

The Clinical Evidence for L-Methylfolate (Deplin®) as Adjunctive Therapy for Patients With MDD

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Achieving sustained remission of major depressive disorder (MDD) with restoration of vocational and interpersonal functions is the primary objective of antidepressant therapy.^{1,2} Failure to accomplish this therapeutic goal is associated with a high probability of relapse or recurrence,¹ the risk of which can be reduced with continuation therapy to preserve remission and maintenance therapy to prevent recurrence and enable recovery.^{2,3} Unfortunately, up to 70% of patients with MDD fail to achieve a complete remission of symptoms following initial antidepressant therapy⁴; and many who do remit experience relapse or recurrence, despite maintenance treatment.⁵ Patients who fail their initial treatment often do not respond to a second antidepressant and frequently experience chronic depression and impaired psychosocial functioning.⁶ Treatment-resistant depression—defined by the Food and Drug Administration (FDA) as MDD with an inadequate response to at least 2 antidepressants given at adequate doses for an adequate duration during the current episode⁷—occurs in up to 30% of patients⁴ and is associated with a substantial burden of disease. Interventions that provide both short-term and sustained remission and subsequently reduce the impact of MDD on functioning and quality of life are critically needed.⁵ In addition, MDD is accompanied by a number of other, equally important needs (Table 1).

Options for Adjunctive Treatment of Depression

Strategies for the early management of patients with an inadequate response to antidepressant therapy

Table 1. Unmet Needs in MDD.

In patients with inadequate response, guidelines that address when to change antidepressants, use adjunctive treatments, or combine antidepressant therapies ^{5,8}
Treatments with a quicker onset and sustained efficacy
Improved short- and long-term safety, tolerability, and side effect profiles of antidepressants and other interventions for unipolar depressive disorder ³
An understanding of the role of biomarkers to guide therapy for individual patients over time, in conjunction with clinical judgment ⁵
Ability to identify which empirically based interventions are capable of improving specific dimension/domain-based outcomes (eg, cognition, fatigue) ⁹
Improved patient and family education and collaboration with other healthcare professionals about treatment options, time to onset of response, side effects, and how to manage side effects at all stages of treatment ³
Alignment of expectations of treatment outcomes between patients and clinicians (eg, patients rank quality of life and positive affect higher, while physicians rank functioning and depressive symptoms higher) ¹⁰
Identification of clinical features and other variables (eg, racial, ethnic, cultural, and biomarkers) in the clinical presentation of MDD and response to treatment ¹¹

(including initial antidepressant therapy) include switching to another antidepressant, use of adjunctive therapy, or combining antidepressant modalities (eg, psychotherapy, electroconvulsive therapy [ECT]).¹² Adjunctive therapy may be more appropriate for patients with a partial response to the antidepressant and includes a multitude of treatment options. Clinicians should first consider the range of treatments with the best empirically based evidence, such as atypical antipsychotics (AAPs), esketamine, lithium, thyroid hormone (T3), vagus nerve stimulation,¹³ transcranial magnetic stimulation,¹⁴ ECT, and L-methylfolate.^{1,12,15} Clinicians should always consider the risk-benefit ratio when choosing an adjunctive treatment, as many of these treatments are associated with adverse events.¹⁶ Among these treatment options, AAPs represent one of the few medication classes with treatment options that are specifically FDA-approved for

adjunctive therapy in MDD. Unlike typical antipsychotics, which act almost exclusively on dopamine neurotransmission, AAPs theoretically work by modulating serotonin and norepinephrine as well as dopamine neurotransmission, which may explain the effectiveness of these agents in MDD.¹⁷ Adding an AAP to antidepressant therapy reduces depressive symptoms in patients with MDD,^{17,18} although the effect size is small and treatment-related side effects, including the possible risk of metabolic syndrome and movement disorders (eg, akathisia, tardive dyskinesia), can be moderate to severe.¹⁹ In clinical trials, intranasal esketamine provided clinically significant improvement of symptoms in patients with treatment-resistant depression with a side effect profile that includes transient, mild to moderate side effects, including increased blood pressure, sedation, and dissociation during the treatment.²⁰

