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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 prescription 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 search 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 Loria-Kohen et al. (2013), demonstrated benefit in the use of folic acid supplementation in lowering depression scores. 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.

## Introduction

The term folate is used to describe natural folates found in foods, folic acid, folinic acid, and L-methylfolate. While folate is readily available in many foods and supplements, low levels of folate can occur due to poor dietary intake, genetic mutations which affect folate methylation, poor absorption in the gastrointestinal tract, excessive alcohol intake, and as a side effect to certain medications (Shelton, Manning, & Barrentine, 2013). L-methylfolate is the usable form of folate and is the only form that can cross the blood brain barrier. Folate is also necessary for the production of the neurotransmitters serotonin, norepinephrine, and dopamine, which are important for maintaining general and mental health. (DynaMed, 2016)

The monoamine hypothesis of depression predicts that depression is the result of low levels of norepinephrine, dopamine and/or serotonin in the brain (McCance, K. L. & Huether, S. E., 2014). According to the Center for Disease Control and Prevention (CDC), more than 15 million adults have experienced depression within the last year. For those patients who seek treatment, many must try multiple medications to find one which is both effective and has few or tolerable side effects. Although the relationship between folate and depression was first recognized in the 1960's, folate supplementation is not routinely recommended or prescribed for the treatment of depression.

## Statement of the Problem

Both the Practice Guideline for the Treatment of Patients with Major Depressive Disorder (Gelenberg et al., 2010) and the American Psychiatric Association list folate as a complementary treatment which can be used in addition to traditional therapies. Neither of these guidelines provides clear recommendations for the type of supplement, dosage ranges, or monitoring that should be used when supplementing with folate in the treatment of depression.

## Research Questions

- In patients treated for depression using traditional antidepressants, should routine folate supplementation be considered as an adjunctive therapy for the reduction of depressive symptoms?
- As an adjunct in treating depression, is folic acid or L-methylfolate more effective?

## 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 depressive 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 ( $t=3.12$ ,  $p<0.01$ ); 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 folate 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 & Micshoulon (2009), provides a good illustration of the various types of folate and the methylation steps necessary for the formation of L-methylfolate.

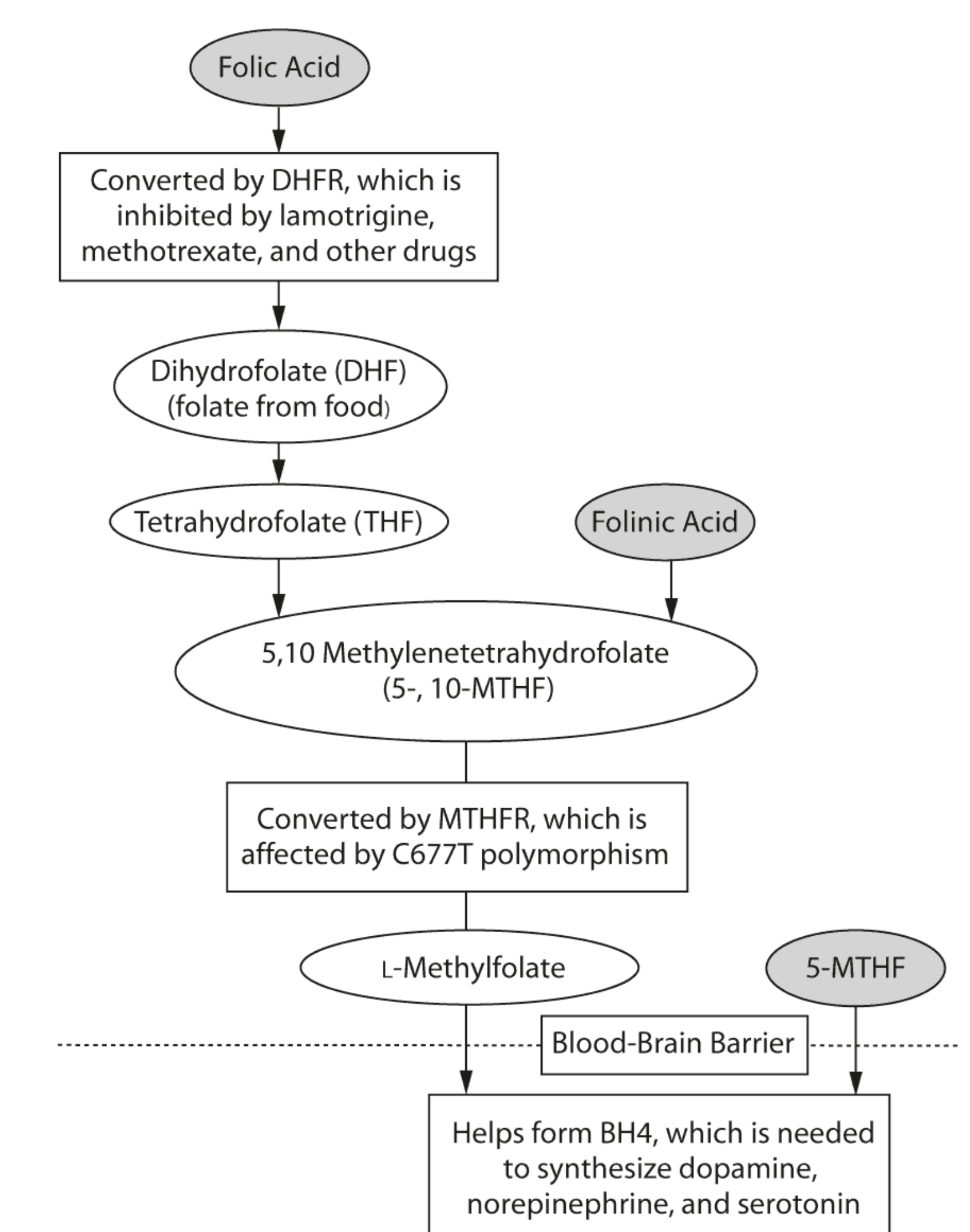
### Folate intake and supplementation for the treatment of depression.

Loria-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 decrease ( $r= -0.581$ ,  $p < 0.05$ ). 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, & Barrentine (2013) reported that 67.9% of study 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 antipsychotics (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 SGA's ( $p < 0.001$ ).

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



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

## Discussion

The literature supports routine folate supplementation as an adjunctive treatment for depression. These studies also verify the relative safety of folate supplementation while showing the inefficiency of testing for folate deficiency. Based on the review of literature, L-methylfolate supplementation is superior to supplementation with folic acid in the treatment of depression when used in addition to traditional antidepressant medications. Also, whether supplementing with folic 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.

## 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 methylation, conditions which cause poor absorption in the gastrointestinal tract, excessive alcohol intake, and medication side effects.
- Cost and applicability of testing
  - Cost varies widely based on 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
    - \$11.95 for a 100-day supply.
  - L-methylfolate 15 mg
    - \$140 for a 30-day supply of Deplin
    - \$174 for a 90-day supply with Rx card
    - \$79.00 for a 90-day supply of generic

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