

What are the treatment options for patients with the MTHFR C677T mutation?

Summary: Patients with the MTHFR C677T mutation have a reduced ability to convert folic acid into its active form, L-methylfolate. Both L-methylfolate and folic acid are possible treatment options for these patients. However, there are currently no guidelines regarding dosage of folic acid or L-methylfolate. Although studies have produced mixed results, some caution may be warranted in the administration of high doses of folic acid as this may mask symptoms of vitamin B12 deficiency. There is also some evidence that high intake of folic acid may exacerbate the neurologic effects of vitamin B12 deficiency.

What is MTHFR?

The methylenetetrahydrofolate reductase (MTHFR) enzyme converts synthetic folic acid and dietary folate into its active form, L-methylfolate, which plays a critical role in neurotransmitter synthesis. Some individuals carry a mutation at the C677T SNP of the MTHFR gene, which results in a 35% reduction in activity for heterozygotes (C/T) and a 70% reduction in activity for homozygotes (T/T).^{1,2} Individuals who carry this mutation will have a reduced capacity to create L-methylfolate.

How can healthcare providers treat individuals with reduced MTHFR activity?

Both L-methylfolate and folic acid are possible treatment options for individuals with reduced MTHFR activity.

L-methylfolate: By bypassing the conversion step mediated by MTHFR, supplementation with L-methylfolate should improve serum and CNS folate levels, which may have an impact on depression response. Studies have found that taking L-methylfolate alone³⁻⁶ or in addition to an antidepressant⁶⁻⁸ improves depression. Only one study has evaluated the MTHFR C677T genotype in depressed patients taking L-methylfolate supplementation. This study found no significant improvement on the HDRS-28 scale for any MTHFR genotype.⁹ However, the study sample was small, and there was a trend for patients with MTHFR variation (CT/TT) benefiting more from L-methylfolate supplementation.

Folic acid: Supplementation with folic acid may compensate for the reduced MTHFR enzyme activity, leading to normal levels of the active L-methylfolate, which may have an impact on depression response. Studies investigating the effect of folic acid supplementation on depression response have produced mixed results.¹⁰⁻¹² There have been more studies investigating the effect of taking folic acid as an adjunct to an antidepressant, but again the results are mixed, with some studies showing an improvement in depression¹³⁻¹⁵ and others, including a meta-analysis, showing no clinical benefit¹⁶⁻¹⁸. There are currently no studies evaluating the MTHFR C677T genotype in depressed patients taking folic acid supplementation.

What dose of folic acid or L-methylfolate should be used?

Assurex Health does not make dosing recommendations, as this is up to the discretion of the healthcare provider. There are currently no guidelines regarding dosage of folic acid or L-methylfolate. For folic acid, there is generally 400 mcg present in a multivitamin and 800 mcg present in a prenatal vitamin. L-methylfolate is available over-the-counter or as a prescription only product.

What are the risks of folic acid supplementation?

Although studies have produced mixed results¹⁹⁻²⁵, some caution may be warranted in the administration of high doses of folic acid, as this may mask vitamin B12 deficiency. Additionally, some studies have shown that high intake of folic acid may exacerbate the neurologic effects of vitamin B12 deficiency.^{19,26,27} Healthcare providers should weigh the benefits of folic acid or L-methylfolate supplementation with possible risks associated with these treatment strategies.

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