L-Methylfolate, the biologically active form of folate that crosses the blood-brain barrier,¹⁵ is also a potentially effective and well-tolerated option for adjunctive treatment of MDD. Studies conducted as early as the 1960s identified an association between folate deficiency and depression,²¹ and patients with depression characteristically demonstrated low serum folate levels or decreased dietary folate intake compared to those without depression.²² In a study of 33 patients with treatment-resistant depression, 36% had low cerebral folate deficiency, defined as normal blood levels of folate together with low cerebrospinal fluid levels of L-methylfolate.²³ Clinically, folate deficiency has been linked to an increased risk of depression with more severe symptoms, protracted episodes, lack of response to antidepressants, lower rates of remission, delayed clinical improvement, and greater risk of relapse.²² The use of folate or derivatives should be considered as adjunctive therapy for patients with MDD demonstrating an inadequate response to antidepressant treatment.²²

In order to cross the blood-brain barrier, folic acid must be converted to L-methylfolate. Conversion of folic acid to L-methylfolate is a multistep process, beginning with intestinal absorption of dietary folic acid (or dietary folate, which is hydrolyzed to folic acid in the gut prior to absorption). Unlike other folate formulations, L-methylfolate bypasses the multistep process required for the biosynthesis of L-methylfolate from dietary folic acid/folate or folinic acid and is unaffected by functional gene-level mutations such as single nucleotide polymorphisms (SNPs), which can disrupt this multistep process.²⁴ In addition, L-methylfolate precursors (metabolites that may accumulate) may bind to folate transport receptors necessary for L-methylfolate to cross the blood-brain barrier and limit the amount of L-methylfolate that can enter the central nervous system.²⁵ The metabolic steps in this process are summarized in **Figure 1**.

After crossing the blood-brain barrier, L-methylfolate modulates the formation of tetrahydrobiopterin (BH4), an essential cofactor that activates tyrosine hydroxylase for the synthesis of norepinephrine and dopamine and tryptophan hydroxylase for the synthesis of serotonin. BH4 is degraded to BH2 during these enzymatic reactions, but it can be generated to BH4 through pathways supported by L-methylfolate. Note that BH4 is irreversibly degraded to XPH2 under conditions of inflammation and oxidative stress (**Figure 1**).²⁶ This pathway is the core explanation for why DEPLIN can be of benefit to patients with an inadequate response to antidepressant therapy.

L-Methylfolate appears to enhance synthesis and sustain optimal levels of serotonin, norepinephrine, and dopamine.²⁵ Studies have shown that L-methylfolate can improve the response to antidepressants in patients with MDD who fail to respond to an adequate trial of an antidepressant.²⁵

Studies have shown that L-methylfolate can improve the response to antidepressants in patients with MDD who fail to respond adequately.

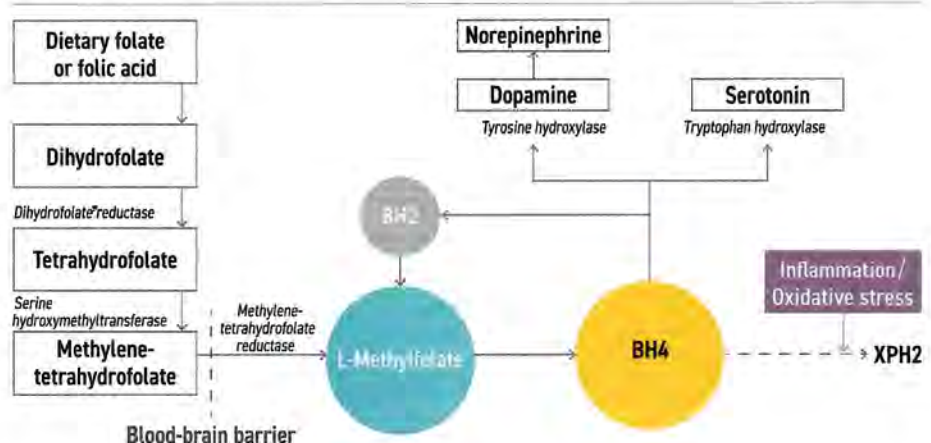
What Is DEPLIN?

