Published in final edited form as:

Menopause. 2009 ; 16(5): 1004–1008. doi:10.1097/gme.0b013e3181a2fa76.

Effect of L-Methionine on Hot Flashes in Postmenopausal Women: A Randomized Controlled Trial

Thomas Guttuso Jr, MD,
University at Buffalo

Michael P. McDermott, PhD,
University of Rochester

Phillip Ng, and
University of Rochester

Karl Kiebertz, MD
University of Rochester

Abstract

Objective—Based on a common mechanism of action with gabapentin, we investigated the effects of L-methionine on hot flashes in postmenopausal women.

Design—After a 1 week baseline period, 51 postmenopausal women experiencing at least 5 moderate-severe hot flashes per day were randomized to 1 of 3 groups in a 13:13:25 ratio: placebo/placebo, placebo/L-methionine, or L-methionine/L-methionine, respectively (Phase 1/Phase 2). Phase 1 was 12 weeks long and Phase 2 was 8 weeks long. Subjects took 1g po bid in Phase 1 and 2g po bid in Phase 2 of either L-methionine or placebo. All subjects also took folate 1mg and methylcobalamin 0.5mg a day to help minimize the L-methionine-induced elevation in serum homocysteine. The primary outcome variable was the percent change in hot flash composite score from baseline to Week 12 obtained from subjects' daily hot flash diaries.

Results—In Phase 1 and Phase 2, there were no significant differences between the L-methionine and placebo groups for any of the hot flash outcome measures. At Week 12, there was a mean 37.4% decrease in hot flash composite score compared to baseline in the L-methionine group and a mean 33.4% decrease in the placebo group ($p = 0.60$). There were expected significant increases in fasting serum homocysteine (1.7 and 5.8 $\mu\text{mol/L}$) and fasting serum methionine (13.9 and 22.3 $\mu\text{mol/L}$) at Weeks 12 and 20, respectively, associated with the 2 dosages of L-methionine therapy relative to placebo therapy.

Conclusion—L-methionine therapy appears to be ineffective in the treatment of hot flashes in postmenopausal women.

Keywords

hot flashes; clinical trial; methionine; amino acid; menopause; homocysteine

Corresponding Author: Thomas Guttuso, Jr., University at Buffalo, 3435 Main Street, 311 BRB, Buffalo, NY 14214, 716-829-2482, 716-829-2463 (fax), tguttuso@buffalo.edu.

Conflict of Interest: Thomas Guttuso, Jr. is the inventor on US Patent 6,310,098, which is owned by the University of Rochester, covering the use of gabapentin and related compounds for treating hot flashes.

Clinicaltrials.gov

<http://clinicaltrials.gov/ct2/show/NCT00081952?term=hot+flash+amino&rank=1>

Registration #: NCT00081952

Introduction

Gabapentin has been shown in several randomized controlled trials (RCTs) to be an effective non-hormonal treatment for hot flashes.^{1–4} It has been theorized that gabapentin's mechanism of action in treating hot flashes stems from decreasing neuronal calcium currents^{5, 6} via interaction with its CNS and PNS binding site, the alpha-2-delta subunit of voltage-gated calcium channels (VGCCs).⁶ Several large neutral amino acids also have an affinity for this binding site that is comparable to that of gabapentin. Of the amino acids that are classified as dietary supplements, L-methionine and L-isoleucine have the first and second-highest affinities in mouse cerebral cortex, respectively, with L-methionine's affinity equal to gabapentin's and about 40% higher than L-isoleucine's.⁷ We initially studied the effects of L-isoleucine on hot flashes since, at that time, elevated serum homocysteine was felt to be a risk factor for cardiovascular disease⁸ and L-methionine therapy was known to elevate serum homocysteine.^{9, 10} In that RCT we showed that L-isoleucine was ineffective in the treatment of hot flashes.¹¹

After the initiation of the isoleucine hot flash RCT, 2 large RCTs were published^{12, 13} and one was presented at the American Heart Association 2006 Scientific Sessions and recently published,¹⁴ all showing that lowering serum homocysteine by 18–27% through the use of B-vitamin therapy led to no cardiovascular benefit. These 3 RCTs in addition to one previously published RCT¹⁵ cumulatively enrolled over 18,000 participants and cast significant doubt on a causative role of homocysteine in cardiovascular disease. This encouraged us to revisit L-methionine therapy in the treatment of hot flashes since it has the same affinity as gabapentin for the proposed therapeutic target.⁷ We conducted a two-phase RCT in postmenopausal women to investigate whether L-methionine was effective in the treatment of hot flashes at a dosage of 2g a day (Phase 1) and 4g a day (Phase 2).

