

The Evolving Pathophysiology of MDD and the Role of Folate

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The clinical manifestations of depression were described more than 2500 years ago,¹ although current terminology including “depression” was not established until the late 19th century,² and the pathophysiology of this common disorder is still being elucidated.³ A recent search of the PubMed database using the key words “depression” + “pathophysiology” identified 3628 articles published within the past 2 years alone. Because major depressive disorder (MDD) is highly variable, complex, multifactorial, and etiologically heterogeneous,^{4,5} its pathophysiology provides the foundation for rational therapy. The proposed underlying pathophysiologic mechanisms broadly include diathesis (vulnerability)-stress,⁶ environmental effects on genes (epigenetics), cellular (oxidative) stress, and neuroinflammation, the latter defined as an inflammatory response within the brain or spinal cord, mediated by proinflammatory cytokines (small protein molecules such as interleukin [IL]-1, IL-6, IL-8, and tumor necrosis factor- α [TNF- α] that are produced by several immune cells), reactive oxygen species (unstable molecules, sometimes called “free radicals,” that can contribute to inflammatory processes), and immune mediators⁷ (Figure 1).

Pathophysiology of MDD: Focus on Inflammation

Bidirectional Relationship Between Depression and Inflammation

The relationship between depression and inflammation is well documented.⁸⁻¹⁰ Patients with MDD typically have increased levels of proinflammatory cytokines and C-reactive protein (CRP).

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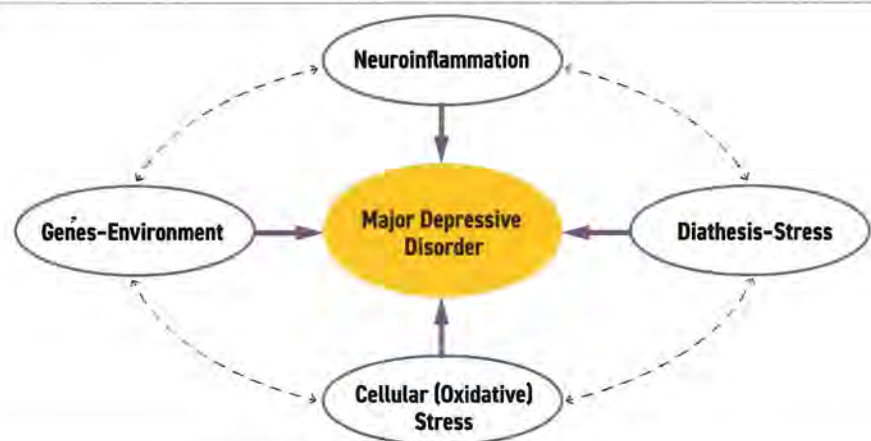
Proinflammatory cytokines and CRP may predict the development of depressive disorders, and administration of proinflammatory cytokines or inflammatory stimuli (eg, typhoid vaccine or endotoxin) can induce depressive symptoms. Patients with MDD show higher cerebrospinal fluid (CSF) levels of proinflammatory cytokines and increased expression in postmortem brains of TNF- α messenger RNA (mRNA), monocyte chemoattractant protein-1 mRNA (MCP-1, a cytokine that regulates migration and infiltration of inflammatory cells), and Toll-like receptor-3 and -4, which play a role in innate immune responses.¹¹ In addition, some viral pathogens induce cytokine production and are associated with depressive symptoms. These findings suggest a bidirectional interaction between cytokines and mood (ie, inflammation increases the risk of depression and depression increases

the risk of inflammation).¹⁰ Conversely, blockade of proinflammatory cytokines can reduce depressive symptoms, and not all patients with MDD display elevated markers of inflammation, which are more common in the presence of stress, nonpsychiatric comorbidities, and obesity.⁸

Evolving Paradigm of the Pathophysiology of Depression

The 3 neurobiological correlates of MDD are 1) dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, 2) depletion of brain serotonin, and 3) alteration of the continuous production of adult-generated neurons in the hippocampus.¹² The HPA axis, sympathetic nervous system, and serotonergic, adrenergic, and dopaminergic central pathways—in concert with genetic factors and glucocorticoid and leptin (a hormone released from adipocytes in adipose tissue) receptors—all play roles in the association between inflammation and MDD.¹³ Briefly, activation of the HPA axis in the central nervous system (CNS), which typically is caused by stress, leads to increased hypothalamic secretion of corticotropin-releasing hormone

Figure 1. Interactive Pathophysiologic Matrix of MDD.



