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Phase II evaluation of S-adenosyl-L-methionine (SAME) for the treatment of hot flashes

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Abstract

Purpose—Hot flashes are a significant source of symptom burden that negatively impacts quality of life (QOL). For women who have contraindications to, or are unwilling to consider, estrogens or antidepressants for bothersome hot flashes, there are limited effective pharmacologic or complementary and alternative medicines.

Methods—This single-arm phase II trial studied the efficacy of S-adenosyl-L-methionine (SAME) for the treatment of hot flashes. Eligible women were required to have reported 14 hot flashes per week for 1 month. The patients were treated with SAME at a dose of 400 mg twice daily to evaluate whether a reduction in hot flash score appeared to be better than the historical placebo response of approximately 25 %. The women kept a daily hot flash diary during a baseline week and then daily during weeks 2–7. The primary endpoint was the change from baseline to week 7 in hot flash score and hot flash frequency. Secondary endpoints included toxicity analyses and the effect of SAME on QOL.

Results—From October 28, 2010 to January 30, 2012, 43 women were treated with SAME. The decrease in mean percent of baseline hot flash score and frequency was 35.4 and 32.6 %, respectively. When compared to the historical placebo response of 25 %, the effect of SAME on hot flash score was not statistically significant ($p=0.09$). Treatment was well tolerated with expected grade 1/2 gastrointestinal toxicity and no negative effect on QOL.

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Conclusions—The use of SAME does not appear to significantly reduce hot flashes more than would be expected with a placebo.

Keywords

SAMe; S-Adenosyl-L-methionine; Hot flashes; Quality of life; Clinical trials

Introduction

Diminished ovarian function as a result of natural menopause or breast cancer treatment leads to a variety of adverse vasomotor symptoms, including hot flashes. More than one third of women, without a history of cancer, will have moderate to severe hot flashes that persist up to 10 years after the onset of natural menopause, which negatively impacts quality of life (QOL) [1]. Hot flashes can be more frequent and severe in women with breast cancer as a result of oophorectomy, chemotherapy, or hormonal manipulation [2, 3]. Estrogens and progesterone analogs are the most effective agents at reducing hot flashes, with reductions of hot flashes by 70–90 % [4, 5]. However, due to concerns related to estrogen's proliferative effect on breast tissue and breast cancer recurrence risk, many women and physicians are unwilling to consider these therapies. In response to these concerns and the significant negative effect of hot flashes on QOL, multiple pharmacologic as well as complementary and alternative medicine (CAM) trials have been conducted in women with and without a history of breast cancer [6].

To date, effective non-hormonal pharmacologic treatments for hot flashes are largely based on well-conducted randomized placebo-controlled clinical trials in the breast cancer population and include antidepressants such as citalopram [7], escitalopram [8], paroxetine [9], desvenlafaxine [10], and venlafaxine [11] as well as antiepileptics including gabapentin [12] and pregabalin [13]. The average reduction in hot flashes in these trials range from 40 to 60 % compared to placebo responses of 20–30 %. In contrast, multiple randomized controlled trials of CAM therapies such as vitamin E [14], soy phytoestrogens [15], black cohosh [16], and flaxseed [17] have failed to show clinically or statistically significant benefits, compared to placebo.

In 1952, S-adenosyl-L-methionine (SAMe) was first discovered and is now known to be formed from the essential amino acid methionine and adenosine triphosphate; this compound functions as a methyl group donor for nucleic acid, proteins, phospholipids, and amines [18]. SAMe is also involved in transsulfuration and aminopropylation pathways and serves as a precursor molecule for cysteine and glutathione as well as polyamine synthesis, respectively. To date, SAMe has been reported to have clinically significant effects in the treatment of osteoarthritis, chronic liver disease, and depression [19]. SAMe has also been shown to increase concentrations of 5-hydroxyindoleacetic acid (5HIA), a serotonin metabolite, which provides an explanation for its antidepressant effect [20, 21]. As serotonin is also known to mediate the thermoregulatory effects of estrogen and resulting vasomotor dysfunction observed in the menopause state [22, 23], it was hypothesized that SAMe could reduce hot flash burden similar to the antidepressant agents described above.

Based on the working mechanistic hypothesis stated above, this single-arm phase II trial was conducted to test whether SAME looked promising enough for the treatment of burdensome hot flashes in women to conduct a more definitive randomized placebo-controlled clinical trial.

Patients and methods

To be eligible for this trial, women had to be 18 years of age or older, have a history of breast cancer (currently without malignant disease and having completed planned chemotherapy and radiation) or no history of breast cancer but who wished to avoid estrogen due to a perceived increased risk of breast cancer, and have burdensome hot flashes (defined as 14 hot flashes per week for 1 month and being a sufficient enough problem that the patient desired therapeutic intervention).

