Impact of the *MTHFR C677T* genetic variant on depression

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Ms. T, age 55, presents to her psychiatrist's clinic with a chief complaint of ongoing symptoms of anhedonia and lethargy related to her diagnosis of major depressive disorder (MDD). She also has a history of peripheral arterial disease, hypothyroidism, and generalized anxiety disorder. Her current antidepressant regimen is duloxetine, 60 mg/d, and mirtazapine, 15 mg at night. She recently elected to undergo pharmacogenetic testing, which showed that she is heterozygous for the methylenetetrahydrofolate reductase (*MTHFR*) *C677T* mutation (*MTHFR C677T* CT carrier). Her test report states that she may have impaired folate metabolism. Her psychiatrist adds L-methylfolate, 15 mg/d, to her current antidepressant regimen.

What is the relationship between folic acid and *MTHFR*?

Methylenetetrahydrofolate reductase is an intracellular enzyme responsible for one of several steps involved in converting dietary folic acid to its physiologically active form, L-methylfolate.[1] Once active, L-methylfolate can be transported into the CNS, where it participates in one-carbon transfer reactions.[2,3] Mutations in the *MTHFR* gene have been associated with decreased activity of the enzyme, which has been shown to result in accumulation of homocysteine and may lead to decreased synthesis of neurotransmitters.[2,4] Commercial pharmacogenetic testing panels may offer *MTHFR* genetic testing to assist with prescribing decisions for patients with mental illness. The most well-characterized mutation currently is *C677T* (rsID1801133), which is a single amino acid base pair change (cytosine [C] to thymine [T]) that leads to increased thermolability and instability of the enzyme.[5] Carrying 1 or 2 T alleles can lead to a 35% or 70% reduction in enzyme activity, respectively. The T variant allele is most

Practice Points

- **Methylenetetrahydrofolate reductase (*MTHFR*) genetic variants may result in impaired folate metabolism**, which may have downstream effects on neurotransmitter synthesis.
- This relationship has a theoretical basis, but **data suggesting a significant relationship between *MTHFR* mutations and major depressive disorder (MDD) have been inconsistent**.
- **Active folate supplementation may have some modest benefit on symptoms of MDD**. However, because studies showing this did not necessarily establish *MTHFR* genetics prior to enrollment, basing the decision to initiate L-methylfolate on *MTHFR* status is not supported by currently available evidence.

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Table 1

Studies assessing *MTHFR* genotype associations with MDD

Study	Design	Sample size (N)	Patient population	MDD assessement method
Moorthy et al[6] (2012)	Cross-sectional observational study	1,956	Patients age ≥65 of Puerto-Rican, African American, and non-Hispanic white ethnicity	CES-D scores
Jiang et al[8] (2015)	Meta-analysis	13 studies	All-comers in China	DSM-IV or Chinese classification of mental disorders systems
Bousman et al[9] (2013)	Longitudinal prospective cohort study	342	Adult Australian primary care patients with DSM-IV depression and a CES-D score ≥16. Ethnicity not reported	CES-D, PHQ-9
Schiepers et al[10] (2011)	Prospective observational study	777	All-comers in family practice in the Netherlands	SLC-DEP scores
Lizer et al[11] (2011)	Cross-sectional observational study	156	Caucasian patients in outpatient ambulatory care and psychiatric care	Compared *MTHFR* genotype in patients with and without prior diagnosis of depression (DSM-IV)
Bjelland et al[12] (2003)	Cross-sectional observational study	5,948	Adult Norwegian ambulatory care patients. Depression was defined as a HADS-D score ≥8, and anxiety as a HADS-A score ≥8	HADS-A and HADS-D

CES-D: Center for Epidemiologic Studies Depression Scale; HADS-A: Hospital Anxiety and Depression Scale-Anxiety (focused on symptoms related to restlessness and worry); HADS-D: Hospital Anxiety and Depression Scale-Depression (focused on anhedonia, psychomotor retardation, and impaired mood); MDD: major depressive disorder; *MTHFR*: methylenetetrahydrofolate reductase; PHQ-9: Patient Health Questionnaire; SCL-DEP: Symptom Checklist 90-Depression