(CRH), followed by increased release of adrenocorticotrophic hormone (ACTH) from the anterior pituitary and then increased secretion of glucocorticoids from the adrenal cortex. Activation of the HPA axis is also associated with increased sympathetic tone, characterized by decreased release of acetylcholine, increased release of norepinephrine, and the release of proinflammatory cytokines in the brain ("inflamed brain"). In addition, there is disruption in synaptic plasticity due to decreased brain-derived neurotrophic factor (BDNF, a key modulator of neuroplasticity) and alterations in dopamine, serotonin, and norepinephrine signaling.⁹ These interactive pathways are summarized in **Figure 2** and together contribute to the

cognitive and emotional features of depression (eg, anhedonia, depressed mood, feelings of decreased self-worth, reduced ability to concentrate, and suicide ideation).¹⁴

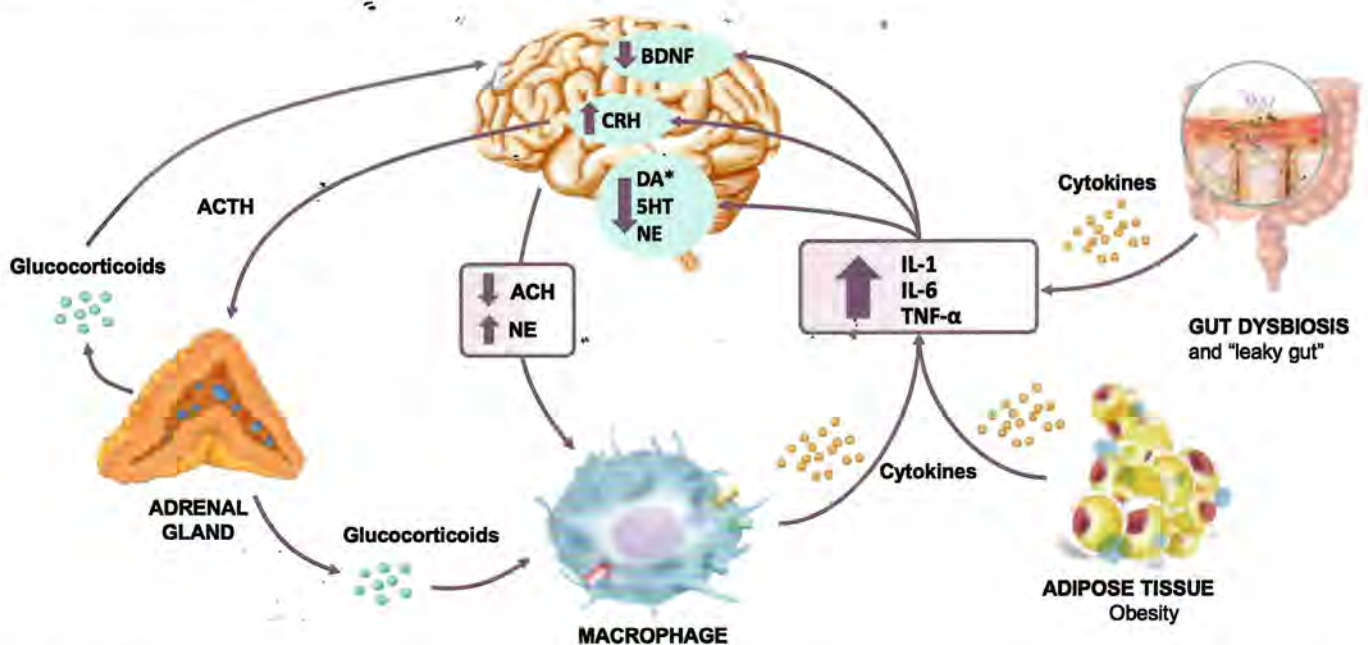
Inflammation plays a key role in the pathophysiology of depression.

In addition to recruiting peripheral immune activating cells, cytokines activate microglia (resident macrophages in the brain).¹¹ Activated microglia then release proinflammatory cytokines such as IL-6 and TNF- α , which induce activation of the HPA axis and subsequent secretion of glucocorticoids by the adrenal cortex. Glucocorticoids in turn modulate

not only the HPA axis but also microglial activation,¹⁸ creating what could be described as a self-perpetuating proinflammatory state.