DEPLIN is a prescription medical food containing the bioactive form of folate, L-methylfolate, for the dietary management of depression and schizophrenia, and is specially formulated to meet the distinctive nutritional requirements of these conditions.²⁷ DEPLIN has been extensively studied as adjunctive treatment for MDD in randomized and open-label clinical trials and real-world settings,^{1,5,15,28-30} and has been in clinical use for more than 15 years.³¹

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. The usual dose of DEPLIN is one 15-mg capsule daily, taken with or without food.²⁷ The rationale for requiring a prescription for DEPLIN underscores the importance of medical monitoring of its use in patients with MDD and avoiding the potential negative outcomes of inadequately treated MDD.

Pharmacokinetic studies show that DEPLIN and folic acid are not interchangeable. In a study comparing the bioavailability of a single oral dose of 5 mg DEPLIN with that of a single oral dose of 5 mg folic acid in persons with homozygosity for the 677C→T mutation of methylenetetrahydrofolate reductase (a genetic polymorphism

Figure 1. Metabolic Steps Required for Folate Formulations to Cross the Blood-Brain Barrier.



BH2=dihydrobiopterin; BH4=tetrahydrobiopterin; XPH2=dihydroxanthopterin.

that is common in people with depression and that can interfere with the metabolism of folate),²⁴ DEPLIN was 7 times more bioavailable at peak concentration than folic acid.³² These results confirm that DEPLIN has a different pharmacokinetic profile than folic acid and is directly available following intestinal absorption, whereas folic acid first must be metabolized to tetrahydrofolate.³²

Short- and Long-Term Clinical Evidence Supporting DEPLIN

Clinical evidence indicates that L-methylfolate supplementation should be used in patients with documented low levels of folate and its metabolites and as adjunctive therapy in patients who do not respond to traditional antidepressant therapies.^{22,25} The well-designed, rigorous, short- and longer-term clinical studies of DEPLIN in patients with MDD were conducted mainly at a dose of 15 mg daily.

The efficacy, safety, and potential role of biomarkers were evaluated in 2 multicenter, randomized, double-blind clinical trials in adult patients with selective serotonin reuptake inhibitor (SSRI)-resistant MDD¹⁵; 2 post hoc analyses of these trials^{5,29}; a 12-month, open-label extension trial¹; a real-world prospective cohort study³⁰; and a retrospective analysis of

patient charts.²⁸ **Table 2** provides an overview of these studies.

In the first randomized, double-blind trial, 148 outpatients were enrolled in 2 consecutive 30-day periods and randomly assigned in a 2:3:3 ratio to receive adjunctive L-methylfolate (DEPLIN) for 60 days (7.5 mg/day for 30 days followed by 15 mg/day for 30 days), placebo for 30 days followed by DEPLIN (7.5 mg/day) for 30 days, or placebo for 60 days, all with continued SSRI therapy.¹⁵ There was no significant difference observed in outcomes across the 3 treatment groups at the 7.5-mg dose. The second randomized, double-blind trial enrolled 75 outpatients and utilized the same design as the first study except the DEPLIN dose was 15 mg/day during both 30-day periods. In the second trial, adjunctive DEPLIN at 15 mg/day showed significantly greater improvement compared with placebo on both primary outcome measures (response rate and degree of change in depression symptom score on the 28-Item Hamilton Depression [HAM-D] Rating Scale) and 2 secondary outcome measures of symptom severity. DEPLIN was well tolerated in both studies, with rates of adverse events no different from those reported for placebo. The investigators concluded that “15 mg/day, but not 7.5 mg/day, of adjunctive

L-methylfolate may constitute an effective, safe, and relatively well tolerated augmentation strategy for patients with major depression who have had no response or a partial response to SSRIs.”¹⁵

15 mg/day of adjunctive DEPLIN “may constitute an effective, safe, and relatively well tolerated augmentation strategy for patients with major depression who have had no response or a partial response to SSRIs.”¹⁵

Given the bidirectional relationship of inflammation to both depression and obesity, as well as the association between low folate status and MDD, 2 post hoc exploratory analyses of the second randomized, double-blind trial were performed to assess the effect of 15 mg DEPLIN vs placebo as a function of baseline biomarker levels or genotype.^{5,29} The analyses focused on biomarkers of inflammation (eg, interleukin-8 [IL-8], tumor necrosis factor- α [TNF- α], high-sensitivity C-reactive protein [hsCRP]) and metabolic status (eg, obesity defined as body mass index [BMI] of ≥ 30 , insulin, and the adipokine leptin),

Table 2. Overview of DEPLIN Clinical Trials in MDD.

