Augmenting Antidepressants With Folate: A Clinical Perspective

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The goal of treatment of depression is full remission, but only a minority of patients will achieve full remission with antidepressant monotherapy. Several forms of augmentation have been found to improve the effect of antidepressants, but in some cases, issues of safety and tolerability may be of concern. Folate in particular has been found to further reduce symptoms in patients with depression when used in conjunction with an antidepressant, and because folate is a water-soluble B vitamin, its safety and tolerability are well established. This strategy would typically be used in patients with low plasma or red blood cell folate levels. Folate augmentation may be used (1) to enhance the efficacy of antidepressants in nonresponders, (2) to enable those who partially respond to antidepressant monotherapy to achieve remission, and (3) to alleviate residual symptoms during antidepressant treatment.
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Although the goal of depression treatment is full remission, remission is often the exception rather than the rule. *Remission* is typically defined as a state with minimal or no depressive symptoms, *response* without remission is a 50% or greater reduction in symptoms from baseline in those who do not achieve remission, *partial response* is typically considered to be a 25% to 49% reduction in depressive symptoms, and *nonresponse* is a less than 25% reduction of depressive symptoms.[1] A large number of patients receiving monotherapy treatment for depression will experience nonresponse, partial response, or response without remission. Davidson and I[2] conducted a review of 36 antidepressant efficacy trials and found that 19% to 34% of patients are nonresponders to antidepressant treatment and 12% to 15% experience only partial response. Thus, nonresponse and partial response are common, and even among responders, a considerable number do not achieve remission.

Even patients considered to be in remission often continue to experience a number of symptoms at either the subthreshold or full threshold level. A study by Nierenberg et al.,[3] from the Depression Clinical and Research Program at Massachusetts General Hospital, found that among patients with major depressive disorder (MDD) considered to be in remission after treatment with fluoxetine, 80% were still experiencing at least 1 residual depressive symptom, more than 30% were still experiencing 3 or more symptoms, and 10% continued to meet criteria for minor or subsyndromal depression. Similarly, my colleagues and I[4] examined residual symptoms among patients considered to be responders who were receiving maintenance treatment with antidepressants. This study found that one third or more of patients had cognitive or physical symptoms, which were likely to be residual symptoms of depression, side effects of medication, or both. As these studies illustrate, even patients considered to be in remission or to be responders to antidepressant treatment often continue to experience depressive symptoms. Clearly, safe treatment alternatives that can improve antidepressant response, address residual symptoms, and help patients achieve remission are needed.

FOLATE AND DEPRESSION

Several observational studies[5–8] have linked depression and poor response to antidepressants to low levels of

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folate. Folate is a water-soluble B vitamin that is found in a variety of foods and occurs in numerous forms.

Folate Monotherapy

The primary rationale for using folate monotherapy for the treatment of depression is that, because folate is a naturally occurring substance in the body, this treatment is well tolerated. Tolerability is an important consideration because many patients who are treated with antidepressants experience side effects that they find sufficiently distressing to discontinue treatment. The safety and potential health benefits of folate are such that, in the United States, all cereal and grain products have been fortified with folate since 1998. Folate is also advised for women who intend to become pregnant and is a daily requirement for the general population, although some research suggests that folic acid supplements should be avoided in people with cancer.[9–11]

Although the efficacy of folate monotherapy for depression has yet to be extensively tested, a few trials have found folate to be effective and well tolerated, although the best dose and form of folate remain unclear. Guaraldi and colleagues[12] treated 20 elderly patients with depression with 50 mg/day of open-label methyltetrahydrofolate (MTHF), which is also known as methylfolate, for 6 weeks and observed a significant reduction ($p < .0001$) in depressive symptoms on the 21-item Hamilton Rating Scale for Depression (HAM-D-21) with no reports of drug-related adverse events. Similarly, a blinded study by Di Palma et al.[13] found that when 36 patients with MDD and alcohol dependence, a condition that might be associated with folate deficiency,[14] were treated with 90 mg/day of MTHF for 4 weeks, they experienced considerable improvement ($p < .01$) in their depressive symptoms according to HAM-D-21 criteria and experienced no adverse side effects. A double-blind multicenter study[15] of 96 patients with depression and dementia conducted by Passeri and colleagues found that patients experienced improvements ($p < .05$) in depressive symptoms on the HAM-D after receiving 50 mg/day of MTHF for 8 weeks. These patients also experienced a significant improvement ($p < .05$) in immediate recall. This study compared MTHF with a low dose (100 mg/day) of trazodone. The antidepressant effects were equal, but the trazodone group did not experience significant improvement in recall ability. Thus, although placebo-controlled data are needed, initial studies indicate that folate monotherapy may be a safe and effective option for the treatment of depression, especially in populations that are vulnerable to medication-related adverse events.

