

L-Methylfolate for Depression

Methylfolate is the active form of folic acid, and a precursor for the synthesis of the monoamine neurotransmitters norepinephrine, dopamine and serotonin [1]. In addition, methylfolate acts as a donor for DNA methylation, a process necessary for epigenetic gene silencing [2]. Methylenetetrahydrofolate reductase (MTHFR) is an enzyme responsible for catalyzing the conversion of folic acid and folate to L-methylfolate. A common variant of this gene significantly reduces the enzymatic activity of MTHFR, resulting in inefficient production of L-methylfolate. Each copy of the variant reduces MTHFR enzyme efficiency by approximately 35% [3].

A number of studies have demonstrated that patients with an *MTHFR* genetic variant resulting in reduced function have a greater risk of developing depression [4, 5]. In addition, several randomized controlled trials have indicated that methylfolate supplements can be an effective antidepressant strategy as an augmentation to serotonin specific reuptake inhibitors (SSRIs) or other antidepressants [6, 7]. One small open label study indicated that methylfolate monotherapy was as effective as augmentation for depression [6]. Supplementation with methylfolate may produce anti-depressant effects by increasing monoamine synthesis, particularly in those patients carrying the MTHFR variant. Methylfolate is available both as an over-the-counter supplement, and as a medical food requiring a prescription.

Recommended Dosage	Side Effects	Drug Interactions
15mg/day [7] (7.5mg 2xD) [8] Use with caution in patients at greater risk for colon cancer as 1mg/day may be associated with colorectal cancer [9]. Manufacturers: Metabolic Maintenance 5MTHF: 10 mg, 90 capsules Life Extension Optimized Folate: 1 mg, 100 capsules Jarrow Formulas Methylfolate 5-MTHF: 400 mcg, 60 capsules Pamlab: Deplin [®] , 7.5, 15 mg (Medical food, requires prescription) Jaymac: Enlyte [®] , 8.73 mg in softgel (Rx, requires prescription)	Sexual dysfunction, somnolence, nausea, dizziness, insomnia, constipation, fatigue (no different than SSRIs alone) [10]	Iron, iron salts, calcium, anticoagulants, tetracyclines

References

1. Robinson, D.M., *Vitamins, Monoamines, and Depression*. Primary Psychiatry, 2009. **16**(2): p. 19-21.
2. Bredy, T.W., Y.E. Sun, and M.S. Kobor, *How the epigenome contributes to the development of psychiatric disorders*. Developmental Psychobiology, 2010. **52**(4): p. 331-342.
3. Gilbody, S., S. Lewis, and T. Lightfoot, *Methylenetetrahydrofolate Reductase (MTHFR) Genetic Polymorphisms and Psychiatric Disorders: A HuGE Review*. American Journal of Epidemiology, 2007. **165**(1): p. 1-13.
4. Wu, Y.L., et al., *Association between MTHFR C677T polymorphism and depression: An updated meta-analysis of 26 studies*. Prog Neuropsychopharmacol Biol Psychiatry, 2013. **46**: p. 78-85.
5. Lok, A., et al., *Interaction between the MTHFR C677T polymorphism and traumatic childhood events predicts depression*. Transl Psychiatry, 2013. **3**: p. e288.
6. Shelton, R.C., et al., *Assessing Effects of L-Methylfolate in Depression Management: Results of a Real-World Patient Experience Trial*. Prim Care Companion CNS Disord, 2013. **15**(4).
7. Papakostas, G.I., et al., *L-methylfolate as adjunctive therapy for SSRI-resistant major depression: results of two randomized, double-blind, parallel-sequential trials*. Am J Psychiatry, 2012. **169**(12): p. 1267-74.
8. Farah, A., *The role of L-methylfolate in depressive disorders*. CNS Spectr, 2009. **14**(1 Suppl 2): p. 2-7.
9. Nahas, R. and O. Sheikh, *Complementary and alternative medicine for the treatment of major depressive disorder*. Can Fam Physician, 2011. **57**(6): p. 659-63.
10. LD, G., O. AY, and D. YA, *L-methylfolate Plus SSRI or SNRI from Treatment Initiation Compared to SSRI or SNRI Monotherapy in a Major Depressive Episode*. Innov Clin Neurosci, 2011. **8**(1): p. 19-28.