L-METHYLFOLATE

THERAPEUTICS

Brands • Deplin
see index for additional brand names

Generic? No

Class

- Medical food (bioavailable form of folate)
- Trimonoamine modulator

Commonly Prescribed for

(bold for FDA approved as medical food indications)

- **Suboptimal folate levels in depressed patients (adjunct to antidepressant)**
- **Hyperhomocysteinemia in schizophrenia patients (adjunct to antipsychotic)**
- Enhancement of antidepressant response at the initiation of treatment
- Cognitive or mood symptoms in patients with MTHFR (methylene tetrahydrofolate) deficiency

How the Drug Works

- Folate is a water-soluble B vitamin (B9) that is essential for cell growth/ reproduction, breakdown/ utilization of proteins, formation of nucleic acids, and other functions
- L-methylfolate, or 6-(S)-5-methyl-tetrahydrofolate, is derived from folate and is the form that enters the brain and works directly as a methyl donor and monoamine synthesis modulator
- That is, it regulates tetrahydrobiopterin (BH4), a critical enzyme cofactor for trimonoamine neurotransmitter synthesis
- Methyl donor for DNA methylation and thus an epigenetic regulator

How Long Until It Works

- Onset of therapeutic actions in depression is usually not immediate, but often delayed 2–4 weeks
- If it is not working within 6–8 weeks for depression, it may require a dosage increase or it may not work at all
- May continue to work for many years to prevent relapse of symptoms

If It Works

- The goal of treatment for depression is complete remission of current symptoms as well as prevention of future relapses
- Treatment most often reduces or even eliminates symptoms, but not a cure since symptoms can recur after medicine is stopped
- Continue treatment until all symptoms are gone (remission)
- Once symptoms gone, continue treating for 1 year for the first episode of depression
- For second and subsequent episodes of depression, treatment may need to be indefinite

If It Doesn't Work

- Many patients with depression only have a partial response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating)
- Other patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Consider increasing dose, switching to another agent or adding an appropriate augmenting agent
- Consider psychotherapy
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)
- Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require antidepressant discontinuation and a switch to a mood stabilizer

Best Augmenting Combos for Partial Response or Treatment Resistance

- L-methylfolate is itself an adjunct to standard treatments for depression or schizophrenia at the initiation of treatment or to augment a partial response

Tests

- Baseline folate levels (serum levels for recent folate intake; red blood cell or CSF levels for long-term folate levels)
- Baseline homocysteine levels (reciprocal relationship with folate levels; high homocysteine levels may be more sensitive in detected folate deficiency than folate levels themselves in some patients)

- May monitor folate levels for patients taking an agent capable of affecting folate metabolism, absorption, or degradation
- May consider genotyping for deficient folate synthesis via MTHFR T alleles or MTHFD1 A alleles

SIDE EFFECTS

How Drug Causes Side Effects
- L-methylfolate does not typically cause side effects

Notable Side Effects
- L-methylfolate does not typically cause side effects

Life-Threatening or Dangerous Side Effects
- Theoretically, rare induction of mania or suicidal ideation and behavior (suicidality)

Weight Gain


- Reported but not expected

Sedation


- Reported but not expected

What to Do About Side Effects
- Wait
- Lower the dose or administer in divided doses
- Switch to another drug

Best Augmenting Agents for Side Effects
- Many side effects cannot be improved with an augmenting agent
- Activation and agitation may represent the induction of a bipolar state, especially a mixed dysphoric bipolar II condition sometimes associated with suicidal ideation, and require the addition of lithium, a mood stabilizer or an atypical antipsychotic, and/or discontinuation of l-methylfolate or the primary antidepressant

DOSING AND USE

Usual Dosage Range
- 7.5–15 mg/day

Dosage Forms
- Tablet 7.5 mg, 15 mg
- Doses above 15 mg/day should be administered in divided doses

How to Dose
- Initial 7.5–15 mg/day

Dosing Tips
- Can be taken with or without food
- L-methyltetrahydrofolate was shown to be 7 times more bioavailable than folic acid
- That means 7.5 mg of the active L enantiomer of methylfolate may be equivalent to 52 mg of folate (usual dose of folate is 100 ug to 1.0 mg)
- If intolerable anxiety, insomnia, agitation, akathisia, or activation occur either upon dosing initiation or discontinuation, consider the possibility of activated bipolar disorder and switch to a mood stabilizer or an atypical antipsychotic

