

Role of S-adenosyl-L-methionine in the treatment of depression: a review of the evidence¹⁻⁴

David Mischoulon and Maurizio Fava

ABSTRACT

Major depression remains difficult to treat, despite the wide array of registered antidepressants available. In recent years there has been a surge in the popularity of natural or alternative medications. Despite this growing popularity, there is limited evidence for the effectiveness of many of these natural treatments. S-adenosyl-L-methionine (SAME) is one of the better studied of the natural remedies. SAME is a methyl donor and is involved in the synthesis of various neurotransmitters in the brain. Derived from the amino acid L-methionine through a metabolic pathway called the one-carbon cycle, SAME has been postulated to have antidepressant properties. A small number of clinical trials with parenteral or oral SAME have shown that, at doses of 200–1600 mg/d, SAME is superior to placebo and is as effective as tricyclic antidepressants in alleviating depression, although some individuals may require higher doses. SAME may have a faster onset of action than do conventional antidepressants and may potentiate the effect of tricyclic antidepressants. SAME may also protect against the deleterious effects of Alzheimer disease. SAME is well tolerated and relatively free of adverse effects, although some cases of mania have been reported in bipolar patients. Overall, SAME appears to be safe and effective in the treatment of depression, but more research is needed to determine optimal doses. Head-to-head comparisons with newer antidepressants should help to clarify SAME's place in the psychopharmacologic armamentarium. *Am J Clin Nutr* 2002;76(suppl):1158S–61S.

KEY WORDS SAME, S-adenosyl-L-methionine, depression, antidepressants, alternative treatments, natural treatments

INTRODUCTION

Major depressive disorder is very common, with a lifetime prevalence of $\approx 17\%$ and a rate almost twice as high in women as in men (1, 2). Despite the increasing number of registered antidepressants (≈ 20 –25) and the increasing number of people seeking antidepressant treatment, many individuals prove to be refractory, demonstrating nonresponse or partial response after an adequate trial of antidepressants.

Between 19% and 34% of depressed patients still do not respond to acute antidepressant treatment, 29–46% may fail to achieve and sustain a full remission (3), and between 15% and 50% will have a recurrence of depression despite continuous antidepressant treatment (4). Registered antidepressants clearly have their limitations, and the importance of other types of treatment is paramount. Some refractory individuals will seek talking

therapies, alternative therapies, or both, including natural remedies, massage, acupuncture, and other treatments.

In recent years there has been a surge in the popularity of natural or alternative medications in the United States and worldwide (5, 6). The terms “natural” and “alternative” in this article refer to medications derived from natural products but not approved by the Food and Drug Administration for their purported indication. Such treatments have been used for thousands of years. More than 70% of individuals worldwide use some sort of alternative treatment, particularly in Europe and Asia, where many of these treatments originated (7). The United States has followed suit, as evidenced by the growing popularity of natural remedies. About 25% of Americans seek and obtain nontraditional treatments and visit practitioners of alternative medicine more frequently than they visit primary care physicians (8).

Despite the growing popularity of alternative medications, they are not as well studied as are more conventional agents, and their efficacy and safety are still not clear (6). There are relatively few well-designed controlled studies with adequate sample sizes, and the question of effectiveness and superiority to placebo is still under debate for most of these treatments (6). Another problem is the mistaken belief among patients that a medication is automatically safe if it is natural (9). In fact, there have been many cases of toxicity, adverse effects, and adverse drug interactions in persons who have used these treatments (6). In addition, the purity and active ingredients of different preparations vary. Finally, insurance companies usually do not cover these treatments, and many patients are unable to absorb the out-of-pocket costs (6). Clearly, additional studies characterizing the safety and effectiveness of natural remedies are required.

S-ADENOSYL-L-METHIONINE AS A POTENTIAL ANTIDEPRESSANT

One of the better-studied natural agents is S-adenosyl-L-methionine (SAME), a major methyl donor in the brain that is involved in the

¹ From the Harvard Medical School, Depression Clinical and Research Program, Massachusetts General Hospital, Boston.

² Presented at the symposium S-Adenosylmethionine (SAME): from Molecular Mechanism to Clinical Implications, held in Santa Barbara, CA, March 7–10, 2001.

³ Supported in part by a NARSAD Young Investigator Award (to DM).

⁴ Address reprint requests to D Mischoulon, Department of Psychiatry, Massachusetts General Hospital, WAC-812, 15 Parkman Street, Boston, MA 02114. E-mail: dmischoulon@partners.org.

