



Depression and the Role of L-methylfolate

Depression is a chronic and recurrent disease affecting more than 18 million people in the United States, ranking it, along with heart disease, cancer and diabetes, among the nation's most common ailments.¹ Sadly, up to 50 percent of patients being treated for depression fail to reach remission.²

Depression is the leading cause of disability in the U.S. for people ages 15 to 44.¹ Beyond its devastating effects on individuals and their families, its societal impact is enormous. It costs society \$83 billion annually including the cost of medication, lost productivity, outpatient doctors' visits and hospitalization.³ Further, there is a high correlation between major depressive disorder and suicide and other medical conditions such as heart attacks.¹ Depression is expected to be the second leading cause of disease burden by 2020.⁴

The Biochemical Origins

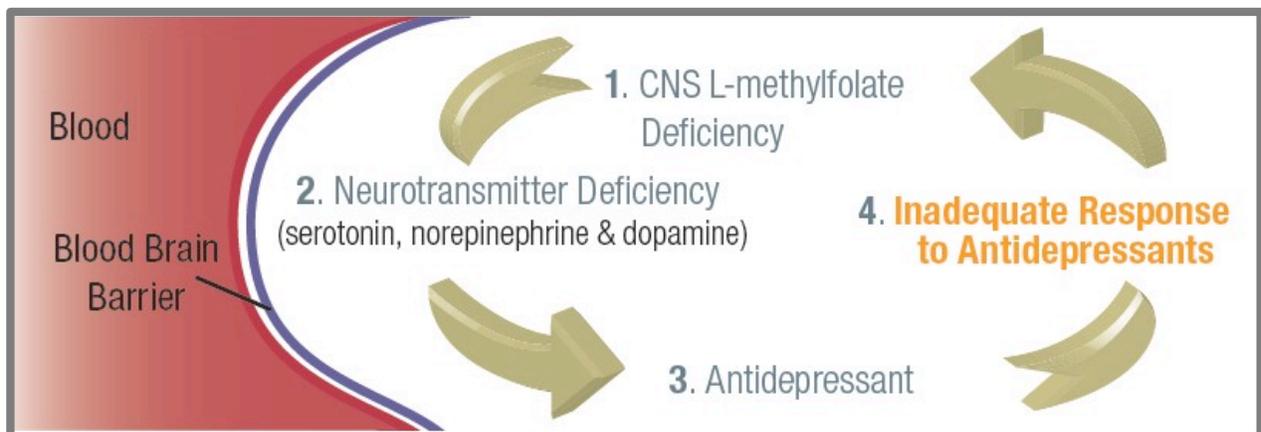
Depression is associated with an imbalance of three chemical messengers (or neurotransmitters) in the brain that regulate mood: serotonin, norepinephrine and dopamine. Antidepressants such as selective serotonin reuptake inhibitors ("SSRIs" e.g. Prozac[®] and Paxil[®]) and serotonin-norepinephrine reuptake inhibitors ("SNRIs" such as Effexor[®] and Cymbalta[®]) are believed to work by addressing this imbalance. However, the landmark Sequenced Treatment Alternatives to Relieve Depression

(STAR*D) study, funded by the National Institute of Mental Health, which was the single largest trial in real-world patients with depression, found that 70 percent of patients will not get well (remission) by taking one antidepressant alone.⁵

There are several hypotheses about why someone may experience less than a full response to antidepressant medications. One explanation is that a single antidepressant may not be able to work effectively if the brain lacks sufficient endogenous quantities of the neurotransmitters associated with mood.

Why Some People Have an Inadequate Response to Antidepressant Therapy

The brain uses a naturally occurring precursor called L-methylfolate to regulate the synthesis, or production, of neurotransmitters. However, as many as 70 percent of people suffering from depression have a genetic factor that limits their ability to convert folate from food or synthetic folic acid, found in vitamin supplements, to L-methylfolate, the only form of folate the brain can use immediately to regulate neurotransmitters.⁶



As illustrated in the chart below, there are additional risk factors for low levels of L-methylfolate in the brain and subsequent neurotransmitter deficiency. These include certain drugs, diseases, lifestyle factors and pregnancy.