Clinical Point

Data suggesting that the *C677T* mutation in *MTHFR* may be associated with depression have been inconsistent

frequent in Hispanics (20% to 25%), Asians (up to 63%), and Caucasians (8% to 20%); however, it is relatively uncommon in African Americans (<2%).[5,6] Another variant, A1289C (rs1801131), has also been associated with decreased enzyme function, particularly when analyzed in combination with *C677T*. However, carrying the 1289C variant allele does not appear to result in as large of a reduction of enzyme function as the 677T variant.[7]

What is the relationship between *MTHFR C677T* and depression?

Some researchers have proposed that the *C677T* mutation in *MTHFR* may be associated with depression as a result of decreased neurotransmitter synthesis, but studies have not consistently supported this hypothesis. Several studies suggest an association between *MTHFR* mutations and MDD[8-10]:

Jiang et al[8] performed a meta-analysis of 13 studies including 1,295 Chinese patients and found that having at least 1 *C677T* variant allele was significantly associated with an increased risk of depression (for T vs C odds ratio 1.52, 95% confidence interval 1.24 to 1.85). The authors noted a stronger association identified in the Northern Chinese population compared with the Southern Chinese population.[8]

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Results	Association identified?
No statistically significant difference in CES-D scores in those with and without at least 1 variant allele within any ethnic group	No
MTHFR C677T was associated with depression in the Chinese population, but associations differ by geographic location	Yes
Over a 5-year period, 677CC patients had more severe symptoms compared with 677TT genotype	Yes
No evidence for association between *MTHFR C677T* and mood decline in healthy individuals at baseline and after a 12-year follow-up	No
No significant differences were found in the frequency of *MTHFR C677T* T allele or the TT genotype between Caucasian patients who were depressed and non-depressed	No
On multivariate analysis, the 677TT genotype was significantly associated with depression but not anxiety or comorbid anxiety and depression	Yes

Bousman et al[9] found that American patients with MDD and the 677CC genotype had greater Patient Health Questionnaire-9 (PHQ-9) scores at assessments at 24, 36, and 48 months post-baseline compared with those with the 677TT genotype (P = .024), which was unexpected based on previously reported associations.[9]

Schiepers et al[10] also assessed the association between the *MTHFR* genotype in a Dutch ambulatory care population over 12 years. There was no association identified between scores on the depression subscale of the Symptom Checklist 90 and *C677T* diplotype.[10]

Table 1[6,8-12] (***page 42***) provides summaries of these and other selected studies on *MTHFR* and MDD. Overall, although a pathophysiological basis for depression and decreased *MTHFR* function has been proposed, the current body of literature does not indicate a consistent link between *MTHFR C677T* genetic variants alone and depression.

Medication changes based on *MTHFR*: What is the evidence?

Some evidence supports the use of active folate supplementation to improve symptoms of MDD.

Shelton et al[3] conducted an observational study that assessed the effects of adding L-methylfolate (brand name: Deplin), 7.5 or 15 mg, to existing antidepressant therapy in 502 patients with MDD who had baseline PHQ-9 scores of at least 5. After an average 95 days of therapy, PHQ-9 scores were reduced by a mean of 8.5 points, with 67.9% of patients achieving at least a 50% reduction in PHQ-9 scores. The study did not take into account patients' *MTHFR* genotype or differentiate results between the 2 doses of L-methylfolate.[3]

Papakostas et al[13] performed 2 randomized, double-blind, parallel-sequential, placebo-controlled trials of L-methylfolate for patients with MDD. The first compared L-methylfolate, 7.5 and 15 mg, to placebo, without regard to *MTHFR* genotype.[13] There was no significant difference between the 7.5-mg dose and placebo, or the 15-mg dose and placebo. However, among the group receiving the 15-mg dose, the response rate was 24%, vs 9% in the placebo group, which approached significance (P = .1). Papakostas et al[13] followed up with a smaller trial comparing the 15-mg dose alone to placebo, and found the response rate was 32.3% in patients treated with L-methylfolate compared with 14.6% in the placebo group (P = .04).[13]

