L-methylfolate in patients with treatment resistant depression: fulfilling the goals of personalized psychopharmacological therapy

Major depressive disorder (MDD) is a highly prevalent psychiatric disorder and reported as one of the most leading cause of disabilities world-wide, affecting approximately 350 million individuals [1]. Depression also leads to considerable maladaptive illness behaviours with increased risk and health care utilization due to comorbid cardiovascular diseases, neurocognitive disorders, chronic pain syndromes, diabetes, and cerebrovascular diseases [2–4]. The predominant neurological theory of MDD is rooted in the monoamine neurotransmitters serotonin (5HT), norepinephrine (NE), and dopamine (DA), in a series of neural circuitries in the brain that contribute to depressive symptoms including anhedonia and depressed mood. Several studies reported that about two third of patients with MDD who were treated with first-line therapies showed some level of response; however, one third of patients remained refractory to treatment leading to poor quality of life and impairment in overall functioning [5]. Often and many times, depressed patients report that antidepressants have been working well during the first 2–3 months, then they have fizzled out and stopped working. Treatment-resistant depressed patients have partial or no response to psychopharmacotherapy, which may include trials of different antidepressants, a combination of psychotropic agents, adjunctive therapy or off-label use of alternative agents [6]. For clinical psychiatrists; rather than a reduction in symptom severity, achieving and maintaining remission is the goal of rational psychopharmacotherapy. There are numerous factors that might contribute to treatment resistance including number of psychiatric/medical comorbidities, environmental stressors such as familial conflicts, marital discordance, postpartum depression, history of physical/sexual abuse, and genetic vulnerabilities [5]. It has long been recognized that there is substantial variation in the response to psychiatric treatment [7]. As a result, understanding an individual’s genetic background can help to predict drug responses and potential risks for adverse events [8]. An emerging and promising strategy is to utilize a person’s pharmacokinetic and pharmacodynamic genetic profile to guide decisions of personalized psychopharmacological therapy.

One of the known associations in treatment-resistant depressed patients is that the presence of methylene tetrahydrofolate reductase (MTHFR) polymorphism which translates into lower serum levels of L-methylfolate and possibly lower folate and monoamine levels in the central nervous system (CNS). A recent meta-analysis indicated higher rates of depression in individuals with the C667 T homozygous mutation for MTHFR [9]. MTHFR is an enzyme responsible for catalysing the conversion of folic acid and folate to L-methylfolate. The mutation of the MTHFR gene is a single nucleotide polymorphism that causes an alanine to valine amino acid substitution [9]. A common variant of this gene significantly reduces the enzymatic activity of MTHFR, resulting in the inefficient production of L-methylfolate. Each copy of the variant reduces MTHFR enzyme efficiency by approximately 35% [9]. Individuals who are homozygous for the T variant have about 30% of the enzyme activity of individuals with the wild-type (CC) variant [9]. Heterozygous (CT) individuals have about 65% of the enzyme activity of CC individuals [9]. More recently, Lok et al. [10] examined the gene-environment relationship between early-life adversity and MTHFR genotype for MDD recurrence and concluded that MTHFR polymorphism combined with traumatic childhood events was predictive of depression. Patients with a history of recurrent depression currently in remission were followed for 5.5 years for depression recurrence. The researchers concluded that the presence of the MTHFR T allele coupled with early-life adversity was most predictive of depression recurrence. Severity of depression was highest in the T/T population and lowest in the C/C population. Severity of depression also correlated with the number and severity of childhood traumatic events [10]. How the MTHFR polymorphism disrupts one carbon metabolism or promotes oxidative stress along with how early-life adversity may trigger or “unlock” certain genes that alter methylation patterns and expression of inflammatory markers will

I said to my soul, be still, and wait without hope For hope would be hope for the wrong thing: wait without love For love would be love of the wrong thing: there is yet faith But the faith and the love and the hope are all in the waiting.