Methods

Subjects

Subjects were recruited from a TV segment on a local news channel and from newspaper advertisements. We screened 378 callers and enrolled 51 eligible subjects; the main 3 reasons for ineligibility were inadequate frequency of hot flashes, disinterest in the study, and perimenopausal state. Eligible subjects could not report having any menses for at least 12 months or report being status-post bilateral oophorectomy for > 6 weeks and have baseline serum FSH > 40 mIU/ml; could not have taken any form of prescription estrogen or progesterone for at least 2 months; could not have had any change in exposure to an antidepressant, a selective estrogen receptor modulator (such as raloxifene or tamoxifen), an aromatase inhibitor (such as anastrozole, letrozole, or exemestane), leuprolide acetate, clonidine, or an over-the-counter hot flash treatment for at least 1 month; and could not have had any exposure to an amino acid supplement, gabapentin, or pregabalin for at least 1 month. Eligible subjects needed to be experiencing at least 5 moderate-severe hot flashes per day for at least 2 months; moderate and severe hot flashes needed to have perspiration associated with the hot flash. The study was approved by the Institutional Review Board at the University at Buffalo and all subjects provided written informed consent to participate.

Randomization and Study Medication

This was a single site study conducted at the University at Buffalo's Student Health Center. Fifty-one women were enrolled between January-May 2007. After a 1 week baseline period, subjects were randomized to 1 of 3 groups (Phase 1/Phase 2) in a 13:13:25 ratio: placebo/placebo, placebo/L-methionine, or L-methionine/L-methionine, respectively. The computer-generated randomization plan was available only to the programmer at the University of

Rochester who generated the plan and the pharmacist at the University at Buffalo who packaged the drug; no other study personnel had access to this plan. Phase 1 was 12 weeks long and Phase 2 was 8 weeks long. We were primarily interested in data from Phase 1; therefore, a 12 week treatment duration was used as recommended by the FDA's Guidance for Industry.¹⁶ We chose an 8-week treatment period for Phase 2 because the data from this phase were of secondary interest and it appears that 8 weeks is the minimum treatment period necessary for demonstrating long-term efficacy of a non-hormonal compound. For example, 3 separate non-hormonal compounds have shown efficacy in hot flash RCTs at early time points (2, 6, and 7 weeks, respectively) only to subsequently lose efficacy at later time points.^{17–19} Subjects took 1g po bid in Phase 1 and 2g po bid in Phase 2 of either L-methionine or identically-appearing placebo capsules containing corn starch and methylcellulose. All subjects also took folate 1mg and methylcobalamin 0.5mg a day (Vitacost, Inc.; vitacost.com) to help minimize the L-methionine-induced elevation in serum homocysteine. The exact identity of the amino acid used in the study was not revealed to the subjects until after the study to help prevent subjects from purchasing L-methionine over-the-counter and taking it during the study.

Evaluations

Subjects completed daily hot flash diaries for a 1 week period before randomization and for the full 20 weeks of both Phase 1 & 2 of the study. Subjects were instructed to keep the diary with them and record each hot flash after it occurred as mild, moderate, or severe.¹⁶ Night sweats were also recorded. Subjects mailed each completed diary directly to the General Clinical Research Center (GCRC) at the University of Rochester, Rochester, NY. The following questionnaires were also completed at baseline, Week 12 and Week 20: The Pittsburgh Sleep Quality Index (PSQI),²⁰ The Greene Climacteric Scale (GCS),²¹ and the Hot Flash Bother Scale (HFBS), which asked subjects to rate on two 10-point Likert scales ranging from 1 ("Not Bothered At All") to 10 ("Extremely Bothered") how much they had been bothered recently by their daytime hot flashes and nighttime hot flashes/night sweats, respectively. Global Satisfaction with Treatment was assessed at Weeks 12 and 20 using a numerical scale ranging from 1 ("Extremely dissatisfied") to 10 ("Extremely satisfied"). Laboratory tests were assayed in the fasting state (no food or study capsules for at least 8 hours) between 8–10 AM and weight was also assessed at randomization, Week 12 and Week 20. Blood samples to be assayed for homocysteine were immediately placed in a 4 degree centigrade refrigerator and centrifuged within 1 hour of the draw. The serum was then immediately poured into a separate tube and homocysteine was assayed the same day. Laboratory testing was performed at Kaleida Health Laboratories, Buffalo, NY and at Strong Memorial Hospital, Rochester, NY. Adverse events were assessed by the PI at each subject visit, by inquiry.