Folate Augmentation

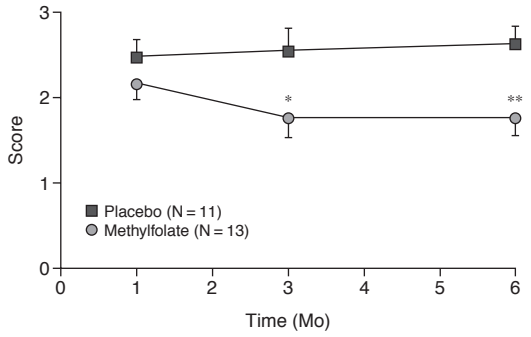
Candidates for augmentation. A number of clinical situations exist in which patients being treated for depression might benefit from folate augmentation. One group of patients who may benefit from folate augmentation is those who have low plasma or red blood cell (RBC) folate levels, given prior observational studies[5–8] linking depression and poor response to antidepressants with low levels of folate.

A second population that might benefit from folate augmentation would be patients who have comorbid conditions that are associated with low folate levels. Iosifescu and colleagues[16–18] have found that a patient's chances of responding to antidepressants progressively decreases as the number of comorbid medical conditions increases. Studies suggest that several medical conditions or treatment for them may be associated with low folate levels, such as diabetes, rheumatoid arthritis, coronary artery disease and stroke, and cardiovascular disease, although data are inconclusive and more research is clearly needed.[19–25]

The third population that might benefit from folate augmentation is those with a central nervous system (CNS) folate deficiency, although measurement of CNS folate levels is not possible. Genetic polymorphisms, such as the methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism, affect folate metabolism and can cause functional forms of folate needed by the body to be unavailable.[26] In the case of CNS folate, the amount of folate that is converted into active forms and manages to cross the blood-brain barrier to affect the activities of the brain cannot be determined. Thus, peripheral measures of folate, such as plasma or RBC folate levels, may not accurately reflect CNS folate levels.

Rationale for augmentation. Patients may receive augmentation either at the same time as the antidepressant is started or later. Antidepressant monotherapy is often only partially effective, and many patients fail to achieve remission with this treatment strategy. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) clinical trials found that only about one third of patients achieved remission with antidepressant monotherapy.[27] Augmenting antidepressant therapy with adjunctive drugs that target specific symptoms of depression may yield higher response and remission rates. For example, my colleagues and I[28] conducted a study in which patients with depression and insomnia were treated with both fluoxetine and eszopiclone. Not only did this drug combination improve the patients' insomnia, but it also resulted in faster onset and enhancement of the antidepressant response and remission rates compared with fluoxetine plus placebo. Implementing augmentation at the start of treatment, rather than after antidepressant monotherapy fails to achieve remission, may increase treatment adherence because patients who perceive little or no benefit are more likely to discontinue medication.[29] Thus, by accelerating treatment response and enhancing antidepressant efficacy, early augmentation may lead to more patients who experience improvement and remain in treatment.

Figure 1. Overall Clinical Outcome Scores in Depressed Patients Treated With Antidepressants and Methylfolate (15 mg/day) or Placebo[a]



[a]Reprinted with permission from Godfrey et al.[32]
*p < .05.
**p < .01.

Augmentation at the start of treatment. Since folate exists in a variety of forms, clinicians must select the best dose and form for augmentation. Coppen and Bailey[30] conducted a study in which patients with major depression were randomly assigned to receive either 500 μg/day of folic acid (N = 62) or placebo (N = 65) in addition to 20 mg/day of fluoxetine from the start of treatment. They found that those who received adjunctive folic acid rather than placebo experienced a greater response to fluoxetine and reported fewer adverse events. However, when men and women were analyzed seperately, only women had substantially improved with folic acid augmentation. Since folic acid is known to lower plasma homocysteine levels, improvement in this study was related to decreased plasma homocysteine levels rather than to increased plasma folate levels. Interestingly, 500 μg/day of folic acid was insufficient to significantly reduce homocysteine levels in men and partly explained folic acid's lack of efficacy in men. A higher dose or a different form of folate may be more suitable for antidepressant augmentation in men. Furthermore, since certain polymorphisms, such as the MTHFR C677T, that impair homocysteine metabolism have been found to be overrepresented in individuals with depression,[31] MTHF may be a more suitable form of folate supplementation because it is able to penetrate the blood-brain barrier. In a study by Godfrey et al.,[32] patients with MDD (N = 24) who were found to be folate deficient were given 15 mg/day of MTHF in addition to psychotropic treatment. These patients experienced a greater reduction of symptoms compared with patients receiving a placebo augmentation (Figure 1).