T. S. Eliot

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be a primary focus of future research. This highlights the importance of understanding complex gene-environment interactions, because they may lead to more personalized psychiatry, which is the ability to choose treatment strategies that account for individual variability, which can achieve a greater response. Specific ethnic groups are at higher risk for the less functional forms of MTHFR. The T/T genotype is present in as many as 10% of Caucasians and up to 22% of Hispanic or Mediterranean populations [11]. Several other groups are also at risk for lower L-methylfolate levels, including patients who are using antiepileptic medications, alcohol/substance dependents, cigarette smokers, and patients with gastrointestinal disorders [12]. Drugs that are known to reduce folate levels include phenytoin, valproic acid, carbamazepine, primidone, phenobarbital, and lamotrigine, which is a specific inhibitor of dihydrofolate reductase (DHFR). DHFR activity is the first step necessary for the conversion of dietary folate or supplemental folic acid to L-methylfolate. Other drugs associated with folate depletion include oral contraceptives, acne medications, metformin, lithium, dopaminergic medications for Parkinson’s disease and methotrexate, which is a specific DHFR inhibitor [12].

L-methylfolate is the only form of folate that crosses the blood–brain barrier and is immediately available for neurotransmitter synthesis [12]. L-methylfolate modulates the synthesis of monoamines, including serotonin, norepinephrine, and dopamine in a 2-step process. First, L-methylfolate acts as an important regulator of a critical cofactor known as tetrahydrobiopterin (BH4), which is necessary for the synthesis of neurotransmitters. The trimonoamine enzymes that require BH4 as a cofactor are tryptophanhydroxylase, the rate-limiting enzyme for 5-HT synthesis and tyrosine hydroxylase, the rate-limiting enzyme for 5-HT synthesis and monoamine synthesis. Tryptophan is transformed to methionine utilizing B12 and L-methylfolate, both necessary cofactors for this transformation. Methionine is then converted to s-adenosylmethionine (SAM), which serves as the methyl donor for all three monoamines serotonin, norepinephrine, and dopamine. Therefore, patients with low CNS L-methylfolate are less able to convert homocysteine to methionine, the first necessary step of the homocysteine cycle [13]. Homocysteine is transformed to methionine utilizing B12 and L-methylfolate, both necessary cofactors for this transformation. Methionine is then converted to s-adenosylmethionine (SAM), which serves as the methyl donor for all three monoamines serotonin, norepinephrine, and dopamine. Therefore, patients with low CNS L-methylfolate are less able to convert homocysteine to methionine, the first necessary step of the homocysteine cycle [13].

L-methylfolate acts as a donor for DNA methylation, a process necessary for epigenetic gene silencing [14]. Unlike antidepressants, which block the reuptake of neurotransmitters in short supply, L-methylfolate allows necessary methyl donation for adequate formation of trimonoamines. L-methylfolate is available by prescription and is regulated by the FDA as a prescription medical food for the specific nutritional requirements of depressed individuals with suboptimal serum, RBC, or CNS folate. It is specifically intended as an adjunctive therapy for depressed patients who have partially responded to antidepressant therapy. However, L-methylfolate may provide benefit to patients with or without serum or RBC folate deficiency, particularly if they are at risk for low production of neurotransmitters [12].