Patients were excluded if they were currently on, or planning to be on, any antineoplastic chemotherapy, androgens, estrogens, or progestational agents. Tamoxifen, raloxifene, and aromatase inhibitors (AI) were allowed only if patients were on a constant dose for 4 weeks prior to the study enrollment and not expected to stop the medication during the trial period. Patients were also excluded if they were pregnant, nursing, or of childbearing potential and unwilling to employ adequate contraception. Women could not have a known allergy to SAME and could not be receiving herbal supplements, therapeutic anticoagulation with warfarin, medications known to have interactions with SAME (meperidine, gabapentin, antidepressants, tramadol, levodopa), or any acute or chronic progressive/unstable systemic disease.

SAME was purchased with research-designated funds from the Nature Made Nutritional Products as SAM-e Complete®. The patients were given a 6-week supply of SAME and were instructed not to take any SAME during the first 7 days but were to keep track of their hot flash frequency and severity every day and complete the hot flash diary. Starting at week 2, the patients were instructed to take SAME 400 mg orally once daily on an empty stomach 30 min prior to breakfast. From weeks 3 to 7, the patients were instructed to take SAME 400 mg orally twice a day on an empty stomach, 30 min prior to breakfast and prior to their evening meal. Each patient was contacted by the study nurse by telephone weekly during weeks 1–7 to assess product tolerability, document compliance, encourage completion of the booklet, and address problems.

The Mayo Clinic institutional review board per United States federal guidelines approved this clinical trial. All patients were required to provide written informed consent prior to trial entry.

Statistical considerations

The primary outcome measure was hot flash activity as recorded via a prospective self-report Hot Flash Diary, completed in a previously validated fashion [24]. The patients recorded both hot flash frequency and severity during each 24-h period over the entire trial period. They were asked to keep track of their hot flashes, as they occurred, in a small

notebook throughout the day in order to accurately complete the hot flash diaries at the end of each day.

The primary study goal was to determine whether there was any reduction in hot flash activity beyond what would be expected with a placebo (25 %). Methodology from earlier phase II trials conducted by this group determined a target reduction of 50 % in order to move to a phase III trial [24]. Similarly, placebo responses in randomized placebo-controlled trials in non-cancer populations' range from 25 to 35 % [25, 26]. The primary endpoint utilized the hot flash score, which was computed by multiplying the frequency by the average severity per day, and calculating the mean per week, as done in previous Mayo/ North Central Cancer Treatment Group (NCCTG) studies [6]. Reduction in score was determined by subtracting baseline score (average during week 1 pre-protocol treatment) from week 7 score (end of treatment). The primary analysis consisted of testing the data for normality then applying a single-sample *t* test or Wilcoxon test on the reduction in score, including 95 % confidence intervals (CIs). The percent change from baseline was also calculated and analyzed in a similar fashion. In an intent-to-treat analysis, a patient was considered to be a success (i.e., have a response) if the patient experienced a 50 % reduction in hot flash score from baseline, otherwise considered a failure. The patients who did not complete the study, and were thus not evaluable for the primary endpoint, were categorized as failures. For the intent-to-treat analysis, chi-square methodology was used.

Secondary endpoint measures included the Hot Flash Related Daily Interference Scale (HFRDIS) [27], the Profile of Mood States (POMS) [28, 29], and a Side Effect Questionnaire (SEQ). The SEQ was completed weekly at the end of each week for weeks 1–7, while the HFRDIS and POMS were completed twice, at the end of week 1 and at week 7. Study personnel called the participants weekly during weeks 1–7 to assess product tolerability, document compliance, address problems, encourage completion of the surveys, and grade toxicities per the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 grading system [30]. Symptoms specifically monitored were insomnia, bloating, nausea, diarrhea, abdominal pain, allergic reaction, headache, anorexia, fatigue, myalgias, neoplasms (benign, malignant, or unspecified), stomach pain, and vomiting.

The POMS was scored according to its specific scoring algorithm resulting in a total score and six subscale scores (anger/hostility, confusion/bewilderment, depression/dejection, fatigue/inertia, tension/anxiety, and vigor/activity). An average of the scores of the 10 individual questions on the HFRDIS was calculated for the HFRDIS total score. Each HFRDIS item and each SEQ item were reported as individual scores. All scores were transposed to a 0–100 point percentage scale where 100 is the best. Changes from week 1 to week 7 were calculated for all scores and changes of 10 points or higher on a 100-point scale were considered clinically meaningful [27]. After normality testing, single-sample *t* tests or Wilcoxon tests were conducted for changes from baseline and descriptive statistics (frequency and percentage) were calculated to summarize AE type and grade.

