CLINICAL MONOGRAPH · ENERGY & NUTRITIONAL

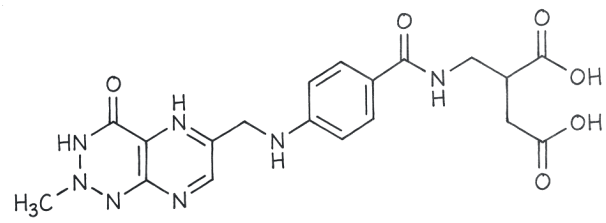
Methylfolate

Active folate (5-MTHF) for methylation pathway support

L-methylfolate (also called 5-MTHF or levomefolate) is the active form of vitamin B9, the form your blood carries and your cells actually use. Ordinary folic acid (the form in supplements and fortified grain products) has to be converted by the body, via an enzyme called MTHFR, before it can do its work. People with common MTHFR genetic variants convert folic acid less efficiently, which is one reason a pre-converted form has clinical appeal [frosst1995] [lamers2006].

L-methylfolate is sold as a medical food under the brand name Deplin for the dietary management of major depression alongside antidepressants [fda_medical_food]. It is not FDA-approved as a drug [fda503a]. The randomized evidence for that use comes from two parallel-sequential trials published by Papakostas and colleagues in 2012, plus follow-on inadequate-responder analyses [papakostas2012]. Folate is also the nutrient that prevents most neural tube defects when taken before and during early pregnancy; the historical evidence for that came from folic acid (the MRC Vitamin Study, 1991), and equivalent red-blood-cell folate is achievable with L-methylfolate at appropriate doses [stover2004; scaglione2014; mrc1991].

RonanRx-compounded L-methylfolate is dispensed only on a patient-specific prescription written by a licensed doctor for an identified patient, typically for patients with documented MTHFR polymorphisms, excipient sensitivities to the manufactured medical-food product, allergen-free formulation needs, or a prescribed strength not commercially available [stover2004]. RonanRx does not sell L-methylfolate directly to patients.



EVIDENCE POSTURE WELL STUDIED EMERGING REVIEWED **2026-05-11**

State-licensed 503A	Pharmacist reviewed	Doctor led	Cold-chain ready	Patient choice preserved

Contents

Click any section to jump there. Page numbers update on render.

FOR CLINICIANS

L-methylfolate ((6S)-5-methyltetrahydrofolate) is the circulating, biologically active form of folate downstream of methylenetetrahydrofolate reductase (MTHFR) [scaglione2014]. Cellular folate metabolism proceeds DHF → THF → 5,10-methylene-THF → 5-MTHF, with the final reduction catalyzed by MTHFR [selhub1999, stover2004]. 5-MTHF is the methyl donor for homocysteine remethylation to methionine by methionine synthase (vitamin B12-dependent) and, via S-adenosylmethionine (SAM), supplies methyl groups for DNA, neurotransmitter, and phospholipid methylation. Two common MTHFR coding variants, C677T (Ala222Val, [frosst1995]) and A1298C (Glu429Ala, [weisberg1998]), reduce MTHFR specific activity; the C677T TT genotype is associated with elevated plasma homocysteine [brattstrom1998] and with reduced response to standard antidepressants in observational and meta-analytic data [lewis2006, gilbody2007].

Oral L-methylfolate bypasses MTHFR. Head-to-head pharmacokinetic and red-blood-cell folate studies show that (6S)-5-MTHF raises plasma and RBC folate at least as effectively as equimolar folic acid in healthy adults and more effectively in C677T variant carriers [lamers2006; prinz2009; pietrzik2010]. Unlike high-dose synthetic folic acid, 5-MTHF does not generate circulating unmetabolized folic acid (UMFA), the appearance of which in serum after folic-acid supplementation has been documented from 100% of NHANES adult samples [pfeiffer2015] down through cohort data [bailey2010; sweeney2012] and has been hypothesized, though not established, to mask vitamin B12 deficiency anemia and to interfere with natural folate transport [morris2007; patanwala2014] [scaglione2014].

For depression: L-methylfolate calcium 15 mg/day (Deplin) was evaluated as adjunctive therapy in SSRI-resistant major depressive disorder in two parallel-sequential RCTs reported by Papakostas et al [obeid2020]. [papakostas2012]; trial 1 (7.5 mg) did not separate from placebo, trial 2 (15 mg) showed superior HDRS-17 response and remission rates over 30 days. Inadequate-responder subgroup analysis in obese and inflammatory-biomarker-high patients [shelton2013, shelton2015] and an MTHFR-genotype-stratified open-label study [mech2016] found enhanced response in patients with elevated BMI, CRP, TNF-α, leptin, or MTHFR C677T/A1298C polymorphism. A 12-month open-label extension confirmed safety and durability [zajecka2016]. Class-level meta-analyses of folate for depression remain mixed, with effect sizes sensitive to formulation (folic acid vs methylfolate vs folinic acid) and adjunctive vs monotherapy framing [almeida2015, roberts2018, fava2009] [scaglione2014]. Folate supplementation also reduces homocysteine in a dose-response fashion regardless of MTHFR genotype [crider2019] [willems2007].

Compounded 503A role: oral capsules at custom strengths (commonly 1, 5, 7.5, 10, 15 mg of the (6S) Metafolin or Quatrefolic salt), allergen-free formulations, sublingual options, and combination products co-prescribed with methylcobalamin or pyridoxal-5-phosphate per patient-specific indication. The brand-name Deplin product is the manufactured medical food and is the reference comparator when documented patient-specific factors render it unsuitable [fda_medical_food].

Why Personalized Methylfolate

The Deplin 15 mg medical-food dose came from two trials in SSRI-resistant adults. That schedule was not calibrated for your MTHFR genotype, your baseline red-blood-cell folate, your homocysteine, your B12 status, or the excipient sensitivities that make a manufactured capsule the wrong fit. With L-methylfolate, the variables that actually move response are individual: C677T versus A1298C status, BMI, inflammatory biomarkers like CRP and TNF-alpha, and whether the patient is taking a folate-interacting anticonvulsant or methotrexate. A single off-the-shelf strength cannot meet that list.

Compounding is where those variables get answered. A 503A pharmacy can dispense the (6S) Metafolin or Quatrefolic salt at strengths the commercial market does not stock (1 mg, 5 mg, 7.5 mg, 10 mg, sublingual options), build allergen-free capsules for patients reactive to the medical-food excipients, and co-formulate with methylcobalamin or pyridoxal-5-phosphate when the prescriber wants the methylation cofactors together. The active ingredient is the same molecule documented in the published pharmacokinetic and depression-adjunct literature, the salt, the strength, and the excipients are written for one patient.

This is the older arrangement: a prescriber who knows the chart, a pharmacist who prepares the medicine, a label with the patient's name. Modern licensing and inspection keep it accountable.

Quick Facts About Methylfolate

Category: Active folate (6S-5-methyltetrahydrofolate, 5-MTHF), the circulating, biologically active form of vitamin B9

Common aliases: L-methylfolate, levomefolate, 6S-5-MTHF, (6S)-5-methyltetrahydrofolic acid, Metafolin (calcium salt), Quatrefolic (glucosamine salt)

Biological role: Methyl donor for homocysteine remethylation to methionine (via methionine synthase + B12), supports SAM-dependent methylation across DNA, neurotransmitters, and phospholipids

Routes studied in humans: Oral capsule/tablet (calcium and glucosamine salts), sublingual

Evidence posture: Bioavailability and homocysteine-lowering well established. Adjunctive efficacy for SSRI-resistant major depression supported by two parallel-sequential RCTs of L-methylfolate 15 mg (Deplin) plus inadequate-responder analyses; effects strongest in biomarker- and genotype-defined subgroups. Class-level folate-for-depression meta-analyses remain mixed.

FDA-approval status: Not FDA-approved as a drug. Marketed L-methylfolate products (Deplin and similar) are classified as medical foods under section 5(b) of the Orphan Drug Act and 21 CFR 101.9(j)(8), for the dietary management of a specific disease (depression with documented folate-pathway deficits). Folic acid is the over-the-counter dietary-supplement form.

Compounded under: 503A, patient-specific prescription only

Important compounding caution: Stereochemistry matters: only the (6S) isomer is biologically active. Pharmacy-grade L-methylfolate should be the (6S) salt (Metafolin calcium or Quatrefolic glucosamine), not racemic 6R,S-5-MTHF. Ingredient identity, salt form, and oxidative stability are part of every compounding record.

SPECIALS: PATIENT-SPECIFIC PRESCRIPTION ONLY

Methylfolate described in this monograph is a 503A compounded preparation. Every dose is made on a prescription, for a named patient, by a licensed pharmacist. It is not a stocked, mass-manufactured product.

- **Made to order, not off a shelf.** No batch sits in a warehouse waiting for buyers. Your prescription triggers the prep.
- **Named-patient label.** The bottle carries one patient's name. The batch records carry one prescription.
- **Dose, strength, and route chosen for the patient.** A prescriber decides what gets compounded, not a manufacturer who set the strength for a trial population.
- **Licensed pharmacist on the hook.** A real person, with a license that can be pulled, signs off on every prep. State inspectors check the facility.
- **Compounded drugs are not FDA-approved.** They should not be evaluated using branded-drug trial data alone. Availability varies by state and prescribed medication.

