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Good, better, best: clinical scenarios for the use of L-methylfolate in patients with MDD

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Abstract

Depression is among the most prevalent mental disorders worldwide, and a substantial proportion of patients do not respond adequately to standard antidepressants. Our understanding of the pathophysiology of depression is no longer limited to the chemical imbalance of neurotransmitters, but also involves the interplay of proinflammatory modulators in the central nervous system, as well as folate metabolism. Additional factors such as stress and metabolic disorders also may contribute. Multiple inflammatory, metabolic, and genetic markers have been identified and may provide critical information to help clinicians individualize treatments for patients to achieve optimal outcomes. Recent advancements in research have clarified underlying causes of depression and have led to possible new avenues for adjunctive treatment. Among these is L-methylfolate, a medical food that is thought to enhance synthesis of monoamines (serotonin, norepinephrine, and dopamine), suppress inflammation, and promote neural health. Clinical studies that assessed supplemental use of L-methylfolate in patients with usual care-resistant depression found that it resulted in improved outcomes. Patients with selective serotonin reuptake inhibitor-resistant depression, and particularly subgroups with biomarkers of inflammation or metabolic disorders or folate metabolism-related genetic polymorphisms (or ≥2 of these factors), had the best responses. Considering this, the goals of this review are to 1) highlight recent advances in the pathophysiology of major depressive disorder as it pertains to folate and associated biomarkers and 2) establish the profiles of patients with depression who could benefit most from supplemental use of L-methylfolate.

Clinical Implications

- For many patients with major depressive disorder, initial therapy with a monoaminergic agent does not sufficiently meet clinical need, as evidenced by low rates of remission and residual depressive symptoms.
- Various factors, including inflammation, metabolic disorders, and stress, contribute to depressive symptoms; thus, supplementation of usual care with adjunctive therapies that can address these factors may further increase response to treatment.
- Recent clinical trials have highlighted the involvement of folate in MDD pathophysiology, and the benefits of supplemental use of L-methylfolate, the biologically active form of folate, in patients with depression.
- Adjunctive therapy with L-methylfolate may be of particular benefit for patients with SSRI-resistant MDD, low folate levels, and/or identified biologic markers associated with inflammation/obesity and/or folate metabolism gene polymorphisms.

Introduction

Depression is one of the most prevalent mental disorders in the United States; more than 16% of individuals suffer from depression in the course of their lifetime.[1] Globally, it is the leading cause of disability and impacts more than 300 million people.[2] Despite the prevalence and severity of the disease, its precise pathophysiology remains unclear. Because of considerable heterogeneity in the neurobiology and genetics of depression, there is a need for a variety of options in order to individualize treatment. Unfortunately, there are no clinically useful biomarkers to guide selection of optimal treatment.[3] The monoaminergic theory of depression, centered around insufficient levels of or abnormal neurotransmission of serotonin (5-hydroxytryptamine [5-HT]), was the most widely accepted explanation for the symptoms of depression for the latter part of the 20th century, and has evolved to encompass the tri-monoamine theory, which also implicates abnormalities of dopamine and norepinephrine.[4,5] Indeed, research in recent decades has determined that specific monoaminergic neurotransmitters modulate various aspects of mood and behavior.[6] For instance, norepinephrine plays a role in alertness, energy, and attention, and low levels may contribute to feelings of anhedonia, a lack of interest in taking pleasure from life. Dopamine, the hallmark neurotransmitter in the reward pathway, is implicated in attention, motivation, and pleasure, while serotonin is implicated in depressed mood, anxiety, and obsessive thoughts.[6] More recently, folate deficiency has been identified as having a role in the pathology of depression.[7] L-methylfolate is thought to be the only form of folate that is able to pass through the blood–brain barrier and is involved in the regeneration of tetrahydrobiopterin (BH4; a critical cofactor for neurotransmitter synthesis), the levels of which are depleted with inflammation or oxidative stress.[8–11] In major depressive disorder (MDD) patients who are unresponsive to antidepressants, L-methylfolate may be a viable treatment option.

This article highlights new advancements in our understanding of the heterogeneous pathogenesis of MDD, particularly those regarding the role of folate inflammation, stress, obesity, and related biomarkers. It also reviews the efficacy and safety data on a prescription form of L-methylfolate that support its clinical use in MDD.

Usual Care and Adjunctive Therapies

Usual care for MDD includes treatments such as selective serotonin reuptake inhibitors (SSRIs) or serotonin and norepinephrine reuptake inhibitors (SNRIs) that target monoamine neurotransmitters, increasing their presence in the synapse by blocking their reuptake by transporters. Despite decades of use, monoaminergic therapies leave several unmet needs for patients: treatment onset may be slow, and many patients do not respond or remit to symptom levels that allow normal function; side effects can be significant; and many patients find it difficult to continue treatment and even discontinue antidepressant use, resulting in withdrawal reactions and/or appearance of new depressive symptoms.[12–16] The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, funded by the National Institutes of Mental Health, found that approximately 30% of patients experienced remission from depression and less than 50% of patients achieved a 50% or greater reduction in baseline depressive symptomology scores with initial SSRI monotherapy.[15] Furthermore, rates of response and remission were found to decrease after every failed treatment.[17] Of the patients who received secondary treatments after failure of initial SSRI therapy, 18%, 21%, and 25% achieved remission with sertraline, sustained-release bupropion, and extended-release venlafaxine treatment, respectively.[17] Only 10% to 16% achieved remission in their third phase of treatment.[18] Thus, treatment of MDD with monotherapy may be incomplete for many patients, and there is a clear need for effective alternative or adjunctive therapies.

There are a number of commonly used adjunctive therapies available to patients for whom monoaminergic-based therapy is insufficient (Table 1).[19–25] Many of them are associated with potentially significant side effects that may put patients at higher risk for other serious health conditions.[19–23] While several are evidence-based, only the atypical antipsychotics aripiprazole, quetiapine, and brexpiprazole are currently approved by the FDA.[26,27] In selecting adjunctive therapies, clinicians should consider the risk–benefit profile of each agent and individualize treatment accordingly. Available evidence suggests that two-thirds of patients taking drugs for depression require the use of at least 1 adjunctive therapy, with many patients cycling through therapy combinations before finding reasonably effective treatment, often a combination of polypharmacy and nonpharmacologic treatments.[28] In particular, patients with treatment-resistant depression are known to experience worse outcomes than those who respond to usual care therapies. Longer duration of untreated depression and the presence of residual symptoms are associated with worse outcomes, including greater cognitive and functional impairment, as well as higher risk of relapse, morbidity, and even mortality.[14,29–32] It is therefore important to identify the proper adjunctive therapy early in the treatment process to improve the possibility of acute full remission and increase the likelihood of longer-term efficacy.[33] Advances in the understanding of depression etiology and pathophysiology may allow clinicians to better identify patients who will respond to particular therapies or adjunctive therapies.