Proinflammatory cytokines also influence the synthesis, release, metabolism, and reuptake of key mood-relevant neurotransmitters in the brain, including the monoamines dopamine, serotonin, and norepinephrine.¹⁸ Serotonin and norepinephrine reuptake inhibitors modulate the development of cytokine-induced depressive-like behavior in research settings. For example, studies have shown that the CSF concentration of IL-6 is elevated in patients with MDD and that there is a significant positive correlation between depression scores and CSF IL-6 levels.¹⁹

Figure 2. Evolving Paradigm of the Pathophysiology of MDD.



*Decreases efficiency of monoamine synthesis. 5HT=5-hydroxytryptamine; ACH=acetylcholine; ACTH=adrenocorticotrophic hormone; BDNF=brain-derived neurotrophic factor; CRH=corticotropin-releasing hormone; DA=dopamine; IL-1=interleukin-1; IL-6=interleukin-6; NE=norepinephrine; TNF- α =tumor necrosis factor-alpha.

Inflammation plays a key role in the pathophysiology of depression via 3 major pathways.⁹ (1) Stress stimulates the release of glucocorticoids from the adrenal cortex, CRH from the hypothalamus, and the peripheral proinflammatory cytokines IL-1, IL-6, and TNF- α .^{9,15} CRH is the primary regulator of HPA axis activation.⁹ (2) HPA overactivity leads to alteration of autonomic balance favoring sympathetic (NE) over parasympathetic (ACH) signaling and increased sympathetic tone, promoting the release of proinflammatory cytokines from macrophages. Sympathetic signaling is activated under stress; parasympathetic signaling is associated with stress reduction. The 2 systems have complementary functions, operating in tandem to maintain homeostasis. Proinflammatory cytokines interfere with monoaminergic (DA, 5HT, and NE) and neurotrophic (eg, BDNF) signaling. (3) In addition, obesity and lipid accumulation in adipocytes, especially abdominal adipocytes, leads to an increased release of inflammatory cytokines.¹⁶ The "leaky gut" theory postulates that many factors including stress and unhealthy diet damage the gut barrier, increase intestinal permeability, and allow lipopolysaccharides (large molecules consisting of a lipid and a polysaccharide that activate peripheral inflammatory cells) to traverse the previously impermeable barrier.¹⁷ Lipopolysaccharides and other endotoxins contribute to an immune-mediated inflammatory response, which includes the release of proinflammatory cytokines.¹⁶

The concentration of the proinflammatory cytokine IL-6 is increased in the CSF of patients with MDD.

Among the many known neurotrophins (growth factors that regulate many aspects of neuronal function), BDNF is the most abundant in the CNS, where it is synthesized mainly in the hippocampus and hypothalamus.²⁰ BDNF modulates neurotransmitter release and neuronal differentiation, adaptation, growth, and survival, collectively defined as neuroplasticity. Reduction of functional neurotrophic factors such as BDNF may contribute to the pathophysiology of depression by attenuating neuroplasticity.²¹ Several studies have demonstrated the reduced expression of BDNF in depressed persons and increased levels of BDNF following antidepressant therapy.²⁰

Relationship Among Obesity, Adipose Tissue, Proinflammatory Cytokines, and Depression

Obesity/Adipose Tissue Contribute Proinflammatory Cytokines

Depression and obesity share alterations in cell-mediated immune responses¹⁴ and demonstrate similar activation of inflammatory and immune pathways leading to neuroinflammation.¹³ In particular, lipid accumulation in the form of white adipose tissue (so-called "bad fat") in the abdomen activates innate immune mechanisms.¹⁶ Specifically, adipocytes in white adipose tissue secrete hormonal and immunostimulatory factors including so-called adipocytokines (ie, adiponectin, leptin, resistin, visfatin) as well as IL-6 and TNF- α , which are believed to be key links between obesity and inflammation.¹⁶ Activated macrophages in white adipose tissue also produce MCP-1, and lipid accumulation in adipocytes increases the production of MCP-1.¹⁶ MCP-1, in turn, leads to further accumulation of mononuclear cells and production of cytokines. This cyclic series of events results

in a chronic inflammatory milieu that appears to mediate the link between obesity and depressive disorders.