How This Differs from a Research-Use-Only Website

A research-use-only website ships a vial from a warehouse. There is no prescription, no pharmacist, no facility inspection, and no way to recall the product if something is wrong with it. If the vial is mislabeled, contaminated, or under-potent, there is nobody whose license is at stake.

A 503A compounding pharmacy is the other thing. The doctor writes the prescription. A licensed pharmacist, whose name is on the label, prepares the medicine in a facility the state inspects. If something goes wrong, there is a person and a license on the hook, and a documented chain of custody on every lot. That accountability is what makes it safe.

What is Methylfolate?

L-methylfolate is (6S)-5-methyltetrahydrofolic acid, a reduced, methylated folate with a single specific stereochemistry at C6 [fda_medical_food]. It is the predominant form of folate in human plasma and the form that crosses the blood-brain barrier via the proton-coupled folate transporter and the reduced folate carrier. Folic acid, by contrast, is a synthetic fully oxidized pteroylmonoglutamate that does not occur in

nature and must be reduced (DHFR → DHF → THF) and then methylated through the folate cycle before it can participate in one-carbon metabolism [stover2004, scaglione2014].

Pharmacy-grade L-methylfolate is supplied as one of two stable salts [fda_medical_food]. Metafolin (calcium L-5-methyltetrahydrofolate) was developed by Merck Eprova; Quatrefolic ((6S)-5-MTHF glucosamine salt) was developed by Gnosis. Both are the (6S) isomer only, racemic 6R,S preparations contain the biologically inactive (6R) diastereomer and are not used in modern clinical formulations [obeid2020].

The L-methylfolate medical-food product Deplin (Alfasigma; formerly Pamlab/Nestlé Health Science) is marketed under FDA medical-food regulation (21 CFR 101.9(j)(8)) for the dietary management of major depressive disorder, with single-active-ingredient capsules at 7.5 mg and 15 mg of L-methylfolate calcium. Multiple branded and generic L-methylfolate products are also marketed as dietary supplements (typically 400 mcg to 5 mg). Folic acid (FDA-approved as a prescription prenatal at 0.4, 1 mg and widely available OTC) is a different molecule and is not interchangeable on a milligram basis [fda_medical_food].

How Methylfolate Works

Folate enters cellular one-carbon metabolism as the reduced cofactor tetrahydrofolate (THF). One-carbon units are transferred between THF, 5,10-methylene-THF, 5,10-methenyl-THF, 10-formyl-THF, and 5-methyl-THF, each form supplying a different methyl-group oxidation state for downstream biosynthesis. Three principal cellular needs are met: thymidylate synthesis (DNA replication and repair, from 5,10-methylene-THF), purine synthesis (from 10-formyl-THF), and methionine regeneration from homocysteine (from 5-methyl-THF) [selhub1999, stover2004].

Methylenetetrahydrofolate reductase (MTHFR) catalyzes the irreversible reduction of 5,10-methylene-THF to 5-methyl-THF, committing the carbon to remethylation rather than to thymidylate or purine synthesis. Once formed, 5-methyl-THF donates its methyl group to homocysteine via methionine synthase (a vitamin-B12-dependent enzyme), regenerating methionine. Methionine is then activated to S-adenosylmethionine (SAM), the universal methyl donor for hundreds of methyltransferase reactions including DNA methylation, neurotransmitter synthesis (serotonin, norepinephrine, dopamine), and phospholipid methylation [bottiglieri2000, selhub1999].

Oral L-methylfolate enters this cycle downstream of MTHFR. It does not require DHFR-mediated reduction (unlike folic acid) and does not require MTHFR activity (which is reduced in C677T and A1298C variant carriers). Once absorbed, 5-MTHF distributes to plasma and is taken up by tissues via the same transporters that handle endogenous 5-MTHF [pietrzik2010, obeid2020].

Biological Role of Methylfolate

Folate (vitamin B9) is an essential water-soluble vitamin. Humans cannot synthesize it and must obtain it from dietary leafy greens, legumes, liver, and folic-acid-fortified grain products (mandatory in the United States since 1998). The total body folate pool is approximately 10, 30 mg, with the liver containing roughly half. Plasma folate is overwhelmingly in the form of 5-methyltetrahydrofolate; only after folic-acid supplementation does meaningful unmetabolized folic acid appear in the circulation [pfeiffer2015, bailey2010] [lamers2006].

Folate deficiency causes megaloblastic anemia (indistinguishable from B12-deficiency anemia on peripheral smear), and severe maternal folate deficiency in early gestation is the principal modifiable cause of neural tube defects. The MRC Vitamin Study (1991) [mrc1991] and the Hungarian periconceptional supplementation trial (Czeizel & Dudás 1992) [czeizel1992] established that 4 mg/day folic acid (MRC; in women with a prior NTD-affected pregnancy) and 0.8 mg/day in a multivitamin (Czeizel; first-occurrence prevention) reduced NTD risk by approximately 70% [lamers2006]. Mandatory U.S. folic-acid fortification of enriched grain products began in 1998; the CDC subsequently estimated that fortification has prevented approximately 1,300 NTD-affected births per year in the United States [williams2015]. The NTD-prevention evidence base is folic-acid-based; 5-MTHF achieves equivalent RBC folate at appropriate dosing but does not have its own NTD-prevention efficacy trial.

Detailed Mechanism of Methylfolate

The MTHFR C677T polymorphism (rs1801133, c.665C>T, p.Ala222Val) was identified by Frosst and colleagues in 1995 as a thermolabile MTHFR variant associated with hyperhomocysteinemia and increased vascular risk [frosst1995]. The A1298C polymorphism (rs1801131, c.1286A>C, p.Glu429Ala) was described by Weisberg and colleagues in 1998 [weisberg1998]. C677T homozygotes (TT, prevalence approximately 10, 15% in non-Hispanic white populations, higher in some Hispanic and East Asian populations) have approximately 30% of wild-type MTHFR specific activity and elevated plasma homocysteine, with the homocysteine elevation modifiable by folate intake [brattstrom1998, klerk2002]. A1298C heterozygotes and homozygotes have a milder activity reduction. Compound C677T/A1298C heterozygosity produces an intermediate phenotype.

Genome-wide and meta-analytic data link MTHFR C677T to several clinical phenotypes: neural-tube defect risk in offspring of TT mothers, modest increased risk of cardiovascular disease and stroke in some homocysteine-elevated populations, and, relevant to the Deplin indication, increased lifetime risk of depression and reduced response to standard antidepressants. The HuGE review by Gilbody and colleagues (2007) summarized psychiatric associations across studies [gilbody2007]; the British Women's Heart and Health Study with meta-analysis by Lewis and colleagues (2006) reported the C677T TT genotype was

associated with increased depression risk [lewis2006]. The Hordaland Homocysteine Study [bjelland2003] found that low plasma folate and C677T TT genotype were each independently associated with depression in a large community sample.

Pharmacokinetically, oral (6S)-5-methyltetrahydrofolate is well absorbed from the proximal small intestine via the proton-coupled folate transporter. Peak plasma 5-MTHF concentrations occur 30, 60 minutes after dosing, with bioavailability comparable to or greater than equimolar folic acid in head-to-head crossover studies [pietrzik2010, prinz2009]. Critically, 5-MTHF does not produce circulating unmetabolized folic acid (UMFA), which appears in serum after folic-acid doses above approximately 200, 400 mcg/day. UMFA has been documented in nearly all NHANES adult and pediatric samples in the post-fortification U.S. [pfeiffer2015, bailey2010]; whether UMFA itself has adverse effects (cognitive effects in B12-deficient older adults, immune effects, masking of B12-deficiency anemia) remains debated rather than established [morris2007, sweeney2012, patanwala2014].

In C677T variant carriers, head-to-head studies show that (6S)-5-MTHF raises plasma and red-blood-cell folate more effectively than folic acid, with the differential pronounced in TT homozygotes [lamers2006, prinz2009, willems2007]. Lamers and colleagues (2006) reported that supplementation with [6S]-5-MTHF increased RBC folate concentrations more than equimolar folic acid in women of childbearing age; Prinz-Langenohl and colleagues (2009) extended this finding specifically in C677T TT and CC women. Pietrzik and colleagues (2010) reviewed the comparative clinical pharmacokinetics and concluded that 5-MTHF is a viable folate-status intervention across MTHFR genotypes.

Methylfolate Research History

Folate research begins in the 1930s and 1940s with Lucy Wills's discovery that a yeast factor (subsequently identified as folic acid) corrected the macrocytic anemia of pregnancy in Bombay. Folic acid was synthesized in 1945; the biochemistry of one-carbon metabolism, including the THF cycle and methionine synthase, was worked out through the 1950s, 1980s by Hoffbrand, Herbert, Stokstad, Selhub, and others, culminating in Selhub's 1999 review of homocysteine metabolism [selhub1999].

The MTHFR C677T variant was discovered by Frosst, Rozen, and colleagues in 1995 as a candidate genetic risk factor for vascular disease [frosst1995]; A1298C followed in 1998 [weisberg1998]. The folate-homocysteine-vascular hypothesis was tested in meta-analyses [brattstrom1998, klerk2002] and large folate-supplementation trials, with mixed cardiovascular outcomes but consistent homocysteine-lowering. The NTD-prevention story matured with the MRC Vitamin Study (1991) and Czeizel & Dudás (1992), followed by mandatory fortification in the U.S [czeizel1992]. and other countries through the late 1990s and 2000s.

