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# S-adenosyl-L-methionine (SAME) and Depression

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Since its introduction in 1999, sales of s-adenosyl-l-methionine (SAME) have placed it among the 25 top-selling dietary supplements in the United States. What makes this particular dietary supplement so popular? Perhaps the myriad of claims surrounding its use have helped. SAME is marketed as an antidepressant; an anti-arthritic; an agent for liver disorders, cholestasis, and migraines; and even as a therapy for fibromyalgia.

### Pharmacology/Mechanism of Action

SAME is naturally synthesized in the body during the metabolism of methionine and functions as a primary methyl group (-CH<sub>3</sub>) donor for a broad range of compounds (proteins, phospholipids, fatty acids, DNA, RNA, porphyrins, choline, carnitine, and creatine). The theoretic rationale for general therapeutic application of SAME is that exogenous administration may bring about restoration of "youthful" levels of this metabolite and thereby induce beneficial changes in individuals whose problems, at least in part, may be attributed to a relative deficiency. Interestingly, activity of methionine adenosyltransferase (the enzyme that forms SAME) is diminished in patients with major depression and schizophrenia, but elevated in mania.<sup>1</sup> SAME crosses the blood-brain barrier and increases concentrations of homovanillic acid and 5-hydroxyindoleacetic acid.<sup>2</sup> It has been suggested that SAME may blunt noradrenergic responsiveness while increasing concentrations of dopamine and serotonin in the CNS.<sup>2,3</sup> Whether this plays a part in the role of SAME's effects in depression has yet to be determined.

### Clinical Trials

Some of the most convincing evidence regarding use of oral SAME in depression comes from three randomized, double-blind, controlled trials (RDBCTs) of SAMYR (BioResearch Inc., Milan, Italy). Kagan and colleagues studied 18 adult male inpatients who met DSM-III criteria for major depression.<sup>4</sup> Patients were randomly assigned to receive SAME or placebo for a total of 21 days. SAME was initially administered as an oral 200 mg tablet once daily, then titrated by day 7 to 800 mg PO bid and continued at this dose for the remainder of the trial. Subjects were evaluated by Hamilton Rating Scale for Depression (HAM-D) and Carroll Rating Scale for Depression (CRSD) scores at various times throughout the trial. No significant differences in age or severity of illness existed between the two treatment groups. Fifteen patients completed the trial and three patients dropped out—one for worsening depression (placebo), one for non-compliance (placebo), and one for documented hypothyroidism (placebo). In the SAME group, six of nine patients experienced a re-

duction in HAMD score by more than 50%; one of six experienced this effect in the placebo group. Mean reductions in scores for the SAME group reached statistical significance ( $P < 0.05$ ) by day 7 and remained significant throughout the 21-day study period. CRSD scores decreased significantly by day 21 ( $P < 0.05$ ). The greatest limitation of this trial is the small study population. Minor limitations include short duration and no information in regard to concomitant medications. *Level II, major limitations (See enclosed insert, "Applying Evidence-Based Medicine to Dietary Supplements," for a complete explanation of the evaluation standards and scales used in rating clinical studies.)*

In 1992, De Vanna and Rigamonti published results from a six-week RDBCT of oral SAME and imipramine in major depression.<sup>5</sup> Thirty patients (9 men, 21 women) with HAMD scores of 18 or higher were randomized to either imipramine (140 mg daily) or SAME (1,600 mg daily). No differences in demographics were detected between the groups. Patients were evaluated frequently by HAMD, Hamilton Rating Scale for Anxiety (HAMA), Montgomery-Asberg's Depression Rating Scale (MADRS), and Zung's Self-Rating Scale for Depression (ZSRS). No concomitant medications were allowed with the exception of limited use of triazolam 0.25 mg for insomnia. Twenty-three patients completed the study. At day 10, statistically significant differences in scores compared to baseline were noted for the MADRS, HAMD, and HAMA ( $P < 0.001$ ) in the SAME treatment group, while only HAMD scores were significantly different from baseline for the imipramine group. By day 20, both MADRS and HAMD yielded similar results for the two treatment groups. At six weeks, all scales suggested efficacy for both treatment groups. The investigators concluded that SAME was effective and well tolerated for major depression. Major limitation includes a lack of statistical power for non-significant findings and a lack of detailed information with respect to certain aspects of the trial (i.e., laboratory studies). *Level II, major limitations*

