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Folate as an Adjunctive Therapy for Treatment Resistant Depression

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Abstract
Numerous medications are available to treat depression, yet many patients do not achieve remission or recovery of their symptoms with traditional therapies alone. Folate supplementation has been shown to be beneficial in the treatment of depression when used in addition to traditional pharmacological therapy. A literature review was conducted to determine the effect of low folate levels on depression and if supplementation with either folic acid or L-methylfolate benefits this patient population. Key terms including folate, folate deficiency, methylfolate nutrition, and depression were used to perform searches of multiple databases and journals including PubMed, CINAHL, PsycInfo, and the American Journal of Psychiatry. Studies such as the one conducted by Loría-Kohen et al. (2013), demonstrated benefit in the use of folic acid supplementation in treatment resistant patients. Researchers including Zajecka et al. (2016) have shown that due to its ability to cross the blood brain barrier, L-methylfolate is the better option in the treatment of depression. Medical providers must determine the best treatment plan based on an individual's personalized needs while also considering the risks, benefits, testing options, and cost of treatment.

Literature Review
Folate Deficiency
Although many consider folate deficiency to be rare in the US, multiple studies have shown that testing for blood folate levels may be inconsistent and that depression symptoms may occur without absolute deficiency. Bottiglieri et al. (2006) found that 30.4% of depressed patients in their study had low levels of red cell folate (<150 μg/L). Compared with the healthy patients, the depressed group had a lower mean red cell folate level (t = 1.12, p < 0.01); even lower levels were observed in the depressed subgroup with high plasma homocysteine levels (t = 4.73, p < 0.01).

Folate methylation and neurotransmitters
Miller (2008) discussed that folic acid is an essential nutrient involved in synthesis of neurotransmitters such as dopamine and serotonin and thus is thought to play an important role in mood and cognition. Figure 1, published by Fava & Michelson (2009), shows a good illustration of the various types of folate and the methylation steps necessary for the formation of L-methylfolate.

Folate intake and supplementation for the treatment of depression
Loría-Kohen et al. (2013) found a positive correlation between folic acid supplementation, decreased homocysteine levels, and decreased levels of depression. As total folate intake increased in the supplemented group, their Beck Depression Inventory scores decreased (p < 0.031, p < 0.035). In contrast, the FoLaTED study showed that patients treated with 5 mg of folic acid provided no clinical benefit in the treatment of depression; adjusted difference between patients treated with folic acid and those with placebo at 25 weeks was insignificant at 1.27 (95% CI, p = 0.27).

Methylfolate supplementation for the treatment of depression
Shelton, Manning, & Barrette (2013) reported that 67.9% of participants had some response to adjunctive treatment with L-methylfolate and 45.7% of participants achieved remission of depressive symptoms. Wade, Kindermann, Hou, and Thase (2014) showed that the addition of L-methylfolate is more effective than the addition of second-generation antidepressants (SGAs) for the treatment of depression. The L-methylfolate group was shown to have higher rates of adherence, lower depression-related costs, and lower general healthcare cost compared to patients taking SGAs (p < 0.001).

Applicability to Clinical Practice
• Without clear guidelines, the decision of whether or not to recommend folate supplementation is a provider decision based on each unique patient presentation.
• Providers must consider the potential causes of low folate levels including poor diet, genetic mutations which affect folate metabolism, conditions which cause poor absorption in the gastrointestinal tract, excessive alcohol intake, and medication side effects.
• Cost and applicability of testing:
  • Genes may be included in insurance and lab.
  • If only those patients with a clear folate deficiency are treated, some patients who may benefit from folate supplementation would not be included.
• Financial cost of supplementation:
  • Folic acid 5 mg: $1.95 for a 90-day supply.
  • L-methylfolate 15 mg: $40 for a 30-day supply of Deplim.
  • $174 for a 90-day supply with RX card
  • $79.00 for a 90-day supply of generic

References


Discussion
The literature supports routine folate supplementation as an adjunctive therapy for treatment resistant depression. These studies also verify the relative safety of folate supplementation while showing the inefficacy of testing for folate deficiency. Based on the review of literature, L-methylfolate supplementation is superior to supplement folic acid in the treatment of depression when used in addition to traditional antidepressant medications. Also, whether supplementing with folate acid or L-methylfolate, the best results were seen with high dose supplementation. Common limitations of current research include small sample sizes and the use of retrospective methods to gather data. Additional long-term studies are needed to confirm the benefits, assess for potential risks, and determine other contributing factors that may affect the decision whether or not to supplement depressed patients with L-methylfolate or folic acid.