The depression line of inquiry developed in parallel. Folate and vitamin B12 deficiencies had been associated with depressive symptoms since the 1960s [bottiglieri2000]; the Hordaland Homocysteine Study [bjelland2003] and a series of meta-analyses linked C677T to depression risk and to reduced

antidepressant response [lewis2006, gilbody2007]. Folic acid as an adjunct to fluoxetine was tested by Coppen & Bailey (2000) in a single-center RCT showing enhanced response in women [coppen2000]; folinic acid (leucovorin) was tested in SSRI-refractory depression by Alpert and colleagues [alpert2002] [williams2015]. L-methylfolate calcium 7.5 and 15 mg as adjunctive therapy in SSRI-resistant MDD was evaluated by Papakostas and colleagues in two parallel-sequential RCTs published in 2012 [papakostas2012], establishing the evidence base for the Deplin medical food [mrc1991]. Subsequent inadequate-responder and biomarker analyses [shelton2013, shelton2015] and an MTHFR-genotype-stratified open-label trial [mech2016] refined the responder profile. Class-level meta-analyses of folate for depression remain mixed [almeida2015, roberts2018, fava2009], reflecting heterogeneity in formulation (folic acid vs methylfolate vs folinic acid), monotherapy vs adjunctive design, and patient selection.

On the unmetabolized folic acid front, Kelly and Pfeiffer's measurement work [pfeiffer2015, bailey2010] documented near-universal UMFA in U.S. serum samples since fortification; the clinical implications remain debated [morris2007, sweeney2012, patanwala2014]. This is one of the principal rationales offered for preferring 5-MTHF to folic acid in patients receiving multi-milligram folate doses, particularly in older adults and B12-deficient patients [crider2019].

Methylfolate Timeline

1991 • MRC Vitamin Study Research Group: 4 mg/day periconceptional folic acid in women with a prior NTD-affected pregnancy reduces NTD recurrence by ~72% (Lancet) [mrc1991]

1992 • Czeizel & Dudás: 0.8 mg folic acid in a periconceptional multivitamin prevents the first occurrence of neural-tube defects (NEJM) [czeizel1992]

1995 • Frosst, Rozen, et al [frosst1995]. identify the MTHFR C677T (Ala222Val) thermolabile variant as a candidate risk factor for vascular disease (Nat Genet)

1998 • Weisberg et al [weisberg1998]. describe the second MTHFR polymorphism A1298C (Glu429Ala) with decreased enzyme activity (Mol Genet Metab)

1998 • U.S. mandatory folic-acid fortification of enriched grain products begins (140 mcg/100 g flour, FDA rule effective January 1, 1998)

1998 • Brattström et al [brattstrom1998]. meta-analysis: MTHFR C677T TT genotype elevates homocysteine but does not independently raise vascular risk after folate adjustment (Circulation)

1999 • Selhub publishes the canonical review of homocysteine metabolism and the folate-B12-methionine axis (Annu Rev Nutr) [selhub1999]

2000 • Coppen & Bailey: 500 mcg folic acid augmenting fluoxetine improves antidepressant response in women (J Affect Disord) [coppen2000]

2002 • Alpert et al [alpert2002]. open-label trial of folinic acid (leucovorin) in SSRI-resistant depression (Ann Clin Psychiatry)

2002 • Klerk et al [klerk2002]. meta-analysis: MTHFR C677T TT genotype is associated with elevated homocysteine and modestly elevated coronary heart disease risk (JAMA)

2003 • Bjelland et al [bjelland2003]. Hordaland Homocysteine Study: low plasma folate and MTHFR C677T TT genotype independently associate with depression (Arch Gen Psychiatry)

2004 • Stover reviews the physiology of folate and vitamin B12 in health and disease (Nutr Rev) [stover2004]

2006 • Lamers et al.: (6S)-5-methyltetrahydrofolate raises RBC folate more than equimolar folic acid in women of childbearing age (Am J Clin Nutr) [lamers2006]

2006 • Lewis et al.: British Women's Heart and Health Study plus meta-analysis, thermolabile MTHFR is associated with depression (Mol Psychiatry) [lewis2006]

2007 • Willems et al.: RBC folate steady state with various folate forms, calcium-L-5-MTHF achieves comparable or superior status to folic acid (Am J Clin Nutr) [willems2007]

2007 • Morris et al.: in NHANES older adults, low B12 + high folate (the post-fortification context) associates with anemia and cognitive impairment (Am J Clin Nutr) [morris2007]

2007 • Gilbody, Lewis & Lightfoot HuGE review: MTHFR genetic polymorphisms and psychiatric disorders (Am J Epidemiol) [gilbody2007]

2009 • Prinz-Langenohl et al.: in C677T TT and CC women, [6S]-5-MTHF raises plasma folate more effectively than folic acid (Br J Pharmacol) [prinz2009]

2009 • Fava & Mischoulon review folate in depression, efficacy, safety, and formulation differences (J Clin Psychiatry) [fava2009]

2010 • Pietrzik, Bailey & Shane: comparative clinical pharmacokinetics of folic acid vs L-5-MTHF (Clin Pharmacokinet) [pietrzik2010]

2010 • Bailey et al.: unmetabolized serum folic acid in a nationally representative U.S [bailey2010]. adult sample (Am J Clin Nutr)

2012 • Papakostas et al.: two parallel-sequential RCTs of L-methylfolate 7.5 mg and 15 mg as adjunctive therapy in SSRI-resistant MDD, trial 2 (15 mg) demonstrates superior HDRS response and remission vs placebo (Am J Psychiatry) [papakostas2012]

2012 • Sweeney, McPartlin & Scott: circulating unmetabolized folic acid review, relationship to folate status and supplementation (Obstet Gynecol Int) [sweeney2012]

2013 • Shelton et al.: biomarker-stratified analysis of adjunctive L-methylfolate 15 mg in SSRI inadequate responders, greater response in obese and inflammation-high patients (J Clin Psychiatry) [shelton2013]

2014 • Scaglione & Panzavolta: 'folate, folic acid and 5-methyltetrahydrofolate are not the same thing', pharmacologic differentiation (Xenobiotica) [scaglione2014]

2014 • Patanwala et al.: folic acid handling by the human gut and implications for fortification and supplementation (Am J Clin Nutr) [patanwala2014]

2015 • Almeida et al [almeida2015]. systematic review and meta-analysis: folate and vitamin B12 RCTs for depression (Int Psychogeriatr)

2015 • Pfeiffer et al.: unmetabolized folic acid is detected in nearly all U.S [pfeiffer2015]. serum samples post-fortification (J Nutr)

2015 • Williams et al. (CDC MMWR): updated estimate of NTDs prevented by U.S [williams2015]. mandatory folic-acid fortification, 1995, 2011

2015 • Shelton et al.: obesity and inflammatory marker association with adjunctive L-methylfolate response in SSRI inadequate responders (J Clin Psychiatry) [shelton2015]

2016 • Mech & Farah: MTHFR genotype-stratified open-label trial of reduced B vitamins (including L-methylfolate) in MDD, homocysteine reduction correlates with clinical response (J Clin Psychiatry) [mech2016]

2016 • Zajecka et al.: 12-month open-label extension of adjunctive L-methylfolate calcium 15 mg confirms long-term safety and tolerability (J Clin Psychiatry) [zajecka2016]

2018 • Roberts et al [roberts2018]. systematic review and meta-analysis: 'caveat emptor', folate in unipolar depression remains mixed at the class level (J Psychopharmacol)

2019 • Crider et al [crider2019]. Bayesian meta-analysis: dose-response relationship between folic-acid intake and blood folate concentrations (Nutrients)

2020 • Obeid et al [obeid2020]. comparative pharmacokinetics: sodium and calcium (6S)-5-MTHF salts vs folic acid (Nutrients)

Clinical Contexts for Methylfolate

Folate-status correction in MTHFR C677T or A1298C variant carriers

WELL STUDIED

Studied, head-to-head pharmacokinetic and red-blood-cell folate evidence supports L-methylfolate as a folate-status intervention that does not require MTHFR activity.

C677T TT homozygotes have approximately 30% of wild-type MTHFR specific activity and elevated plasma homocysteine [frosst1995, brattstrom1998, klerk2002]. Head-to-head crossover and parallel-group studies in C677T-genotyped women demonstrated that (6S)-5-MTHF raises plasma and red-blood-cell folate more effectively than equimolar folic acid [lamers2006; prinz2009; pietrzik2010]. Folate supplementation lowers homocysteine in a dose-dependent fashion across MTHFR genotypes [crider2019] [willems2007; weisberg1998]. The clinical use is folate-status repletion, not a specific disease treatment; cardiovascular outcomes from homocysteine lowering have been mixed in large folate-supplementation RCTs [obeid2020].

Major depressive disorder, adjunctive use with SSRIs/SNRIs in inadequate responders

WELL STUDIED

Well-studied for the manufactured L-methylfolate calcium 15 mg medical food (Deplin); not an FDA-approved drug indication. Compounded preparations have no separate efficacy program.

