

## L-methylfolate: Another weapon against depression

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**When added to antidepressants, L-methylfolate may lead to faster, greater reduction of depressive symptoms**

Combination therapies for major depressive disorder (MDD) may enhance antidepressant efficacy and long-term results by working synergistically to regulate monoamines availability. Low levels of serum and red blood cell folate are linked to severe symptoms of depression and some patients are less likely to respond to antidepressants.<sup>1</sup> Even in patients with normal serum or red blood cell folate levels, CNS folate levels may be suboptimal.<sup>1</sup>

L-methylfolate is the centrally active derivative of folate that regulates synthesis of trimonoamines serotonin, dopamine, and norepinephrine and is a key regulator of the cofactor tetrahydrobiopterin (BH4). BH4 is required by tryptophan hydroxylase for serotonin synthesis and by tyrosine hydroxylase for dopamine and norepinephrine synthesis.<sup>2</sup>

Evidence suggests adding L-methylfolate to selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) when starting pharmacotherapy leads to greater reduction of depressive symptoms in a shorter time compared with SSRI or SNRI monotherapy.<sup>1</sup> In a study of patients with MDD who partially responded or did not respond to SSRIs, adjunctive L-methylfolate, 15 mg/d, produced greater response rates compared with SSRIs plus placebo.<sup>3</sup> L-methylfolate also was well tolerated in combination with SSRI or SNRI therapy. The rates of adverse effects were not significantly different in patients taking L-methylfolate plus an SSRI or SNRI compared with those taking SSRI or SNRI monotherapy.<sup>1</sup>

MDD patients who may benefit from L-methylfolate include those with low levels of folate and its active metabolites—such as L-methylfolate—and inadequate response to antidepressants. Patients who have an alcohol use disorder, eating disorders, genetic C677-T polymorphism (present in half of the general population), or gastrointestinal disorders are at risk for low folate levels, as well as those who are pregnant.<sup>2</sup>

Folic acid needs to be converted to L-methylfolate to cross the blood-brain barrier, whereas L-methylfolate can be used directly by the brain.<sup>2</sup> Therefore, patients who take medications that can interfere with the conversion of folate to L-methylfolate might benefit from adjunctive L-methylfolate. These medications include lamotrigine, valproate, oral contraceptives, metformin, warfarin, fenofibrates, and certain retinoids.<sup>1</sup> Patients with C677-T polymorphism and patients from Hispanic or Mediterranean populations have shown impaired ability to convert folic acid to L-methylfolate.<sup>2</sup>

### References

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### Disclosure

Dr. Fluitt reports no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.