Advances in Depression Pathophysiology Research

A growing body of literature has identified factors in depression etiology and pathophysiology that may predict response to certain treatments. These findings have largely implicated inflammatory markers, metabolic abnormalities, and stress as major categories contributing to depression symptoms in certain patients. In addition to uncovering their roles in causing and maintaining depression episodes, research into these processes has revealed diagnostic tools and biomarkers that can assist clinicians in determining the best adjunctive therapies for each individual patient.

Inflammation and inflammatory biomarkers

Inflammation and depression are directly correlated and form a bidirectional loop that plays a critical role in the mechanism behind depression in a subgroup of MDD patients,[34] potentially causing downstream metabolic and behavioral effects.[35] Increased inflammation causes the central nervous system (CNS) to elicit or intensify depressive symptoms such as negative mood, fatigue, anhedonia, increased pain sensitivity, an altered sleep pattern, and cognitive deficits.[34,36] Depression also can promote inflammation by decreasing the sensitivity of the immune system to glucocorticoid hormones that stop the inflammatory response.[35] Furthermore, in MDD, there is a lack of parasympathetic activity to counter the continual sympathetic activity, which results in elevated norepinephrine and epinephrine levels and low acetylcholine levels, which ultimately results in release of inflammatory mediators from immune cells.[37]

The link between inflammation and depression lies in the cytokines, which elevate inflammatory signaling in the CNS, which subsequently leads to depressive symptoms.[34] Cytokines can activate indoleamine 2,3-dioxygenase (IDO), which converts tryptophan, a key component of serotonin, into kynurenine, thereby decreasing the production and availability of serotonin in the brain.[34,38] Other factors involved in the bidirectional pathway of inflammation and depression include psychological stressors, sensitization of cells to neurotoxic peptides, and oxidative and nitrosative stress.[36] Cytokines can affect production, metabolism, and transport of neurotransmitters that are responsible for mood (ie, dopamine, norepinephrine, serotonin, and glutamate).[34,38,39] Additionally, cytokines may lead to a decrease in GABA release, which can further exacerbate inflammation in the CNS.[38] Elevated levels of proinflammatory cytokines in the CNS may deleteriously influence neurotransmitters that are central to depression pathophysiology by increasing the activity of transporters that clear

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Table 1. Adjunctive therapies in the management of depression.[19–25]

Class	Modality/agent	Known side effects
Pharmacotherapy	Lithium	• Narrow therapeutic index, risk of lithium toxicity • Fine hand tremor • Downbeat nystagmus • Nausea • Headache • Weight gain • Hypercholesterolemia • Hypothyroidism • Nephrogenic diabetes insipidus • Permanent kidney damage
	Thyroid hormone	• Increased risk of cardiovascular disease • Dysrhythmias • Fractures
	Anticonvulsant medication	• Reduced effectiveness of contraceptives • Increased risk of depression and suicide • Sedation • Drowsiness • Cerebellar symptoms such as nystagmus, tremor, and incoordination
	Second-generation (atypical) antipsychotics	• Weight gain • Metabolic complications including dyslipidemia, hypertriglyceridemia, glucose dysregulation, diabetes mellitus • Hyperprolactinemia • Extrapyramidal symptoms and tardive dyskinesia • Neuroleptic malignant syndrome • QTc prolongation
	Bupropion	• Headache • Tremors • Seizures • Agitation • Jitteriness • Mild cognitive dysfunction • Insomnia • Gastrointestinal upset
	Mirtazapine	• Dry mouth • Sedation • Weight gain • Increased serum cholesterol • Agranulocytosis
	Buspirone	• Dizziness • Nausea • Headache • Nervousness • Lightheadedness • Excitement
	CNS stimulants	• Insomnia • Stomach ache • Headache • Anorexia • Risk of abuse • Acute toxicity
	Serotonin norepinephrine reuptake inhibitors (SNRIs)	• Increased blood pressure • Nausea • Vomiting • Sexual dysfunction • Activation • Increased pulse rate • Dilated pupils • Dry mouth • Excessive sweating • Constipation
Somatic therapies	Electroconvulsive therapy	• Increased heart rate and blood pressure • Increase in cardiac workload and intracranial pressure • Arrhythmias • Confusion • Anterograde amnesia • Note: this therapy requires anesthesia

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Table 1. *Continued.*

Class	Modality/agent	Known side effects
	Nerve stimulation (eg, transcranial, vagal)	• Risk of postsurgical infection • Hoarseness or voice alteration during stimulation • Coughing • Dyspnea • Neck discomfort • Interaction with implanted devices
	Transcranial magnetic stimulation (TMS)	• Transient scalp discomfort • Headache
Psychotherapy	Cognitive and behavioral, interpersonal, psychodynamic, or other[a]	• No known side effects
Complementary and alternative treatments	Folate and its metabolites	• Low-risk intervention
	St John's wort	• Note: St John's wort is not regulated by the FDA and therefore may lack standardization of ingredients, composition, and potency • Substantial drug-drug interactions including antiretrovirals, immunosuppressants, antineoplastic agents, anticoagulants, oral contraceptives, and hormone replacement therapy
	S-adenosylmethionine	• Note: *S*-adenosylmethionine is not regulated by the FDA and therefore may lack standardization of ingredients, composition, and potency
	Omega-3 fatty acids	• No known side effects
	Light therapy	• Low-risk intervention
	Acupuncture	• No substantial risks
	Exercise/physical activity	• Ischemia • Musculoskeletal symptoms

[a]Examples include problem-solving, marital, family, and group therapy.

Table 2. Evidence for inflammatory biomarkers implicated in depression.