Bidirectional Relationship Between Depression and Obesity

Studies have confirmed a bidirectional relationship between depression and obesity, ie, depression increases the risk of obesity and obesity increases the risk of depression.¹⁶

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A meta-analysis of 15 longitudinal studies confirmed a bidirectional association between depression and obesity (especially abdominal adiposity).²⁵ Specifically, obese persons had a 55% increased risk of developing depression over time, and depressed persons had a 58% increased risk of becoming obese.²⁵

Results from a well-characterized cohort of almost 66,000 US women followed between 1996 and 2006 in the Nurses' Health Study also provided evidence that depression and obesity are bidirectional.²⁶ Depression was associated with a significantly² increased risk of obesity at follow-up, and this association was more apparent in women with physician-diagnosed depression and who used antidepressant medication. The converse analysis showed that baseline obesity was also associated with a moderately increased risk of depression at follow-up. Both associations were only partially explained by lifestyle factors and baseline comorbidities.

Research suggests several mechanisms for the relationship between depression and obesity.²⁷ Some experts propose that depression causes or contributes to obesity through its potential effect on binge eating and that pharmacotherapy for depressive disorders may lead to weight gain. Alternatively, others suggest that

NHANES Survey Identifies a Connection Between Obesity and Depression

Data from the National Health and Nutrition Examination survey, a continuous survey of a nationally representative sample of about 5000 persons across the United States,²² were analyzed for the years 2005–2010 and found that almost 43% of adults with depression were obese (defined as BMI ≥ 30 kg/m²) compared with 33% without depression.²³ Women with depression were more likely to be obese than women without depression, a finding that was consistent across all age groups. Among men, rates of obesity did not differ by depression status until age 60 and over, after which men with depression were more likely to be obese than men of the same age without depression.²³ The survey also found that 1) as the severity of depression increased, so did the percentage of all adults with obesity; 2) both moderate to severe depressive symptoms and antidepressant use were associated with increased obesity; 3) moderate to severe depressive symptoms were associated with a higher rate of obesity both in persons who were taking antidepressant medication and in those who were not; and 4) antidepressant use was associated with a higher rate of obesity regardless of severity of depressive symptoms. The highest prevalence of obesity (54.6%) was seen in persons who had moderate or severe depressive symptoms and took antidepressant medication. However, it could not be determined whether depression preceded obesity or the opposite, as both were assessed concurrently in this epidemiological study.²³ In contrast, longitudinal studies have demonstrated a bidirectional relationship between depression and obesity (ie, depression increases risk of obesity and obesity increases the risk of depression).²⁴

obesity causes or contributes to depression. For example, the stigma attached to obesity (particularly among women) may contribute to depression, and limitation of activity due to obesity or obesity-related chronic disorders may increase the risk of depression. Finally, depression and obesity may be linked through some common cause or third factor, either environmental or biological. There is evidence to suggest that inflammation represents the underlying link between adiposity and depression and their effects on comorbidities.²⁸

Inflammation and Increased Monoamine Synthesis May Lead to Antidepressant Treatment Resistance

Studies have shown that inflammation is associated with greater depressive symptom severity, resistance to commonly used antidepressants, a differential response to the selective serotonin reuptake inhibitor (SSRI) escitalopram versus the tricyclic antidepressant nortriptyline or the norepinephrine-dopamine reuptake inhibitor bupropion, and a higher likelihood of hospitalization in patients with MDD.^{9,29,30}

Chamberlain et al measured blood CRP levels in 4 groups: patients with treatment-resistant MDD, treatment-responsive patients with MDD not currently experiencing symptoms, patients with depression who were not currently receiving medication, and healthy volunteers.³¹ Mood assessments were performed with the Hamilton Rating Scale for Depression (HAM-D). Compared with healthy volunteers, CRP was elevated significantly in the treatment-resistant group but not significantly in the treatment-responsive and untreated groups, demonstrating an association between CRP and treatment resistance.³¹ The authors concluded that MDD is associated with increased CRP, particularly in treatment-resistant depression.³¹

Using a somewhat similar study design, Lindqvist et al measured the blood levels of IL-6, TNF- α , CRP, and biomarkers of oxidative stress in

untreated patients with MDD and healthy controls.³² The investigators then treated about half the MDD patients with an SSRI for 8 weeks and repeated the measurements; all patients with MDD were assessed with the HAM-D before and after treatment. Compared with healthy controls, MDD patients had significantly higher levels of IL-6, TNF- α , and 2 markers of oxidative stress (F2-isoprostanes and 8-OH 2-deoxyguanosine). Compared with MDD responders to SSRI antidepressant treatment, nonresponders had significantly higher levels of F2-isoprostanes at baseline and after treatment. Nonresponders showed a significant increase in 8-OH 2-deoxyguanosine over the course of treatment, whereas responders showed a significant decrease in IL-6 during treatment. The authors concluded that antidepressant response was associated with changes in inflammatory and oxidative stress markers.³²

Inflammation contributes to an inadequate response to typical antidepressants.