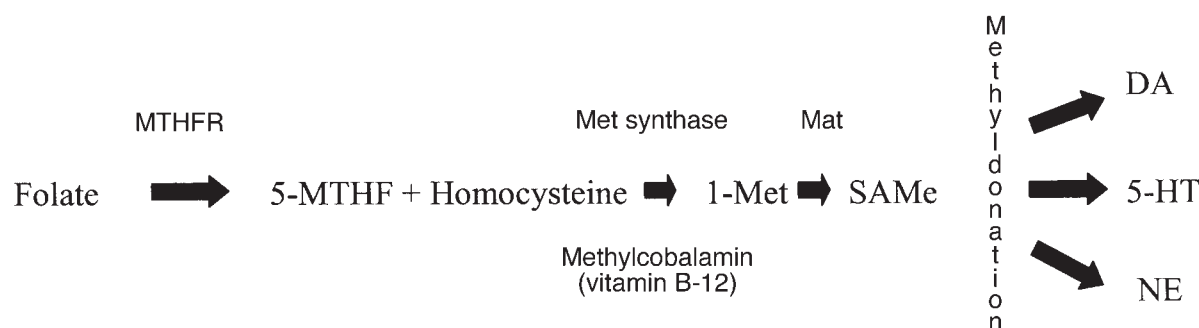


FIGURE 1. Pathway of *S*-adenosyl-L-methionine (S-AdoMet). S-AdoMet is synthesized as part of a multistep pathway involving the vitamins folic acid and B-12. The end product then donates methyl groups in the reactions involved in the synthesis of the key neurotransmitters serotonin, norepinephrine, and dopamine. Deficiencies of these neurotransmitters are thought to be involved in the development of depression and other mood disorders. It has been postulated that exogenous addition of S-AdoMet may result in increased synthesis of these neurotransmitters, which may account for its antidepressant effect. MTHFR, methylenetetrahydrofolate reductase (EC 1.7.99.5); MTHF, methyltetrahydrofolate; 1-Met, methionine; Mat, methionine adenosyltransferase (EC 2.5.1.6); Met synthase, methionine synthase (EC 4.2.99.10); DA, dopamine; 5-HT, serotonin (5-hydroxytryptophan); NE, norepinephrine. Adapted from reference 11.

pathways for synthesis of hormones, neurotransmitters, nucleic acids, proteins, and phospholipids (10, 11) (Figures 1 and 2). S-AdoMet is required for the synthesis of norepinephrine, dopamine, and serotonin, and also plays a role in other intracellular metabolic pathways (10).

Routinely prescribed in Europe for nearly 30 y, S-AdoMet has gained popularity in the United States since its release as an over-the-counter dietary supplement in 1998–1999. Given its range of activity, S-AdoMet has been proposed as a potential treatment for many medical conditions, particularly major depression (10). Marketed as an agent for improving mood and emotional well-being, S-AdoMet has been featured in the national media and the popular press and has steadily attracted the attention of patients and clinicians.

S-AdoMet is synthesized from the amino acid L-methionine through a metabolic pathway called the one-carbon cycle, which relies, in part, on adequate concentrations of the vitamins folate and B-12 (Figure 1) (10, 11). Deficiencies of both of these vitamins have also been linked to depression. For example, between 10% and 30% of depressed patients may have low folate concentrations, and these patients appear to respond less well to

antidepressants (12). Vitamin B-12 is converted to methylcobalamin, which is also involved in the synthesis of the various central nervous system neurotransmitters. Vitamin B-12 deficiency may result in an earlier age of onset of depression (13). The common mediator of this effect may be reduced S-AdoMet. Correction of folate and vitamin B-12 deficiencies may alleviate depressive symptoms and augment the response to antidepressant therapy, perhaps because of the resultant increase in S-AdoMet concentrations.

S-AdoMet's relation to mood is suggested by several lines of evidence. For instance, low S-AdoMet concentrations have been observed in the cerebrospinal fluid of depressed persons (14). Conversely, there is a positive correlation between an increase in plasma S-AdoMet concentrations and an improvement in depressive symptoms (15). The activity of the enzyme methionine adenosyltransferase (EC 2.5.1.6), which is involved in the manufacture of S-AdoMet, has been shown to be low in depressed schizophrenic patients but high in manic patients (16–18). This finding supports the role of S-AdoMet as a mood-elevating agent.