Evidence/effect	Biomarkers
Biomarker levels elevated in patients with MDD compared with healthy individuals	CRP[36,44,45] IL-6[36,44,45,47,48] IL-1[44,47] TNF-α[45,47,48]
Elevated level of biomarker associated with worse disease severity or outcomes	CRP[49,50]
Biomarker level decreases with MDD treatment	CRP[51] IL-6[45,46,51,52] IL-1[52] TNF-α[46,52]
Biomarker level predicts response to specific MDD treatment	CRP (escitalopram, bupropion–SSRI combination)[42,53] IL-1 (exercise)[54] IL-17 (bupropion–SSRI combination)[55] PDGF (bupropion–SSRI combination)[56]

Abbreviations: CRP, C-reactive protein; IL, interleukin; MDD, major depressive disorder; PDGF, platelet-derived growth factor; TNF, tumor necrosis factor.

monoamine neurotransmitters from neuronal synapses, by decreasing the synthesis of monoamines, and by increasing excitatory and potentially neurotoxic glutamate activity through N-methyl-D-aspartate (NMDA) receptor activation and reduced astrocytic reuptake.[38] Moreover, they are known to decrease neuroplasticity and cause oxidative stress by generating nitrogen and oxygen radicals, which can promote oxidative neurotoxicity.[38,40,41]

Serologic markers of systemic inflammation are potentially useful tools that may inform clinicians about optimal treatment paradigms and antidepressant selection for individual patients.[42] Antidepressants have been shown to affect the immune system and levels of proinflammatory cytokines.[43] Specific inflammatory biomarkers that have been implicated in MDD are detailed as follows and in Table 2.[36,42,44–56]

C-reactive protein (CRP) and interleukins 6 (IL-6) and 1 (IL-1)

IL-6 and IL-1, which are secreted by activated macrophages and are upstream of CRP, were initially hypothesized to be causative inflammatory agents in depression.[57] Following decades of research, CRP—a nonspecific marker of inflammation as well as other acute-phase processes including tissue damage and infection[58]—has emerged as a major inflammatory biomarker in MDD. A meta-analysis of studies evaluating the potential relationship between CRP levels and depression found a significantly positive relationship overall (effect size, 0.22; 95% CI, 0.15–0.28; $p < 0.001$).[44] Similar findings were reported for IL-6 (effect size, 0.25; 95% CI, 0.18–0.31; $p < 0.001$) and IL-1 (effect size, 0.35; 95% CI, 0.03–0.67; $p = 0.03$). Additional meta-analyses have largely confirmed these results,[36,45–48] with some suggesting a stronger link between CRP and depression,

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compared with IL-6 or IL-1. IL-6 and IL-1β levels may be particularly elevated in patients with late-life depression (ie, age >60 or >70 years).[59,60] Elevated CRP levels have also been associated with worse outcomes, more severe symptoms,[49] and higher rates of suicide[50] in this clinical setting.

Some patients with MDD show signs of inflammatory response, including increased expression of proinflammatory cytokines and their receptors.[61] Inflammation has been associated with inadequate response to antidepressant treatment.[61] Conventional antidepressants increase synaptic availability of monoamines and also increase neurogenesis through brain-derived neutrophic factor (BDNF).[61] Cytokines impact synthesis, release, and reuptake of monoamines by decreasing serotonin and dopamine availability and increasing expression of monoamine reuptake transporters, thus weakening their signal.[38,62,63] Nonresponsiveness to antidepressant treatment and increased inflammatory markers in treatment-resistant patients may be attributed to these effects of the cytokines.[61] Increasing evidence supports the role of CRP to guide anti-inflammatory treatment in depressed patients. In a trial conducted by Raison et al, it was shown that baseline concentrations of CRP >5 mg/L correlated with better response to infliximab.[64] Furthermore, this study demonstrated the effectiveness of anti-inflammatory medications for the treatment of depression in subjects with higher baseline CRP levels, as evidenced by greater improvement in Hamilton Depression Rating Scale (HDRS)-17 scores and improvement in symptoms.[64]

Findings from meta-analyses have further detailed the relationship between CRP levels and MDD treatment.[46,51] Recently, using data from 2 independent prospective studies, researchers have shown that baseline CRP levels predict response to MDD treatment.[42,53] Uher et al[53] analyzed data from the Genome-Based Therapeutic Drugs for Depression study to evaluate whether baseline CRP level correlated with reduction in depression severity with escitalopram and nortriptyline. Patients with CRP levels of less than 1 mg/L had a greater reduction in depression severity with escitalopram versus nortriptyline (β, 3.27; 95% CI, 1.65–4.89; $p < 0.001$). In escitalopram-treated patients, the increase in baseline CRP level was associated with worsening of disease severity ($p < 0.001$). In nortriptyline-treated patients, there was a trend toward improvement in severity with increased CRP level. Using data from the Combining Medications to Enhance Depression Outcomes (Co-MED) trial, Jha et al[42] also evaluated the potential relationship between biomarker levels and response to treatment with SSRI monotherapy compared with bupropion–SSRI combination. Overall, higher baseline CRP levels were associated with greater reduction in disease severity in patients treated with bupropion–SSRI combination ($r = -0.63$) compared with SSRI monotherapy ($r = 0.40$). In patients with a CRP level of less than 1 mg/L, there was a numerical trend toward improved outcomes with SSRI monotherapy versus bupropion–SSRI combination ($p = 0.057$).

Less is known about potential relationships between IL-6 or IL-1 and treatment response. Meta-analyses[45,46,51,52] have demonstrated that IL-6 levels decrease with MDD treatment; however, there may not be a difference in outcomes by treatment response. A similar relationship has been shown for IL-1.[46,52] Another study showed a positive correlation between change in IL-1β level and depressive symptoms in patients who underwent an exercise program to manage depression.[54]

Tumor necrosis factor α (TNF-α)

Meta-analyses have also found levels of TNF-α to be higher in depressed patients than in nondepressed patients.[45–48] In a preclinical model, levels of TNF-α decreased after administration of bupropion.[65] Levels have been demonstrated to decrease with MDD treatments in some but not all clinical studies.[46,52] Elevated TNF-α levels have been associated with failure to respond to antidepressant medications,[45] but have been shown to improve response to infliximab treatment ($p < 0.05$)[64] and exercise programs.[54]

Interleukin 17 (IL-17)

Results from preclinical analyses and clinical studies have demonstrated that T-helper 17 cells accumulate in the brain and periphery during depressive states,[66,67] suggesting a potential role for IL-17 cytokines produced by these T cells.[68] An analysis of the Co-MED trial data demonstrated that elevated levels of IL-17 at baseline were associated with greater effectiveness of bupropion and SSRI in combination, but not with SSRI monotherapy or venlafaxine–mirtazapine combination therapy.[55] These findings also suggested the converse, that patients with low levels of IL-17 had a poorer response to bupropion–SSRI in combination compared with other studied treatments.

Platelet-derived growth factor (PDGF)

PDGF signaling was recently shown to have a role in neuroinflammation.[69] It has been hypothesized that secretion of PDGF, a peripheral marker of neuroinflammation, increases following damage to the blood–brain barrier due to inflammation or stress.[56] An analysis of data from the Co-MED trial[56] found that treatment with bupropion–SSRI combination therapy was associated with decreased severity of depression and anhedonia in patients with higher versus lower levels of PDGF at baseline.