The hot flash eligibility requirement was derived using data from NCCTG 95-92-53 [14], which illustrated that we could expect a standard deviation of roughly two hot flashes per day (14 per week). A 50 % reduction in frequency would amount to a decrease of seven hot

flashes per week, even if severity did not change. This study was powered considering the enrollment of 30 patients. With 30 observations (patients) and a one-sided test with a 5 % type I error rate, there was over 80 % power to detect a 50 % reduction, which equates to a moderate effect size of a decrease of 0.5 standard deviations (seven per week) [24]. All analyses were carried out using SAS[®] software, Version 9.

Results

Patients

A total of 45 patients were enrolled from October 28, 2010 to January 30, 2012 (Fig. 1). Two patients were ineligible (one due to beginning treatment prior to registration and one due to having an IUD placed after beginning treatment). Forty-three patients with a history of breast cancer ($n=18$) and without ($n=25$) initiated treatment. Nine of the treated patients did not complete the trial (four refused further treatment, two of whom cited lack of efficacy, and five stopped treatment due to gastrointestinal (GI) adverse events). Three patients, who completed the trial, did not complete the QOL assessment booklets, thus changes from baseline could not be calculated. Overall, 31 completed per protocol and were evaluable for the primary efficacy analysis. All 43 patients were included in an intent-to-treat responder analysis. The demographics, clinical, and other characteristics of the eligible patients are described in Table 1. In response to a single question about self-reported adherence to the study medication, 82 % reported always taking the medication as prescribed, 15 % reported usually, and only 3 % reported their adherence as rarely.

Efficacy

This study did not meet the 50 % reduction threshold (Table 2). The mean percent decrease in hot flash score was 35.4 %, and compared to the historical placebo response of 25 %, the effect of SAME on hot flash score was not statistically significant ($p=0.09$). The mean percent reduction in hot flash frequency was 32.6 %, and this was also non-significant ($p=0.14$). The mean hot flash score and frequency data over time, as shown as percent of baseline with 95 % CIs are shown in Fig. 2. The intent-to-treat analysis indicates that 31 (72.1 %) of the 43 patients did not achieve a 50 % reduction in hot flash score ($p=0.004$). This result for hot flash frequency is the same. A comparison of the characteristics of the responders versus non-responders revealed no significant differences between the two groups. Of the 33 patients who responded to the week 7 phone call, 18 (54.5 %) reported satisfaction with hot flash control during the trial period and 15 (45.5 %) did not.

Toxicity and QOL

The self-reported SEQ indicated nine symptoms improved and five symptoms got worse (Table 3). Compared to baseline values, statistically significant improvements occurred for abnormal sweating ($p<0.001$), trouble sleeping ($p=0.003$), fatigue ($p=0.02$), and muscle or joint aches/pains ($p=0.01$). The patients experienced a statistically significant worsening in sleepiness. Online resource 1 shows maximum reported AE grades as measured by the CTCAE experience regardless of attribution. There was no grade 4 AEs. However, three instances of grade 3 AEs were observed, which included one insomnia, one neoplasm which

were deemed unrelated to study medication, and another insomnia that was deemed possibly related.

All POMS and HFRDIS scores showed improvement from baseline (Table 4). Modest but statistically significant improvements existed in the total mood disturbance of the POMS (mean change of 3, $p=0.04$) as well as the fatigue/inertia subscale (mean change of 10.9, $p=0.004$). Similarly, statistically significant improvements (from baseline) were observed in several individual questions of the HFRDIS: mood (mean change 13.9, $p<0.001$), sleep (mean change of 21.6, $p<0.001$), and concentration (mean change of 12.8, $p=0.001$); however, the total QOL showed a non-significant trend towards improved QOL (mean change of 7.8, $p=0.06$).

Discussion

This is the first published study to investigate the effect of S-adenosyl-L-methionine (SAME) for the treatment of burdensome hot flashes in women. In this single-arm phase II trial, the use of SAME failed to reduce hot flashes by 50 %, which was the predetermined threshold needed for further study. There was only a modest signal of activity (35 % reduction in the hot flash score), which commensurates with published placebo arms in randomized trials [24, 25, 31]. Though we were not powered to perform a subset analysis, a thorough comparison of the characteristics of the 12 women who had at least a 50 % reduction with those who did not provided no information about a potential subgroup who might benefit from SAME. Some women with breast cancer responded and some women without breast cancer responded while some women on endocrine therapy and also some not on endocrine therapy responded. There was no trend for a pattern in response. In addition, SAME demonstrated a tolerable toxicity profile and a slight improvement in QOL as measured by two validated tools (POMS [28] and HFRDIS [27]).

