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)
**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 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

**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

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**THE ART OF PSYCHOPHARMACOLOGY**

**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
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