Microglial cells and extracellular vesicles

Microglial cells are associated with depression, although the exact mechanism behind this is unclear.[70,71] Elevated microglial cell numbers have been observed in patients with depression and depressive symptoms.[70] Microglial cells serve as the immunologic guards of the brain through their anti-inflammatory and neuroprotective role, and their abnormal activation results in release of inflammatory mediators, which may be a factor behind the immune response in depression.[70,71] Activated microglia cells release microvesicles that contain IL-1β, IL-1β processing enzyme caspase-1, IL-6, TNF-α, the P2X7 receptor, reactive oxygen species, and reactive nitrogen species, and can cause inflammation in the brain.[62,70] Extracellular vesicles are also released by reactive microglia and are important in intercellular communication and neuroinflammation through transport of mRNA, microRNA, and proteins.[70]

Metabolic disorders

The prevalence of obesity is rising, which not only increases the risk of cardiovascular disease but also increases the rates of depression.[72] Obese individuals have up to a 2-fold increased probability of developing depression, with significantly increased risk in those with higher body mass index (BMI) and in females.[73–76] A BMI of 30 kg/m^2 or more, increased waist-to-hip ratio, and particularly abdominal fat have been shown to increase the risk of MDD and to predict lower response to usual care antidepressants.[75,77,78] Inflammation and abdominal fat serve as the link between obesity and MDD, as well as worse antidepressant response. It has therefore been suggested that BMI measurements could be used to direct patient care in depression.

Metabolic disorders are not limited to obesity or high BMI: diabetes and insulin resistance are also associated with increased levels of depression.[79] Insulin resistance is associated with increased CRP levels and BMI, specifically abdominal fat.[80] In the Framingham Heart Study, the odds ratios of insulin resistance with abdominal obesity, as measured by subcutaneous adipose tissue and visceral adipose tissue, were 2.48 (95% CI, 2.24–2.74; $p < 0.0001$) and 3.46 (95% CI, 3.08–3.90; $p < 0.0001$), respectively.[80] Improving dietary factors, addressing insulin resistance and/or diabetes, and promoting a regimen of exercise may reduce depressive symptomology.[81,82] Physical exercise has many benefits, such as decreased risk of cardiovascular and metabolic disease; reduced inflammatory parameters, including CRP; improved psychological functioning and mood; and increased neurotransmitters such as serotonin, dopamine, and norepinephrine.[82–84] In addition, markers of obesity, insulin resistance, and metabolic syndrome have been correlated with increased levels of CRP in patients with depression, as well as increased severity of depressive symptoms.[85,86]

Cardiovascular disease

Cholesterol is essential for CNS development and function, synapse formation, dendrite formation, and axonal guidance.[87] Interference with any of these mechanisms can result in disruption in neurotransmission and diminished synaptic plasticity, both of which are found in patients with depression.[87] Studies have demonstrated an increased risk of cardiovascular disease and cardiac-related death in patients who have depression.[88,89] Though the exact link between cardiovascular disease and MDD has not yet been clearly defined, altered cholesterol metabolism and atherosclerosis have been thought to contribute to the risk of depression, as evidenced by abnormal cholesterol levels in MDD patients.[87,90] Patients with MDD have been observed to have lower high-density lipoprotein cholesterol levels and elevated low-density lipoprotein cholesterol levels, indicating a positive correlation between depression and cholesterol metabolism.[78,87,91,92]

Notably, serotonin plays an important role in platelet aggregation. Increased serotonin in the cardiovascular system may cause arrhythmia and subsequent heart block or valvular fibrosis.[93] During occlusive coronary thrombus formation, serotonin may increase clot stability and ischemia, as a result of its vasoconstrictive properties. Administration of SSRIs limits the uptake of blood serotonin by platelets, inhibits platelet aggregation, and increases risk of bleeding.[94]

Stress

Stress, both chronic and acute, may be neurotoxic in nature, associated with increased levels of inflammatory markers, weakening of the blood–brain barrier, and peripheral cytokine entry into the brain.[95] Life stressors, in combination with genetic predisposition, put individuals at a higher risk for developing depression.[96] Stress may induce an inflammatory response in the brain (through an overstimulated immune system and overactivated sympathetic nervous system) and increase glucocorticoid levels.[63] In some patients, activation of the hypothalamic–pituitary–adrenal axis is observed, which increases stress hormones such as corticotrophin-releasing hormone and adrenocorticotropic hormone.[63]

Proinflammatory cytokines and acute-phase reactants, such as CRP, IL-6, and TNF-α, are involved in stress-induced inflammation.[63] Through increased inflammatory cytokine expression, stress can provoke depressive symptoms and lead to changes in behavior.[63] Stress also leads to the release of hormones, such as cortisol and dehydroepiandrosterone (DHEA), that are associated with the development of depressive symptoms.[96] These factors can lead to hyperactivity of neural networks such as the hypothalamic–pituitary axis, which may be responsible for depressive symptomology resulting from chronic or acute stress.[97] Stress may also cause reductions in 5-HT1A receptor binding and changes in serotonin activity, which may contribute to anxiety and depression.[96] Indeed, stressful life events, especially early life adversity are associated with a higher risk of depression.[98–100] Early life adversity, which includes abuse, neglect, distress, and negative experiences during the infancy/toddler age, has been shown to impact neurobiological development, resulting in depressive behavior.[99] Furthermore, maternal depression is a risk factor for depression in children and remission in the treatment of depressed mothers has been shown to reduce psychopathology in their children.[101]

Key takeaways

The emerging evidence discussed here suggests that factors including inflammation, metabolic abnormalities, and stress may contribute to the pathophysiology of depression. Furthermore, it is possible that when these elements have contributed to an individual patient's depression, that patient may be less likely to respond adequately to antidepressant monotherapy, especially therapies that are predominantly serotonergic, such as SSRIs or SNRIs. These patients may be better served by early adjunctive interventions.