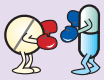
Overdose
- Doses up to 90 mg/day of methylfolate (45 mg l-methylfolate) have been studied without any additional adverse events
- L-methylfolate is generally regarded as safe
- A toxic dose of l-methylfolate is not known at this time

Long-Term Use
- Safe

Habit Forming
- No

How to Stop
- Taper not necessary

Pharmacokinetics
- Mean elimination half-life approximately 3 hours for d,l-methylfolate
- L-methylfolate is naturally stored in most cells and used by the body when needed; therefore, l-methylfolate may not follow typical drug pharmacokinetic patterns



Drug Interactions

- L-methylfolate may reduce plasma levels of certain anticonvulsants, including phenytoin, carbamazepine, fosphenytoin, phenobarbital, primidone, or valproate
- L-methylfolate may reduce plasma levels of pyrimethamine
- Patients taking folate-lowering drugs (e.g., anticonvulsants, cholestyramine, colestipol, cycloserine, aminopterin, methotrexate, sulfasalazine, pyrimethamine, triamterene, trimethoprim, isotretinoin, fluoxetine, nonsteroidal anti-inflammatory drugs (NSAIDs), methylprednisolone, pentamidine) or who smoke or drink heavily may require higher doses of l-methylfolate

Other Warnings/ Precautions

- Folic acid may mask symptoms of B12 deficiency (e.g., pernicious anemia), although this may be less likely with l-methylfolate
- Use with caution in patients with bipolar disorder unless treated with concomitant mood-stabilizing agent
- Monitor patients for activation of suicidal ideation, especially children and adolescents
- Folic acid, when administered in doses above 800 mcg, may increase the amount of unmetabolized folic acid, which has been linked to accelerated growth of existing neoplasms in the colon; l-methylfolate may be less likely than folic acid to accelerate the growth of existing neoplasms

Do Not Use

- If there is a proven allergy to folate or folic acid

SPECIAL POPULATIONS

Renal Impairment

- Dose adjustment not necessary

Hepatic Impairment

- Dose adjustment not necessary

Cardiac Impairment

- Dose adjustment not necessary

Elderly

- Dose adjustment not necessary

Children and Adolescents

- Use with caution, observing for activation of known or unknown bipolar disorder and/or suicidal ideation, and inform parents or guardian of this risk so they can help observe child or adolescent patients
- Safety and efficacy have not been established

Pregnancy

- L-methylfolate has not been formally assigned a pregnancy risk category; there are no controlled studies in humans or animals
- At recommended doses, folic acid is pregnancy risk category A [adequate, well-controlled studies in pregnant women have failed to demonstrate risk to the fetus]
- At high doses, folic acid is pregnancy risk category C [no controlled studies in humans]
- Because pregnant women are advised to take folic acid or prenatal vitamins that contain folic acid, it is important to ask the patient about any supplements or vitamins she may be taking and consider this when deciding whether to prescribe l-methylfolate

Breast Feeding

- Some drug is found in mother's breast milk

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Patients who need efficacy greater than an antidepressant alone at the initiation of treatment
- Patients with partial or inadequate response to antidepressants

Potential Disadvantages

- Patients with adequate folate levels

Primary Target Symptoms

- Depressed mood
- Cognitive symptoms

Pearls

- Numerous studies suggest that low plasma, red blood cell, and/or cerebrospinal fluid levels of folate may be associated with depression in some patients
- Treatment with l-methylfolate seems to be safe, has few if any side effects, and is generally less expensive than augmenting with a second antidepressant
- L-methylfolate is able to cross the blood-brain barrier and support the synthesis of monoamines

Suggested Reading

Bottiglieri T. Homocysteine and folate metabolism in depression. Prog Neuropsychopharmacology Biol Psychiatry 2005;29:1103–12.

Fava M, Mischoulon D. Folate in depression: efficacy, safety, differences in formulations, and clinical issues. J Clin Psychiatry 2009;70 (suppl 5):12–7.

Miller AL. The methylation, neurotransmitter, and antioxidant connections between folate and depression. Altern Med Rev 2008;13(3):216–26.

Stahl SM. L-methylfolate: A vitamin for your monoamines. J Clin Psychiatry 2008;69(9):1352–3.