Studies also indicate that low-grade inflammation—defined as elevated serum levels of proinflammatory cytokines and CRP and/or activated circulating or resident immune cells including microglia—contributes to an inadequate response to antidepressants (eg, SSRIs/SNRIs, TCAs).³³ A systematic review of 19 studies found that elevated serum levels of IL-6 and CRP identify a form of MDD with a relatively poor outcome and nonresponsiveness to agents with a predominantly serotonergic mechanism of action.³³

What are the therapeutic implications of these findings? Most important is that monoamine-modulating antidepressants may not be very effective in the setting of increased inflammatory signals and oxidative stress, both of which can reduce the central synthesis of monoamine

neurotransmitters. Increasing the synthesis of serotonin, norepinephrine, and dopamine with L-methylfolate (also known as 5-methyltetrahydrofolate) may enhance the effectiveness of antidepressants that are dependent on adequate levels of these monoamines.³⁴

Role of Folate in Physiology and MDD Pathophysiology

Folate functions as a coenzyme or cosubstrate in the metabolism of amino acids, the conversion of homocysteine to methionine, and the synthesis of DNA and RNA.³⁵ Methylation of deoxyuridylate to thymidylate in the formation of DNA is required for proper cell division, and impairment of this reaction can lead to megaloblastic anemia, one of the hallmarks of folate deficiency. Folate also has a role in neurotransmitter synthesis in the brain.³⁵

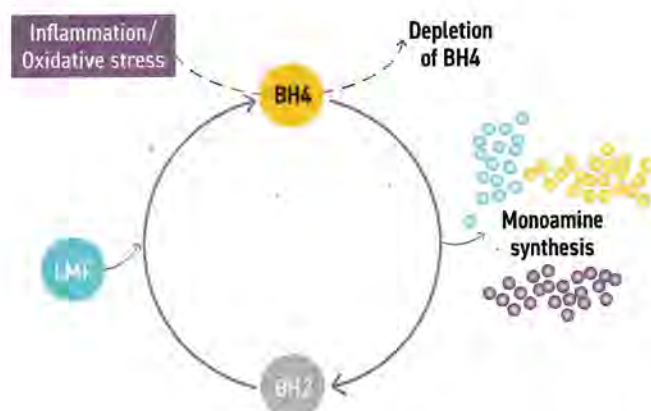
L-Methylfolate, Monoamine Synthesis, and Inflammation

The conversion of dietary folate to L-methylfolate is a multi-step process. A key step in this process is the conversion of dihydrofolate to the bioactive form L-methylfolate by the enzyme methylenetetrahydrofolate reductase (MTHFR).³⁴ L-Methylfolate is the only form of folate that crosses the blood-brain barrier and is immediately available for synthesis of serotonin, norepinephrine, and dopamine.³⁶

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L-Methylfolate is a cofactor in the metabolic pathway leading to the synthesis of monoamine neurotransmitters (**Figure 3**). L-Methylfolate modulates the formation of tetrahydrobiopterin (BH4),

Figure 3. Role of L-Methylfolate in the Synthesis of Monoamine Neurotransmitters.



BH2=dihydrobiopterin; BH4=tetrahydrobiopterin; LMF=L-methylfolate.

a critical cofactor for the synthesis of monoamines that activates the rate-limiting enzymes tyrosine hydroxylase for the synthesis of norepinephrine and dopamine and tryptophan hydroxylase for the synthesis of serotonin.³⁴ During this process, BH4 is oxidized to dihydrobiopterin (BH2), which can be regenerated to BH4 through pathways supported by L-methylfolate.³⁷ However, BH4 is highly labile and is relatively unstable in the presence of inflammation and oxidative stress, resulting in its oxidation and irreversible degradation to dihydroxanthopterin (XPH2).³⁷ Proinflammatory cytokines such as IL-6 have been shown to reduce BH4 in sympathetic neurons, and cytokine influences on BH4 through oxidative stress may be a mechanism for inflammation to reduce monoamine availability in important regions of the brain.³⁷

Association Between Folate and Depression

Research has demonstrated that low serum or red blood cell (RBC) folate levels are associated with increased risk for depression, more severe depressive symptoms, longer and more severe depressive episodes, no response to antidepressant therapy, lower probability of achieving remission, later onset of clinical improvement, and

increased risk of depressive symptom relapse.³⁸⁻⁴¹

Low serum or RBC folate levels are associated with an increased risk for depression.