The Role of Folate in Depression

Following the active uptake of the reduced form of folate across the blood–brain barrier, it is transported into neuronal cells through the cerebrospinal fluid and is involved in the methylation of homocysteine, synthesis of methionine and *S*-adenosylmethionine (SAMe), and other methylation-dependent pathways in depression.[7] A growing body of literature supports the importance of folate in cognition and the cognitive deficits that are associated with psychiatric conditions. Folate levels have been found to correlate with performance in various cognitive tasks[102] and are inversely correlated with dementia and Alzheimer disease risk.[103,104] Antibodies against folate receptors have been found in patients with psychiatric conditions,[105] and maternal folate deficiency increases the risk of psychiatric illness in children.[106] In studies of folate and depression, higher folate intake was correlated with a lower risk of depression and anxiety, and folate levels were found to be inversely correlated with depression risk.[107,108] In a prospective clinical study, folate levels were shown to be notably lower in patients with depression than in the control group ($p < 0.01$).[109] Furthermore, decreased levels of folate have been shown to be associated with lower cognitive performance, lower psychomotor speed, and greater depressive symptoms, suggesting a concentration–response relation.[102,104,108,110]

Several mechanistic links may exist between folate and depression (Figure 1).[7,8,111–114] Folate has been associated with a reduction in gray matter loss, suggesting a neuroprotective effect[114]; it is required for the health and functioning of DNA through its role in methylation[115]; and it is necessary for proper functioning of the 1-carbon metabolism cycle. Proper functioning of the 1-carbon metabolism cycle is critical for neural development, neural health in adulthood, and inflammation signaling pathway function,[116] which has been implicated in mood regulation.[117] Folate can

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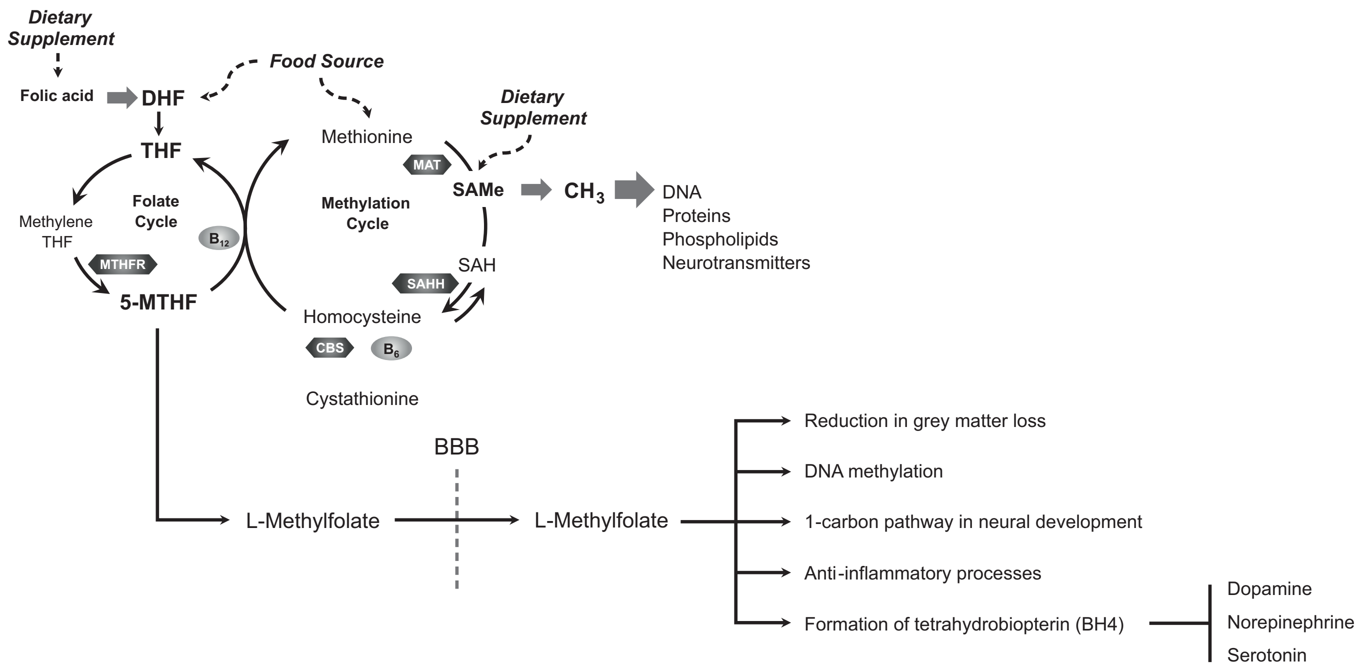

Figure 1. L-Methylfolate enters the brain and influences numerous neural processes to promote neurological health and function.[7,8,111–114] BBB, blood–brain barrier; CBS, cystathionine β synthase; DHF, dihydrofolate; MAT, methionine adenosyltransferase; 5-MTHF, 5-methyltetrahydrofolate; MTHFR, methyltetrahydrofolate reductase; MTR, methionine synthase; SAH, *S*-adenosylhomocysteine; SAHH, *S*-adenosylhomocysteine hydrolase; SAMe, *S*-adenosylmethionine; THF, tetrahydrofolate.

positively impact lipid profiles and reduce oxidative stress, and folate-related genes can impact mood through stress-related mechanisms.[118–120] Furthermore, during inflammation or oxidative stress, folate may be involved in the biochemical reactions, leading to the synthesis of the monoaminergic neurotransmitters that are implicated in the pathophysiology of depression.[117]

Underscoring the link between folate and depression are genetic mutations and polymorphisms to folate-related genes that have been identified in conjunction with neurological disorders.[121] The gene encoding the enzyme methylenetetrahydrofolate reductase (MTHFR) of the 1-carbon pathway, and the genes encoding the enzymes methionine synthase (MTR) and methionine synthase reductase (MTRR),[122] are necessary for converting dietary dihydrofolate or folic acid to L-methylfolate, the biologically active form of folate that can pass through the blood–brain barrier. L-methylfolate has a higher bioavailability than folic acid and is the only form of folate that is able to cross the blood–brain barrier.[123]

MTHFR is an essential enzyme responsible for the irreversible final step in folic acid reduction to produce L-methylfolate, therefore, a mutation in the *MTFHR* gene cannot be bypassed by any of the intermediate metabolites, as this would require metabolism through MTHFR.[112] Numerous pharmacogenomics studies have revealed the strong correlation between *MTHFR* polymorphisms and depression, validating its importance in this clinical setting.[120,124–126] Furthermore, the precise polymorphism present may determine whether a patient demonstrates a normal, intermediate, or poor metabolizer phenotype.[127] Patients with *MTHFR* variants may not synthesize adequate amounts of monoaminergic neurotransmitters, limiting the effectiveness of SSRI/SNRI antidepressants. Indeed, animal studies of folate in depression suggest that folate may improve symptoms of depression or augment the effects of antidepressants.[128]

Given its established role in the pathophysiology of depression, both the American Psychiatric Association[23] and the British Association for Psychopharmacology[129] have recommended folate in general, and L-methylfolate specifically, as augmentation/adjunctive strategies for patients with depression. According to the American Psychiatric Association, folate is recommended as a reasonable adjunctive strategy with little risk, as supported by modest evidence.[23] The British Association for Psychopharmacology recommends using L-methylfolate as the "next step" in patients who are not responsive to drugs for depression.[129]

Clinical Evidence for the Use of L-Methylfolate

A prescription formulation of L-methylfolate (Deplin®, Alfasigma USA, Inc.; Covington, LA) is a medical food with a recommended dosage of 15 mg/day for use under clinician supervision for the dietary management of depression, and meets distinctive nutritional requirements for patients with depression.[130,131] The efficacy of this formulation of L-methylfolate used adjunctively for the treatment of MDD has been analyzed in 2 double-blind, randomized, placebo-controlled clinical trials (Table 3),[33,111,113,132–134] which together represent the largest number of patients treated with any form of folate ever studied for MDD.[33,111,113,132,133] Results from these large-scale and best-designed clinical trials provide robust evidence regarding the safety and efficacy of various doses of L-methylfolate and its potential place in therapy for MDD. Furthermore, notable findings from these studies provide valuable insight into which candidates would achieve optimal outcomes and may benefit most from L-methylfolate treatment.