In another RDBCT, Salmaggi et al enrolled 80 women between 45 and 59 years who suffered from depression related to onset of natural or surgical menopause.<sup>6</sup> Patients on estrogen replacement therapy were excluded. Patients were randomly assigned to either SAME (1,600 mg/d PO) or placebo and assessed at regular intervals for 30 days by the HAMD, Rome Depression Inventory (RDI), Clinical Global Impression Improvement Scale (CGIIS), and Minnesota Multiphasic Personality Inventory (MMPI). No significant demographic differences were detected between groups. Ten patients in each group dropped out due to "reduced compliance." From day 10 forward, statistically greater improvements were seen in HAMD scores for SAME treatment as compared to placebo and baseline. This also held true for RDI scores. At trial endpoint, scores for the MMPI and CGIIS demonstrated statistical significance in favor of SAME. The investigators concluded that oral SAME was an effective treatment for depressive symptoms in postmenopausal women with major depressive disorder or dysthymia. This trial is limited primarily by short duration. *Level II, minor limitations*

Several detailed reviews<sup>7-9</sup> and at least two meta-analyses<sup>10,11</sup> have examined the available evidence for SAME in the therapy of depression. The most recent meta-analysis included almost 800 patients in trials that used oral ( $> 1,600$  mg/d) or parenteral ( $> 200$  mg/d) SAME for short-term ( $< 12$  weeks) treatment of depression vs. placebo or tricyclic antidepressants.<sup>11</sup> Overall, SAME was superior to placebo in treating depressive disorders and nearly as effective as standard tricyclic antidepressants. The reviews appear to echo these conclusions.<sup>7-9</sup> However, it is important to realize that these reviews and meta-analyses included trials of oral and parenteral formulations and many suffered severely from a lack of sound study design.

### **SAME Supplementation and Serum Levels**

Despite the availability of a sensitive assay for SAME, no true therapeutic range for SAME serum levels has been defined. Although SAME serum levels change with both SAME and tricyclic treatment,<sup>2</sup> attempts to correlate SAME serum levels with successful responses in depressed subjects have not been successful.<sup>2,7</sup>

### **Adverse Events**

In general, SAME appears to be well tolerated. The majority of side effects are mild to moderate in nature and of brief duration, with an overall incidence of 20%.<sup>12</sup> Although few patients have withdrawn from trials because of SAME side effects, this agent is not devoid of significant adverse events.

The majority of reported adverse effects are gastrointestinal (heartburn, nausea, vomiting, diarrhea), and can be quite severe,<sup>13</sup> but also include insomnia, dizziness, and headache.<sup>14,15</sup> Anaphylaxis has been documented with parenteral SAME administration.<sup>14</sup> The subject also experienced dizziness and cognitive impairment that slowly resolved over two months.

Psychoactivation or a "switch" reaction to mania/ hypomania has been documented in several trials.<sup>4,15,16</sup> The frequency with which this occurs is concerning given the small number of subjects studied.

### **Contraindications**

Information on use of SAME in pregnancy and lactation is unavailable. Also, there is no information on actual or potential contraindications other than hypersensitivity to SAME or any components in the formulation involved.

Patients with a history of bipolar (manic) disorder may be at risk of a manic episode with use of SAME.

Hyperhomocysteinemia (elevated plasma homocysteine) is a relatively rare disorder, but is associated with a dramatically increased risk of thrombosis and premature cardiovascular disease.<sup>17</sup> Since SAME participates in the trans-sulfuration pathway of methionine, it poses a theoretical, but potentially dangerous risk in those individuals susceptible to elevated homocysteine levels (defective or absent cystathionine beta-synthase and/or deficiencies of vitamins B<sub>6</sub> or B<sub>12</sub>). The actual risk remains to be determined.

### **Interactions**

There are no reports of drug or food interactions with SAME. It is prudent that patients taking SAME avoid other antidepressants or mood-altering agents.

### **Formulation/Dosage**

GNC and Nature Made distribute the only stable salt form of SAME available in the United States. Twenty-tablet bottles retail at approximately \$18-20. Oral doses in depression trials were 1,600 mg/d—approximately \$225 for a 30-day supply.

### **Conclusion**

SAME is an intriguing compound, and useful anti-depressant activity has been demonstrated in small RDBCTs. However, enthusiasm for this entity must be tempered by the lack of information surrounding SAME's adverse effect profile. More data are needed before SAME can be evaluated appropriately in the face of the more commonly utilized modern antidepressants and their more clearly defined risk/benefit ratios.

### **Recommendation**

Current evidence does not strongly support a recommendation for use. Future studies must include larger numbers of patients and a dose-response component to identify a minimally effective and maximally tolerated dose, and specifically characterize the incidence of mania/hypomania. Also of concern is the theoretical risk of elevating homocysteine levels in patients prone to hyperhomocysteinemia.

Patients inquiring about the use of SAME for depression should be counseled about weak efficacy evidence, safety issues, the difference in doses used in trials and those recommended in product labeling, and its high cost. Patients should also be instructed to discuss the use of this dietary supplement with their primary health care (or mental health

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