A meta-analysis of 43 studies that included 8510 persons with depression and 27,282 without depression was performed to identify an association with folate.³⁸ The results showed that individuals with depression had significantly lower serum folate levels compared to those without depression; dietary intake of folate and serum folate levels differentiated those with depression from those without depression.³⁸ All studied populations—adult, geriatric, perinatal, and child/adolescent—had significantly lower levels of serum folate than their nondepressed counterparts, although RBC folate levels did not identify a difference. The authors noted that, despite the large burden of disease and mortality associated with depression, the best available treatment modalities including antidepressant therapy are not effective for almost 60% of patients, which suggests that core underlying mechanisms of depression are not being targeted.³⁸ They concluded that clinicians should

consider folate supplementation for their patients, although additional research is warranted.³⁸

Genetic Polymorphisms Impair Conversion of Dietary Folate and Folic Acid to L-Methylfolate

The *MTHFR* gene encodes MTHFR.⁴² Single nucleotide polymorphisms (SNPs) have been identified in *MTHFR* that are associated with impaired folate metabolism, lower plasma folate concentrations, changes in folate form distribution, and elevated plasma homocysteine concentrations, all of which have been correlated with MDD.^{42,43} One common SNP that reduces the activity of MTHFR is the C677T polymorphism of *MTHFR*, a point mutation with the substitution of the nucleotide cysteine for thymine at position 677, causing the substitution of the amino acid alanine with valine in the enzyme.⁴⁴ This SNP encodes a thermolabile MTHFR that is less active at higher temperatures.⁴⁵ Individuals with 2 copies of this variant tend to have lower serum folate levels compared to controls. More than 25% of Hispanics, up to 15% of North American Caucasians, and 6% of African Americans are estimated to be homozygous for the C677T variant. Supplementation with folate as folic acid, folinic acid, or L-methylfolate has been shown to reduce depressive symptoms in MDD.⁴⁶ Because L-methylfolate is not MTHFR-dependent regardless of a patient's genotype,⁴⁷ this formulation may offer advantages in depressed patients with a reduced-function *MTHFR* variant and decreased MTHFR activity.

Summary and Conclusions

MDD may be associated with increased neuroinflammation, which is known to interfere with monoamine turnover, possibly reducing the efficacy of antidepressant agents.

- Depression is a complex heterogeneous disorder, the pathophysiology of which includes

diathesis (vulnerability)-stress, epigenetics, cellular (oxidative) stress, and neuroinflammation.

- Pathogenetic mechanisms in depression include activation of the HPA axis (CRH-ACTH-glucocorticoid pathway); increase in sympathetic tone and proinflammatory cytokines; decreased BDNF with loss of neuroplasticity; and alterations in dopamine, serotonin, and epinephrine signaling.
- Obesity and the leaky gut contribute proinflammatory cytokines to the underlying inflammatory process.
- Inflammation and the associated increase in monoamine synthesis may result in reduced effectiveness of and increased resistance to antidepressant therapy.
- Clinicians can consider obtaining CRP levels in their depressed patients to help rule out an underlying inflammatory process that may be contributing to the depressive disorder.
- L-Methylfolate is a key cofactor in the metabolic pathway leading to synthesis of monoamine neurotransmitters, and reduced folate levels are associated with reduced levels of monoamine neurotransmitters.
- SNPs may impair the functioning of MTHFR, thereby limiting the synthesis of L-methylfolate, which results in more treatment-resistant MDD.
- Unlike other folate formulations, L-methylfolate is not MTHFR-dependent and may be a better choice in depressed patients with a reduced-function *MTHFR* variant and decreased MTHFR activity.
- Deplin® is a branded form of L-methylfolate, the biologically active form of folate that crosses the blood-brain barrier to support the synthesis of monoamines. Dietary supplements containing folic acid or other forms of folate available over-the-counter (OTC) are not

subject to the same labeling and manufacturing regulations as are medical foods such as DEPLIN.