SAME has been evaluated as an antidepressant in numerous studies with a mild to moderate effect when compared to placebo [19, 32]. As a primary methyl donor, SAME is known to be involved with the synthesis of monoaminergic neurotransmitters and has been shown to increase 5HIA, a serotonin metabolite, which provides an explanation for its antidepressant effect [20, 21] and a proposed mechanism of action for the current trial. While the effect on hot flashes was not sufficiently positive to warrant a placebo-controlled phase III trial, the improved mood noted on the HFRDIS subscale corroborates its action as an antidepressant. Similar results were seen in a negative trial of desipramine on hot flashes despite improvements in mood [33]. Taken together, these findings continue to support the concept that the effectiveness of anti-depressants on hot flashes remains independent of their anti-depressant effect.

Several aspects of this trial might account for the lack of a significant observed benefit. The method of administration and studied dose could have influenced the current findings. SAME has poor oral bioavailability due to extensive first-pass metabolism. A large double-blind randomized trial of intramuscular (IM) SAME at a dose of 400 mg showed equivalence to imipramine for treating depression [34]. Though it is possible that IM or intravenous (IV) SAME might be more efficacious for hot flashes, cerebrospinal fluid SAME levels appear to

increase with either oral or IV administration [35] and other data suggest comparable antidepressant efficacy with IM versus oral treatment [36]. The hassles of IM/IV treatment limit consideration of testing this administration approach for the treatment of hot flashes. Higher dosing of SAME (up to 1600 mg/day) have been used in multiple trials for depression [19, 32]; however, a linear dose effect with lower doses of newer antidepressants has not been observed to be associated with decreased efficacy in hot flash reduction [7].

A particularly interesting post hoc finding was the improvement in fatigue as measured by patient-reported side effects via the SEQ and the fatigue/inertia subscale of the POMS. Significant fatigue is a common complaint of women undergoing treatment for breast cancer as well as in those who have completed therapy [37]. The mechanism of action for this finding remains to be known; however, it might be due to its influence on inflammation and pain [18, 38]. Supporting this hypothesis, two separate randomized clinical trials testing SAME for the treatment of fibromyalgia found modest improvements in fatigue in their subset analyses [39, 40]. Given the exploratory nature of this finding, SAME should be considered for testing for cancer-related and post-menopausal fatigue.

SAME at 400 mg orally twice daily had a tolerable toxicity profile with the most common adverse effects being grade 1/2 insomnia, bloating, nausea, and diarrhea, understanding that these findings might all be from a nocebo effect, as there was no placebo arm to better understand background 'toxicity' rates. GI toxicity is the most common adverse effect seen in other trials of SAME as well. The four patients that discontinued therapy in the current trial did so due to GI toxicity.

Some perceived limitations of this study would include its small sample size, single-arm design, and heterogeneous population. The sample size was supported by meta-analytic work that demonstrated that this is a reasonable sample size for a pilot study assessing hot flash interventions [24]. While it is plausible that outcomes might have been different if patients were used as their own control, the modest effect suggests against this. Moreover, the use of a historical placebo response and requirement for a single-arm open-label trial to meet a 50 % reduction threshold was based on a large body of research in both cancer and non-cancer trials with relatively similar inclusion criteria showing consistent placebo responses of 25–35 % [25, 31, 41]. Lastly, although patients with and without breast cancer and various endocrine therapies added heterogeneity, clinical trial evidence supports that serotonergic agents have relatively similar efficacy in populations irrespective of breast cancer history or use of endocrine agents and provides evidence to support the inclusion of both cohorts in hot flash trials [6, 26, 31, 41]. Strengths include the use of a prospective self-report daily diary for hot flash measurement, high degree of adherence to the protocol treatment, and the use of validated QOL tools.

Complementary and alternative medicine therapies continue to be used by many women for hot flashes, with the highest use among women with a history of breast cancer [42]. Despite a compelling mechanism based on its antidepressant activity, SAME appears to be yet another CAM agent with minimal observed efficacy for hot flashes, when tested objectively.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