Statistical Analysis

The primary outcome measure was percent change in hot flash composite score from baseline to Week 12 as determined by subjects' daily hot flash diaries. The hot flash composite score combines frequency and severity into one score by assigning the numbers 1, 2, and 3 to mild, moderate, and severe hot flashes, respectively, and then summing across all hot flashes. Secondary outcome variables included percent change in hot flash frequency (number of hot flashes per day) from baseline to Week 12, changes from baseline to Week 12 in the PSQI Global Score, GCS Total Score, HFBS Score, fasting serum homocysteine level, weight, laboratory test results, and Global Satisfaction with Treatment at Week 12. Changes from baseline to Week 20 were also considered in the statistical analyses.

For Phase 1, the statistical analyses were performed according to the intention-to-treat principle and included data from all randomized subjects. The hot flash diary outcomes were analyzed using a repeated measures analysis of variance model that included terms for treatment group

(L-methionine, placebo), week (categorical), and the interaction between treatment group and week. This allowed estimation of the treatment effects separately for each week (including the primary time point at Week 12) along with associated 95% confidence intervals. All available data from all randomized subjects were included in these analyses, with maximum likelihood used to estimate the model parameters of interest in the setting of missing data.²² Changes from baseline to Week 12 in the other outcome variables were compared between the L-methionine and placebo groups using Wilcoxon rank sum tests, with missing data at Week 12 imputed with the last available observation. Treatment effects were estimated using the Hodges-Lehmann estimates of the group differences in population medians and their associated 95% confidence intervals.²³

For Phase 2, the hot flash diary outcomes were analyzed as in Phase 1 (repeated measures analysis of variance), with a focus on estimating treatment effects at Week 20. The significance of group differences in mean changes from Baseline to Week 20 in the other clinical and laboratory outcomes was examined using Wilcoxon rank sum tests, with a focus on the comparison between the L-methionine/L-methionine group ($n = 25$) and the placebo/placebo group ($n = 13$). The statistical analyses for these outcome variables in Phase 2 were exploratory and did not use imputation for missing data.

A comparison of the means between the daytime and nighttime Hot Flash Bother Scale scores among the 51 subjects at baseline was performed using a paired t-test.

The sample size of 51 subjects was chosen to provide 80% power to detect a group difference (L-methionine – placebo) in mean response of 30% for the primary outcome variable of percent change from baseline to Week 12 in hot flash composite score, using a t-test and a two-tailed significance level of 5%. The chosen effect size of 30% was based on that observed using similar dosages of gabapentin to the L-methionine dosage used here² and that L-methionine and gabapentin have the same affinity for the proposed therapeutic target.⁷ The calculation also assumed a standard deviation of 37.5% for the primary outcome variable based on results from the L-isoleucine hot flash trial.¹¹

All statistical analyses were performed through the GCRC at the University of Rochester.

Results

The baseline characteristics are summarized in Table 1 by treatment received in Phase 1. The L-methionine and placebo groups were generally comparable, with the L-methionine group having a slightly higher hot flash frequency at baseline. Four subjects withdrew from Phase 1 of the study (3 L-methionine subjects for nausea, lack of benefit, and loss-to-follow-up, and 1 placebo subject for worsening hot flashes). Five subjects withdrew from Phase 2 of the study, all of whom were taking L-methionine in Phase 2 (3 for worsening hot flashes and 2 were lost to follow-up) (Figure 1).