Papakostas et al. have shown that L-methylfolate can be an effective antidepressant strategy as an augmentation to selective serotonin reuptake inhibitors (SSRIs) [15]. In a novel sequenced parallel comparison design; they reported results from two trials concluding that L-methylfolate at 15 mg/day is an effective and well-tolerated treatment for patients with MDD who were SSRI non-responders. Patients fulfilling the criteria for unipolar major depression without psychosis received treatment with an SSRI at adequate doses for at least 8 weeks. The primary outcome measures were the difference in response rates on the 17-item HAM-D along with the degree of improvement in the HAM-D. In the first trial of 148 patients, no significant difference was found for either primary outcome measure between SSRI plus L-methylfolate at 7.5 mg/day versus SSRI monotherapy. However, a subgroup of patients in the first trial who had L-methylfolate 15 mg/day demonstrated a greater response rate than the placebo group. This led to the design of the second trial with 75 patients, in which only the higher dosage of 15 mg/day of L-methylfolate was used for augmentation. In this trial, L-methylfolate at 15 mg/day plus an SSRI was superior in both outcome measures to SSRI monotherapy. Response rates for the L-methylfolate-plus-SSRI group (32.3%) were higher than the SSRI-plus-placebo group (14.6%), and the corresponding differences in the degree of improvement on the HAM-D were higher (−5.58 versus −3.04). In addition, L-methylfolate augmentation did not lead to any significant differences in terms of gastrointestinal side effects, sedation, weight gain, and sexual dysfunctions. The number needed to treat for response in the second trial was approximately six in favour of adjunctive L-methylfolate compared to the placebo, which is comparable to results reported for other augmentation strategies in patients with MDD, such as use of atypical antipsychotics [16]. In a randomized controlled trial, Reynolds et al. reported that methylfolate monotherapy was as effective as a standard antidepressant for depression [17]. Overall 8 of 19 (42%) patients treated with L-methylfolate (25 mg of active L-methylfolate)
and 7 of 20 (35%) patients treated with Amitriptyline (150 mg/day) for 6 weeks responded. No side effects were reported with L-methylfolate, while three patients were withdrawn from the study due to unacceptable side effects with Amitriptyline. Another interesting finding was the relationship between antidepressant response to L-methylfolate and the rise in red cell folate levels. All the patients who were responders to L-methylfolate treatment exhibited a noticeable rise in red blood cell folate at 6 weeks [17].

If MDD is hypothesized as a low serotonergic state, then we can imagine a serotonergic neuron producing a less than the desired amount of neurotransmitter. When an SSRI/SNRI is prescribed, less serotonin returns to the neuron via reuptake inhibition and it begins to accumulate in the post-synaptic cleft, where it can serve its role in neurotransmission. Although it is possible that additional stressors might worsen the clinical state of the depressed patients, it is possible that the prescribed antidepressant no longer binding effectively to the serotonin reuptake site or it is likely that tolerance developed. What might be occurring is that the prescribed antidepressant worked effectively in the beginning and that over several weeks of reuptake inhibition, it effectively drained serotonin from the neurons. Something similar was shown in prior research involving partial responders to fluoxetine who experienced depressive symptom relapse after tryptophan-depletion challenges [18]. Augmentation of SSRI/SNRI with L-methylfolate might help maintain serotonin levels in certain depressed patients and also contribute to a more sustained treatment effect. This may increase the chance of achieving remission, and in those who have reached remission, it may reduce the risk of symptom relapses.

Conclusions

L-methylfolate 15 mg/day added to SSRIs or as monotherapy can be an effective and well-tolerated treatment strategy for MDD patients who are partial or non-responders to antidepressant therapy. L-methylfolate can be particularly effective in patients with a C667T homozygous mutation for MTHFR. As psychiatry advances at the molecular level, we will gain more understanding of how individuals with certain genotypes may be more vulnerable to particular stressors compared to individuals with other genotypes. Certain traumatic events or stressors may require specific psychotherapy interventions, such as cognitive–behavioural therapy, eye movement desensitization and reprocessing (EMDR), or even anaerobic exercise. Biological interventions aimed at oxidative stress, one carbon metabolism or blockage of certain DNA–protein interactions could be the norm. Better understanding the role of MTHFR and its relationship to MDD may be one of the first steps in this long due process. L-methylfolate appears to be the optimal compound for augmentation, as it is the active form utilized by the CNS and readily crosses the blood–brain barrier. It is a necessary cofactor for the synthesis of monoamine neurotransmitters. Many depressed patients are at risk for low levels of CNS folate due to lifestyle, medications, and genetics, but even those with normal CNS folate may benefit from L-methylfolate augmentation. There are no known drug interactions and no reports of mania induction. L-methylfolate is a well-tolerated medication which stands out as one of the safest of available augmentation options. Replication of results in independent cohorts is needed, as well as additional research to further clarify the antidepressant role of L-methylfolate. We recommend genetic testing for the MTHFR polymorphism wherever feasible. Once identified as treatment-resistant depression, patients are likely to be positive for MTHFR polymorphism and therefore genetic testing may not even be required for recommended treatment (L-methylfolate, 15 mg/day) to begin with.