Importantly, adjunctive use of L-methylfolate was found to be efficacious and has been determined to work especially well in certain subsets of patients, including those with SSRI-resistant depression.[111] Overall, adverse events with L-methylfolate and with placebo were similar (Table 4),[111] with minimal changes in weight, supine and standing heart rate, and supine and standing diastolic and systolic blood pressure.

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Table 3. Clinical evidence for the use of L-methylfolate in the treatment of depression.

Study	Design	Size	Efficacy Outcomes	Safety Outcomes	Conclusion
Ginsberg et al, 2011[132]	Retrospective analysis of L-methylfolate as adjunctive therapy to SSRI/SNRI in adult patients with MDD	95 patients received L-methylfolate 147 patients received SSRI/SNRI monotherapy	CGI-S scores met threshold for major improvement after 60 days in 18.5% of patients on L-methylfolate adjunctive therapy, compared with 7.04% of those on monotherapy Calculated NNT for ≥2 point reduction in CGI-S score at 60 days: 9	No statistically significant difference between adverse events in each group; numerical trend (not significant) toward reporting of weight gain at visits with monotherapy compared with L-methylfolate combination Calculated NNH for antidepressant discontinuation due to adverse events: 6	Combination was more effective in improving symptoms of depression and function; L-methylfolate safe and well tolerated
Papakostas et al, 2012, study 1[111]	Patients with SSRI-resistant MDD were randomized to placebo or L-methylfolate 7.5 mg/day for 60 days, or placebo for 30 days and then L-methylfolate, in addition to SSRIs	148 patients	No significant differences between groups were found Calculated NNT for pooled response rate: 200	Safe and well tolerated, lacked side effects of other usual care therapies Calculated NNH for somatic adverse events: 10	7.5 mg/day may not be a sufficient dose for clinical efficacy
Papakostas et al, 2012, study 2[111]	Patients with SSRI-resistant MDD were randomized to placebo or L-methylfolate 15 mg/day for 60 days, or placebo for 30 days and then L-methylfolate, in addition to SSRIs	75 patients	Efficacy was significantly greater for patients who also received L-methylfolate, which reduced symptoms by up to 84% Calculated NNT for pooled response rate: 6	Safe and well tolerated, lacked side effects of other usual care therapies Calculated NNH for somatic adverse events: 7	15 mg/day may be a clinically effective dose of L-methylfolate for adjunctive use
Papakostas et al, 2014[133] Fava et al, 2013[113]	Post hoc analysis of study reported by Papakostas et al, 2012[111]	74 patients	Evaluated hsCRP, BMI, genetic polymorphisms, and other biomarkers. Patients with genetic markers at baseline in the L-methylfolate group had a significantly ($p \leq 0.05$) greater pooled mean change from baseline in HDRS-28 scores than did that subgroup of patients in the placebo arm	N/A	Combinations of baseline biological and genetic markers predicted significantly ($p \leq 0.05$) greater reductions in depression rating scores. Adjunctive L-methylfolate demonstrated greater mean change in HDRS-28 scores from baseline compared with placebo (-6.8 ± 7.2 vs -3.7 ± 6.5, $p = 0.017$). Greatest pooled mean changes in genetic markers were found in *MTHFR 677 CT/TT + MTR 2756 AG/GG, GCH1 TC/TT + COMT GG, and GCH1 TC/TT + COMT CC*
Shelton et al, 2015[134]	Exploratory post hoc analysis of study reported by Papakostas et al, 2012[111]	69 patients	Response to supplemental L-methylfolate was significantly greater than	N/A	Combinations of elevated BMI plus inflammatory markers were predictive

Table 3. *Continued.*

Study	Design	Size	Efficacy Outcomes	Safety Outcomes	Conclusion
			placebo for patients with BMI ≥30 kg/m^2 ($p = 0.001$) or elevated levels of IL-8 ($p = 0.025$); pooled effects after correction for multiple testing were demonstrated for patients with BMI ≥30 kg/m^2 plus elevated levels of IL-8, IL-12, TNF-α, hsCRP, or leptin ($p < 0.03$)		of better treatment response with adjunctive L-methylfolate
Zajecka et al, 2016[33]	Extension of study reported by Papakostas et al, 2012[111] 12-month, open-label, long-term maintenance study of patients receiving L-methylfolate following a 30-day, double-blind, placebo-controlled trial	68 patients	92% of patients achieved response within 3–6 months; 75% of patients showing a response at baseline achieved full remission; 60% of SSRI nonresponders achieved remission during the long-term maintenance phase of the trial; no reported recurrence in patients who recovered	Safety profile comparable to placebo	Potential benefits of adjunctive L-methylfolate 15 mg over 12 months included high rates of response; remission; and absence of recurrence

Abbreviations: BMI, body mass index; CGI-S, Clinical Global Impressions-Severity; HDRS-28, 28-item Hamilton Depression Rating Scale; hsCRP, high-sensitivity C-reactive protein; MDD, major depressive disorder; *MTHFR*, methylenetetrahydrofolate reductase gene; *MTR*, methionine synthase gene; *MTRR*, methionine synthase reductase gene; N/A, not applicable; NNH, number needed to treat in order for 1 person to experience harm; NNT, number needed to treat in order for 1 person to benefit; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Table 4. Reported adverse events using adjunctive therapy to SSRIs with L-methylfolate or placebo in SSRI-resistant depression.[111]

Adverse event	Placebo[a] $n = 54$	L-methylfolate 15 mg/day[a] $n = 42$
Gastrointestinal	8 (14.8)	7 (16.7)
Sleep	3 (5.5)	1 (2.4)
Psychological	9 (16.7)	4 (9.5)
Somatic	16 (29.6)	6 (14.3)
Infectious	7 (13.0)	5 (11.9)
Cardiovascular	0 (0)	0 (0)
Sexual	0 (0)	1 (2.4)
Miscellaneous	5 (9.3)	1 (2.4)

Data are n (%).
[a]Ns are based on the total numbers of patients who received placebo or 15 mg of L-methylfolate, respectively, at some point during the trial.