In Phase 1 of the study, there were no significant differences between the L-methionine and placebo groups for any of the hot flash or clinical outcome variables (Figure 2 and Table 2). For the hot flash composite score, the mean percent changes from baseline to Week 12 (estimated from the repeated measures analysis of variance model) were -37.4% in the L-methionine group and -33.4% in the placebo group ($p = 0.60$). There were significant increases in fasting serum homocysteine and L-methionine levels (1.7 and $13.9 \mu\text{mol/L}$, respectively) associated with 2g a day of L-methionine relative to placebo.

In Phase 2 of the study, there were again no significant changes in any of the hot flash outcomes associated with double-dose (4g a day) L-methionine therapy as compared to placebo (Table

3). Fasting serum homocysteine and L-methionine levels showed large increases after 8 weeks of L-methionine 4g a day (Table 3).

At baseline, the 51 participating subjects reported being more bothered by their nighttime hot flashes/night sweats than by their daytime hot flashes according to the Hot Flash Bother Scale scores measured on the 10-point Likert scale (mean nighttime – daytime difference = -0.84 , 95% CI -1.54 to -0.15 , $p = 0.02$).

Discussion

This study demonstrated that L-methionine is ineffective in the treatment of hot flashes in postmenopausal women. This lack of efficacy was apparently not due to inadequate intestinal absorption of L-methionine as serum levels of L-methionine and homocysteine rose significantly at both 2g and 4g of L-methionine a day. We hypothesized that these dosages of L-methionine would be effective in the treatment of hot flashes since L-methionine has the same affinity for the theoretical hot flash therapeutic target as does gabapentin⁹, and gabapentin has repeatedly been shown to be an effective hot flash treatment even at much lower dosages.^{1–4} L-methionine may not have the same physiological effects at this binding site as does gabapentin.

The compound pregabalin is closely related structurally and functionally to gabapentin²⁴ and is currently being studied in a RCT to determine its effectiveness in the treatment of hot flashes.²⁵ Positive results from the pregabalin trial would help to validate the alpha-2-delta subunit of VGCCs as a therapeutic target in the treatment of hot flashes.

In this study, the 2 dosages of L-methionine were associated with 16% and 61% increases in homocysteine, respectively, compared to baseline. Observational studies have linked elevated homocysteine with increased risk for cardiovascular disease; however, RCTs have repeatedly failed to show any cardiovascular benefit associated with lowering homocysteine by 18–27% through the use of B-vitamin therapy. Based on these data, elevated homocysteine is more likely to represent a biomarker for cardiovascular risk rather than a causative agent itself. It is unclear if the L-methionine-induced elevations in homocysteine in this study are clinically significant.

It is not surprising that subjects at baseline reported being more bothered by their nighttime hot flashes/night sweats than their daytime hot flashes since night sweats frequently interfere with sleep. Sleep disruption is commonly associated with the menopausal transition and the presence of chronic insomnia is positively associated with the severity of hot flashes.²⁶

Conclusion

L-methionine therapy appears to be ineffective in the treatment of hot flashes in postmenopausal women.

Acknowledgments

Support: This publication was made possible by Grant Number 1K23-AT-1709-01 from the National Center for Complementary and Alternative Medicine (NCCAM) and by the University of Rochester Clinical and Translational Science Institute, Grant Numbers UL1 RR024160, KL2 RR024136, and TL1 RR024135 from the National Center for Research Resources (NCRR). Both Centers are components of the National Institutes of Health (NIH). This publication's contents are solely the responsibility of the authors and do not necessarily represent the official views of NCCAM, NCRR or NIH.