- Freeman EW, Sammel MD, Sanders RJ. Risk of long-term hot flashes after natural menopause: evidence from the Penn Ovarian Aging Study cohort. *Menopause*. 2014; 21(9):924–932. doi: [10.1097/GME.0000000000000196](https://doi.org/10.1097/GME.0000000000000196). [PubMed: 24473530]
- Couzi RJ, Helzlsouer KJ, Fetting JH. Prevalence of menopausal symptoms among women with a history of breast cancer and attitudes toward estrogen replacement therapy. *J Clin Oncol*. 1995; 13(11):2737–2744. [PubMed: 7595732]
- Carpenter JS, Andrykowski MA, Cordova M, Cunningham L, Studts J, McGrath P, Kenady D, Sloan D, Munn R. Hot flashes in postmenopausal women treated for breast carcinoma: prevalence, severity, correlates, management, and relation to quality of life. *Cancer*. 1998; 82(9):1682–1691. [PubMed: 9576289]
- Loprinzi CL, Michalak JC, Quella SK, O’Fallon JR, Hatfield AK, Nelimark RA, Dose AM, Fischer T, Johnson C, Klatt NE, et al. Megestrol acetate for the prevention of hot flashes. *N Engl J Med*. 1994; 331(6):347–352. doi: [10.1056/NEJM199408113310602](https://doi.org/10.1056/NEJM199408113310602). [PubMed: 8028614]
- The 2012 hormone therapy position statement of: The North American Menopause Society. *Menopause*. 2012; 19(3):257–271. doi: [10.1097/gme.0b013e31824b970a](https://doi.org/10.1097/gme.0b013e31824b970a). [PubMed: 22367731]
- Loprinzi CL, Barton DL, Sloan JA, Novotny PJ, Dakhil SR, Verdirame JD, Knutson WH, Kelaghan J, Christensen B. Mayo Clinic and North Central Cancer Treatment Group hot flash studies: a 20-year experience. *Menopause*. 2008; 15(4 Pt 1):655–660. doi: [10.1097/gme.0b013e3181679150](https://doi.org/10.1097/gme.0b013e3181679150). [PubMed: 18427355]
- Barton DL, LaVasseur BI, Sloan JA, Stawis AN, Flynn KA, Dyar M, Johnson DB, Atherton PJ, Diekmann B, Loprinzi CL. Phase III, placebo-controlled trial of three doses of citalopram for the treatment of hot flashes: NCCTG trial N05C9. *J Clin Oncol*. 2010; 28(20):3278–3283. doi: [10.1200/JCO.2009.26.6379](https://doi.org/10.1200/JCO.2009.26.6379). [PubMed: 20498389]
- Freeman EW, Guthrie KA, Caan B, Sternfeld B, Cohen LS, Joffe H, Carpenter JS, Anderson GL, Larson JC, Ensrud KE, Reed SD, Newton KM, Sherman S, Sammel MD, LaCroix AZ. Efficacy of escitalopram for hot flashes in healthy menopausal women: a randomized controlled trial. *Jama*. 2011; 305(3):267–274. doi: [10.1001/jama.2010.2016](https://doi.org/10.1001/jama.2010.2016). [PubMed: 21245182]
- Stearns V, Beebe KL, Iyengar M, Dube E. Paroxetine controlled release in the treatment of menopausal hot flashes: a randomized controlled trial. *Jama*. 2003; 289(21):2827–2834. doi: [10.1001/jama.289.21.2827](https://doi.org/10.1001/jama.289.21.2827). [PubMed: 12783913]
- Sun Z, Hao Y, Zhang M. Efficacy and safety of desvenlafaxine treatment for hot flashes associated with meno-pause: a meta-analysis of randomized controlled trials. *Gynecol Obstet Investig*. 2013; 75(4):255–262. doi: [10.1159/000348564](https://doi.org/10.1159/000348564). [PubMed: 23548358]
- Bordeleau L, Pritchard KI, Loprinzi CL, Ennis M, Jugovic O, Warr D, Haq R, Goodwin PJ. Multicenter, randomized, cross-over clinical trial of venlafaxine versus gabapentin for the management of hot flashes in breast cancer survivors. *J Clin Oncol*. 2010; 28(35):5147–5152. doi: [10.1200/JCO.2010.29.9230](https://doi.org/10.1200/JCO.2010.29.9230). [PubMed: 21060031]
- Loprinzi CL, Dueck AC, Khoiratty BS, Barton DL, Jafar S, Rowland KM Jr, Atherton PJ, Marsa GW, Knutson WH, Bearden JD 3rd, Kottschade L, Fitch TR. A phase III randomized, double-blind, placebo-controlled trial of gabapentin in the management of hot flashes in men (N00CB). *Ann Oncol*. 2009; 20(3):542–549. doi: [10.1093/annonc/mdn644](https://doi.org/10.1093/annonc/mdn644). [PubMed: 19129205]
- Moraska AR, Atherton PJ, Szydlo DW, Barton DL, Stella PJ, Rowland KM Jr, Schaefer PL, Krook J, Bearden JD, Loprinzi CL. Gabapentin for the management of hot flashes in prostate cancer

survivors: a longitudinal continuation Study-NCCTG Trial N00CB. *J Support Oncol.* 2010; 8(3): 128–132. [PubMed: 20552926]