In a post hoc analysis by Papakostas et al,[111,113,133] changes from baseline in the 28-item HDRS-28 score were significantly greater with L-methylfolate versus placebo across all investigated plasma markers, which included a SAMe:SAH (*S*-adenosylhomocysteine) ratio of less than 2.71, high-sensitivity CRP (hs-CRP) levels of 2.25 mg/L or greater, and 4-hydroxy-2-nonenal blood levels of 3.28 μg/mL or less ($p \leq 0.05$). There were also statistically significant improvements from baseline in most genetic markers in the L-methylfolate group ($p < 0.05$). Subgroups of patients with *MTR* 2756 AG/GG or *MTRR* 66 AG/GG genotypes had greater mean changes from baseline in HDRS-28 scores than those with homozygous dominant genotypes ($p < 0.05$). Combinations of biomarkers and/or genetic markers (eg, *MTHFR* 677 CT/TT+*MTR* 2745 AG/GG) had varying effect sizes but also were associated with marked improvements in HDRS-28 scores ($p \leq 0.05$; number needed to treat in order for 1 person to benefit [NNT], 1–4). Another post hoc analysis by Shelton et al[134] determined that patients with BMI ≥30 kg/m^2 or elevated levels of IL-8 ($p = 0.025$) had significantly greater clinical responses with adjunctive L-methylfolate. After correction for multiple testing, pooled effects were demonstrated for patients with BMI ≥30 kg/m^2 plus elevated levels of IL-8, IL-12, TNF-α, hsCRP, or leptin ($p < 0.03$).

Clinical Scenarios for L-Methylfolate use in MDD: Good, Better, and Best

The positive clinical trial findings for L-methylfolate use as an adjunctive treatment for depression suggest that certain patient characteristics may be especially predictive of response. These characteristics, along with the good, better, and best scenarios in which L-methylfolate use may be more or less likely to improve a patient's symptoms, are summarized in Figure 2[8,23,111,113,130,131,133–136] and described in detail below.

Good scenario

Overall, L-methylfolate and other forms of folate are considered to be low-risk adjunctive interventions in patients with MDD, and are associated with general health benefits.[23] Individuals who prefer nutritional products with limited side effects may find L-methylfolate an attractive adjunctive option,[8] as well as those

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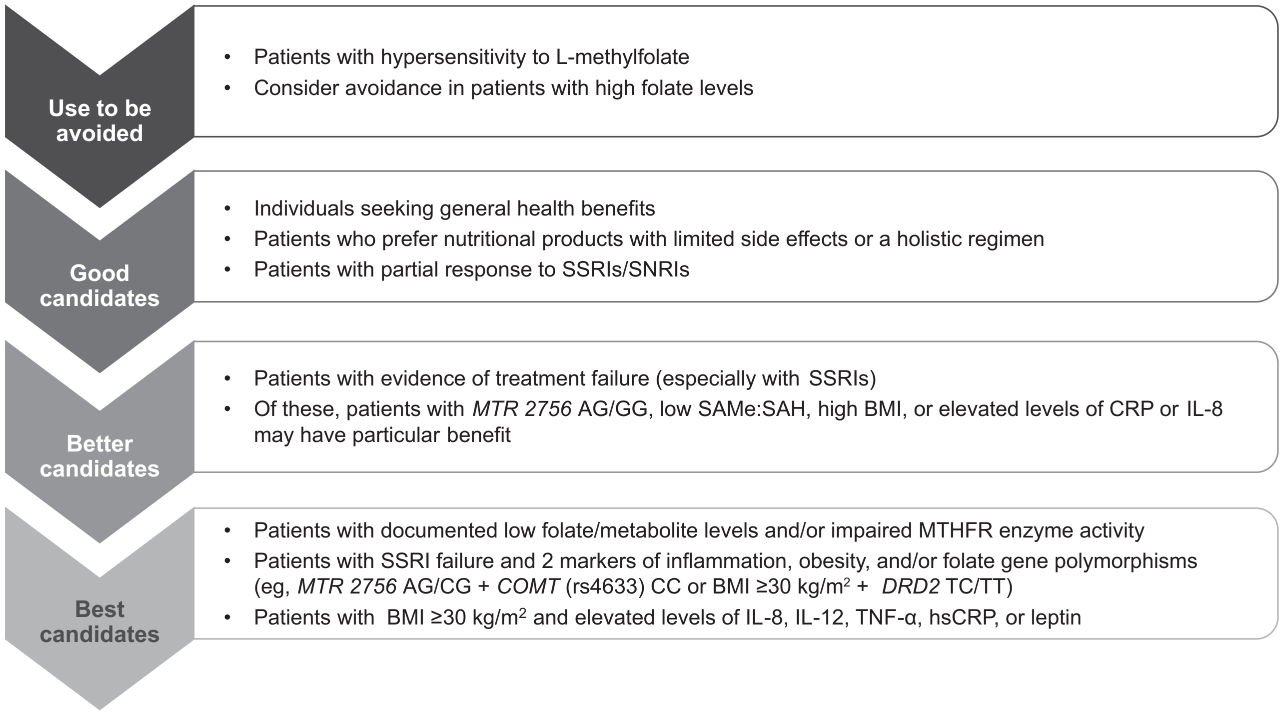

Figure 2. Good, better, best: candidates for the adjunctive use of L-methylfolate to treat depression.[8,23,111,113,130,131,133-136] MTHFR, methyltetrahydrofolate reductase; SSRI, selective serotonin reuptake inhibitor.

who attempt a holistic regimen including exercise induction[23] to manage more mild depressive symptoms. Patients with a partial response to SSRI/SNRIs may augment treatment with L-methylfolate to achieve better outcomes. In a retrospective study, patients who were treated with SSRI/SNRIs supplemented with L-methylfolate had greater improvements in depressive symptoms than patients who were treated with SSRI/SNRIs alone ($p = 0.01$),[132] without alteration of the SSRI/SNRI side effect profile.

