Safety and efficacy of S-adenosylmethionine (SAMe) for osteoarthritis

A meta-analysis

KAREN L. SOEKEN, PHD; WEN-LIN LEE, RN, PHD; R. BARKER BAUSELL, PHD; MARIA AGELLI, MD, MS; AND BRIAN M. BERMAN, MD
Baltimore, Maryland

KEY POINTS FOR CLINICIANS

- S-adenosylmethionine (SAMe) is as effective as NSAIDs in offering pain relief and improving functional limitation with less risk of side effects.
- When compared with placebo, SAMe improved functional limitations of osteoarthritis, but there was no improvement in pain.
- The tolerability of SAMe was similar to that of placebo and greater than that of NSAIDs.

■ OBJECTIVE We assessed the efficacy of S-adenosylmethionine (SAMe), a dietary supplement now available in the United States, compared with that of placebo or nonsteroidal anti-inflammatory drugs (NSAIDs) in the treatment of osteoarthritis (OA).
■ STUDY DESIGN This was a meta-analysis of randomized controlled trials.
■ DATA SOURCES We identified randomized controlled trials of SAMe versus placebo or NSAIDS for the treatment of OA through computerized database searches and reference lists.
■ OUTCOMES MEASURED The outcomes considered were pain, functional limitation, and adverse effects.
■ RESULTS Eleven studies that met the inclusion criteria were weighted on the basis of precision and were combined for each outcome variable. When compared with placebo, SAMe is more effective in reducing functional limitation in patients with OA (effect size [ES] = .31; 95% confidence interval [CI], .098 - .519), but not in reducing pain (ES = .22; 95% CI, -.247 to .693). This result, however, is based on only 2 studies. SAMe seems to be comparable with NSAIDs (pain: ES = .12; 95% CI, -.029 to .273; functional limitation: ES = .025; 95% CI, -.127 to .176). However, those treated with SAMe were less likely to report adverse effects than those receiving NSAIDs.
■ CONCLUSIONS SAMe appears to be as effective as NSAIDs in reducing pain and improving functional limitation in patients with OA without the adverse effects often associated with NSAID therapies.
■ KEY WORDS S-adenosylmethionine; osteoarthritis; meta-analysis; systematic review [non-MeSH]; complementary therapy [non-MeSH]. (*J Fam Pract 2002; 51:425–430*)

One alternative therapy for osteoarthritis (OA) is S-adenosylmethionine (SAMe), a naturally occurring sulphur-containing physiologic compound synthesized from amino acid L-methionine and adenosine triphosphate (ATP).[1,2] Although scientists are not certain how it works to control pain, SAMe plays a key role in 3 major pathways: transmethylation, transsulfuration, and aminopropylation.[2] SAMe was introduced in the United States in 1999 as a dietary supplement to promote joint health, mobility, and joint comfort. On the basis of a 1987 review of 12 clinical studies involving more than 20,000 patients, SAMe has been touted as "the prototype of a new class of safe drugs for the treatment of osteoarthritis."[3] However, the majority of the patients in those studies (97%) were enrolled in a single open field trial.

Although systematic reviews have demonstrated the benefit of other alternative strategies for OA, such as glucosamine and chondroitin,[4,5] there has been no systematic review of SAMe for OA. Because individual studies of SAMe vary in their sample sizes and report conflicting results, we conducted a meta-analysis to assess the efficacy of SAMe for OA as compared with that of placebo or NSAIDs. We also examined whether study quality, drug dosage, or length of treatment is associated with the effect, and we identified needs for future research.

From the University of Maryland School of Nursing (K.L.S.); the Complementary Medicine Program, University of Maryland, School of Medicine (K.L.S., W.L.L., R.B.B., B.M.B.); and the Department of Epidemiology and Preventive Medicine, University of Maryland, School of Medicine (M.A.), Baltimore. The authors report no conflicts of interest. All requests for reprints should be addressed to Karen L. Soeken, PhD, Complementary Medicine Program, University of Maryland, School of Medicine, Kernan Hospital Mansion, 2200 Kernan Drive, Baltimore, MD 21207-6697. E-mail: ksoeken@compmed.umm.edu.