Risk Factors for Low CNS L-methylfolate^{7,8}	
Genetics	MTHFR C→T Polymorphism can reduce L-methylfolate levels in plasma and CNS
Drugs	Anticonvulsants such as lamotrigine and valproate, methotrexate, sulphasalazine, oral contraceptives, metformin, niacin and fenofibrates
Disease	Diabetes, atrophic gastritis, Crohn's, colitis, renal failure and hypothyroidism
Lifestyle	Excess alcohol, smoking and poor nutrition
Pregnancy	Mother's supply is depleted to support the fetal growth

Individuals with Deficient L-methylfolate are:^{8,9}

- Six times more likely *not* to respond to antidepressants and less likely to achieve remission
- Thirteen times more likely to have a relapse of their depression
- At risk for increased severity of a depressive episode, length of an episode and delayed improvement
- Likely to have significant reduction in the production of serotonin, norepinephrine and dopamine, neurotransmitters that regulate mood

The Case for Early Combination Therapy

Research has found that many patients with persistent depression can get well after trying several treatment strategies, but their odds of overcoming depression diminish as additional treatments are employed. An inadequate response to antidepressants has been associated with higher relapse rates, higher medical costs and co-morbidities.

Most patients do not beat depression with a single antidepressant and no single antidepressant medication is dramatically superior in achieving disease remission. As a result, many experts now suggest that patients should be prescribed combinations of medications at the start of treatment or earlier in their treatment plan.

This combination therapy approach at the beginning of treatment can also improve a patient's willingness to continue taking antidepressant medication as he or she may see faster improvement in symptoms. In other chronic diseases, such as hypertension and arthritis, combination therapy is the norm.

There is a downside to combination drug therapy: a greater potential for side effects and drug interactions. L-methylfolate, however, is a medical food that is used in addition to an antidepressant. In a trial using L-methylfolate in combination with an antidepressant compared antidepressants with a placebo, adverse events were reported to be similar to a single antidepressant alone. By providing dietary management with L-methylfolate in addition to antidepressant therapy, twice as many patients maintained therapy without discontinuing due to

adverse events.

For additional information, including possible side effects, visit www.Deplin.com or see full prescribing information.

¹ The National Institute of Mental Health (NIMH). (n.d.). The Numbers Count: Mental Disorders in America. Retrieved from: <http://www.nimh.nih.gov/health/publications/the-numbers-count-mental-disorders-in-america/index.shtml>.

² Zajecka, John. Treating Depression to Remission. *J Clin Psychiatry*. 2003;64[suppl 15]:7-12.

³ Greenberg P, Kessler R, Birnbaum H, et al. The Economic Burden of Depression in the United States: How Did It Change Between 1990 and 2000? *J Clin Psychiatry*. 2003;64:1465-75.

⁴ Michaud M, Murray C, Bloom R. Burden of Disease – Implications for Future Research. *JAMA*. 2001;285(5):535-539.

⁵ Trivedi M, Rush A, Wisniewski S, 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.

⁶ Kelly C, McDonnell A, Johnston T, et al. The MTHFR C677T polymorphism is associated with depressive episodes in patients from Northern Ireland. *J Psychopharmacol*. 2004;18(4):567-71.

⁷ Fava M & Rush J. 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;75:139–53.

⁸ Papakostas GI, Iosifescu DV, Renshaw PF, et al. Brain MRI white matter hyperintensities and one-carbon cycle metabolism in non-geriatric outpatients with major depressive disorder (Part II). *Psychiatry Res*. 2005;140(3):301-7.

⁹ Papakostas GI et al. Serum Folate, Vitamin B12, and Homocysteine in Major Depressive Disorder, Part 2: Predictors of Relapse During the Continuation Phase of Pharmacotherapy. *J Clinical Psychiatry*. 2004;65(8):1096-8.