14. Barton DL, Loprinzi CL, Quella SK, Sloan JA, Veeder MH, Egner JR, Fidler P, Stella PJ, Swan DK, Vaught NL, Novotny P. Prospective evaluation of vitamin E for hot flashes in breast cancer survivors. *J Clin Oncol.* 1998; 16(2):495–500. [PubMed: 9469333]
15. Quella SK, Loprinzi CL, Barton DL, Knost JA, Sloan JA, LaVasseur BI, Swan D, Krupp KR, Miller KD, Novotny PJ. Evaluation of soy phytoestrogens for the treatment of hot flashes in breast cancer survivors: a North Central Cancer Treatment Group Trial. *J Clin Oncol.* 2000; 18(5):1068–1074. [PubMed: 10694559]
16. Pockaj BA, Gallagher JG, Loprinzi CL, Stella PJ, Barton DL, Sloan JA, Lavasseur BI, Rao RM, Fitch TR, Rowland KM, Novotny PJ, Flynn PJ, Richelson E, Fauq AH. Phase III double-blind, randomized, placebo-controlled crossover trial of black cohosh in the management of hot flashes: NCCTG Trial N01CC1. *J Clin Oncol.* 2006; 24(18):2836–2841. doi:[10.1200/JCO.2005.05.4296](https://doi.org/10.1200/JCO.2005.05.4296). [PubMed: 16782922]
17. Pruthi S, Qin R, Terstreich SA, Liu H, Loprinzi CL, Shah TR, Tucker KF, Dakhil SR, Bury MJ, Carolla RL, Steen PD, Vuky J, Barton DL. A phase III, randomized, placebo-controlled, double-blind trial of flaxseed for the treatment of hot flashes: North Central Cancer Treatment Group N08C7. *Menopause.* 2012; 19(1):48–53. doi:[10.1097/gme.0b013e318223b021](https://doi.org/10.1097/gme.0b013e318223b021). [PubMed: 21900849]
18. Bottiglieri T. S-Adenosyl-L-methionine (SAME): from the bench to the bedside—molecular basis of a pleiotrophic molecule. *Am J Clin Nutr.* 2002; 76(5):1151S–1157S. [PubMed: 12418493]
19. Hardy ML, Coulter I, Morton SC, Favreau J, Venuturupalli S, Chiappelli F, Rossi F, Orshansky G, Jungvig LK, Roth EA, Suttrop MJ, Shekelle P. S-Adenosyl-L-methionine for treatment of depression, osteoarthritis, and liver disease. *Evid Rep Technol Assess (Summ).* 2003; 64:1–3. [PubMed: 12899148]
20. Bottiglieri T, Laundry M, Martin R, Carney MW, Nissenbaum H, Toone BK, Johnson AL, Reynolds EH. S-Adenosylmethionine influences monoamine metabolism. *Lancet.* 1984; 2(8396):224. [PubMed: 6146777]
21. Otero-Losada ME, Rubio MC. Acute changes in 5-HT metabolism after S-adenosyl-L-methionine administration. *Gen Pharmacol.* 1989; 20(4):403–406. [PubMed: 2473938]
22. Bethea CL, Lu NZ, Gundlach C, Streicher JM. Diverse actions of ovarian steroids in the serotonin neural system. *Front Neuroendocrinol.* 2002; 23(1):41–100. doi:[10.1006/frne.2001.0225](https://doi.org/10.1006/frne.2001.0225). [PubMed: 11906203]
23. Moses-Kolko EL, Berga SL, Greer PJ, Smith G, Cidis Meltzer C, Drevets WC. Widespread increases of cortical serotonin type 2A receptor availability after hormone therapy in euthymic post-menopausal women. *Fertil Steril.* 2003; 80(3):554–559. [PubMed: 12969697]
24. Sloan JA, Loprinzi CL, Novotny PJ, Barton DL, Lavasseur BI, Windschitl H. Methodologic lessons learned from hot flash studies. *J Clin Oncol.* 2001; 19(23):4280–4290. [PubMed: 11731510]
25. Shams T, Firwana B, Habib F, Alshahrani A, Alnoub B, Murad MH, Ferwana M. SSRIs for hot flashes: a systematic review and meta-analysis of randomized trials. *J Gen Intern Med.* 2014; 29(1):204–213. doi:[10.1007/s11606-013-2535-9](https://doi.org/10.1007/s11606-013-2535-9). [PubMed: 23888328]
26. Drewe J, Bucher KA, Zahner C. A systematic review of non-hormonal treatments of vasomotor symptoms in climacteric and cancer patients. *Springerplus.* 2015; 4:65. doi:[10.1186/s40064-015-0808-y](https://doi.org/10.1186/s40064-015-0808-y). [PubMed: 25713759]
27. Carpenter JS. The Hot Flash Related Daily Interference Scale: a tool for assessing the impact of hot flashes on quality of life following breast cancer. *J Pain Symptom Manag.* 2001; 22(6):979–989.
28. Curran S, Andrykowski M, Stadts J. Short form of the profile of mood states (POMS-SF): psychometric information. *Psychol Assess.* 1995; 7:80–83.
29. Wyrwich KW, Yu H. Validation of POMS questionnaire in postmenopausal women. *Qual Life Res.* 2011; 20(7):1111–1121. doi:[10.1007/s11136-011-9846-2](https://doi.org/10.1007/s11136-011-9846-2). [PubMed: 21279447]
30. Institute, NC. Common terminology criteria for adverse events. v4.02009. (NIH publication # 09–7473)

