S-adenosylmethionine (SAMe) for Treatment of Depression

December 1999; Volume 2: 133-135
By Barak Gaster, MD

A young woman sits in your exam room complaining of chronic headaches and sleep disturbances. She is clearly depressed, but when you raise the possibility of an antidepressant she shudders. “A chemical like that in my body? Never.” And therein lies the source of the multimillion dollar nutritional supplement industry aimed at people suffering from depression.

The most recent addition to the growing cadre of “natural mood-enhancers” in the United States is SAMe, a common intermediary molecule found throughout the body, whose formal biochemical name is S-adenosylmethionine. The efficacy claims for SAMe in commercial advertising are subtle, as required by law, but they are glowing nonetheless. Unfortunately, although a modest amount of data suggests that the parenteral form of SAMe is probably effective, there are minimal data to support the efficacy of oral SAMe.

History
SAMe was first discovered in 1953 in Italy. Reports that SAMe could treat depression were widely disseminated in Europe in the early 1970s, and in 1977 it became commercially available there for that purpose. SAMe was not available in the United States until the spring of 1999.

Mechanism of Action
SAMe is a ubiquitous methyl-donor molecule located throughout the body. It plays a key role in numerous metabolic pathways that involve the transfer of methyl groups. SAMe is not present in the diet in a significant amount, but is formed in the body by the combination of adenosine triphosphate (ATP) and the amino-acid methionine. (See Figure 1.) SAMe then donates its methyl group to any of a wide range of molecules and is subsequently transformed to homocysteine.1

As it is for other common conditions for which SAMe is sometimes used (osteoarthritis and liver disease), the mechanism by which SAMe might treat depression is a mystery. Possible hypotheses include: increasing the synthesis of neurotransmitters such as serotonin and norepinephrine, increasing the responsiveness of neurotransmitter receptors, and increasing the fluidity of cell membranes through the production of phospholipids.2 Unfortunately, the evidence for any of these hypotheses is scant.

Pharmacology
Oral SAMe has a very low bioavailability, estimated to be < 1%, so its usefulness as an oral agent is open to question.3 In a study by Bell et al, only 71% of the patients treated with oral SAMe had a rise in their serum SAMe concentrations.4 Parenterally administered SAMe does appear to cross the blood brain barrier.5 The half-life, metabolism, and excretion of SAMe have not been well defined.

Clinical Studies
Although there have been more than 40 trials evaluating SAMe for depression, almost all have been of parenteral formulations. Only five trials have tested oral forms of SAMe.4,6-9 Only three of these were randomized controlled trials (RCTs), and all were extremely small. One trial of 15 patients tested SAMe vs. placebo,6 and two trials, one with 17 patients4 and one with 23 patients,7 compared SAMe to a tricyclic antidepressant (TCA).

All three RCTs suffered from serious methodological flaws, including failure to provide baseline data, failure to perform an intention-to-treat analysis, and failure to report the response rates of the study subjects. In the single placebo controlled trial, patients with severe depression who were given oral SAMe experienced more of an improvement in
their depression scores than those who received placebo, a result that was statistically significant despite the very small sample size. The two trials comparing SAMe to a TCA showed no significant difference between the two, but both studies were too small to draw conclusions from a null result. Review articles often claim that SAMe has a faster onset of action than TCAs, but the results from the two trials comparing oral SAMe to a TCA do not support this. The rapid onset of action reported in early studies of parenterally administered SAMe is probably attributable more to the parenteral dosing route rather than to the SAMe itself, since parenterally administered TCAs also appear to have a faster onset of action than oral TCAs. The numerous trials that have tested the parenteral dosing of SAMe have generally shown it to be effective. Given SAMe’s questionable absorption from the gastrointestinal tract, however, it is not valid to extrapolate this data to the use of oral SAMe.

**Adverse Effects**
The primary adverse event associated with the use of SAMe has been mania, manifested by pressured speech and the display of grandiose ideas. Four trials have reported this effect in 5-30% of study subjects, none of whom had a history of mania. In all of these subjects except one, patients’ thought processes seemed to return to normal when SAMe was discontinued. In one patient, however, mania was still present three months after SAMe was discontinued. SAMe otherwise appears to be well tolerated. It does not appear to cause anticholinergic side effects, as do TCAs. Some patients taking oral SAMe report nausea. Because homocysteine levels have been implicated in the development of coronary atherosclerosis, the fact that SAMe is transformed to homocysteine raises an additional safety concern. It is not known whether the administration of SAMe raises homocysteine levels or has an effect on the development of coronary artery disease. A literature search revealed no drug or supplement interactions with SAMe.

**Contraindications**
SAMe is contraindicated in patients with a history of mania or bipolar disorder.

**Formulation and Dosage**
Studies testing parenteral forms of SAMe have used a wide variety of doses, ranging from 45-400 mg/d. Parenteral SAMe is not commercially available in the United States. The five trials of oral SAMe all used 1,600 mg/d, divided in two equal doses. Oral SAMe is available in 200 mg tablets. Distributor instructions typically recommend that patients take 400 mg twice per day, but this dose has never been tested in trials. Although it is routinely recommended that SAMe be taken on an empty stomach because of its poor bioavailability, no data are available to suggest that this dosing schedule increases SAMe absorption. SAMe is significantly more expensive than common pharmaceutical agents that are used to treat depression. (See Table 1.)

<table>
<thead>
<tr>
<th>Therapeutic Agent</th>
<th>Usual Dosage</th>
<th>Cost (30-day supply)</th>
</tr>
</thead>
<tbody>
<tr>
<td>St. John’s wort</td>
<td>300 mg tid</td>
<td>$15</td>
</tr>
<tr>
<td>Desipramine</td>
<td>150 mg qd</td>
<td>$44</td>
</tr>
<tr>
<td>Sertraline (Zoloft®)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
50 mg qd
$71

Paroxetine (Paxil®)
20 mg qd
$74

Fluoxetine (Prozac®)
20 mg qd
$81

SAMe
800 mg bid
$240

Average cost based on the author's phone survey of national pharmacy chains and online nutritional supplement distributors, October 1999.

Conclusion
A significant amount of evidence suggests that intramuscular or intravenous SAMe may be effective in treating serious depression. SAMe is very poorly absorbed, however, and there are very little data to support the efficacy of oral SAMe. SAMe may potentially be harmful by inducing mania or by increasing serum levels of homocysteine.

Recommendation
Oral SAMe cannot currently be recommended for the treatment of depression given its uncertain absorption, its high cost, and its significant potential for causing mania.

Dr. Gaster is Acting Assistant Professor of Medicine at the University of Washington in Seattle.

References