Better scenario

L-Methylfolate may be of better clinical utility in patients who have evidence of MDD treatment failure, particularly with SSRIs. As described above, use of L-methylfolate is associated with better efficacy in patients with SSRI-resistant depression.[111] These outcomes are particularly improved in patients with the *MTR* 2756 AG/GG genotype, a low SAMe:SAH ratio, high BMI, or elevated levels of CRP or IL-8.[113,133,134] These findings are important because treatment considerations post–SSRI failure may include atypical antipsychotics, which are associated with a risk of tardive dyskinesia, potentially irreversible. Atypical antipsychotics might also be inappropriate in obese patients due to their class-related metabolic side effects (ie, weight gain; increased levels of insulin, glucose, and low-density lipoprotein cholesterol; diabetes mellitus; and hypertriglyceridemia).[137–139] Use of these agents may also put patients at greater risk for cardiovascular complications, including stroke and coronary heart disease,[139] which are also associated with high CRP levels.[58]

Best scenario

Patients with MDD and BMI ≥30 kg/m^2, documented low levels of folate or its metabolites, and/or impaired MTHFR enzyme activity have a clear rationale for the adjunctive use of L-methylfolate.[8,113,136] In some patients, low folate levels can result from alcohol abuse, hypothyroidism, eating disorders, pregnancy, gastrointestinal disorders, or from taking certain medications; thus, clinicians should consider adding L-methylfolate to the treatment regimen of patients with any of these factors.[8] Findings from the post hoc analysis of clinical trials with L-methylfolate[133] demonstrated the largest effect sizes versus placebo and NNT = 1 for L-methylfolate in patients whose depression failed to respond to SSRI therapy and had 2 of the studied biologic markers associated with inflammation/obesity and/or folate metabolism gene polymorphisms (eg, *MTR* 2756 AG/CG + *COMT* (rs4633) CC or BMI ≥30 kg/m^{2} + *DRD2* TC/TT). Additionally, pooled effects have been shown for patients with BMI ≥30 kg/m^2 plus elevated levels of IL-8, IL-12, TNF-α, hsCRP, or leptin.[134] Therefore, identification of more than 1 of these factors is an especially important indication that adjunctive L-methylfolate use may improve a patient's clinical outcome.

When to avoid use of L-methylfolate

Although it is an effective, low-risk option, L-methylfolate may not be suitable for all patients. L-methylfolate should not be used in patients with hypersensitivity to the product.[130,131] In general, high folate levels may increase the risk for cardiovascular disease.[135] Similarly, while moderate folate levels have been associated with reduction in the risk of several cancer types, the risk of adenoma recurrence and colorectal cancer may be higher with both low and high levels of folate.[135] Patients who exhibit signs of manic, hypomanic, or mixed episodes should have their diagnosis and treatment reevaluated[23] and should not necessarily initiate or continue folate supplementation. In particular, findings from a clinical study in bipolar depression[140] suggest potential dampening of the effects of lamotrigine, which is known to inhibit dihydrofolate reductase and the formation of L-methylfolate,[141] when coadministered with folate. Augmentation with L-methylfolate or folinic acid, which do

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not require conversion by dihydrofolate reductase, may mitigate this effect.[141]

Additional considerations

Promotion of wellness

Considerations for adding L-methylfolate to a patient's treatment include its use in addition to diet and exercise modifications and its introduction early in the course of treatment. Dietary supplementation with folate alone is not sufficient for treatment, since it requires enzyme conversion and must be reduced to the active form.[112] As previously mentioned, genetic mutations in the enzymes involved in the folate pathway may impair enzymatic conversion to L-methylfolate and affect L-methylfolate levels, especially in patients with depression and people with higher risk for low folate levels (eg, pregnant women, people who abuse alcoholic, people with eating disorders). In this subset of patients, supplementation with L-methylfolate would be beneficial. L-methylfolate, as opposed to atypical antipsychotics, is not known to produce fatigue,[111] and therefore may be conducive to starting or maintaining exercise regimens and to supporting general wellness initiatives for patients with MDD. Because physical activity has recently been recognized by the European Psychiatric Association as being therapeutic for people with severe mental illness, including depression,[82] and because exercise has clearly demonstrated antidepressant effects,[142–144] consideration of L-methylfolate use aligns well with recommendations for diet/exercise and promotion of wellness in patients with MDD.

Safety profile

Importantly, L-methylfolate is well tolerated, and its safety profile is similar to that of placebo when used as adjunctive therapy in MDD.[33,111,132] Use of L-methylfolate is not associated with the sexual, cardiovascular, metabolic (ie, weight gain), and neurologic side effects associated with atypical antipsychotics and SSRI/SNRIs.[23,111,145] In addition to metabolic and weight gain side effects, atypical antipsychotics have been associated with movement disorders such as akathisia, extrapyramidal symptoms, and tardive dyskinesia.[146,147]

Quality of life and patient satisfaction

Patients who used L-methylfolate as augmentation for the management of MDD reported major improvements in functioning at work, at home, and in social situations.[123] The percentage of patients who had reported functioning being very difficult or extremely difficult decreased from 50% to 13% following L-methylfolate treatment. Furthermore, patient satisfaction reached a rating of 7 out of 9 after treatment from 5.2 prior to treatment, with 1 being "not at all satisfied" and 9 being "very satisfied."

Availability and interpretation of genetic testing

Pharmacogenetic testing was recently shown to improve treatment outcomes, identify patients likely to have treatment resistance, reduce side effect burden, and facilitate selection of genetically appropriate medications in depression management.[148,149] These tests may provide clinicians with better insight in the management of depression by identifying genetic markers, such as mutations in enzymes involved in the metabolism of folate, that may guide treatment decisions. Overall, while the concept of pharmacogenetic testing is promising in MDD, more research is needed before clinical use may become routine.[149]

Considering the positive correlation between *MTHFR* polymorphisms and the risk of depression, genetic testing may be a promising avenue for identifying patients who may benefit from L-methylfolate supplementation in this clinical setting.[124] Salivary or blood genetic testing kits for *MTHFR* variants, typically *C677T* and *A1298C*, are commercially available[150] and can be performed in most conventional laboratories.[151] The salivary genetic test is available through companies that offer complete genetic profiling; however, it is not recommended to be used for the diagnosis of depression.[151]

Conclusions

L-methylfolate has been well studied in multiple clinical trials, and findings support its consideration for use as an adjunctive therapy in any depression management program, and especially in patients with characteristics suggestive of potential responsiveness, such as low folate levels, mutations in genes coding enzymes involved in the metabolism of folate, BMI greater than 30 kg/m^2, and elevated markers of inflammation, including CRP. Use of L-methylfolate in the clinical setting of MDD should be considered in conjunction with other treatments and forms of holistic management, in a multimodal team approach. Supplementation with L-methylfolate fits well with the changing paradigm of MDD management, with the ultimate goal of producing wellness instead of focusing solely on symptom reduction. Future studies with L-methylfolate could help to further confirm its role in the management of MDD.

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