Study	Design	Patients	Treatment Arms	Primary Endpoint
Trial 1 ¹⁵	Multicenter, randomized, double-blind (two 30-day phases) trial in SSRI-resistant MDD	N=148; ≥ 12 QIDS-SR, tx with SSRI ≥ 8 weeks (stable for ≥ 4 weeks)	• PBO $\rightarrow$ PBO • PBO $\rightarrow$ 7.5 mg • 7.5 mg $\rightarrow$ 15 mg	• Improvement in HAM-D17 • Response ^a rates according to HAM-D17
Trial 2 ¹⁵	Multicenter, randomized, double-blind (two 30-day phases) trial in SSRI-resistant MDD	N=75; ≥ 12 QIDS-SR, tx with SSRI ≥ 8 weeks (stable for ≥ 4 weeks)	• PBO $\rightarrow$ PBO • PBO $\rightarrow$ 15 mg • 15 mg $\rightarrow$ 15 mg	• Improvement in HAM-D17 • Response ^a rates according to HAM-D17
Post hoc analyses ^{5,29}	Exploratory analyses evaluating effects of biological, inflammatory, and/or genetic markers on treatment response	N=74	—	Effect of biomarkers on response to HAM-D28
Open-label extension ¹	12-month, open-label, extension trial of Trials 1 and 2	N=68	15 mg	Reduction in HAM-D17 score at 12 months
Real-world study ³⁰	Prospective cohort study evaluating patients prescribed DEPLIN	N=502	7.5 mg or 15 mg	Reduction in PHQ-9 from baseline

^aResponse defined as a reduction of $\geq 50\%$ in HAM-D17 score during treatment or a final score of ≤ 7 . HAM-D17=Hamilton Depression Rating Scale-17 item; HAM-D28=Hamilton Depression Rating Scale-28 item; MDD=major depressive disorder; PBO=placebo; PHQ-9=Patient Health Questionnaire; QIDS-SR=Quick Inventory of Depressive Symptomatology–Self-Rated; SSRI=selective serotonin reuptake inhibitor; tx=treatment.

as well as genotypes of enzymes involved in folate metabolism.^{5,29}

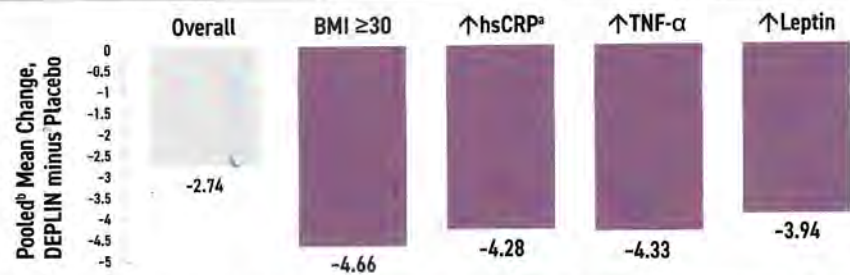
The first post hoc analysis showed that adjunctive treatment with DEPLIN 15 mg resulted in a significantly greater improvement (pooled mean change from baseline for HDRS-17) vs placebo in patients with elevated biomarkers suggestive of inflammation, including TNF- α , IL-8, and hsCRP, as well as obesity, defined as BMI of ≥ 30 (Figure 2).²⁹ These results remained significant even after correcting for obesity, indicating that the effects of the inflammatory biomarkers were significant independent of obesity.²⁹ This suggests that patients with obesity (BMI of ≥ 30) and elevated inflammatory markers (hsCRP, TNF- α , and IL-8) would show an increased response to DEPLIN. The randomized clinical studies demonstrated the overall benefit of DEPLIN, and its use should not be limited only to these populations.

Patients with obesity (BMI of ≥ 30) and elevated levels of inflammatory markers (hsCRP, TNF- α , and IL-8) showed an increased response to DEPLIN 15 mg, although treatment with DEPLIN for depression should not be limited to patients with these characteristics.