METHODS

Literature search and data sources

We conducted computerized searches using the term "arthritis" and all synonyms for SAMe: "S-Adenosylmethionine," "Ademetionine," "S-adenosyl-L-methionine," "Adenosyl-l-methionine," "Samyr," "Gumbaral," "Sammy," and "SAM-e." Results were then combined into the optimally sensitive search strategy for retrieving all clinical trials.[6,7] All languages were included. Our database search included MEDLINE (1966- September 2000), EMBASE (1987-2000), CAMPAIN (Complementary and Alternative Medicine and Pain), Science Citation Index, International Pharmaceutical Abstracts, The Cochrane Complementary Medicine Field Registry, National Institutes of Health Office of Dietary Supplements Database, and Micromedix. We also hand searched the 3 journals with the highest impact factors for rheumatology (*Arthritis and Rheumatism*, *British Journal of Rheumatology*, and *Journal of Rheumatology*, 1985-1999),[8] English-language journals from which we had already retrieved articles, and complementary medicine journals (inception to 1999). In addition, we examined bibliographies from retrieved articles, books, and Web sites related to SAMe and contacted manufacturers of SAMe for previously unidentified research studies.

Inclusion criteria

Criteria for inclusion were established a priori. Studies had to include a sample of patients with a diagnosis of OA; be a randomized controlled trial; compare SAMe with placebo or NSAID; and report data for at least 1 of the outcome variables: pain, functional limitation, and adverse effects. Two raters independently screened studies to determine whether they met the inclusion criteria and agreed in their assessments.

Quality assessment and data extraction

Two raters independently rated study quality of the English studies using the 5-point Jadad scale[9] that assesses random allocation, double-blinding, and the reporting of withdrawals and dropouts. An additional rating item concerned concealed allocation. Only 1 of the 2 raters assessed the quality of the 4 non-English articles. Two reviewers also independently extracted descriptive information and outcomes that reflected pain, functional impairment, and adverse effects. Any differences in ratings and data extraction were discussed and a consensus was reached.

For pain and functional impairment we computed the difference in the average response between treatment groups and control groups, standardized to account for differences in the measurement scale across studies. The result is a difference effect size (ES) with a positive ES favoring SAMe. We also applied a correction factor[10] that adjusts for the positive bias in the ES estimate for small samples. For the binary outcome of adverse effects, we computed the odds ratio (OR) for the individual trials.[11] An OR of less than 1 indicated that treatment with SAMe was more effective than the control.

Heterogeneity in the strategy to measure pain was expected. Either individual studies pooled several pain items (eg, day pain and resting pain) that were rated using a 4- or 5-point rating scale or Visual Analog Scale (VAS), or studies used a single-item VAS. Functional limitation reflects stiffness, swelling, and joint mobility as rated by the physician according to the degree of joint movement (eg, flexion, extension, abduction, adduction, and rotation). In some studies, this score also included a pain item. Adverse effects refer to patient reports of nonspecific gastrointestinal complaints, mucocutaneous symptoms, and central nervous systems disturbances. Finally, a pooled dropout rate because of side effects was computed across studies as a measure of the tolerability of SAMe.

Statistical analysis

Outcomes for each subject measured at multiple time points tend to be correlated, which introduces dependency between corresponding ESs. To avoid this dependency, we computed the ES for the end-of-treatment only, rather than for all time points. Although dependency is also a concern when results are reported for more than one outcome within a study,[12-14] we did not control for this. Following the test for homogeneity or consistency within the set of ESs using the Q statistic with $\alpha = .10$,[11] we computed the weighted mean ES with 95% confidence intervals (CI) across studies for each outcome, weighting for sample size (the inverse of the variance). The choice of a fixed-effects model was dependent on the finding of homogeneity of results.

To assess sensitivity of the results, we examined the relationship of the ES to the dosage of SAMe, length of treatment, and study quality rating. Subgroup analyses examined differences related to the location of the OA to estimate the robustness of results. Finally, we assessed potential publication bias informally by using the funnel plot of ES by precision, and statistically through the rank correlation between the standardized ES and standardized study variance.[15]

RESULTS

Description of studies

Twenty studies were identified through our search

and 11 of them[16-26] met the inclusion criteria (Table). We excluded one duplicate study[27] and one study whose sample included persons with rheumatoid arthritis.[28] Other excluded studies compared the routes of administration of SAMe,[29] compared SAMe plus ketoprofen with ketoprofen alone,[30] or were not randomized controlled trials.[31-34] Four of the included studies[18,20,21,25] were published in Italian; the others were published in English. The majority of studies (7 of 11) were conducted in Italy.