31. Loprinzi CL, Sloan J, Stearns V, Slack R, Iyengar M, Diekmann B, Kimmick G, Lovato J, Gordon P, Pandya K, Guttuso T Jr, Barton D, Novotny P. Newer antidepressants and gabapentin for hot flashes: an individual patient pooled analysis. *J Clin Oncol*. 2009; 27(17):2831–2837. doi:[10.1200/JCO.2008.19.6253](https://doi.org/10.1200/JCO.2008.19.6253). [PubMed: 19332723]
32. Williams AL, Girard C, Jui D, Sabina A, Katz DL. S-Adenosylmethionine (SAME) as treatment for depression: a systematic review. *Clin Invest Med*. 2005; 28(3):132–139. [PubMed: 16021987]
33. Barton DL, Loprinzi CL, Atherton P, Raymond J, Shanafelt T, Hines S, Palmieri F, Rummans T, Adjei AA, Sloan J. Phase II evaluation of desipramine for the treatment of hot flashes. *Support Cancer Ther*. 2007; 4(4):219–224. doi:[10.3816/SCT.2007.n.018](https://doi.org/10.3816/SCT.2007.n.018). [PubMed: 18632520]
34. Pancheri P, Scapicchio P, Chiaie RD. A double-blind, randomized parallel-group, efficacy and safety study of intramuscular S-adenosyl-L-methionine 1,4-butanedisulphonate (SAME) versus imipramine in patients with major depressive disorder. *Int J Neuropsychopharmacol*. 2002; 5(4):287–294. doi:[10.1017/S1461145702003085](https://doi.org/10.1017/S1461145702003085). [PubMed: 12466028]
35. Bottiglieri T, Godfrey P, Flynn T, Carney MW, Toone BK, Reynolds EH. Cerebrospinal fluid S-adenosylmethionine in depression and dementia: effects of treatment with parenteral and oral S-adenosylmethionine. *J Neurol Neurosurg Psychiatry*. 1990; 53(12):1096–1098. [PubMed: 2292704]
36. Delle, Chiaie R.; Pancheri, P.; Scapicchio, P. Efficacy and tolerability of oral and intramuscular S-adenosyl-L-methionine 1,4-butanedisulfonate (SAME) in the treatment of major depression: comparison with imipramine in 2 multicenter studies. *Am J Clin Nutr*. 2002; 76(5):1172S–1176S. [PubMed: 12418499]
37. Schmidt ME, Chang-Claude J, Vrieling A, Heinz J, Flesch-Janys D, Steindorf K. Fatigue and quality of life in breast cancer survivors: temporal courses and long-term pattern. *J Cancer Surviv*. 2012; 6(1):11–19. doi:[10.1007/s11764-011-0197-3](https://doi.org/10.1007/s11764-011-0197-3). [PubMed: 22160661]
38. Gutierrez S, Palacios I, Sanchez-Pernaute O, Hernandez P, Moreno J, Egido J, Herrero-Beaumont G. SAME restores the changes in the proliferation and in the synthesis of fibronectin and proteoglycans induced by tumour necrosis factor alpha on cultured rabbit synovial cells. *Br J Rheumatol*. 1997; 36(1):27–31. [PubMed: 9117169]
39. Di Benedetto P, Iona LG, Zidarich V. Clinical evaluation of s-adenosyl-1-methionine versus transcutaneous electrical nerve stimulation in primary fibromyalgia. *Curr Ther Res*. 1993; 53(2):222–229.
40. Jacobsen S, Danneskiold-Samsøe B, Andersen RB. Oral S-adenosylmethionine in primary fibromyalgia. Double-blind clinical evaluation. *Scand J Rheumatol*. 1991; 20(4):294–302. [PubMed: 1925418]
41. Bardia A, Novotny P, Sloan J, Barton D, Loprinzi C. Efficacy of nonestrogenic hot flash therapies among women stratified by breast cancer history and tamoxifen use: a pooled analysis. *Menopause*. 2009; 16(3):477–483. doi:[10.1097/gme.0b013e31818c91ca](https://doi.org/10.1097/gme.0b013e31818c91ca). [PubMed: 19188850]
42. Harris PF, Remington PL, Trentham-Dietz A, Allen CI, Newcomb PA. Prevalence and treatment of menopausal symptoms among breast cancer survivors. *J Pain Symptom Manag*. 2002; 23(6):501–509.