The second post hoc analysis confirmed the effect of elevated inflammatory biomarkers (hsCRP, S-adenosylmethionine [SAM]/S-adenosylhomocysteine [SAH] ratio, 4-hydroxynonenal [4-HNE]) on treatment response with DEPLIN. In addition, despite a limited sample size, it showed that the presence of most (but not all) genetic polymorphisms related to folate metabolism also predicted a greater response to DEPLIN.⁵

These 2 analyses suggest that the presence of certain inflammatory biomarkers and genetic markers may help identify patients with SSRI-

Figure 2. Post Hoc Analysis of DEPLIN 15 mg/day vs Placebo on Pooled Mean Change From Baseline for HDRS Stratified by Biomarkers and Obesity (BMI of ≥ 30) in 69 Patients With No or Partial Response to SSRI Monotherapy.²⁹



^ahsCRP levels above the median value of (log) 5.01 were considered to be associated with systemic inflammation.

^bPooled across study groups from 2 randomized clinical trials. BMI=body mass index; HDRS=Hamilton Depression Rating Scale; hsCRP=high-sensitivity C-reactive protein; TNF- α =tumor necrosis factor-alpha.

resistant MDD who may be particularly responsive to adjunctive therapy with DEPLIN 15 mg.⁵

The long-term efficacy, safety, and tolerability of DEPLIN 15 mg was investigated in a 12-month open-label extension of the 2 randomized, double-blind trials.¹ Outcome criteria included response ($\geq 50\%$ improvement in the Hamilton Depression Rating Scale [HDRS-17] total score from the start of the double-blind study), remission (total HDRS-17 score of ≤ 7), recovery (≥ 6 months of remission from the start of the open-label study), relapse (HDRS-17 score of >15 within 6 months of achieving remission), and recurrence (HDRS-17 score of >15 after 6 months of remission at the time of recovery). Sustained recovery was defined as recovery that was sustained through the final study visit at 12 months from the start of the open-label trial.¹

Patients continuing management of their condition with DEPLIN 15 mg after the double-blind acute therapy trial showed additional and sustained reduction in depression scores, indicating further improvement in depression symptoms over time (Table 3).¹

Overall, 61% of patients achieved remission and 38% achieved full recovery, which were sustained over the 12 months.¹ Among non-responders at the end of the double-blind trial, 60% of 53 patients converted to remission and 26% converted to full recovery (statistical significance not reported). There were no recurrences in patients who recovered, no serious adverse events, and no discontinuations as a result of adverse events. As in the double-blind trials, DEPLIN had a safety and tolerability profile comparable to placebo.¹ Despite the limitation of the

Table 3. Outcomes of Subjects in 12-Month Open-Label Phase of DEPLIN 15 mg (N=68).¹

Status at End of Double-Blind Acute Phase	Achieved Remission During Open-Label Phase	Achieved Recovery	Sustained Recovery
Remission (n=11)	NA	91% (n=10)	100%
Response without remission (n=4)	75% (n=3)	50% (n=2)	100%
Nonresponse (n=53)	60% (n=32)	26% (n=14)	100%
Total	61% (n=35/57)	38% (n=26/68)	100%

NA=not applicable. Adapted with permission.¹

open-label study design, the authors concluded that DEPLIN may be an early option in patients who do not respond adequately to antidepressant monotherapy.¹

Patients in the long-term (12-month) extension trial showed additional and sustained reductions in depressive symptoms with DEPLIN 15 mg/day. As in the double-blind trials, DEPLIN had a safety and tolerability profile comparable to placebo.

A real-world prospective cohort study evaluated 554 patients with MDD, 502 of whom received DEPLIN along with their antidepressant for 3 months (adjunctive therapy) and 52 of whom were treated with DEPLIN alone (monotherapy).³⁰ Depressive symptoms, quality of life, and medication satisfaction were assessed with the self-reported Patient Health Questionnaire-9 (PHQ-9).³⁰ In this clinical setting, patients who received adjunctive DEPLIN along with their antidepressant achieved statistically significant improvements in depressive

symptoms, quality of life, and functioning and reported greater satisfaction with DEPLIN compared with their previous medication.