Sequential augmentation for treatment-resistant depression or residual symptoms. Folate augmentation may be implemented after a patient fails to achieve remission with antidepressant monotherapy, or after a patient achieves remission but continues to experience residual symptoms. As the study by Nierenberg et al.[3] illustrated, residual symptoms are common among patients being treated for depression, even among patients considered to be in remission. Alpert and colleagues[33] conducted a study of 22 patients who had experienced only partial response or nonresponse to at least 4 weeks of antidepressant treatment. After 8 weeks of augmentation with 15 to 30 mg/day of leucovorin, a form of folinic acid that is converted into MTHF, the sample experienced a significant reduction in depressive symptoms, although only 19% reached remission. Subjects in this sample were not folate deficient at baseline. A further study[34] found that folate augmentation may enhance lithium response in patients being treated for bipolar and unipolar depression. A substantial number of these subjects (N = 75) had low folate levels at baseline. After receiving 200 μg/day of folic acid in addition to lithium for 1 year, the patients with higher end-of-trial folate levels (13.0 ng/mL or greater) experienced a 40% reduction in their affective morbidity. These patients had already responded to lithium when folate was added, indicating that folate may be effective for reducing residual symptoms.

CONCLUSION

From the psychiatrist's perspective, folate has a number of uses for the treatment of depression. Folate monotherapy may benefit certain populations. Folate augmentation can be used to enhance antidepressant efficacy from the start of treatment or, for patients who are already on antidepressant treatment, folate augmentation can be used to boost antidepressant efficacy in an attempt to convert partial responders or nonresponders into responders or remitters. Although folate use typically occurs in the context of low plasma or red blood cell folate levels, individuals with normal peripheral levels of folate may also benefit from folate treatment, especially since peripheral folate levels may not accurately reflect CNS folate levels. Further research is needed in order to determine which forms of folate are able to cross the blood-brain barrier to affect CNS folate levels and which doses are most effective.

Drug names: eszopiclone (Lunesta), fluoxetine (Prozac and others), lithium (Eskalith, Lithobid, and others), methylfolate (Deplin, Cerefolin NAC).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, eszopiclone, leucovorin, and methyltetrahydrofolate are not approved by the U.S. Food and Drug Administration for the treatment of depression.

REFERENCES

1. Nierenberg AA, Dececco LM. Definition of antidepressant treatment response, remission, nonresponse, partial response, and other relevant outcomes: a focus on treatment-resistant depression. J Clin Psychiatry 2001;62(suppl 16):5–9
2. Fava M, Davidson KG. Definition and epidemiology of treatment-resistant depression. Psychiatr Clin North Am 1996;19:179–200