Although the Shelton et al[3] and Papakostas et al[13] studies showed some improvement in

Clinical Point

Some evidence supports the use of active folate supplementation to improve symptoms of MDD

Clinical Point

Available data do not confirm the relevance of *MTHFR* functional status to symptom response

Table 2

Studies assessing active folate supplementation in MDD

Study	Design	Sample size (N)	Population	Treatment
Shelton et al[3] (2013)	Prospective observational study (no placebo)	554	Adults prescribed L-methylfolate for the treatment of depression *MTHFR C677T* status was not assessed	L-methylfolate (brand name: Deplin), 7.5 mg or 15 mg
Papakostas et al[13] (2012)	Two multicenter, randomized, double-blind, sequential parallel comparison trials	Trial 1: 148	Adults with MDD, score ≥12 on QIDS-SR, having received treatment with SSRI at adequate dose (≥20-mg fluoxetine, paroxetine, citalopram, ≥10-mg escitalopram, ≥50-mg sertraline) at time of screening *MTHFR C677T* status was not assessed	Trial 1: L-methylfolate (brand name: Deplin), 7.5 mg vs 15 mg vs placebo
		Trial 2: 61		Trial 2: L-methylfolate (brand name: Deplin), 15 mg vs placebo
Mech and Farah[15] (2016)	Randomized, double-blind, placebo-controlled trial	330	Adults with MDD with at least one *MTHFR C677T* or A1298C variant (did not provide breakdown of these mutations in the study population)	EnLyte supplement containing L-methylfolate, 7 mg, and many other ingredients
Godfrey et al[16] (1990)	Double-blind, placebo-controlled trial	41	Adults referred to psychiatric hospital with history of MDD or schizophrenia with folate deficiency (<200 ug/L)	Methylfolate, 15 mg/d

CGI: Clinical Global Impression; HAM-D: Hamilton Depression Rating Scale; MADRS: Montgomery-Åsberg Depression Scale; MDD: major depressive disorder; *MTHFR*: methylenetetrahydrofolate reductase; PHQ-9: Patient Health Questionnaire; QIDS-SR: Quick Inventory of Depressive Symptomatology-Self-Report; QOL: Quality of Life Questionnaire; SSRI: selective serotonin reuptake inhibitor

depressive symptom scores among patients who received L-methylfolate supplementation, an important consideration is if *MTHFR* genotype may predict patient response to this therapy.

Papakostas et al[14] performed a post hoc analysis of their earlier study to assess potential associations amongst multiple other biomarkers of inflammation and metabolic disturbances hypothesized by the authors to be associated with MDD, as well as body mass index (BMI), with treatment outcome.[14] When change in the Hamilton Depression Rating Scale-28 (HDRS-28) was analyzed by *C677T* and A1298C variant groups (677 CT vs TT and 1298 AC vs CC), no statistically significant improvements were identified (*C677T* mean change from baseline –3.8 points, $P = .087$; A1298C mean change from baseline –0.5 points, $P = .807$).[14] However, statistically significant improvements in HDRS-28 scores were observed