Overall, the response rate was 67.9% and the remission rate was 45.7%, with a compliance rate of >90%. Interestingly, treatment response rates were similar for patients who took DEPLIN as monotherapy or adjunctive therapy.³⁰

A retrospective chart review compared outcomes in 242 patients with MDD and a Clinical Global Impression–Severity (CGI-S) score of 4 to 5, 147 of whom were treated with an SSRI or a serotonin and norepinephrine reuptake inhibitor (SNRI) alone and 95 with an SSRI or SNRI plus DEPLIN 7.5 mg or 15 mg daily.²⁸ DEPLIN-treated patients showed a significantly greater improvement in CGI-S scores at 60 days and a significantly more rapid improvement at both doses with no between-group difference in adverse events.²⁸

Appropriate Patient Types for DEPLIN Therapy

Based on the results of these studies and other factors, what are the patient selection criteria for DEPLIN in MDD? Data from clinical trials show that DEPLIN is effective adjunctive therapy

for MDD in patients who have had no or only partial response to antidepressant treatment.^{5,28,30} The data also show that DEPLIN is beneficial for long-term use,¹ with no significant differences in adverse events compared to placebo and none of the adverse events associated with other adjunctive agents, such as weight gain or movement disorders.^{1,15,28}

Evidence suggests specific patient selection criteria include obesity, clinical and/or laboratory evidence of inflammation or an underlying inflammatory process, and/or certain polymorphisms of genes regulating folate metabolism (Table 4).^{5,29} In addition, a number of factors and conditions can lead to low folate states, and patients who have MDD with certain clinical profiles particularly may benefit from DEPLIN. These profiles are summarized in Table 4 and include medications such as anticonvulsants, antibiotics, methotrexate, and oral contraceptives.²⁴ Tailoring the assessment for these factors should involve a current and prospective monitoring of the medical illness, other newer treatments, and possibly laboratory or genetic markers.

Table 4. Patients With MDD Who May Benefit From DEPLIN (But Not Limited to These Patients).

• No or partial response to antidepressant therapy ^{15,28,30}
• Obesity ²⁹
• Clinical evidence of a chronic inflammatory state or a disorder associated with inflammation ^{5,29}
• Biomarkers suggestive of an inflammatory process ^{5,29}
• Systemic metabolic disorders (eg, diabetes, ³³ cardiovascular disease ³⁴)
• Gut dysbiosis ³⁵
• Functional polymorphism(s) of folate metabolism genes ^{5,24,32}
• Concurrent use of medication known to reduce folate levels and/or inhibit dihydrofolate reductase, which is required for the first conversion step of both dietary folate and folic acid supplements to L-methylfolate – Antibiotics²⁴ – Anticonvulsants used as mood stabilizers (valproate, lamotrigine)^{24,25} – Metformin³⁶ – Oral contraceptives³⁷ – Methotrexate and other folic acid antagonists²⁴
• Need to avoid side effects of AAPs ¹⁶ and/or not candidates for esketamine
• Alcohol abuse ^{24,38}
• Preference for nutritional products with perceived holistic/wellness health benefits ¹⁶

When there is an inadequate response to current antidepressant therapy, clinicians are encouraged to consider assessing for the multiple factors that may contribute to the lack of achieving and sustaining remission, including the impact of potentially modifiable factors, genetics, and inflammation (eg, obesity), and continue to monitor and tailor treatment to the individual's needs over time.

Summary and Conclusions

Up to 70% of patients with MDD experience an inadequate response to antidepressant therapy, and many are unable to tolerate adjunctive therapy with AAPs. DEPLIN is a prescription medical food, and it is 7 times more bioavailable at peak concentrations than OTC/supplement folic acid. Clinical studies support its use as adjunctive therapy across a range of patients with MDD with no response or a partial response to antidepressant monotherapy. These studies also suggest that obesity and biomarkers of inflammation may be predictive of a greater response to DEPLIN. DEPLIN is effective for short- and long-term use in this setting, with a favorable tolerability and safety profile characterized by no significant differences in adverse events compared with placebo and none of the adverse events associated with some other adjunctive agents for MDD. Therefore, clinicians should consider the use of DEPLIN early in the course of treatment or whenever there may be an inadequate response to antidepressant therapy.

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