Authors' objectives
To perform a comprehensive literature review and synthesis of evidence on the use of S-adenosyl-L-methionine (SAMe) for the treatment of depression, osteoarthritis and liver disease.

Searching
Five extensive searches were conducted of 25 named databases using a search strategy that was provided in an appendix to the review. There were no language restrictions. The reference lists of retrieved articles were searched for additional relevant studies.

Study selection
Study designs of evaluations included in the review
The inclusion criteria specified the inclusion of randomised controlled trials (RCTs), controlled clinical trials, meta-analyses and systematic reviews.

Specific interventions included in the review
The inclusion criteria specified interventions using SAMe.

Participants included in the review
The inclusion criteria specified patients with depression, osteoarthritis, or chronic liver disease. Studies not focusing on one of these three diseases were excluded. Animal or in vitro studies were excluded unless human clinical data were also included.

Outcomes assessed in the review
The inclusion criteria for the outcomes were not specified a priori. For each of the four conditions (depression, osteoarthritis, cholestasis of pregnancy, and intrahepatic cholestasis associated with liver disease), the reviewers chose the clinically relevant outcomes and clinically comparable follow-up times that were reported most often. These included both dichotomous and continuous outcome measures. The outcome measures used in the review were the Hamilton Rating Scale for Depression (HRSD) for depression, pain for osteoarthritis, and pruritis and bilirubin for the analysis of liver disease studies.

How were decisions on the relevance of primary studies made?
Two authors independently selected the papers for the review. Any disagreements were resolved by consensus.

Assessment of study quality
The authors used a quality review form to assess the included studies, based on the scoring system developed by Jadad. The quality assessment considered the study design, appropriateness of randomisation, blinding, description of withdrawals and drop-outs, and concealment of allocation. Two authors independently reviewed the papers for validity. Any disagreements were resolved by consensus.

Data extraction
Two authors independently extracted the data for the review using a specialised data collection instrument. Any disagreements were resolved by consensus or, if consensus was not reached, by a senior physician researcher. Details were extracted on the study design, the technical quality of the study, the number and characteristics of the patients, patient recruitment information, the intervention, the types of outcome measures, and the time between the intervention and outcome measurement.
To be included in the analysis, the studies had to include sufficient statistical information for the calculation of an effect size or risk ratio, as appropriate. Studies lacking a follow-up mean were excluded. If standard deviations (SDs) were not provided, or could not be calculated from the given data, then the SD was imputed. A related study focusing on the osteoarthritis section of this review was also included in this abstract (see Other Publications of Related Interest).

Methods of synthesis
How were the studies combined?
For depression and osteoarthritis, the studies were sufficiently clinically homogeneous to allow a pooled analysis. Too few studies compared SAMe with active therapy for intrahepatic cholestasis to conduct a pooled analysis. Twenty remaining studies were too heterogeneous with respect to diagnosis (a wide variety of liver conditions) and outcomes to permit a pooled analysis.

Pooled risk ratios, along with 95% confidence intervals (CIs), were calculated for dichotomous outcomes; pooled effect sizes were calculated for continuous outcomes. A pooled random-effects model (DerSimonian and Laird) was used where appropriate.

Publication bias was assessed using funnel plots, adjusted rank correlation tests, and regression asymmetry tests.

How were differences between studies investigated?
The authors used a chi-squared statistic to test for heterogeneity and conducted sensitivity analyses of subgroups of studies to determine the robustness of the review conclusions.

Results of the review
A total of 102 studies were included in the review: 47 studies of SAMe for the treatment of depression, 14 for the treatment of osteoarthritis, and 41 for the treatment of a variety of liver diseases.

Compared with placebo, treatment with SAMe was associated with an improvement of approximately 6 points in the HDRS score for depression. This degree of improvement is clinically significant and is equivalent to a partial response to treatment.

Compared with conventional therapy, SAMe was not associated with a statistically significant difference in outcomes.

Compared with placebo, one large randomised clinical trial showed a small to moderate effect in favour of SAMe for osteoarthritis.

Compared with non-steroidal anti-inflammatory agents, SAMe was not associated with a statistically significant difference in outcomes.

For cholestasis of pregnancy, treatment with SAMe was associated with a large effect in decreasing pruritus and in decreasing bilirubin levels in comparison with placebo. In two clinical trials, conventional therapy (ursodeoxycholic acid) was favoured over SAMe for the treatment of pruritis.

For intrahepatic cholestasis, treatment with SAMe for pruritis was associated with a risk ratio of 0.45 (95% CI: 0.37, 0.58) in comparison with placebo. This means that patients treated with SAMe were twice as likely as placebo-treated patients to have a reduction in pruritis.

Authors’ conclusions
The authors stated that the data in this review indicate that SAMe is more effective than placebo for the relief of symptoms of depression, the pain of osteoarthritis, and pruritis in cholestasis of pregnancy and intrahepatic cholestasis. SAMe was more effective than placebo in reducing bilirubin for cholestasis of pregnancy and serum bilirubin for intrahepatic cholestasis. Treatment with SAMe was equivalent to standard therapy for depression and osteoarthritis, but not for liver disease.
CRD commentary
This was a very well-conducted systematic review. The review question and inclusion and exclusion criteria were all clearly stated. The literature search was extensive and publication bias was explored using three separate investigative tests. The validity of the included studies was assessed by the reviewers. The process of the review was adequately reported and the statistical analyses were all performed using appropriate statistical methods. Heterogeneity was investigated, while sensitivity analyses also looked at the validity of the review results. The conclusions follow from the results of this review, although the need for further evidence in this area of research should be noted.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors made many recommendations for future research. The risk benefit ratio of SAMe compared with conventional therapy is needed, as are dose escalation studies using the oral formulation of SAMe for the treatment of depression, osteoarthritis, or liver disease. Such trials would need large numbers of participants with homogeneous diagnoses and should focus on significant clinical outcomes. For liver conditions other than cholestasis, smaller trials are needed to find out which patients would benefit most from SAMe, and which interventions (dose and route of administration) are most effective. Additional small clinical trials of an exploratory nature should be performed to investigate other uses of SAMe, e.g. to decrease the effectiveness latency of conventional antidepressants and to treat postpartum depression.

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Bibliographic details

Original Paper URL
http://www.ahrq.gov/clinic/epcsums/samesum.htm

Other publications of related interest

This additional published commentary may also be of interest. Baime MJ. Review: SAMe reduces symptoms in depression, osteoarthritis, and liver disease. ACP Journal Club 2003;139:20.

Indexing Status
Subject indexing assigned by CRD

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.