S-adenosyl-l-methionine (SAMe) as antidepressant: meta-analysis of clinical studies

Bressa GM

CRD summary
This review found that s-adenosyl-l-methionine was superior to placebo and as effective as tricyclic antidepressant medication. Limitations in the analysis mean that the author’s conclusions should be treated with caution.

Authors' objectives
To investigate the short-term efficacy of s-adenosyl-l-methionine (SAMe) as an antidepressant compared with placebo and standard tricyclic antidepressants.

Searching
MEDLINE was searched for articles published from 1973 to 1992, and bibliographies were handsearched. Study authors and the manufacturers of SAMe were contacted for unpublished data.

Study selection
Study designs of evaluations included in the review
Double-blind randomised controlled trials (RCTs) were eligible for inclusion. Standard and crossover trials were included in the review.

Specific interventions included in the review
Studies that compared parenteral (>=200 mg/day) or oral (>= 1,600 mg/day) SAMe with placebo or standard tricyclic medication over 12 weeks or less were eligible for inclusion. SAMe was administered in varying dosages, as oral, intravenous or intramuscular treatments. Treatment duration ranged from 14 to 42 days. The tricyclics used in the control arms were imipramine, desipramine, amitriptyline and chlorimipramine, in varying dosages.

Participants included in the review
Studies of adults with a diagnosis of depressive syndrome were eligible for inclusion. The diagnosis of depressive syndrome was either clinical or based on the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-III or DSM III-R).

Outcomes assessed in the review
Studies using the Hamilton Depression Rating Scale (HAM-D) as before and after measures were eligible for inclusion. To be included, studies had to report data to enable quantification of the effect size.

How were decisions on the relevance of primary studies made?
The author did not state how the papers were selected for the review or how many reviewers performed the selection.

Assessment of study quality
The author did not state that they assessed validity. However, the author selected only studies with random allocation and double-blind design and that treated data using intention-to-treat principles.

Data extraction
The author did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

The outcomes were categorised as partial response to treatment (defined as a reduction in HAM-D scores of 25% or more) or full response to treatment (defined as a reduction in HAM-D scores of 50% or more). The percentage reductions in HAM-D scores, which were used to calculate the numbers of patients partially and fully responding to treatment for each group, were extracted. For each trial the following data were calculated: rate of responders for each treatment group; effect size r (corresponds approximately to the difference in the rate of responders between treatment groups) using the BESD method; odds ratio and corresponding 95% confidence intervals (CIs) for the odds of failure of
treatment (a reduction of less than 25% in HAM-D scores) in the intervention and control groups.

**Methods of synthesis**

**How were the studies combined?**
The total number of responders in each treatment group was calculated and summed across studies, as was the rate of responders by treatment group. The studies were combined in a meta-analysis using Stouffer's Z test of pooled probabilities, global effect sizes and the odds ratio with its 95% CI.

**How were differences between studies investigated?**
Statistical heterogeneity was calculated using the chi-squared test for heterogeneity of p-values and effect size. Separate meta-analyses were carried out for SAMe compared with placebo and SAMe compared with tricyclic antidepressants, and for the outcomes 'partial or full response to treatment' and 'full response only to treatment'.

**Results of the review**
Thirteen studies were included (n=381).

S-adenosyl-l-methionine (SAMe) compared with placebo (six RCTs including one crossover study, n=180).

Significantly more people showed a full or partial response to SAMe compared with placebo. The effect size was moderate (r=0.38) and there was evidence of significant statistical heterogeneity (p<0.011). When only full responders were considered (five studies), SAMe continued to show significant benefits in alleviating symptoms of depression compared with placebo although the effect size was small (r=0.17). There was evidence of significant heterogeneity for effect size (p=0.04).

SAMe compared with tricyclic antidepressants (seven RCTs, n=201).

There was no significant difference between SAMe and tricyclic antidepressants in the proportion of patients showing partial or full response to medication. The effect size was negligible (0.07) and showed evidence of significant heterogeneity (p=0.048). When only full responders were considered, there continued to be no significant differences between the groups.

**Authors' conclusions**
S-adenosyl-l-methionine was superior to placebo in treatment of depressive syndromes and comparable to standard tricyclic antidepressant medication.

**CRD commentary**
Inclusion criteria for the participants, intervention and study design were clearly defined. Restricting outcomes to studies using the HAM-D might have resulted in relevant studies being omitted. Only studies with a short-term follow-up were included, which means that any conclusions can only be interpreted in light of this relatively brief timeframe. Attempts were made to identify unpublished data, but only one database was used to search for studies and it is unclear whether any language restrictions were imposed. Relevant studies might therefore have been missed and bias introduced. There was insufficient information about the study selection and data extraction processes to rule out the possibility of bias and error. Although a formal quality assessment was not undertaken, only double-blind RCTs were included; all included studies were therefore of a relatively high quality and are likely to have produced reliable results.

There was insufficient information on the characteristics of the included studies to determine the extent to which the findings can be generalised. The methods used to synthesise the studies were confusing and, in some cases, inappropriate. The author summed data across individual study arms, which ignores the randomisation in the included studies and so is not an appropriate method of analysis. The use of effect sizes was confusing; the use of standard methods of meta-analysis based on relative risks would have been easier for the reader to interpret. There was evidence of statistically significant heterogeneity for some meta-analyses and these analyses should therefore be interpreted with caution. Limitations in the analysis mean that the author's conclusions should be treated with caution.
Implications of the review for practice and research

Practice: The author stated that given that SAMe is a naturally occurring substance with relatively few side-effects, it is potentially an important treatment for depression. However, it should be noted that the author did not assess the occurrence of adverse events in the review.

Research: The author did not state any implications for further research.

Bibliographic details

Indexing Status
Subject indexing assigned by NLM

MeSH
Antidepressive Agents, Tricyclic /administration & dosage /therapeutic use; Clinical Trials, Phase III as Topic; Depressive Disorder /drug therapy /psychology; Double-Blind Method; Placebos; Prospective Studies; S-Adenosylmethionine /administration & dosage /pharmacology /therapeutic use; Treatment Outcome

AccessionNumber
12007005871

Date bibliographic record published
07/02/2008

Date abstract record published
09/08/2008

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.