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References

1. Balmuth E. From black bile to the brain: tracing melancholia and depression. Max Planck Phdnet. May 29, 2017. Accessed August 1, 2021. <https://www.phdnet.mpg.de/offspring-blog/2017/from-black-bile-to-the-brain>
2. Reynolds HE, Wilson JVK. Depression and anxiety in Babylon. *J R Soc Med*. 2013;106(12):478-481.
3. Zhang Y, Anoopkumar-Dukie S, Davey AK. SIRT1 and SIRT2 modulators: potential anti-inflammatory treatment for depression? *Biomolecules*. 2021;11(3):353.
4. Belleau EL, Treadway MT, Pizzagalli DA. The impact of stress and major depressive disorder on hippocampal and medial prefrontal cortex morphology. *Biol Psychiatry*. 2019;85(6):443-453.
5. Athira KV, Bandopadhyay S, Samudrala PK, Naidu VGM, Lahkar M, Chakravarty S. An overview of the heterogeneity of major depressive disorder: current knowledge and future perspective. *Curr Neuropsychopharmacol*. 2020;18(3):168-187.
6. Arnau-Soler A, Adams MJ, Clarke TK, et al. A validation of the diathesis-stress model for depression in Generation Scotland. *Translat Psychiatry*. 2019;9(1):25.
7. DiSabato DJ, Quan N, Godbout JP. Neuroinflammation: the devil is in the details. *J Neurochem*. 2016;139(suppl 2):136-153.
8. Miller AH. Beyond depression: the expanding role of inflammation in psychiatric disorders. *World Psychiatry*. 2020;19(1):108-109.
9. Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. *Trends Immunol*. 2006;27(1):24-31.
10. Beurel E, Toups M, Nemeroff CB. The bidirectional relationship of depression and inflammation: double trouble. *Neuron*. 2020;107(2):234-256.
11. Enache D, Pariante CM, Mondelli V. Markers of central inflammation in major depressive disorder: a systematic review and meta-analysis of studies examining cerebrospinal fluid, positron emission tomography and post-mortem brain tissue. *Brain Behav Immun*. 2019;81:24-40.
12. Troubat R, Barone P, Leman S, et al. Neuroinflammation and depression: a review. *Eur J Neurosci*. 2021;53(1):151-171.
13. Ouakinin SRS, Barreira DP, Gols CJ. Depression and obesity: integrating the role of stress, neuroendocrine dysfunction and inflammatory pathways. *Front Endocrinol (Lausanne)*. 2018;9:431.
14. Jokela M, Virtanen M, Batty GD, Klivimäki M. Inflammation and specific symptoms of depression. *JAMA Psychiatry*. 2016;73(1):87-88.
15. Maletic V, Robinson M, Oakes T, Iyengar S, Ball SG, Russell J. Neurobiology of depression: an integrated view of key findings. *Int J Clin Pract*. 2007;61(12):2030-2040.
16. Shelton RC, Miller AH. Eating ourselves to death (and despair): the contribution of adiposity and inflammation to depression. *Prog Neurobiol*. 2010;91(4):275-299.
17. Liang S, Wu X, Jin F. Gut-brain psychology: rethinking psychology from the microbiota-gut-brain axis. *Front Integr Neurosci*. 2018;12:33.
18. Miller AH, Maletic V, Raison CL. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. *Biol Psychiatry*. 2009;65(9):732-741.
19. Lindqvist D, Janelidze S, Hagell P, et al. Interleukin-6 is elevated in the cerebrospinal fluid of suicide attempters and related to symptom severity. *Biol Psychiatry*. 2009;66(3):287-292.
20. Arosio B, Guerini FR, Voshaar RCO, Aprahamian I. Blood brain-derived neurotrophic factor (BDNF) and major depression: do we have a translational perspective? *Front Behav Neurosci*. 2021;15:626906.