Papakostas et al. (2012) reported two parallel-sequential randomized double-blind placebo-controlled trials of L-methylfolate calcium as adjunctive therapy in adults with SSRI-resistant major depression: trial 1 (7.5 mg) showed no separation from placebo, trial 2 (15 mg) showed significantly greater HDRS-17 response and remission rates over 30 days [papakostas2012]. Biomarker- and BMI-stratified analyses in the inadequate-responder population [shelton2013, shelton2015] identified obesity, elevated CRP, TNF-α, and leptin as predictors of enhanced L-methylfolate response. An MTHFR genotype-stratified open-label trial [mech2016] reported that homocysteine reduction with reduced B vitamins (L-methylfolate, methylcobalamin, pyridoxal-5-phosphate) correlated with clinical improvement. A 12-month open-label extension confirmed tolerability and durability [zajecka2016]. Class-level folate-for-depression meta-analyses are mixed [almeida2015, roberts2018, fava2009], reflecting heterogeneity in formulation, monotherapy vs adjunctive design, and selection criteria. Earlier work on folic acid augmenting fluoxetine [coppen2000] and folinic acid in SSRI-refractory depression [alpert2002] is supportive but uses different molecules.

Periconceptional folate status for neural tube defect prevention WELL STUDIED

Studied as a folate-status intervention; the underlying NTD-prevention evidence base is folic-acid-based, not 5-MTHF-specific.

Periconceptional folic acid reduces the risk of neural tube defects by approximately 70%, established by the MRC Vitamin Study [mrc1991] in women with a prior NTD-affected pregnancy and by Czeizel & Dudás [czeizel1992] for first-occurrence prevention. The CDC estimated that U.S. mandatory folic-acid fortification has prevented approximately 1,300 NTD-affected births per year [williams2015]. (6S)-5-MTHF raises plasma and red-blood-cell folate at least as effectively as equimolar folic acid in healthy women of childbearing age [lamers2006, willems2007, obeid2020], supporting its use as a folate-status intervention; however, no NTD-prevention efficacy trial of 5-MTHF exists. Patient-specific compounded 5-MTHF for periconceptional folate status is prescribed when patients cannot tolerate manufactured folic-acid prenatals or carry MTHFR polymorphisms.

Hyperhomocysteinemia in MTHFR variant carriers WELL STUDIED

Studied as a homocysteine-lowering intervention. Whether lowering homocysteine reduces cardiovascular or cognitive outcomes is a separate, mixed evidence question.

Folate intake lowers plasma homocysteine in a dose-dependent fashion across MTHFR genotypes [crider2019, brattstrom1998, klerk2002]. (6S)-5-MTHF achieves this without requiring MTHFR activity and without generating unmetabolized folic acid [pietrzik2010, obeid2020]. The clinical question of whether homocysteine reduction translates to cardiovascular event reduction was tested in several large folate-B12-B6 trials (HOPE-2, VISP, NORVIT, VITATOPS, SEARCH) with predominantly null cardiovascular event findings despite consistent homocysteine reduction; this brief does not re-litigate that literature but notes it as context for clinical decision-making.

Off-Label Uses of Methylfolate

MTHFR-related infertility and pregnancy outcome support EMERGING

Emerging, case series and pharmacokinetic rationale; no powered RCT data specific to 5-MTHF for pregnancy outcomes.

Case-series reports describe successful pregnancy outcomes in MTHFR variant carriers switched from folic acid to (6S)-5-MTHF [servy2018, servy2019], on a pharmacokinetic rationale that variant carriers convert folic acid less efficiently and may accumulate unmetabolized folic acid [lamers2006]. Powered RCT evidence in fertility populations is not available; use is clinician-driven on a patient-specific basis [prinz2009].

B12-deficient older adults: alternative to high-dose folic acid EMERGING

Emerging, proposed on the basis of unmetabolized folic acid concerns in B12-deficient older adults; not driven by an RCT comparing 5-MTHF vs folic acid for clinical endpoints in this population.

Morris and colleagues reported associations between high folate / low B12 status and anemia, macrocytosis, and cognitive impairment in older Americans in the post-fortification era [morris2007]. Unmetabolized folic acid appears in nearly all U.S. serum samples [pfeiffer2015, bailey2010] and has been hypothesized to interact with B12 metabolism. (6S)-5-MTHF does not generate UMFA [pietrzik2010, obeid2020], which is the principal rationale offered for substituting 5-MTHF in B12-deficient older adults receiving multi-milligram folate. The clinical-outcome evidence supporting that substitution is not yet established.

Compounded Methylfolate (503A)

Compounded L-methylfolate is dispensed under 503A only on a patient-specific prescription written by a licensed clinician for an identified patient [fda_medical_food]. Documented patient-specific needs typically fall into four categories: (1) excipient sensitivity to a component of the manufactured Deplin medical-food capsule or to dietary-supplement L-methylfolate products; (2) allergen-free formulation requirements (gluten, dairy, soy, dye, or excipient avoidance); (3) a prescribed strength not commercially available (custom strengths between 1 mg and 15 mg, or sublingual presentations); or (4) combination products (L-methylfolate plus methylcobalamin ± pyridoxal-5-phosphate) prescribed for a documented clinical indication where a single-active manufactured product is not appropriate [fda503a] [papakostas2012; shelton2013].

Because Deplin is regulated as a medical food rather than as an FDA-approved drug, the 503A 'essentially-a-copy' framework that governs compounding of brand-name drugs applies differently [fda_medical_food]. Compounded L-methylfolate is not a copy of an FDA-approved drug because there is no FDA-approved L-methylfolate drug; nevertheless, RonanRx documents a patient-specific clinical reason for each compounded preparation and does not dispense L-methylfolate as a routine substitute for over-the-counter dietary-supplement L-methylfolate without documented clinical rationale.

Stereochemistry is a non-negotiable quality attribute [fda_medical_food]. Only (6S)-5-methyltetrahydrofolate is biologically active; racemic 6R,S preparations contain the (6R) diastereomer, which is not metabolically usable and may compete with the (6S) form at folate transporters [obeid2020]. RonanRx uses Metafolin (calcium L-5-methyltetrahydrofolate) or Quatrefolic ((6S)-5-MTHF glucosamine salt), both single-stereoisomer pharmaceutical-grade APIs with established stability data and certificates of analysis. Compounded preparations are oxidation-sensitive; appropriate packaging (amber, low-oxygen, desiccant) and beyond-use dating reflect the stability characteristics of the salt form [scaglione2014].

The published clinical evidence base for L-methylfolate is generated overwhelmingly with the Metafolin calcium salt at single-active doses of 7.5 and 15 mg [fda_medical_food] [shelton2015; zajecka2016]. Combination products and non-Metafolin salts have less direct clinical-outcome evidence. Compounded

combination products are dispensed on documented patient-specific clinical reasoning, not as a generic preference.

Methylfolate Formulations and Routes

Form	Concentration	Description
Oral capsule (compounded, Metafolin calcium or Quatrefolic glucosamine salt)	Custom strengths from 1 mg to 15 mg per capsule; allergen-free excipient profile documented per batch	Capsules compounded under USP General Chapter <795> with documented API source (Metafolin or Quatrefolic), gravimetric and analytical verification, oxidation-protective packaging, and beyond-use dating reflecting the stability characteristics of the salt form.
Sublingual tablet or troche (compounded)	Custom strengths, typically 1, 5 mg per unit	Sublingual formulations developed for patients with documented oral-absorption concerns or swallowing difficulty; pharmacokinetic equivalence to oral capsules is not formally established for compounded sublingual forms and is treated as an individual clinical decision.
Combination capsule (L-methylfolate plus methylcobalamin ± pyridoxal-5-phosphate)	Custom, L-methylfolate 1, 15 mg; methylcobalamin 1, 2 mg; pyridoxal-5-phosphate 25, 50 mg	Combination products compounded on patient-specific prescriptions for documented clinical indications (e.g., MTHFR-stratified depression adjunct per the Mech 2016 reduced-B-vitamin protocol).
Manufactured medical food (reference product)	7.5 mg or 15 mg L-methylfolate calcium per capsule (Deplin)	Deplin is the manufactured single-active L-methylfolate calcium medical food regulated under FDA medical-food provisions (21 CFR 101.9(j)(8)) for the dietary management of major depressive disorder. Marketed by Alfasigma (formerly Pamlab / Nestlé Health Science). Compounded preparations are not bioequivalent to Deplin and are dispensed only on documented patient-specific clinical need.
Dietary-supplement L-methylfolate (reference context)	400 mcg to 5 mg per tablet/capsule (numerous brands)	Over-the-counter L-methylfolate dietary supplements are marketed under DSHEA without an FDA pre-market approval requirement. They are not interchangeable with medical-food Deplin or with prescription folic-acid prenatals.

Routes used in published literature: oral, sublingual.

