L-Methylfolate as Adjunctive Therapy for Selective Serotonin Reuptake Inhibitor-Resistant Major Depressive Disorder: Results of Two Randomized, Double-blind, Parallel-Sequential Trials


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ABSTRACT

Background: Two multi-center, randomized, double-blind, placebo-controlled trials of L-methylfolate used as an adjunct to selective serotonin reuptake inhibitors (SSRIs) were conducted. To enhance the clinical comparability of the study (the sequential parallel comparison design or SPCCD) was employed.

Methods: In the first study, patients were randomized in a multi-center, 60-day, SPCCD-blind study, which was divided into two, 30-day phases (phases I and II). Patients were randomized, in a 2:1 fashion, to receive either adjunct L-methylfolate (15 mg/day) or placebo for 30 days followed by L-methylfolate for 30 days (7.5 mg/day), or placebo for 60 days. 150 patients were randomized during each phase of the study. The second trial, which involved a total of 75 patients, was designed in identical fashion, to all patients a target dose of 15 mg/day of L-methylfolate throughout both phases.

Results: In the first trial, there was no difference in outcome between the treatment groups. The results of the second trial indicated greater efficacy for subjects in the L-methylfolate groups. L-methylfolate improved all primary outcome measures and significantly improved depressive symptoms as measured by the Hamilton Depression Rating Scale (HDRS). The L-methylfolate dose effect was not significant.

Conclusion: 15 mg of L-methylfolate may represent an effective, safe, and relatively inexpensive treatment for patients who failed to adequately respond to MDD who are SSRIs partial- and non-responders. Future research is needed in order to further clarify the antidepressive potential of L-methylfolate and other agents of the one-carbon cycle.

INTRODUCTION

A number of studies have demonstrated (Coppen et al., 1999; Coppen & Bailey, 2000; Coppen et al., 2002; Copper et al., 1996; Godfrey et al., 1990; Guaraldi et al., 1993; Guaraldi et al., 2002) that levels of L-methylfolate can be improved in patients with depression and that L-methylfolate may be effective in the treatment of depression.

METHODS

Trial Design: First Trial

The study was a 24-week, 60-center, randomized, double-blind, SPCCD trial of adjunct L-methylfolate for SSRI-resistant MDD. The study was divided into two, 30-day phases (phases I and II). Institutional review board (IRB)-approved written informed consent was obtained from all study patients before any study procedures were conducted. Eligibility was assessed, primarily, during the screen visit, and, secondarily, during the baseline visit and throughout the study. Patients found eligible during the baseline visit were enrolled in a study according to the SPCCD (Fava et al., 2003). Specifically, eligibility was assessed for patients who completed the first phase of treatment in one of three treatment groups in a 2:1 fashion. One group of patients randomized probability matching to receive placebo, and one group to receive L-methylfolate in appearance during phases I and II (placebo-placbo group).

Trial Design: Second Trial

The second trial was conducted in another 60-center, SPCCD-blind study, which was divided into two, 30-day phases (phases I and II). Patients were randomized, in a 2:1 fashion, to receive either placebo or L-methylfolate for 30 days and then L-methylfolate for 30 days (7.5 mg/day) or placebo for 60 days. 150 patients were randomized during each phase of the study. The second trial, which involved a total of 75 patients, was designed in identical fashion, to all patients a target dose of 15 mg/day of L-methylfolate throughout both phases.

RESULTS

The second group (randomization probability 3:1) received two dummies pills during phase I and one dummypill during phase II. The third group (randomization probability 1:1) received one dummypill during phase I and one 7.5 mg L-methylfolate pill during phase II (placebo-placbo group). The third group (randomization probability 1:3) received one dummypill and one 7.5 mg L-methylfolate pill during phase I and two 7.5 mg L-methylfolate pills during phase II (placebo-placbo group). 30 patients were withdrawn from the study during phases I and II. All patients were instructed to return any excess medication at each visit. Therefore, the number of study medications counted for each patient were recorded and used to calculate the study drug record. Protocol violation was defined as less than 80% compliance by pill count. The Hamilton Depression Rating Scale (HDRS) for depression, (Montgomery and Åsberg, 1979, 1990, CGI-S, CGI-I, Global Impression Severity and Improvement scorings (CG-I-S, -I-G, -I-D, -I-Y 1976), were administered during all post-screen visits.

Inclusion criteria:

- Age 18-65.
- Patients meeting the criteria for the primary outcome measure (response according to the Hamilton Depression Scale (HDRS) and the CGI-S or CGI-I, Global Impression Severity and Improvement scorings (CG-I-S, -I-G, -I-D, -I-Y 1976), and the clinical global impression severity scale (CGI-S, p=0.01)). The number needed to treat (NNT) for response was between 5 and 6 in favor of adjunct 15mg of L-methylfolate versus placebo.

Conclusion: 15mg, but not 7.5mg of adjunctive L-methylfolate may represent an effective, safe, and relatively inexpensive treatment for patients who failed to adequately respond to MDD who are SSRIs partial- and non-responders. Future research is needed in order to further clarify the antidepressive potential of L-methylfolate and other agents of the one-carbon cycle.

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REFERENCES

Huang (2007) method for continuous measures

Efficacy Results of Study II

HDRS-17 Mean Score Reduction

Table 1 – Efficacy Results in Second Study

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Adjunct L-methylfolate</th>
<th>Placebo</th>
<th>Placebo vs. Adjunct L-methylfolate</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Responder</td>
<td>36.8% (7)</td>
<td>15.7% (3)</td>
<td>21.1%</td>
<td>0.01</td>
</tr>
<tr>
<td>CGI-S Mean score reduction (SD)</td>
<td>-4.6 (0.6)</td>
<td>-4.3 (0.6)</td>
<td>0.40</td>
<td>0.16</td>
</tr>
</tbody>
</table>

Gastrointestinal 12 (10.7%) 10 (7.0%) 0.07
Sleep 9 (8.0%) 1 0.45
Psychological 15 (13.3%) 7 (8.1%) 0.43
Cardiovascular 26 (23.2%) 10 (27.0%) 0.60
Infectious 10 (9.2%) 9 (24.3%) 0.06
Sexual 9 (8.1%) 0.04
Miscellaneous 8 (7.1%) 0.45

* N is based on total number of subjects that received placebo or L-methylfolate at some point during the trial.