3. Nierenberg AA, Keefe BR, Leslie VC, et al. Residual symptoms in depressed patients who respond acutely to fluoxetine. J Clin Psychiatry 1999;60:221–225
4. Fava M, Graves LM, Benazzi F, et al. A cross-sectional study of the prevalence of cognitive and physical symptoms during long-term antidepressant treatment. J Clin Psychiatry 2006;67:1754–1758
5. Lerver V, Kanevsky M, Dwolatzky T, et al. Vitamin B_{12} and folate serum levels in newly admitted psychiatric patients. Clin Nutr 2006; 25:60–67
6. Papakostas GI, Petersen T, Lebowitz BD, et al. The relationship between serum folate, vitamin B_{12}, and homocysteine levels in major depressive disorder and the timing of improvement with fluoxetine. Int J Neuropsychopharmacol 2005;8:523–528
7. Tolmunen T, Voutilainen S, Hintikka J, et al. Dietary folate and depressive symptoms are associated in middle-aged Finnish men. J Nutr 2003;133:3233–3236
8. Papakostas GI, Petersen T, Mischoulon D, et al. Serum folate, vitamin B_{12}, and homocysteine in major depressive disorder, pt 1: predictors of clinical response in fluoxetine-resistant depression. J Clin Psychiatry 2004;65: 1090–1095
9. Neuhouser ML, Beresford SA. Folic acid: are current fortification levels adequate? Nutrition 2001;17:868–872
10. Kim YI. Does a high folate intake increase the risk of breast cancer? Nutr Rev 2006;64:468–475
11. Kim YI. Folate and colorectal cancer: an evidence-based critical review. Mol Nutr Food Res 2007;51:267–292
12. Guaraldi GP, Fava M, Mazzi F, et al. An open trial of methyltetrahydrofolate in elderly depressed patients. Ann Clin Psychiatry 1993;5: 101–105
13. Di Palma C, Urani R, Agricola R, et al. Is methylfolate effective in relieving major depression in chronic alcoholics? a hypothesis of treatment. Curr Ther Res 1994;55:559–567
14. Glória L, Cravo M, Camillo ME, et al. Nutritional deficiencies in chronic alcoholics: relation to dietary intake and alcohol consumption. Am J Gastroenterol 1997;92:485–489
15. Passeri M, Cucinotta D, Abate G, et al. Oral 5′-methyltetrahydrofolic acid in senile organic mental disorders with depression: results of a double-blind multicenter study. Aging (Milano) 1993;5:63–71
16. Iosifescu DV, Nierenberg AA, Alpert JE, et al. The impact of medical comorbidity on acute treatment in major depressive disorder. Am J Psychiatry 2003;160:2122–2127
17. Iosifescu DV, Bankier B, Fava M. Impact of medical comorbid disease on antidepressant treatment of major depressive disorder. Curr Psychiatry Rep 2004;6:193–201
18. Iosifescu DV, Nierenberg AA, Alpert JE, et al. Comorbid medical illness and relapse of major depressive disorder in the continuation phase of treatment. Psychosomatics 2004;45:419–425
19. Hartman M, van Ede A, Severens JL, et al. Economic evaluation of folate supplementation during methotrexate treatment in rheumatoid arthritis. J Rheumatol 2004;31:902–908
20. Golbahar J, Aminzadeh MA, Sharifkazemi MB, et al. Association of red blood cell 5-methyltetrahydrofolate and severity of coronary artery disease: a cross-sectional study from Shiraz, southern Iran. Heart Vessels 2005;20:203–206
21. Sahin M, Tutuncu NB, Ertugrul D, et al. Effects of metformin or rosiglitazone on serum concentrations of homocysteine, folate, and vitamin B_{12} in patients with type 2 diabetes mellitis. J Diabetes Complications 2007; 21:118–123
22. MacKenzie KE, Wiltshire EJ, Gent R, et al. Folate and vitamin B_6 rapidly normalize endothelial dysfunction in children with type 1 diabetes mellitus. Pediatrics 2006;118:242–253
23. Bazzano LA, Reynolds K, Holder KN, et al. Effect of folic acid supplementation on risk of cardiovascular diseases: a meta-analysis of randomized controlled trials. JAMA 2006;296:2720—2726
24. Flight I, Clifton P. Cereal grains and legumes in the prevention of coronary heart disease and stroke: a review of the literature. Eur J Clin Nutr 2006;60:1145–1159
25. Ignarro LJ, Balestrieri ML, Napoli C. Nutrition, physical activity, and cardiovascular disease: an update. Cardiovasc Res 2007;73:326–340
26. Mischoulon D, Raab MF. The role of folate in depression and dementia. J Clin Psychiatry 2007;68(suppl 10):28–33
27. Trivedi MH, Rush AJ, Wisniewski SR, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry 2006;163:28–40
28. Fava M, McCall WV, Krystal A, et al. Eszopiclone co-administered with fluoxetine in patients with insomnia coexisting with major depressive disorder. Biol Psychiatry 2006;59:1052–1060
29. Fava M, Rush AJ. Current status of augmentation and combination treatments for major depressive disorder: a literature review and a proposal for a novel approach to improve practice. Psychother Psychosom 2006; 75:139–153
30. Coppen A, Bailey J. Enhancement of the antidepressant action of fluoxetine by folic acid: a randomized, placebo controlled trial. J Affect Disord 2000;60:121–130
31. Kelly CB, McDonnell AP, Johnston TG, et al. The MTHFR C677T polymorphism is associated with depressive episodes in patients from Northern Ireland. J Psychopharmacol 2004;18:567–571
32. Godfrey PSA, Toone BK, Carney MWP, et al. Enhancement of recovery from psychiatric illness by methylfolate. Lancet 1990;336:392–395
33. Alpert JE, Mischoulon D, Rubenstein GE, et al. Folinic acid (leucovorin) as an adjunctive treatment for SSRI-refractory depression. Ann Clin Psychiatry 2002;14:33–38
34. Coppen A, Chaudhry SSC. Folic acid enhances lithium prophylaxis. J Affect Dis 1986;10:9–13