Methylfolate Dosing

Route	Population	Range	Duration	Study type
Oral	Adults with major depressive disorder, adjunctive to an SSRI/SNRI in inadequate responders	L-methylfolate calcium 15 mg once daily (the dose evaluated in Papakostas 2012 trial 2 and the labeled medical-food strength for Deplin). The 7.5 mg dose was not effective in trial 1.	Initial response evaluated at 30 days in the pivotal trial; long-term tolerability and durability documented through 12 months in the open-label extension [zajecka2016]	Randomized double-blind placebo-controlled trial (Papakostas 2012) plus open-label extension and biomarker-stratified inadequate-responder analyses
Oral	Adults with MTHFR C677T or A1298C polymorphism, folate-status repletion	Typical 1, 5 mg/day of (6S)-5-MTHF (Metafolin or Quatrefolic salt). Higher doses (up to 15 mg) used clinically when co-prescribed for the depression adjunct indication; doses above 5 mg are not required for folate-status repletion in most patients [crider2019, pietrzik2010].	Indefinite while clinically indicated	Pharmacokinetic and red-blood-cell folate studies
Oral	Periconceptional folate-status in women of reproductive potential	(6S)-5-MTHF doses providing folate-status equivalent to 400, 800 mcg/day folic acid (typical 400 mcg, 1 mg of 5-MTHF for low-risk women; up to 4, 5 mg/day for women with a prior NTD-affected pregnancy on the folic-acid evidence base). NTD-prevention efficacy is established for folic acid, not for 5-MTHF specifically.	From at least one month preconception through the first trimester at minimum	RBC folate equivalence (5-MTHF) extrapolated from folic-acid NTD-prevention RCTs

Doctor-prescribed and titrated. For the depression-adjunct indication, the evidence-based dose is L-methylfolate calcium 15 mg once daily as documented in the Papakostas 2012 trial 2 [papakostas2012]; the

7.5 mg dose did not separate from placebo in trial 1 of the same study [obeid2020]. For folate-status repletion in MTHFR variant carriers, 1, 5 mg/day is generally sufficient on pharmacokinetic grounds. Doses above 15 mg/day are not supported by published clinical evidence [pietrzik2010].

L-methylfolate is taken once daily with or without food. Onset of antidepressant adjunct effect was assessed at 30 days in the pivotal trial; biomarker- and BMI-stratified post-hoc analyses [shelton2013, shelton2015] and the genotype-stratified open-label trial [mech2016] suggest that response is enriched in obese, inflammation-high, or MTHFR-polymorphism-positive subgroups. Patients on monoamine-oxidase inhibitors should not initiate methylfolate-containing adjuncts without specialist input; routine concomitant medication review at initiation is standard [lamers2006; prinz2009; crider2019].

Methylfolate Safety

L-methylfolate at doses up to 15 mg/day has been well tolerated in published trials [13]. In the Papakostas 2012 parallel-sequential RCTs, the most common adverse events with L-methylfolate 15 mg vs placebo were nausea, headache, fatigue, and insomnia at rates similar to placebo; treatment-emergent adverse-event-driven discontinuation was not meaningfully different between groups [23]. The 12-month open-label extension [27] confirmed long-term tolerability with no signal of new safety concerns at 15 mg/day.

The principal safety consideration with any high-dose folate is the theoretical concern that folate can mask the hematologic features of vitamin B12 deficiency (megaloblastic anemia) while permitting B12-deficiency neuropathy to progress unchecked. This concern is rooted in the era of high-dose folic-acid supplementation and the post-fortification observation that low-B12 / high-folate older adults have a higher rate of anemia and cognitive impairment [18]. Whether (6S)-5-MTHF carries the same masking potential is mechanistically less concerning (it does not generate UMFA) but is not absent, methionine synthase still requires B12, and the methyl-trap hypothesis applies. Routine B12 status assessment prior to and during high-dose folate or methylfolate therapy is standard practice [13].

Hypersensitivity reactions to L-methylfolate are uncommon but reported; patients with documented folate hypersensitivity should not initiate [13]. There is no signal of hepatotoxicity, nephrotoxicity, or cardiovascular toxicity at the doses studied. Long-term cancer-related signals from high-dose folic-acid trials (e.g., colorectal adenoma recurrence in the AFPPS trial) have not been replicated for 5-MTHF, but trial duration and population were limited [12].

Contraindications

L-methylfolate is contraindicated in patients with known hypersensitivity to L-methylfolate or to excipients of the prescribed formulation. There are no other absolute contraindications documented for the molecule. Caution is appropriate in patients with untreated vitamin B12 deficiency (folate or methylfolate may correct megaloblastic anemia while neurologic B12-deficiency disease progresses) and in patients with seizure

disorders on folate-interacting anticonvulsants (phenytoin, phenobarbital, primidone), where folate status changes can alter anticonvulsant concentrations [6].

Concurrent use with methotrexate, pyrimethamine, trimethoprim, or other dihydrofolate-reductase inhibitors warrants prescriber awareness: L-methylfolate enters the folate cycle downstream of DHFR and is less likely than folic acid to reverse the intended anti-folate effect, but interaction is not zero and should be reviewed against the indication for the anti-folate agent (oncologic vs anti-inflammatory dosing of methotrexate are managed differently) [13].

Drug interactions

Folate-interacting anticonvulsants, phenytoin, phenobarbital, primidone, carbamazepine, valproate, can lower folate status; conversely, folate supplementation can lower anticonvulsant plasma concentrations and worsen seizure control in some patients. Monitor anticonvulsant levels when initiating or adjusting methylfolate.

Methotrexate, pyrimethamine, trimethoprim-sulfamethoxazole, and sulfasalazine are dihydrofolate-reductase or folate-pathway inhibitors. L-methylfolate enters the folate cycle downstream of DHFR, so it does not directly reverse DHFR inhibition the way leucovorin does, but co-administration warrants explicit prescriber rationale, particularly with oncologic-dose methotrexate.

Capecitabine, fluorouracil, and pemetrexed package inserts include guidance regarding concurrent folate supplementation (with both efficacy and toxicity implications depending on the drug); decisions about methylfolate co-administration during cancer chemotherapy must be made by the prescribing oncologist.

Monoamine-oxidase inhibitors (MAOIs) are not a documented L-methylfolate interaction, but the depression-adjunct context, where patients are typically on SSRIs or SNRIs, sometimes prompts MAOI considerations; standard antidepressant pharmacology rules apply.

Routine clinical chemistry: folate intake affects red-blood-cell folate, plasma folate, and homocysteine measurements [6][13][10]. Document recent supplementation history before interpreting folate-status laboratory results.

Adverse events

Adverse events reported in the L-methylfolate clinical trial literature are predominantly mild and not significantly elevated over placebo [13]. The Papakostas 2012 parallel-sequential trials reported nausea, headache, fatigue, and insomnia in <10% of L-methylfolate 15 mg-treated participants vs comparable placebo rates; treatment-emergent serious adverse events were rare and not attributable to L-methylfolate [23]. The 12-month open-label extension [27] reported similar tolerability with no new safety signals at 15 mg/day.

Outside the trial setting, adverse-event reports include hypersensitivity (rash, urticaria), gastrointestinal upset, irritability or anxiety with initiation in some patients (which may reflect methyl-donor effects on

monoamine turnover and is sometimes managed by dose reduction or methylcobalamin co-prescription), and rare cases of bronchospasm. Cancer-recurrence and cardiovascular-event signals from high-dose folic-acid trials have not been demonstrated for 5-MTHF in the available trial population; durations and sample sizes are smaller for 5-MTHF than for folic acid [13].

Monitoring Methylfolate Therapy

Baseline assessment should include vitamin B12 status (serum B12 ± methylmalonic acid in older adults or in patients at risk of deficiency), plasma homocysteine if clinically indicated, and a medication review for folate-interacting agents (anticonvulsants, methotrexate, anti-folate antimicrobials) [morris2007; scaglione2014]. MTHFR genotyping is sometimes ordered but is not required to prescribe L-methylfolate; genotype-stratified analyses [mech2016] inform decision-making rather than gate it.

On therapy: reassess the indication-specific response (depressive-symptom score, homocysteine concentration, or folate-status biomarker) at 4, 12 weeks depending on indication [morris2007]. For the depression adjunct, response was assessed at 30 days in the pivotal trial [papakostas2012]. Long-term monitoring follows the underlying psychiatric or medical condition rather than a methylfolate-specific schedule.

Methylfolate in Special Populations

Methylfolate Evidence Quality

Evidence supporting L-methylfolate as a folate-status intervention is strong: head-to-head pharmacokinetic and red-blood-cell folate studies vs equimolar folic acid in healthy adults and in MTHFR-genotyped subjects, dose-response meta-analysis of folate intake and blood folate concentration [crider2019], and consistent homocysteine-lowering across MTHFR genotypes [brattstrom1998, klerk2002, crider2019] establish (6S)-5-MTHF as a viable alternative to folic acid that does not generate unmetabolized folic acid [fda503a].

Evidence supporting L-methylfolate as an antidepressant adjunct rests on the two parallel-sequential RCTs reported by Papakostas et al [fda503a] [patanwala2014; scaglione2014]. (2012) [papakostas2012], trial 1 (7.5 mg, negative) and trial 2 (15 mg, positive on HDRS-17 response and remission at 30 days), together with biomarker- and BMI-stratified inadequate-responder analyses [shelton2013, shelton2015], an MTHFR-genotype-stratified open-label trial [mech2016], and a 12-month open-label safety extension [zajecka2016]. Older folate-augmentation trials with folic acid [coppen2000] and folinic acid [alpert2002] are supportive but use different molecules [pfeiffer2015; prinz2009]. Class-level folate-for-depression

meta-analyses [almeida2015, roberts2018, fava2009] remain mixed, with heterogeneity by formulation, monotherapy vs adjunctive design, and selection criteria.

Evidence supporting periconceptional 5-MTHF for NTD prevention is indirect, the NTD-prevention RCT evidence base is folic-acid-based [mrc1991, czeizel1992, williams2015] and (6S)-5-MTHF is used as a folate-status equivalent on pharmacokinetic and RBC-folate grounds [lamers2006, willems2007, obeid2020] [fda503a]. Evidence for off-label uses (MTHFR-related infertility; B12-deficient older adults) is at the case-series or hypothesis level [servy2018, servy2019, morris2007] and does not support efficacy claims.