References

1. Butt DA, Lock M, Lewis JE, Ross S, Moineddin R. Gabapentin for the treatment of menopausal hot flashes: a randomized controlled trial. *Menopause* 2008;15:310–318. [PubMed: 17917611]
2. Guttuso T Jr, Kurlan R, McDermott MP, Kiebertz K. Gabapentin's effects on hot flashes in postmenopausal women: a randomized controlled trial. *Obstet Gynecol* 2003;101:337–345. [PubMed: 12576259]
3. Pandya KJ, Morrow GR, Roscoe JA, et al. Gabapentin for hot flashes in 420 women with breast cancer: a randomised double-blind placebo-controlled trial. *Lancet* 2005;366:818–824. [PubMed: 16139656]
4. Reddy SY, Warner H, Guttuso T Jr, et al. Gabapentin, Estrogen, and Placebo for Treating Hot Flushes: A Randomized Controlled Trial. *Obstet Gynecol* 2006;108:41–48. [PubMed: 16816054]
5. Stefani A, Spadoni F, Giacomini P, Lavaroni F, Bernardi G. The effects of gabapentin on different ligand- and voltage-gated currents in isolated cortical neurons. *Epilepsy Res* 2001;43:239–248. [PubMed: 11248535]
6. Sutton KG, Martin DJ, Pinnock RD, Lee K, Scott RH. Gabapentin inhibits high-threshold calcium channel currents in cultured rat dorsal root ganglion neurones. *Br J Pharmacol* 2002;135:257–265. [PubMed: 11786502]
7. Thurlow RJ, Brown JP, Gee NS, Hill DR, Woodruff GN. [3H]gabapentin may label a system-L-like neutral amino acid carrier in brain. *Eur J Pharmacol* 1993;247:341–345. [PubMed: 8307106]
8. Clarke R, Daly L, Robinson K, et al. Hyperhomocysteinemia: an independent risk factor for vascular disease. *N Engl J Med* 1991;324:1149–1155. [PubMed: 2011158]
9. Ditscheid B, Funfstuck R, Busch M, Schubert R, Gerth J, Jahreis G. Effect of L-methionine supplementation on plasma homocysteine and other free amino acids: a placebo-controlled double-blind cross-over study. *Eur J Clin Nutr* 2005;59:768–775. [PubMed: 15870821]
10. van der Griend R, Biesma DH, Banga JD. Postmethionine-load homocysteine determination for the diagnosis hyperhomocysteinaemia and efficacy of homocysteine lowering treatment regimens. *Vasc Med* 2002;7:29–33. [PubMed: 12083731]
11. Guttuso T, McDermott MP, Su H, Kiebertz K. Effects of L-isoleucine and L-valine on hot flashes and serum homocysteine: a randomized controlled trial. *Obstet Gynecol* 2008;112:109–115. [PubMed: 18591315]
12. Bona KH, Njolstad I, Ueland PM, et al. Homocysteine lowering and cardiovascular events after acute myocardial infarction. *N Engl J Med* 2006;354:1578–1588. [PubMed: 16531614]
13. Lonn E, Yusuf S, Arnold MJ, et al. Homocysteine lowering with folic acid and B vitamins in vascular disease. *N Engl J Med* 2006;354:1567–1577. [PubMed: 16531613]
14. Albert CM, Cook NR, Gaziano JM, et al. Effect of folic acid and B vitamins on risk of cardiovascular events and total mortality among women at high risk for cardiovascular disease: a randomized trial. *Jama* 2008;299:2027–2036. [PubMed: 18460663]
15. Toole JF, Malinow MR, Chambless LE, et al. Lowering homocysteine in patients with ischemic stroke to prevent recurrent stroke, myocardial infarction, and death: the Vitamin Intervention for Stroke Prevention (VISP) randomized controlled trial. *Jama* 2004;291:565–575. [PubMed: 14762035]
16. U.S. Department of Health and Human Services FDA. Guidance for Industry: Estrogen and estrogen/progestin drug products to treat vasomotor symptoms and vulvar and vaginal atrophy symptoms—recommendations for clinical evaluation. [Accessed 6 July 2008]. Available at: <http://www.fda.gov/cder/guidance/5412dft.pdf>
17. Bergmans MG, Merkus JM, Corbey RS, Schellekens LA, Ubachs JM. Effect of Bellergal Retard on climacteric complaints: a double-blind, placebo-controlled study. *Maturitas* 1987;9:227–234. [PubMed: 3323851]
18. Upmalis DH, Lobo R, Bradley L, Warren M, Cone FL, Lamia CA. Vasomotor symptom relief by soy isoflavone extract tablets in postmenopausal women: a multicenter, double-blind, randomized, placebo-controlled study. *Menopause* 2000;7:236–242. [PubMed: 10914616]
19. Evans ML, Pritts E, Vittinghoff E, McClish K, Morgan KS, Jaffe RB. Management of postmenopausal hot flashes with venlafaxine hydrochloride: a randomized, controlled trial. *Obstet Gynecol* 2005;105:161–166. [PubMed: 15625158]

20. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28:193–213. [PubMed: 2748771]
21. Barentsen R, van de Weijer PH, van Gend S, Foekema H. Climacteric symptoms in a representative Dutch population sample as measured with the Greene Climacteric Scale. *Maturitas* 2001;38:123–128. [PubMed: 11306200]
22. Little, RJA.; Rubin, DB. *Statistical Analysis with Missing Data*. Vol. Second Edition. Hoboken, NJ: John Wiley and Sons; 2002.
23. Hettmansperger, T. *Statistical Inference Based on Ranks*. New York: John Wiley and Sons; 1984.
24. Fink K, Dooley DJ, Meder WP, et al. Inhibition of neuronal Ca(2+) influx by gabapentin and pregabalin in the human neocortex. *Neuropharmacology* 2002;42:229–236. [PubMed: 11804619]
25. ClinicalTrials.gov. Pregabalin in Treating Women With Hot Flashes. [Accessed 20 December 2008]. Available at: <http://clinicaltrials.gov/ct2/show/NCT00702949?term=lyrica+hot+flash&rank=1>
26. Ohayon MM. Severe hot flashes are associated with chronic insomnia. *Arch Intern Med* 2006;166:1262–1268. [PubMed: 16801508]

Figure 1.
Flow Diagram

Figure 2.

Hot Flash Composite Scores by Week from Study Phase 1

The values plotted are the adjusted group means estimated from a repeated measures analysis of covariance model that included terms for treatment group, week, and the interaction between treatment group and week.

Table 1

Subject Characteristics at Baseline by Treatment Assigned for Phase 1

Characteristic	L-Methionine (n=25)	Placebo (n=26)
Age (y)	54.5 (4.9)	54.1 (6.0)
Daily hot flash frequency	11.3 (3.4)	9.3 (4.0)
Daily moderate & severe hot flash frequency	8.6 (3.2)	7.4 (3.5)
Daily hot flash composite score	22.3 (6.9)	19.1 (8.1)
Duration of amenorrhea (mo) [†]	50.0 (24.0 – 120.0)	48.0 (22.0 – 120.0)
Duration experiencing hot flashes (mo) [†]	36.0 (24.0 – 90.0)	60.0 (36.0 – 108.0)
Surgical menopause (no., %)	4 (16%)	4 (15%)
Non-Hispanic white (no., %)	24 (96%)	21 (81%)
Non-Hispanic black (no., %)	1 (4%)	4 (15%)
Daytime hot flash bother score	6.9 (1.7)	6.9 (2.3)
Nighttime hot flash bother score	7.6 (2.2)	7.9 (2.4)
PSQI- global score	9.0 (3.3)	10.0 (3.9)
GCS- total score	18.8 (6.6)	21.4 (9.7)
Fasting serum homocysteine (μmol/L)	7.6 (2.7)	7.2 (1.9)
FSH (mIU/ml)	110.8 (41.4)	98.0 (32.2)
LH (mIU/ml)	49.9 (14.4)	45.8 (13.3)
Cortisol (μg/dl)	10.1 (2.9)	10.5 (3.8)
Weight (lb)	155.3 (38.9)	175.8 (47.9)

PPHFS- Patient Perceived Hot Flash Score; PSQI- Pittsburgh Sleep Quality Index; GCS-Greene Climacteric Scale; FSH- Follicle Stimulating Hormone; LH- Luteinizing Hormone. Values are mean (standard deviation) unless otherwise indicated.

[†] Reported as median (25th percentile – 75th percentile).

