L-methylfolate represents a therapeutic option in the management of depression by enhancing BH4 synthesis and modulating the synthesis of all three monoamines in a 2-step process involving tetrahydrobiopterin (DHFR) and 5,10-methylene-THF (MTHFD1) in the serotonergic, noradrenergic and dopaminergic pathways. L-methylfolate is the only form of folate that crosses the blood-brain barrier and is metabolized by monoamine oxidase A (MAO-A) and MAO-B. Various surrogate markers have been explored for L-methylfolate and biomarkers consisting of L-methylfolate plasma levels, body mass index (BMI), and MTHFR (methylentetrahydrofolate reductase) C677T genotype have been studied in a phase 2 study in SSRI-resistant MDD patients. Among 75 outpatients with SSRI-resistant MDD, the addition of 15 mg/day of adjunctive L-methylfolate to SSRI therapy resulted in a statistically significant (p=0.001) greater improvement in mean change in HDRS-28 (21.5) compared to placebo (0.5). A numerically greater treatment effect was observed in patients with an allelic variant in the MTHFR (methylentetrahydrofolate reductase) C677T genotype (p=0.001). This study was supported by a grant from Pamlab, LLC.

**Method**

- **Patient inclusion criteria**
  - Ages 18-65 years and meeting HDRS-28 criteria for a current episode of MDD.
  - Places of residence: Boston, MA and Austin, TX
  - Patients had to be on a stable SSRI dose for the past 4 weeks.
  - Patients with baseline L-methylfolate levels below vs. above the median. A numerically greater treatment effect was observed in patients with baseline L-methylfolate levels below vs. above the median. A numerically greater treatment effect was observed in patients with an allelic variant in the MTHFR (methylentetrahydrofolate reductase) C677T genotype. This was a multi-center, randomized, double-blind study of adjunctive L-methylfolate for SSRI-resistant MDD.

- **Study intervention**
  - Placebo
  - Citalopram
  - Escitalopram
  - Sertraline

- **Study assessments**
  - Study assessments occurred every 10 days.
  - Changes in the HDRS-28 were stratified by biomarkers measured at baseline: L-methylfolate, BMI, MTHFR C677T genotype.

- **Statistical analysis**
  - Differences in mean changes in HDRS-28 between patients on placebo vs. L-methylfolate were evaluated and compared using the seemingly unrelated regression approach proposed by Tamura and Huang (2007) adjusting for baseline HDRS-28 score.

**Results**

- **Overall Comparison**
  - 75 patients (57% women) were randomized to treatment; 74 provided data
  - Placebo: 15 mg/day
  - L-methylfolate 15 mg/day
  - Citalopram: 14
  - Escitalopram: 12
  - Sertraline: 11

- **MTHFR C677T Genotype**
  - Among non-responders, no difference was observed for mean change in HDRS-28 between L-methylfolate and placebo.
  - Among responders, a trend towards a greater treatment effect was noted with L-methylfolate.

- **BMI**
  - Among obese subjects (BMI ≥30 kg/m²), mean change in HDRS-28 was significant (p=0.001) greater with L-methylfolate.

**Conclusion**

- **L-methylfolate 15 mg/day added to SSRI can be an effective and well-tolerated adjunctive treatment strategy for MDD patients who are partial- or non-responders to antidepressant therapy.**

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**References**

- As compiled in the references section of the study, which includes all relevant studies.

**Appendix**

- **Table 1.** Summary of treatment comparisons.
- **Table 2.** Summary of patient demographics.

**Figure 1.** Flowchart of the study population.

**Figure 2.** Baseline Characteristics of Study Population.

**Figure 3.** Pooled-Phase Mean Change in HDRS-28 Score Stratified by Baseline BMI.

**Figure 4.** Pooled-Phase Mean Change in HDRS-28 Score Stratified by MTHFR C677T Genotype.

**Figure 5.** Pooled-Phase Differences in Mean Change Treated Minus Placebo in HDRS-28 Score for the MTHFR C677T Genotype.