TABLE

Characteristics of studies included in meta-analysis

Study, by first author	Sample size: treatment/ control	Jadad score*	SAMe intervention†	Control group
Bradley[16]	24/24 (site A) 17/17 (site B)	5 (2+2+1)	(A) 400 mg/day IV for 5 days; (B) 600 mg/day for 23 days	Placebo
Capretto[17]	53/58	4 (1+2+1)	600 mg/day for 30 days	Ibuprofen 1200 mg/day
Caroli[18]	30/30	4 (1+2+1)	1200 mg/day for 42 days	Aspirin 3000 mg/day
Caruso[19]	(1) 248/241 (2) 248/245	4 (1+2+1)	1200 mg/day for 30 days	(1) Placebo (2) Naproxen 750 mg/day
Ceccato[20]	48/47	4 (1+2+1)	400 mg/day IV for 30 days	Ibuprofen 1200 mg/day
Cucinotta[21]	20/20	4 (1+2+1)	600 mg/day for 30 days	Ibuprofen 1200 mg/day
Maccagno[22]	24/24	4 (1+2+1)	1200 mg/day for 84 days	Piroxicam 20 mg/day
Marcolongo[23]	75/75	5 (2+2+1)	1200 mg/day for 30 days	Ibuprofen 1200 mg/day
Müller-Fassbender[24]	18/18	3 (1+1+1)	1200 mg/day for 28 days	Ibuprofen 1200 mg/day
Pelligrini[25]	50/50	3 (1+2+0)	600 mg/day for10 days; 5-day washout	Sulindac 200 mg/day
Vetter[26]	18/18	3 (1+1+1)	1200 mg/day for 28 days	Indomethacin 150 mg/day

IV denotes intravenously.
*Numbers in parentheses are randomization + blinding + dropouts.
†Interventions are oral, unless otherwise noted.

Quality assessment

Percent agreement between raters for the items on the Jadad scale averaged 87.5%. Following discussion, the raters reached consensus for all items. Using Jadad's criteria, all studies were rated of high quality (score ≥ 3), although only 2 studies[16,23] included a description of the method of randomization. None of the studies addressed allocation concealment.

Study characteristics

Ten of the 11 studies used a parallel groups design including one with 3 arms[19]; the 11th one[25] used a crossover design (Table W1).* The SAMe dosage in 6 studies was 1200 mg per day orally[18,19,22-24,26]; 3 studies used 600 mg per day orally[17,21,25]; and one used 400 mg per day intravenously.[20] In one study[16] the dosage varied. Duration of treatment ranged from 10 days to 84 days; a duration of 28 or 30 days was used in 8 of the studies. A variety of NSAIDs served as active comparators and 2 studies[16,19] used placebo.

The studies involved 1442 subjects with a mean age of 60.3 years, of whom 70.1% were women. Mean duration of OA was 5.7 years, ranging from 2.6 years to 9.1 years. In 5 studies, the majority of subjects had OA of the knee; across all studies 54.2% of the subjects had OA of the knee.

*Please see Table W1 on the JFP Web site (www.jfponline.com) for an expanded table with inclusion criteria, concomitant medications, age of patients, sex, duration of disease, and location of OA.

Analysis of outcomes

Pain. Twelve ESs from 7 studies[16,18-20,22,23,25] were computed for pain, ranging from -.501 to +.794. Because of borderline heterogeneity of the results for SAMe versus placebo (Q[2] = 5.41; P = .067), a more conservative random effects model was used to compute the mean ES of .223 (P = .352; 95% CI, -.247 to .693). Homogeneity was present for SAMe versus

NSAIDs (Q[8] = 9.31, *P* = .317) and on the basis of a fixed effects model, the weighted mean ES was .122 (*P* = .057; 95% CI, -.029 to .273). Among the studies of SAMe versus NSAIDs, effect size was not related to study quality (*P* = .32), length of intervention (*P* = .31), or dosage of SAMe (*P* = .97). Finally, there was no evidence of publication bias according to the funnel *P* lot (Figure W1)* or the rank order correlation (*P* = .297) for studies of SAMe versus NSAIDs.

Functional limitation. Six studies[17-20,24,26] contributed 10 effect sizes for functional limitation. The length of the intervention phase was 28 days to 42 days for all 6 studies. Only one study[19] compared SAMe with placebo (ES = .309; *P* = .002; 95% CI, .098 - .519). Among the studies comparing SAMe with NSAIDs, there was homogeneity of results (Q[8] = 2.53; *P* = .96) with a weighted mean ES of .025 (95% CI, -.127 to .176), indicating no difference between SAMe and NSAIDs with respect to functional limitation. There was no relationship of ES to study quality (*P* = .30), length of treatment (*P* = .71), or dosage of SAMe (*P* = .48). Both the funnel plot (Figure W2)** and the rank correlation of standardized ES and variance (*P* = .097) suggested no evidence of publication bias with respect to the functional limitation outcome for SAMe versus NSAIDs.

Adverse effects. Two studies[16,19] reported adverse effects when comparing SAMe with placebo. Results were homogenous (Q[2] = 2.035; *P* = .362), with a pooled OR of 1.37 (95% CI, .81 - 2.32). Among the studies comparing SAMe with NSAIDs results also were homogeneous (Q[6] = 4.41; *P* =.622), with a pooled OR of .424 (95% CI, .294 - .611). Again, the effect size was not related to quality of study (*P* = .409), length of treatment (*P* = .367), or dosage of SAMe (*P* = .341). That is, those treated with SAMe were 58% less likely to experience side effects than those treated with NSAIDs. Further, this was independent of study quality, dosage of SAMe, or the length of the intervention.