Evidence specifically supporting compounded L-methylfolate preparations is, like other compounded products, absent as a separate efficacy program, compounded use is justified case by case by patient-specific clinical factors that the manufactured Deplin medical food or over-the-counter dietary-supplement L-methylfolate products cannot accommodate [fda503a] [bailey2010; sweeney2012; pietrzik2010].

Major Methylfolate Clinical Studies

Study	Design	Participants	Duration	Finding
Papakostas et al. (2012, Am J Psychiatry), L-methylfolate adjunctive trials in SSRI-resistant MDD	Two parallel-sequential, randomized, double-blind, placebo-controlled trials in adults with SSRI-resistant major depressive disorder	223	30 days primary, 60 days total	Trial 1 (L-methylfolate 7.5 mg) did not separate from placebo. Trial 2 (L-methylfolate 15 mg) produced significantly higher HDRS-17 response (32.3% vs 14.6%) and remission rates vs placebo as adjunct to ongoing SSRI therapy, pivotal evidence for the Deplin medical-food indication [papakostas2012].
Shelton et al. (2013, J Clin Psychiatry), Biomarker-stratified L-methylfolate response	Pooled inadequate-responder analysis from the Papakostas 2012 program, stratified by biomarkers (BMI, CRP, TNF-α, leptin)	—	30-day randomized period	L-methylfolate 15 mg produced greater HDRS-17 response in patients with elevated BMI, CRP, TNF-α, and leptin, supports inflammation- and obesity-enriched responder profile [shelton2013].

Study	Design	Participants	Duration	Finding
Shelton et al. (2015, J Clin Psychiatry), Obesity and inflammation predictors of L-methylfolate response	Pre-specified pooled biomarker analysis from the Papakostas 2012 trials	—	—	Obesity and inflammatory-marker elevations were associated with greater response to adjunctive L-methylfolate 15 mg vs placebo in SSRI inadequate responders [shelton2015].
Mech & Farah (2016, J Clin Psychiatry), MTHFR genotype-stratified reduced B vitamins in MDD	Randomized double-blind trial in patients with MDD positive for MTHFR C677T or A1298C polymorphism, comparing reduced B vitamins (L-methylfolate + methylcobalamin + pyridoxal-5-phosphate) vs placebo	—	8 weeks	Clinical response correlated with homocysteine reduction during therapy with reduced B vitamins in MTHFR-variant-positive MDD patients [mech2016].
Zajecka et al. (2016, J Clin Psychiatry), 12-month open-label L-methylfolate safety	Open-label extension of adjunctive L-methylfolate calcium 15 mg in SSRI inadequate responders	—	12 months	Long-term efficacy, safety, and tolerability of L-methylfolate 15 mg as adjunctive therapy with SSRIs, confirmed durability and absence of new safety signals [zajecka2016].
Coppen & Bailey (2000, J Affect Disord), Folic-acid fluoxetine augmentation	Randomized, placebo-controlled trial of 500 mcg folic acid as fluoxetine augmentation	127	10 weeks	Folic acid significantly enhanced antidepressant action of fluoxetine in women but not in men, early evidence for folate augmentation that motivated subsequent L-methylfolate work [coppen2000].
Alpert et al. (2002, Ann Clin Psychiatry), Folinic	Open-label trial of leucovorin (folinic acid) as	—	8 weeks	Folinic acid produced clinically meaningful response in a subset of

Study	Design	Participants	Duration	Finding
acid in SSRI-refractory depression	adjunctive treatment for SSRI-refractory MDD			SSRI-refractory patients, early signal supporting reduced-folate adjuncts [alpert2002].
Almeida et al. (2015, Int Psychogeriatr), Folate / B12 RCT meta-analysis for depression	Systematic review and meta-analysis of randomized placebo-controlled trials of folate and vitamin B12 for depression	—	—	No clear short-term antidepressant effect for folate or B12 supplementation across pooled RCTs; possible benefit on longer-term outcomes and depression prevention [almeida2015].
Roberts et al. (2018, J Psychopharmacol), 'Caveat emptor' folate-for-depression meta-analysis	Systematic review and meta-analysis of folate (folic acid, methylfolate, folinic acid) in unipolar depression	—	—	Heterogeneity by formulation and design; class-level effect on depression remains uncertain. Recommends caution in pooling folic acid with reduced folates [roberts2018].
Frosst et al. (1995, Nat Genet), Discovery of MTHFR C677T	Genetic association study identifying a thermolabile MTHFR variant as a candidate risk factor for vascular disease	—	—	The C677T (Ala222Val) MTHFR variant produces a thermolabile enzyme with reduced specific activity and is associated with elevated plasma homocysteine, foundational genetic finding [frosst1995].
Weisberg et al. (1998, Mol Genet Metab), MTHFR A1298C	Genetic and biochemical characterization of a second MTHFR polymorphism	—	—	The A1298C (Glu429Ala) variant is associated with decreased MTHFR enzyme activity and an intermediate phenotype

Study	Design	Participants	Duration	Finding
				when combined with C677T [weisberg1998].
Brattström et al. (1998, Circulation), MTHFR C677T meta-analysis	Meta-analysis of MTHFR C677T genotype, homocysteine, and vascular disease	—	—	C677T TT genotype elevates homocysteine but does not independently elevate vascular risk after folate adjustment, established the folate-modifiable phenotype [brattstrom1998].
Lewis et al. (2006, Mol Psychiatry), MTHFR C677T and depression meta-analysis	British Women's Heart and Health Study + meta-analysis of MTHFR C677T and depression	—	—	C677T TT genotype is associated with depression risk; one of the foundational genetic-epidemiology findings motivating L-methylfolate development for depression [lewis2006].
Gilbody, Lewis & Lightfoot (2007, Am J Epidemiol), MTHFR HuGE review	Human Genome Epidemiology review of MTHFR polymorphisms and psychiatric disorders	—	—	Across the published literature, MTHFR variants modestly associate with depression, schizophrenia, and bipolar disorder; effect sizes are small but consistent [gilbody2007].
Bjelland et al. (2003, Arch Gen Psychiatry), Hordaland Homocysteine Study	Large community-based cross-sectional analysis of folate, B12, homocysteine, and MTHFR C677T in anxiety and depression	5948	—	Low plasma folate and C677T TT genotype each independently associate with depression, foundational epidemiologic evidence [bjelland2003].
		1817		

Study	Design	Participants	Duration	Finding
MRC Vitamin Study Research Group (1991, Lancet), NTD recurrence prevention	Randomized double-blind trial of 4 mg folic acid for prevention of recurrent neural-tube defects		Periconceptional supplementation	Periconceptional folic acid 4 mg/day reduced NTD recurrence by approximately 72%, landmark trial establishing folate's NTD-prevention role [mrc1991].
Czeizel & Dudás (1992, NEJM), NTD first-occurrence prevention	Randomized controlled trial of periconceptional multivitamin (0.8 mg folic acid) for first-occurrence NTD prevention	4753	—	Periconceptional folic-acid-containing multivitamin reduced first-occurrence NTDs by approximately 70%, extending the MRC finding to the general obstetric population [czeizel1992].
Lamers et al. (2006, Am J Clin Nutr), 5-MTHF vs folic acid RBC folate	Randomized supplementation trial in women of childbearing age comparing (6S)-5-methyltetrahydrofolate vs equimolar folic acid	—	24 weeks	(6S)-5-MTHF increased red-blood-cell folate concentrations more than equimolar folic acid in women of childbearing age, pharmacokinetic foundation for 5-MTHF as a folate-status intervention [lamers2006].
Prinz-Langenohl et al. (2009, Br J Pharmacol), Genotype-stratified 5-MTHF PK	Randomized crossover comparing [6S]-5-MTHF vs folic acid in C677T TT and CC women	—	—	(6S)-5-MTHF raised plasma folate more effectively than folic acid in both wild-type and TT homozygous C677T women, with the differential more pronounced in TT carriers [prinz2009].
Pietrzik, Bailey & Shane (2010, Clin Pharmacokinet),	Comparative review of folic acid vs L-5-methyltetrahydrofolate	—	—	(6S)-5-MTHF bioavailability is comparable to or

Study	Design	Participants	Duration	Finding
Comparative PK review	clinical pharmacokinetics and pharmacodynamics			greater than folic acid; key differentiator is absence of unmetabolized folic acid in circulation with 5-MTHF [pietrzik2010].
Willems et al. (2007, Am J Clin Nutr), RBC folate steady-state with various folate forms	Pharmacokinetic calculation of red-blood-cell folate steady state and elimination after daily supplementation	—	—	Calcium-L-5-MTHF achieves comparable or superior RBC folate steady-state concentrations to folic acid across daily doses [willems2007].
Obeid et al. (2020, Nutrients), (6S)-5-MTHF salts PK	Pharmacokinetic comparison of sodium and calcium salts of (6S)-5-methyltetrahydrofolic acid vs folic acid	—	—	Both (6S)-5-MTHF salt forms produced bioavailability comparable to or exceeding folic acid; salt selection has minor PK implications [obeid2020].
Pfeiffer et al. (2015, J Nutr), Universal UMFA in US population	Analysis of NHANES serum samples for unmetabolized folic acid	—	—	Unmetabolized folic acid is detected in nearly all serum samples from U.S [pfeiffer2015]. children, adolescents, and adults in the post-fortification era, establishes the population exposure context.
Bailey et al. (2010, Am J Clin Nutr), UMFA in NHANES adults	Nationally representative analysis of unmetabolized serum folic acid in U.S. adults aged 60 years and older	—	—	UMFA concentrations correlate with folic-acid intake from supplements and fortification, quantifies the magnitude of UMFA exposure in older adults [bailey2010].