21. Yang T, Nie Z, Shu H, et al. The role of BDNF on neural plasticity in depression. *Front Cell Neurosci*. 2020;14:82.
22. About the National Health and Nutrition Examination Survey. Centers for Disease Control and Prevention. Reviewed September 15, 2017. Accessed September 14, 2021. https://www.cdc.gov/nchs/nhanes/about_nhanes.htm
23. Pratt LA, Brody DJ. Depression and obesity in the U.S. adult household population, 2005–2010. *NCHS Data Brief*. 2014;(167):1–8.
24. Shelton RC, Miller AH. Inflammation in depression: is adiposity a cause? *Dialogues Clin Neurosci*. 2011;13(1):41–53.
25. Luppino FS, de Wit LM, Bouvy PF, et al. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. *Arch Gen Psychiatry*. 2010;67(3):220–229.
26. Pan A, Sun Q, Czernichow S, et al. Bidirectional association between depression and obesity in middle-aged and older women. *Int J Obes (Lond)*. 2012;36(4):595–602.
27. Simon GE, Ludman EJ, Linde JA, et al. Association between obesity and depression in middle-aged women. *Gen Hosp Psychiatry*. 2008;30(1):32–39.
28. Capuron L, Lassein J, Castanon N. Role of adiposity-driven inflammation in depressive morbidity. *Neuropsychopharmacology*. 2017;42(1):115–128.
29. Jha MK. Anti-inflammatory treatments for major depressive disorder: what's on the horizon? *J Clin Psychiatry*. 2019;80(6):18ac12630.
30. Uher R, Tansey KE, Dew T, et al. An inflammatory biomarker as a differential predictor of outcome of depression treatment with escitalopram and nortriptyline. *Am J Psychiatry*. 2014;171(12):1278–1286.
31. Chamberlain SR, Cavanagh J, de Boer P, et al. Treatment-resistant depression and peripheral C-reactive protein. *Br J Psychiatry*. 2019;214(1):11–19.
32. Lindqvist D, Dhabhar FS, James SJ, et al. Oxidative stress, inflammation and treatment response in major depression. *Psychoneuroendocrinology*. 2017;76:197–205.
33. Artiga-Henríquez G, Simon MS, Burger B, et al. Low-grade inflammation as a predictor of antidepressant and anti-inflammatory therapy response in MDD patients: a systematic review of the literature in combination with an analysis of experimental data collected in the EU-MOODINFLAME consortium. *Front Psychiatry*. 2019;10:458.
34. Stahl SM. L-Methylfolate: a vitamin for your monoamines. *J Clin Psychiatry*. 2008;69(9):1352–1353.
35. Folate: Fact Sheet for Health Professionals. National Institutes of Health Office of Dietary Supplements. Updated March 29, 2021. Accessed August 12, 2021. <https://ods.od.nih.gov/factsheets/folate-HealthProfessional/>
36. Kose S, Sayar K. L-Methylfolate in patients with treatment-resistant depression: fulfilling the goals of personalized psychopharmacological therapy. *Psychiatry Clin Psychopharmacol*. 2018;28(4):359–362.
37. Haroon E, Raison CL, Miller AH. Psychoneuro-immunology meets neuropsychopharmacology: translational implications of the impact of inflammation on behavior. *Neuropsychopharmacology*. 2012;37(1):137–162.
38. Bender A, Hagan KE, Kingston N. The association of folate and depression: a meta-analysis. *J Psychiatr Res*. 2017;95:9–18.
39. Levitt AJ, Joffe RT. Folate, B12, and life course of depressive illness. *Biol Psychiatry*. 1989;25(7):867–872.
40. Wesson VA, Levitt AJ, Joffe RT, et al. Change in folate status with antidepressant treatment. *Psychiatry Res*. 1994;53(3):313–322.
41. Abou-Saleh MT, Coppen A. Serum and red blood cell folate in depression. *Acta Psychiatr Scand*. 1989;80(1):78–82.
42. Cho K, Amin ZM, An J, Rambaran KA, Johnson TB, Alzghari SK. Methylenetetrahydrofolate reductase A1298C polymorphism and major depressive disorder. *Cureus*. 2017;9(10):e1734.
43. DeVos L, Chanson A, Liu Z, et al. Associations between single nucleotide polymorphisms in folate uptake and metabolizing genes with blood folate, homocysteine, and DNA uracil concentrations. *Am J Clin Nutr*. 2008;88(4):1149–1158.
44. Liew SC, Das Gupta E. Methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism: epidemiology, metabolism and the associated diseases. *Eur J Med Genet*. 2015;58(1):1–10.
45. Dean L, Pratt VM, Scott SA, et al. Methylenetetrahydrofolate deficiency. In: Pratt VM, Scott SA, Pirmohamed M, et al, eds. *Medical Genetics Summaries*. National Center for Biotechnology Information; 2012.
46. Fava M, Mischoulon D. Folate in depression: efficacy, safety, differences in formulations, and clinical issues. *J Clin Psychiatry*. 2009;70(suppl 5):12–17.
47. Willems FF, Boers GHJ, Blom HJ, Aengevaeren WRM, Verheugt FWA. Pharmacokinetic study on the utilisation of 5-methyltetrahydrofolate and folic acid in patients with coronary artery disease. *Br J Pharmacol*. 2004;141(5):825–830.