L-Methylfolate (Deplin®): A medical food for depression?

The Bottom Line

Limited evidence (from before the adoption of widespread dietary supplementation of folate) suggested that folate might be beneficial in depression by augmenting the effects of antidepressants. However, no direct evidence suggests that the medical food supplement L-methylfolate (Deplin®) is the most effective form of supplementation. It is also unclear whether patients must be deficient in folate to receive benefit or whether this prescription supplement has significant clinical application in an era of widespread vitamin fortification of foods.

Key Points

- L-Methylfolate is a medical food for treatment of folate deficiency that is being marketed as an option for individuals with partial or no response to antidepressants
- As a medical food, L-methylfolate has not undergone US Food and Drug Administration (FDA) review
- L-Methylfolate crosses the blood–brain barrier where it is utilized in the synthesis of neurotransmitters
- The evidence is limited that folate supplementation augments antidepressant effectiveness
- How L-methylfolate compares with other forms of folate supplementation has not been determined

The Pitch

L-Methylfolate is being marketed as a prescription-only medical food “approved or indicated for” augmentation of antidepressant therapy for depressed patients who have low plasma and/or low red blood cell folate. According to marketing literature¹:

- Low folate concentrations have been associated with both an increased incidence of depression and an inadequate response to treatment
- More than one-half of the general population has a reduced ability to metabolize folic acid into methylfolate due to methylenetetrahydrofolate reductase (MTHFR) polymorphism, with a higher rate of mutation among people with depression
- Methylfolate is the form of folic acid able to cross the blood–brain barrier and aid in the synthesis of neurotransmitters

Context

In studies performed prior to the FDA mandate that all grain products be fortified with folic acid in the United States, folate deficiency was associated with an increased risk of depression and a poorer response to treatment.² This association has led to the use of various forms of folate for the treatment of depression.

Folates occur in many forms (folic acid; folinic acid or leucovorin; tetrahydrofolate; methylenetetrahydrofolate; and methyltetrahydrofolate, also known as methylfolate or L-methylfolate). Most forms must be converted through multiple steps including reduction by MTHFR into methylfolate, which is able to cross the blood–brain barrier. Once in the central nervous system, methylfolate aids in the production of norepinephrine, dopamine, and serotonin. Some limited evidence suggests that a small percentage of the general population has a variant MTHFR gene, which leads to an enzyme with less than 50% of normal activity.³

L-Methylfolate or methylfolate is classified as a medical food, which is defined as a food “formulated to be consumed under the supervision of a physician and is intended for the specific dietary management of a disease
or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation.” With this designation, medical foods may be “prescription only,” but do not undergo premarket review or approval by the FDA.

An oral dose of 7.5 mg methylfolate (the dose in Deplin tablets) is equivalent to 52.5 mg folic acid supplementation. Concerns related to high-dose folate supplementation (≥15 mg folic acid) include significant drug interactions with many anticonvulsants, and an increased incidence of sleep alterations, malaise, irritability, and hyperactivity. 5

The Data
The Cochrane Collaboration performed a review of folates for depressive disorders in 2003. 2 Two of the 3 articles included in this review utilized methylfolate, while the third used folic acid. 4 6 8 Folates were used to augment other antidepressants in 2 studies and compared directly with trazodone in the third. All used a Hamilton Depression Rating Scale (HDRS) to measure symptoms and effectiveness. Notably, 1 study required low folate concentrations prior to randomization while the other 2 populations had concentrations within the normal range.

When pooling the results of the 2 trials using methylfolate for augmentation, the weighted mean difference (WMD) in HDRS score between the groups favored treatment with folate (WMD –2.65; 95% confidence interval [CI], −4.93 to −0.038). 7 8 When folic acid was compared with trazodone among patients with dementia and depression, there was somewhat greater improvement with folic acid, but the difference did not reach statistical significance (WMD −1.00; 95% CI, −3.21 to 1.21). 6 Adverse events and drop-out rates were similar between groups in all evaluated studies.

The Cochrane reviewers concluded that folate supplementation may be effective when used in addition to conventional anti-depressants, and may be effective with or without low folate concentrations. 2 Several other small, uncontrolled studies with various folate preparations have also shown modest improvement in depression-related symptoms.

Summary
Folate supplementation may be effective for augmenting antidepressant therapy in partial or nonresponders, but the form of supplementation needed is not clear. However, most studies were published prior to folic acid fortification in foods, leaving questions about efficacy now that fortification is commonplace.

Folic acid is inexpensive, but L-methylfolate (Deplin, 7.5 mg) will cost $47.00 a month. 1 An appropriate strategy may be to check folate status in partial or nonresponders to therapy and suggest supplementation if necessary.

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REFERENCES