Study	Design	Participants	Duration	Finding
Morris et al. (2007, Am J Clin Nutr), Folate, B12, anemia, cognition in older adults	NHANES-based analysis of folate and B12 status in relation to anemia, macrocytosis, and cognitive impairment in older Americans	—	—	Low B12 combined with high folate associated with anemia and cognitive impairment in the post-fortification era, motivated concern about high-dose folic acid in B12-deficient older adults [morris2007].
Scaglione & Panzavolta (2014, Xenobiotica), Pharmacologic differentiation	Review of folate, folic acid, and 5-methyltetrahydrofolate pharmacology	—	—	Folate, folic acid, and 5-MTHF differ in chemistry, metabolism, and pharmacokinetics; the terms are not interchangeable, foundational pharmacology reference for compounding decisions [scaglione2014].
Crider et al. (2019, Nutrients), Folate dose-response Bayesian meta-analysis	Systematic review and Bayesian meta-analysis of folic-acid dose and blood folate change	—	—	Predictable dose-response relationship between folic-acid intake and red-blood-cell folate concentration, informs dose selection for folate-status repletion across MTHFR genotypes [crider2019].
Williams et al. (2015, MMWR), US fortification NTD prevention update	Updated CDC estimate of neural-tube defects prevented by mandatory folic-acid fortification in the US, 1995, 2011	—	—	Mandatory U.S. folic-acid fortification has prevented approximately 1,300 NTD-affected births per year, public-health benchmark for folate-status intervention [williams2015].

Methylfolate Pharmacokinetics & Pharmacodynamics

Pharmacokinetics

Oral (6S)-5-methyltetrahydrofolate is absorbed from the proximal small intestine via the proton-coupled folate transporter (SLC46A1) and the reduced folate carrier (SLC19A1). Peak plasma concentrations occur 30, 60 minutes after dosing; bioavailability is comparable to or greater than equimolar folic acid in head-to-head crossover studies in healthy adults [pietrzik2010, prinz2009, obeid2020]. Distribution to red blood cells over weeks of dosing reflects incorporation into the long-lived erythroid folate pool; red-blood-cell folate is the conventional steady-state biomarker and is increased more by (6S)-5-MTHF than by equimolar folic acid in C677T variant carriers [lamers2006, prinz2009, willems2007].

Unlike folic acid, (6S)-5-MTHF enters the folate cycle directly and does not generate circulating unmetabolized folic acid [pfeiffer2015; bailey2010; sweeney2012]. UMFA appears in plasma after folic-acid doses above approximately 200, 400 mcg/day and is detectable in nearly all post-fortification U.S. serum samples. The clinical significance of UMFA remains debated but the absence of UMFA is a documented pharmacokinetic differentiator of 5-MTHF [scaglione2014].

Elimination is via urinary excretion of folate catabolites and biliary recirculation. Steady-state red-blood-cell folate is reached over weeks to months following the lifespan of the erythrocyte pool [willems2007, crider2019]. Compounded preparations may differ from manufactured Deplin in salt form, excipient profile, and dissolution; PK characteristics published for Metafolin or Deplin should not be assumed to translate without local stability data [patanwala2014].

Pharmacodynamics

The principal pharmacodynamic effects of L-methylfolate are increased red-blood-cell and plasma folate, decreased plasma total homocysteine via methionine synthase-mediated remethylation, and, in the depression-adjunct setting, symptomatic improvement in patients with elevated BMI, inflammatory biomarkers, or MTHFR C677T/A1298C polymorphism [shelton2015; mech2016]. Homocysteine reduction is dose-dependent and reproducible across MTHFR genotypes [crider2019, brattstrom1998, klerk2002].

Hypothesized central effects relate to SAM-dependent monoamine synthesis (tetrahydrobiopterin regeneration and BH4-dependent tyrosine and tryptophan hydroxylation) and to one-carbon-dependent neurotransmitter and phospholipid methylation [bottiglieri2000, stover2004]. These mechanisms are biochemically plausible but not directly measured in the depression-adjunct clinical trials [papakostas2012; shelton2013].

Comparing Methylfolate Formulations

The manufactured medical-food reference is Deplin (Alfasigma), L-methylfolate calcium (Metafolin salt) at 7.5 mg or 15 mg per capsule [fda_medical_food] [zajecka2016]. Multiple over-the-counter dietary-supplement L-methylfolate products are also available (typically 400 mcg to 5 mg per unit; Metafolin or Quatrefolic salt) [papakostas2012; shelton2013]. Folic acid is a structurally and pharmacologically distinct molecule that is not interchangeable on a milligram basis [scaglione2014, obeid2020].

Compounded L-methylfolate preparations vary in salt form (Metafolin vs Quatrefolic), excipient profile, and dosage form (capsule, sublingual, combination product). They are not bioequivalent to Deplin and are not interchangeable on a mass basis without considering the salt form's stoichiometry of active drug [fda_medical_food]. The published depression-adjunct trial evidence is generated with Metafolin calcium; non-Metafolin salts have less direct outcome data [shelton2015].

Methylfolate Storage and Handling

(6S)-5-Methyltetrahydrofolate is oxidation-sensitive in its free-acid form; the calcium (Metafolin) and glucosamine (Quatrefolic) salt forms are stabilized for room-temperature storage when packaged appropriately [obeid2020]. Compounded capsules are stored at controlled room temperature (20, 25°C, 15, 30°C excursions permitted) in amber, low-oxygen, desiccated packaging per the pharmacy's stability data and beyond-use date assignment under USP <795>.

Patients should be educated to keep capsules in the original closed container, away from heat and humidity, and to inspect for color change (a yellow-to-brown drift may indicate oxidation). Discoloration warrants pharmacy consultation [usp_795].

Methylfolate Compounding & Operations

503A compounding

Compounded L-methylfolate is prepared under 503A on patient-specific prescriptions in state-licensed compounding pharmacies. RonanRx prepares oral capsules and sublingual presentations per USP General Chapter <795>, the official compendial standard for nonsterile pharmaceutical compounding, with documented active ingredient sourcing (Metafolin calcium or Quatrefolic glucosamine, single (6S) stereoisomer), gravimetric and analytical verification, oxidation-protective packaging, and full lot traceability [fda503a; usp_795; obeid2020].

Beyond-use dating, ingredient identity verification, and stability assessment follow USP <795> requirements. Each compounded batch is documented per state board of pharmacy retention rules with full

traceability from API lot through dispensing. Stereochemistry verification (confirmation that the API is the (6S) isomer, not racemic 6R,S) is part of the incoming-material specification.

Pharmacist review

Each prescription for compounded L-methylfolate undergoes pharmacist review prior to dispensing [fda503a]. The review confirms: a documented patient-specific clinical reason that the manufactured Deplin medical-food product or commercially available OTC L-methylfolate is not appropriate (excipient sensitivity, allergen-free formulation need, non-commercial strength, or documented combination-product indication); appropriate concomitant medication review including folate-interacting anticonvulsants, anti-folate antimicrobials, and methotrexate; vitamin B12 status assessment for older adults or patients on multi-milligram doses; and a prescribed regimen consistent with published evidence (15 mg/day for the SSRI-resistant MDD adjunct indication per Papakostas 2012; 1, 5 mg/day for folate-status repletion in MTHFR variant carriers) unless the prescriber documents a patient-specific reason for variance [papakostas2012, pietrzik2010, mech2016].

RonanRx does not fill prescriptions that read as routine substitution of compounded for over-the-counter L-methylfolate without documented clinical rationale. The medical-food vs drug regulatory distinction is reviewed at intake: compounded L-methylfolate is not an FDA-approved drug and is not marketed as a treatment for any indication; prescribers and patients are advised that the published clinical evidence base, particularly for the SSRI-resistant MDD adjunct indication, is generated with manufactured Deplin (Metafolin calcium 15 mg) and does not transfer to compounded preparations without separate documentation of clinical equivalence [fda503a; fda_medical_food].

Quality and traceability

Active pharmaceutical ingredients are sourced from FDA-registered facilities with documented certificates of analysis confirming (6S) stereochemistry, salt form (Metafolin calcium or Quatrefolic glucosamine), assay, and limits for related substances. Each batch is recorded with lot numbers traceable to API source, compounding date, beyond-use date, and dispensing pharmacist of record. Finished product lot records are retained per state board of pharmacy retention requirements.

Cold chain

L-methylfolate capsules in stabilized salt form (Metafolin or Quatrefolic) are not a cold-chain product and are shipped at ambient temperature with appropriate moisture and light protection. Patients should store at controlled room temperature in the original closed container. Cold-chain considerations apply only if a specific compounded preparation's stability data require refrigerated storage, which is uncommon for these salt forms [obeid2020].

Frequently Asked Questions About Methylfolate

Is L-methylfolate the same as folic acid?