Treatment period	Outcome assessment	Results	Conclusions
90 days	PHQ-9 survey, QOL survey, and medication satisfaction survey	PHQ-9 scores reduced by mean of 8.5 points ($P < .001$) Study did not break down any differences between the 2 doses of L-methylfolate	Patients treated with L-methylfolate achieved statistically significant improvements in depressive symptoms
30 days	HAM-D score (primary), QIDS-SR score, CGI score	Trial 1: No significant difference observed between the 7.5-mg or 15-mg dose and placebo	Adjunctive treatment with L-methylfolate 15 mg/d may be a safe and effective strategy for patients with MDD inadequately managed by SSRIs
30 days		Trial 2: Response rate was 32.3% in those receiving 15 mg, compared with 14.6% in patients receiving placebo (P = .04)	
8 weeks	MADRS score	MADRS scores decreased by 12 points in patients receiving the supplement and by 1.3 points in the placebo group ($P < .001$)	The combination of reduced B vitamins and micronutrients resulted in improvement in depressive symptoms in patients with an *MTHFR* polymorphism
6 months	HAM-D, Beck Depression Inventory self-rating scale, serum folate, serum vitamin B12	The mean clinical outcome score was lower in the methylfolate group compared with the placebo group at 3 months ($P < .01$) and 6 months ($P < .001$) After 3 and 6 months of treatment, folate levels were above the upper limit of assay in the methylfolate group. A smaller increase was observed in the placebo group	Disturbances of methylation in the nervous system may contribute to depression and schizophrenia

Clinical Point

There are likely multiple inherited and environmental factors affecting patients' response to L-methylfolate

compared with baseline when the *C677T* genotype was pooled with other biomarkers, including methionine synthase (MTR 2756 AG/GG, –23.3 points vs baseline, $P < .001$) and a voltage-dependent calcium channel (CACNAIC AG/AA, –9 points vs baseline, $P < .001$), as well as with BMI ≥30 kg/m^2 (–9.9 points vs baseline, $P = .001$).[14]

Mech and Farah[15] performed a randomized, double-blind, placebo-controlled study of the use of EnLyte, a supplement containing 7-mg L-methylfolate, in patients with at least 1 variant of *MTHFR* (either *C677T* or A1298C) over an 8-week period. In addition to L-methylfolate, this supplement contains other active ingredients, including leucovorin (or folinic acid), magnesium ascorbate, and ferrous glycine cysteinate. Montgomery-Åsberg Depression Scale (MADRS) scores improved by 12 points in patients who received the supplement and by 1.3 points in patients who received

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placebo. However, because the supplement contained many ingredients, the response observed in this study cannot be attributed to L-methylfolate alone.[15]

Table 2[3,13,15,16] (***page 44***) contains summaries of these and other selected studies assessing active folate supplementation in MDD.

CASE CONTINUED

Over the next several weeks, Ms. T experiences some modest improvement in mood while taking L-methylfolate and her antidepressant regimen, and she experiences no notable adverse effects. Unfortunately, after 3 months, Ms. T discontinues the supplement due to the cost.

The value of *MTHFR* testing

Ms. T's case is an example of how clinicians may respond to *MTHFR* pharmacogenetic testing. Although L-methylfolate has shown some benefit in several randomized clinical trials, available data do not confirm the relevance of *MTHFR* functional status to symptom response. Additionally, there is likely interplay among multiple factors affecting patients' response to L-methylfolate. Larger randomized trials prospectively assessing other pharmacogenetic and lifestyle factors may shed more light on which patients would benefit.

Based on available data, the decision to prescribe L-methylfolate should not necessarily hinge on *MTHFR* genetics alone. Both patients and clinicians must be aware of the potentially prohibitive cost if L-methylfolate is recommended, as prescription insurance may not provide coverage (eg, a recent search on GoodRx.com showed that generic L-methylfolate was approximately $40 for 30 tablets; prices may vary). Additionally, clinicians should be aware that L-methylfolate is regulated as a medical food product and is not subject to strict quality standards required for prescription medications. Future prospective studies assessing the use of L-methylfolate specifically in patients with a *MTHFR* variants while investigating other relevant covariates may help identify which specific patient populations would benefit from supplementation.

Related Resources

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Drug Brand Names

Citalopram • Celexa
Duloxetine • Cymbalta
Escitalopram • Lexapro
Fluoxetine • Prozac
L-methylfolate • Deplin
Mirtazapine • Remeron
Paroxetine • Paxil
Sertraline • Zoloft

Clinical Point

The decision to prescribe L-methylfolate should not necessarily hinge on *MTHFR* genetics alone

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Clinical Point

Prescription insurance may not provide coverage for the cost of L-methylfolate

Negative symptoms of schizophrenia

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