, especially since peripheral folate levels may not reflect CNS folate levels. Factors associated with response in normofolatemic individuals need to be identified.

More placebo-controlled studies with rigorous methodologies and large sample sizes are needed to elucidate the roles of the different folate compounds in the treatment of MDD. The ability of different folate forms to cross the blood-brain barrier requires further investigation to determine the most efficacious doses to benefit mood. Further, clinicians need to know which depressed populations may be particularly suited to folate augmentation and whether medical or psychiatric comorbidity affects response to folate therapy. For example, depressed populations that may be appropriately treated with folate include those who are vulnerable to medication-related adverse events but might be able to tolerate folate and those who are folate-deficient or at risk of deficiency, such as elderly people who have nutritional problems, individuals with recent alcoholism, and women of childbearing age who take medications that interfere with folate metabolism.

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