Table 2
Treatment Effects on Primary and Secondary Outcome Variables from Study Phase 1

Variable [†]	L-Methionine (n=25)	Placebo (n=26)	Treatment Effect [‡]	95% CI	P
Hot Flash Frequency (% change)	-37.2 (32.2)	-31.4 (43.4)	-5.7	(-27.1, 15.7)	0.59
Hot Flash Composite Score (% change)	-37.4 (38.1)	-33.4 (45.7)	-6.3	(-29.8, 17.3)	0.60
Daytime Hot Flash Bother Score	-1.5 (3.2)	-1.7 (2.9)	0.5	(-1.0, 2.0)	0.53
Nighttime Hot Flash Bother Score	-1.7 (2.4)	-1.8 (2.8)	0.0	(-1.0, 2.0)	0.98
PSQI Global Score	-1.8 (3.9)	-1.2 (3.5)	-1.0	(-2.0, 1.0)	0.46
GCS Total Score	-3.6 (7.0)	-4.2 (9.7)	0.0	(-4.0, 4.0)	0.89
Global Satisfaction with Treatment	4.7 (3.1)	5.1 (3.3)	0.0	(-3.0, 1.0)	0.81
Fasting Serum Homocysteine (μmol/L)	1.2 (2.5)	-0.5 (1.2)	1.4	(0.4, 2.6)	0.004
Fasting Serum Methionine (μmol/L)	16.2 (34.4)	2.3 (5.5)	5.7	(2.2, 9.7)	0.003
Fasting Serum Phenylalanine (μmol/L)	7.5 (11.8)	-3.2 (11.4)	10.0	(3.4, 17.5)	0.005
FSH (mIU/ml)	-2.8 (26.6)	-2.1 (22.1)	1.8	(-15.0, 17.4)	0.98
LH (mIU/ml)	-3.8 (13.1)	-4.8 (9.6)	0.1	(-6.0, 5.8)	0.99
Cortisol (μg/dl)	-0.5 (3.3)	-0.8 (3.9)	-0.2	(-2.1, 2.1)	0.83
Weight (lb)	0.3 (3.9)	-0.6 (4.7)	1.0	(-1.0, 3.0)	0.49

CI- Confidence Interval; PSQI- Pittsburgh Sleep Quality Index; GCS- Greene Climacteric Scale.

[†]Values are presented as mean (standard deviation) change from baseline to Week 12 except for Global Satisfaction with Treatment, for which the mean score at Week 12 is presented.

[‡]Treatment effect is estimated from a repeated measures analysis of variance model for the hot flash diary outcomes, and is the Hodges-Lehmann estimate of the group difference (L-Methionine – placebo) in population medians for the other outcome variables; see text for details.

Table 3

Changes from Baseline to Week 20 in Outcome Variables (Study Phase 2)

Variable	L-Methionine / L-Methionine (n = 25)	Placebo / Placebo (n = 13)	P
Hot Flash Frequency (% change)	-43.3 (29.5)	-50.6 (46.0)	0.93
Hot Flash Composite Score (% change)	-45.6 (36.0)	-53.2 (47.0)	0.64
Daytime Hot Flash Bother Score	-1.7 (2.9)	-2.5 (4.3)	0.83
Nighttime Hot Flash Bother Score	-2.9 (2.5)	-3.1 (4.3)	0.79
PSQI Global Score	-1.6 (4.1)	-1.5 (4.3)	0.81
GCS Total Score	-6.7 (5.9)	-3.8 (6.1)	0.20
Global Satisfaction with Treatment	5.7 (3.8)	6.9 (3.7)	0.49
Fasting Serum Homocysteine (μmol/L)	4.6 (6.4)	-1.2 (1.5)	0.0002
Fasting Serum Methionine (μmol/L)	23.9 (51.4)	1.6 (3.3)	0.003
Fasting Serum Phenylalanine (μmol/L)	-1.1 (10.1)	-8.2 (11.9)	0.09
FSH (mIU/ml)	7.6 (14.4)	-1.0 (7.4)	0.06
LH (mIU/ml)	-10.6 (7.6)	-12.7 (9.7)	0.57
Cortisol (μg/dl)	-2.3 (2.9)	-2.2 (5.3)	0.94
Weight (lb)	1.0 (3.9)	-4.4 (8.2)	0.20

PSQI- Pittsburgh Sleep Quality Index; GCS- Greene Climacteric Scale. Values are presented as mean (standard deviation) change from baseline except for Global Satisfaction with Treatment for which the mean score at Week 20 is presented.