Fig. 1.
Consort diagram

Fig. 2.
Mean hot flash score and frequency per week

Table 1

Baseline patient characteristics

	Total (N=43)
Race	
White	40 (93 %)
Black or African American	1 (2 %)
Asian	2 (5 %)
Tamoxifen therapy	
Yes	8 (19 %)
No	35 (81 %)
Aromatase inhibitor therapy	
Yes	5 (12 %)
No	38 (88 %)
Average hot flashes per day	
2–3	3 (7.0 %)
4–9	21 (49 %)
>=10	19 (44 %)
Duration of flash symptoms (months)	
<9	5 (12 %)
9	38 (88 %)
Breast cancer history	
Yes	18 (42 %)
No	25 (58 %)

Table 2

Mean hot flash score and frequency during study period

Efficacy variable	Statistic	Week 1 (baseline) (N=41)	Week 7 (N=31)	Week 7 (minus baseline) (N=31)	Week 7 (percent of baseline) (N=31)	95 % CI of the percent of baseline	p value *
Hot flash score	Mean	16.7	9.9	-5.7	64.6	(49.2–80.0)	0.0903 ^a
	Median	14.7	6.4	-5.1	57.3		
Hot flash frequency	Mean	9.0	5.8	-2.8	67.4	(52.3–82.5)	0.1443 ^b
	Median	8.4	4.7	-2.6	71.4		

CI confidence interval*
p value that the mean reduction in hot flash score and frequency is at least 25 %^a
t test^b
Wilcoxon

Table 3

Mean change in symptoms measured by the side effect questionnaire

Symptoms	Total (N=43)	Mean change from baseline ^a (SD)	<i>p</i> value
Abnormal sweating	32	25 (34.5)	<0.001 ^b
Trouble sleeping	32	17.5 (30.7)	0.003 ^b
Fatigue	29	11.7 (25.2)	0.02 ^b
Muscle or joint aches/pain	32	10 (20.6)	0.01 ^c
Trouble concentrating	32	7.5 (20.2)	0.06 ^c
Swelling of hands/feet	32	2.8 (18.9)	0.64 ^c
Anxiousness	32	2.8 (16.7)	0.32 ^c
Constipation	32	2.5 (25)	0.80 ^c
Diarrhea	29	1.4 (18.3)	0.42 ^c
Headache	29	0 (16)	0.96 ^c
Nausea	29	−1.4 (18.1)	0.80 ^c
Lack of coordination	32	−3.8 (14.8)	0.25 ^c
Appetite	29	−4.1 (17.8)	0.23 ^c
Dry mouth	29	−4.1 (22.4)	0.40 ^c
Sleepiness	29	−15.5 (25.6)	0.003 ^b

SD standard deviation

^a Adverse events were reported using a 0–100 scale where 0 is as bad as it can be and 100 is no event; a positive change indicates symptom improvement during the study period

^b *t* test

^c Wilcoxon

Table 4

Mean change in quality of life measures

QOL measure	Total (N=43)	Mean change from baseline ^a (SD)	<i>p</i> value
POMS			
POMS total	30	3.0 (7.8)	0.04 ^b
Fatigue/inertia	30	10.9 (18.7)	0.004 ^b
Anger/hostility	30	2.8 (10.1)	0.13 ^b
Tension/anxiety	30	2.3 (10.8)	0.18 ^c
Confusion/bewilderment	30	1.2 (10.6)	0.54 ^c
Depression/dejection	30	0.7 (8.8)	0.61 ^c
Vigor/activity	30	0.5 (13.9)	0.85 ^b
HFRDIS			
HFRDIS total	31	8.6 (14.4)	0.002 ^b
Mood	31	13.9 (16.3)	<0.001 ^b
Sleep	32	21.6 (30.0)	<0.001 ^b
Concentration	32	12.8 (21.3)	0.001 ^c
Overall QOL	32	7.8 (21.1)	0.06 ^c
Enjoyment of life	32	5.9 (17.4)	0.08 ^c
Social activities	32	5.3 (17.0)	0.09 ^c
Leisure activities	32	4.7 (15.2)	0.11 ^c
Work	32	4.4 (19.3)	0.21 ^b
Relationships with others	32	3.4 (15.6)	0.29 ^c
Sexuality	32	2.8 (23.7)	0.59 ³

Abbreviation: *SD* standard deviation, *POMS* Profile of Mood States, *HFRDIS* Hot Flash Related Daily Interference Scale, *QOL* quality of life^a All questions were converted to a 0–100 scale where 100 is the best QOL and a positive change indicates improvement during the study period^b *t* test^c Wilcoxon