No. Folic acid is a synthetic, fully oxidized form of vitamin B9 that the body must reduce and methylate (via DHFR and then MTHFR) before it can be used [stover2004] [pietrzik2010]. L-methylfolate ((6S)-5-MTHF) is the already-methylated active form that the body uses directly and that crosses the blood-brain barrier. People with common MTHFR variants (C677T, A1298C) convert folic acid less efficiently, which is one reason a pre-converted form has clinical appeal [scaglione2014; frosst1995; weisberg1998].

Is L-methylfolate an FDA-approved drug?

No. L-methylfolate is sold under the brand name Deplin as a 'medical food' regulated under FDA medical-food provisions (21 CFR 101.9(j)(8)) for the dietary management of major depressive disorder [papakostas2012]. Medical foods are not FDA-approved as drugs; they are subject to a separate regulatory framework and require physician supervision [fda_medical_food]. Over-the-counter L-methylfolate dietary supplements are also widely available at lower doses.

What does L-methylfolate do for depression?

L-methylfolate calcium 15 mg/day was studied as an adjunct to SSRIs in patients with SSRI-resistant major depressive disorder in two parallel-sequential randomized trials published by Papakostas et al [papakostas2012; shelton2013; shelton2015]. in 2012. The 15 mg dose produced significantly higher HDRS-17 response and remission rates than placebo at 30 days when added to ongoing SSRI therapy; the 7.5 mg dose did not. Subsequent biomarker analyses suggest the response is enriched in patients with elevated BMI, CRP, or MTHFR polymorphisms [mech2016].

Should I take L-methylfolate if I have an MTHFR polymorphism?

MTHFR C677T and A1298C are common variants, combined heterozygosity is present in roughly half the population. People with the C677T TT genotype have reduced MTHFR enzyme activity and tend to have higher homocysteine on standard folic-acid intake [weisberg1998]. L-methylfolate bypasses MTHFR and raises red-blood-cell folate more effectively than folic acid in TT carriers in head-to-head studies [lamers2006; prinz2009; pietrzik2010]. Whether this translates to a clinical benefit for a given person depends on the clinical context, having an MTHFR variant alone is not a disease and does not by itself indicate a need for L-methylfolate [frosst1995].

Is L-methylfolate better than folic acid for preventing neural tube defects?

The randomized-trial evidence base for NTD prevention is folic-acid-based, the MRC Vitamin Study (1991) and the Czeizel & Dudás trial (1992) used folic acid at 0.4, 4 mg/day [mrc1991; czeizel1992]. L-methylfolate

raises red-blood-cell folate at least as effectively as equimolar folic acid in healthy women of childbearing age, but no NTD-prevention efficacy trial of L-methylfolate exists [lamers2006; willems2007; obeid2020]. For low-risk women without MTHFR considerations, standard folic-acid prenatals remain the evidence-based choice; L-methylfolate is a reasonable folate-status alternative for women who cannot tolerate folic-acid products or who carry MTHFR variants.

What are the most common side effects?

L-methylfolate at 15 mg/day was well tolerated in the Papakostas 2012 trials and the 12-month open-label extension, nausea, headache, fatigue, and insomnia were reported at rates similar to placebo [papakostas2012; zajecka2016]. Some patients report irritability or anxiety with initiation, which may reflect methyl-donor effects and is sometimes managed by dose reduction or methylcobalamin co-prescription. Hypersensitivity reactions are uncommon but possible.

What's the concern about 'unmetabolized folic acid'?

Above approximately 200, 400 mcg/day, folic acid exceeds the body's capacity to reduce it via DHFR, and unmetabolized folic acid (UMFA) appears in the bloodstream [pfeiffer2015; bailey2010] [scaglione2014]. UMFA has been documented in nearly all post-fortification U.S. serum samples. Whether UMFA itself causes adverse effects, masking B12-deficiency anemia, altering natural folate transport, immune effects, remains debated rather than established [pietrzik2010]. L-methylfolate does not produce circulating UMFA, which is the principal pharmacokinetic rationale for preferring it over high-dose folic acid in certain patients [sweeney2012; morris2007; patanwala2014].

Who should not take L-methylfolate?

Patients with known hypersensitivity to L-methylfolate or its excipients should not initiate. Caution applies in untreated vitamin B12 deficiency (folate can correct megaloblastic anemia while permitting B12-deficient neurologic disease to progress) and on folate-interacting anticonvulsants [morris2007; stover2004; scaglione2014]. Decisions about concurrent methotrexate, pyrimethamine, or other anti-folate agents require explicit prescriber review.

Does RonanRx sell L-methylfolate directly to patients?

No. Compounded L-methylfolate requires a patient-specific prescription written by a licensed doctor for an identified patient with a documented clinical reason that the manufactured Deplin medical-food product or commercial dietary-supplement L-methylfolate is not appropriate, plus pharmacist review before dispensing. RonanRx is not a direct-to-consumer storefront [fda503a; fda_medical_food].

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How to Access Methylfolate

Compounded Methylfolate is dispensed under 503A on a patient-specific prescription. Depending on your role, the next step looks different.

FOR PRESCRIBING CLINICIANS

Offer this medication

A pharmacist will follow up within two business days. We'll cover state availability, supported formulations, and what integration looks like for your clinic.

ronanrx.com/request-partnership-call

PATIENT WITH A DOCTOR

Receive your prescription

If your doctor has prescribed Methylfolate, sign up so we can prepare and ship your medication. The signup wizard collects intake and connects you to the prescribing workflow.

ronanrx.com/patients

PATIENT WITHOUT A DOCTOR

Find a partner clinic

RonanRx prescribes through partner clinics — we don't initiate prescriptions on this site. Read how the referral process works and how to find a partner clinic in your state.

ronanrx.com/find-clinic

Other compounds RonanRx makes

This monograph is one of many in the RonanRx formulary. Every compound below is prepared under 503A on a patient-specific prescription. Browse the full catalog at ronanrx.com/medications and ronanrx.com/peptides, or scan the codes at right for each index.

Medications

Peptides

MEDICATIONS (40)

Alpha-Lipoic Acid (ALA) — Antioxidant & mitochondrial
Coenzyme Q10 (CoQ10) — Antioxidant & mitochondrial
Glutathione — Antioxidant & mitochondrial
NAD+ / NMN — Antioxidant & mitochondrial
Compounded Topical Anesthetics (BLT, LET) — Dermatology
Topical Minoxidil — Dermatology
Topical Tretinoin — Dermatology
Compounded Magnesium — Energy & nutritional
Cyanocobalamin — Energy & nutritional
High-Dose Vitamin D — Energy & nutritional
Hydroxocobalamin — Energy & nutritional
Iron (Compounded) — Energy & nutritional
L-Carnitine — Energy & nutritional
Methylcobalamin (B12) — Energy & nutritional
Methylfolate — Energy & nutritional
Anastrozole — Hormone optimization
Clomiphene & Enclomiphene — Hormone optimization
DHEA — Hormone optimization
Estradiol — Hormone optimization
Estriol — Hormone optimization
Human Chorionic Gonadotropin (HCG) — Hormone optimization
Pregnenolone — Hormone optimization
Progesterone — Hormone optimization
Testosterone — Hormone optimization
Compounded Metformin — Metabolic & weight
Compounded Semaglutide — Metabolic & weight
Compounded Tirzepatide — Metabolic & weight
Lipotropic Injection (MIC, MICC) — Metabolic & weight
Low-Dose Naltrexone (LDN) — Metabolic & weight
Naltrexone-Bupropion Combination — Metabolic & weight
Topiramate — Metabolic & weight
Bremelanotide / PT-141 — Sexual health
Compounded Sildenafil — Sexual health
Compounded Tadalafil — Sexual health
Trimix Injection — Sexual health
Compounded Gabapentin — Sleep & recovery
Compounded Melatonin — Sleep & recovery
Compounded T3 (Liothyronine) — Thyroid
Compounded T3/T4 Combinations — Thyroid
Compounded T4 (Levothyroxine) — Thyroid

PEPTIDES (21)

Sermorelin — Available now

Tesamorelin — Available now

AOD-9604 — Growth-hormone axis (under FDA review)

CJC-1295 — Growth-hormone axis (under FDA review)

GHRP-2 / GHRP-6 — Growth-hormone axis (under FDA review)

Hexarelin — Growth-hormone axis (under FDA review)

Ipamorelin — Growth-hormone axis (under FDA review)

MK-677 / Ibutamoren — Growth-hormone axis (under FDA review)

5-Amino 1MQ — Metabolic & longevity (under FDA review)

Epitalon / Epithalon — Metabolic & longevity (under FDA review)

MOTS-C — Metabolic & longevity (under FDA review)

Thymosin Alpha-1 / Thymalin — Metabolic & longevity (under FDA review)

DSIP, Delta Sleep-Inducing Peptide — Neuro & cognitive (under FDA review)

Selank — Neuro & cognitive (under FDA review)

Semax — Neuro & cognitive (under FDA review)

Vasoactive Intestinal Peptide (VIP) — Neuro & cognitive (under FDA review)

BPC-157 — Tissue repair (under FDA review)

KPV — Tissue repair (under FDA review)

LL-37 — Tissue repair (under FDA review)

Pentadeca Arginate (PDA) — Tissue repair (under FDA review)

TB-500 / Thymosin Beta-4 — Tissue repair (under FDA review)