References

[1] Kessler RC, Bromet EJ. The epidemiology of depression across cultures. Annu Rev Public Health. 2013;34:119–138.
[2] Penninx BW, Beekman AT, Honig A, et al. Depression and cardiac mortality: results from a community-based longitudinal study. Arch Gen Psychiatry. 2001;58(3):221–227.
[3] Fishbain DA, Cutler R, Rosomoff HL, et al. Chronic pain-associated depression: antecedent or consequence of pain? A review. Clin J Pain. 1997;13(2):116–137.
[4] Egede LE, Zheng D, Simpson K. Comorbid depression is associated with increased health care use and expenditures in individuals with diabetes. Diabetes Care. 2002;25(3):464–470.
[5] Al-Harbi KS. Treatment-resistant depression: therapeatic trends, challenges, and future directions. Patient Prefer Adherence. 2012;6:369–388.
[6] Keller MB, Boland RJ. Implications of failing to achieve successful long-term maintenance treatment of recurrent unipolar major depression. Biol Psychiatry. 1998;44(5):348–360.
[7] Mrazek DA. Psychiatric pharmacogenomic testing in clinical practice. Dialogues Clin Neurosci. 2010;12:69–76.
[8] Vegter S, Boersma C, Rozenbaum M, et al. Pharmacoeconomic evaluations of pharmacogenetic and genomic screening programmes: a systematic review on content and adherence to guidelines. Pharmacoeconomics. 2008;26:569–587.
[9] Gilbody S, Lewis S, Lightfoot T. Methylene tetrahydrofolate reductase (MTHFR) genetic polymorphisms and psychiatric disorders: a HuGE review. Am J Epidemiol. 2007 Jan 1;165(1):1–13.
[10] Lok A, Bockting CL, Koeter MW, et al. Interaction between the MTHFR C677T polymorphism and
traumatic childhood events predicts depression. Transl Psychiatry. 2013 Jul 30;3:e288.

[11] Kelly CB, McDonnell AP, Johnston TG, et al. The MTHFR C677T polymorphism is associated with depressive episodes in patients from Northern Ireland. J Psychopharmacol. 2004;18(4):567–571.

[12] Farah A. The role of L-methylfolate in depressive disorders. CNS Spectr. 2009;14(1 Suppl 2):2–7.

[13] Folstein M, Liu T, Peter I, et al. The homocysteine hypothesis of depression. Am J Psychiatry. 2007;164(6):861–867.

[14] Bredy TW, Sun YE, Kobar MS. How the epigenome contributes to the development of psychiatric disorders. Dev Psychobiol. 2010 May;52(4):331–342.

[15] Papakostas GI, Shelton RC, Zajecka JM, et al. L-methylfolate as adjunctive therapy for SSRI-resistant major depression: results of two randomized, double-blind, parallel-sequential trials. Am J Psychiatry. 2012 Dec;169(12):1267–1274.

[16] Nelson JC, Papakostas GI. Atypical antipsychotic augmentation in major depressive disorder: a meta-analysis of placebo controlled randomized trials. Am J Psychiatry. 2009;166:980–991.

[17] Reynolds EH, Creglin R, Bottiglieri T, et al. Methylfolate as monotherapy in depression. A pilot randomised controlled trial. J Neurol Psychol. 2015;3(1):5.

[18] Delgado PL, Miller HL, Salomon RM, et al. Tryptophan-depletion challenge in depressed patients treated with desipramine or fluoxetine: implications for the role of serotonin in the mechanism of antidepressant action. Biol Psychiatry. 1999;46(2):212–220.

Samet Kose, MD, PhD
Editor, Psychiatry and Clinical Psychopharmacology, Franklin, TN, USA
sametkose@gmail.com http://orcid.org/0000-0003-0841-004X

Kemal Sayar, MD
Marmara University, Department of Psychiatry, Istanbul, Turkey
http://orcid.org/0000-0001-6909-3012