As an additional indication of tolerability we compared the overall dropout rates due to side effects. The dropout rate was highest (6.9%) among those treated with NSAIDs, followed by those receiving placebo (5.0%). The dropout rate for SAMe users was lowest at 2.6%. The only significant difference was between those treated with SAMe and with NSAIDs (*P* = .001).

DISCUSSION

Results of this meta-analysis indicate that SAMe has a comparable effect to that of NSAIDs in reducing pain and functional limitation. In addition, there was significantly less likelihood of patients reporting adverse effects with the use of SAMe. When SAMe is compared with placebo, however, there is no differential effect on pain according to 2 studies, although there is minimal improved functional limitation according to one study. This improvement corresponds to a 15% decrease in functional limitation in the SAMe group as compared with placebo. The likelihood of adverse effects was similar in the 2 groups. Given the combined sample sizes in this meta-analysis, there was a more than 90% power to detect a moderate difference between groups at a .05 level of significance.

Several reporting issues were noted during the extraction of study data. Some researchers did not adequately describe study dropouts and how they were handled. Sample characteristics may have been reported for the initial sample, but there was no mention of the characteristics of the final sample, so that bias in subject loss could not be assessed in any studies that did not use intention-to-treat analysis. Some authors reported intervention results on the basis of the location of the OA, but only reported characteristics (age, sex, duration of disease) for the full sample. This precluded examining the relationship of intervention effect size to demographic characteristics. Finally, because not all authors provided complete descriptive statistics, we based the computation of the ES for one study on post-test scores only, rather than on the change from baseline, a strategy that could underestimate the ES. This potential underestimation occurred in a study with one of the larger sample sizes that, in turn, would carry more weight in the analysis.

Limitations

Potential limitations must also be noted in our analysis. First, in 6 of the studies, the SAMe dosage of 1200 mg per day exceeded the dosing recommendations for SAMe. These recommendations include 800 mg per day for 2 weeks followed by 400 mg per day as a maintenance dose, or to increase from 200 mg per day to 1200 mg per day over a 19-day period followed by 400 mg per day thereafter.[35] Dosage was not related to the ES, however, in studies comparing SAMe with NSAIDs. Second, most studies used a short intervention (28 to 30 days). It may be that NSAIDs are more effective in the long run, that a longer treatment period is needed for patients to realize the effect of SAMe, or that there are more adverse side effects with SAMe over time. It is not yet clear how effective SAMe is over time. Those studies that did have an intervention longer than 30 days[18,22] did not compare SAMe with ibuprofen. In general, concomitant medications for treatment of

*Available at www.jfponline.com.
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OA were not permitted, but 3 studies[24-26] failed to provide this information. Finally, most of the studies looked at OA of the knee and/or hip, so generalizability of the results to other locations of OA is limited. Although we included subgroup analyses by location of OA, statistical power for subgroup analysis was low because of the smaller number of subjects for whom data were available.

CONCLUSIONS

Although SAMe appears to offer pain relief and improve functional limitations associated with OA without the side effects of NSAIDs, it must be remembered that SAMe is not considered a drug in the United States and is therefore not subject to federal regulations. (In contrast, Samyr is a prescription drug in Italy and is available in 200 mg and 400 mg doses.) Recent testing by ConsumerLab.com of over-the-counter brands of SAMe in the United States found, on average, that for 6 of the 13 brands tested, less than half the amount of SAMe stated on the label was actually present.[36] Patients who use SAMe in the United States may fail to experience relief because of this dose inconsistency.

We offer several suggestions for further research. First, the long-term effectiveness of SAMe for the treatment of OA has not been investigated in a randomized controlled trial. Since OA is the most prevalent form of arthritis, the long-term effectiveness of SAMe should be assessed in this manner. Second, given that SAMe has been shown to decrease depression,[1] it seems prudent to use multivariate techniques to examine both depression and OA outcomes (pain and functional limitation) to determine whether the effect of SAMe is directly on the joint or indirectly mediated through depression. Perhaps in the short term SAMe does decrease pain through decreasing depressive symptoms, but in the long term the effectiveness related to pain may diminish. Third, whether SAMe treats the symptoms of the disease or alters the course of the disease by increasing the production of new cartilage, as suggested by animal models, has not been investigated. Finally, can use of SAMe enhance the effectiveness of other nonpharmacologic modalities? These questions should all be investigated before we can make a determination about the efficacy and safety of SAMe for the treatment of OA.

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