S-AdoMet has been studied in clinical trials to determine its mood-elevating effect in depressed patients (10, 19). A few published

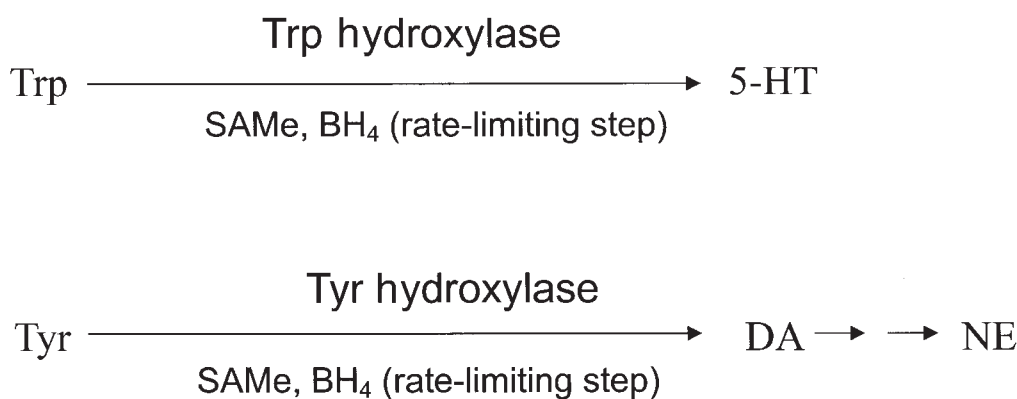


FIGURE 2. *S*-Adenosyl-L-methionine (S-AdoMet) and synthesis of neurotransmitters. The neurotransmitter serotonin (5-hydroxytryptophan; 5-HT) is synthesized from the amino acid tryptophan in a series of chemical reactions, of which the rate-limiting step is catalyzed by the enzyme tryptophan hydroxylase (EC 1.14.16.4). Similarly, the neurotransmitters dopamine (DA) and norepinephrine (NE) are synthesized from the amino acid tyrosine in a series of chemical reactions dependent on tyrosine hydroxylase (EC 1.14.16.2). S-AdoMet functions as a methyl-donating cofactor in the rate-limiting step in these synthetic reactions. BH₄, tetrahydrobiopterin. Adapted from reference 11.



clinical studies showed that parenteral (intravenous or intramuscular) SAME is superior to placebo and is as effective as tricyclic antidepressants (10, 19). Trials of oral SAME suggest an efficacy comparable to that of tricyclic antidepressants and superior to placebo at doses between 200 and 1600 mg/d (10). Some studies, however, have yielded equivocal results because of problems with dissolution and stability of early oral SAME preparations (10). Current oral SAME preparations are more stable and more amenable to systematic study. SAME has not been compared against newer antidepressants such as the selective serotonin reuptake inhibitors.

In 6 of at least 8 placebo-controlled studies with sample sizes ranging from 40 to 100, SAME was superior to placebo and was equivalent to placebo in the other 2 studies (10). In 6 of 8 comparison studies with tricyclic antidepressants, SAME was equivalent in efficacy to tricyclic antidepressants and more effective than imipramine in one study (10). Doses (oral, intramuscular, or intravenous) of SAME in these studies ranged from 200 to 1600 mg/d.

SAME may have a relatively faster onset of action than do conventional antidepressants (20–30). In one study, some patients improved within a few days and most did within 2 wk (10, 28). Likewise, 2 studies showed that the combination of SAME and low-dose tricyclic antidepressants resulted in an earlier onset of action than did tricyclic antidepressants alone (29, 30).

Other reports suggest that SAME is effective in treating cognitive deficits seen in dementia (31). Decreased folate and vitamin B-12 and decreased membrane fluidity were found in patients with Alzheimer disease, and SAME may protect against these deleterious effects (31, 32). Other studies have suggested that SAME may relieve distress during the puerperium (33). In addition, SAME has been shown to reduce psychological distress during opioid detoxification (34) and may be useful in depressed persons with alcoholism (35). A recent open study suggests effectiveness at doses ranging from 800 to 3600 mg/d in depressed patients with Parkinson disease (36). Studies by Martinez-Chantar (37) and others have shown that treatment with SAME may improve outcomes in patients with alcoholic liver disease, resulting in increased survival or a delay in the need for transplantation. Finally, SAME may be useful in medically ill, depressed patients for whom conventional agents may be contraindicated (38).


SAME is well tolerated and relatively free of adverse effects. There is no apparent associated hepatotoxicity or anticholinergic effects. Side effects include mild insomnia, lack of appetite, constipation, nausea, dry mouth, sweating, dizziness, and nervousness (10). Increased anxiety, mania, or hypomania have been reported in patients with bipolar depression (10, 39, 40); therefore, patients with a history of bipolar disorder should be advised not to take SAME unless they are also taking a mood stabilizer.

SAME is relatively expensive; prices for a 200-mg tablet range from \$0.75 to \$1.25. This high monetary cost may limit access to this medication for many patients, particularly for those who require high doses (> 200 mg) to achieve the desired effect. Some internet-based companies who sell directly to customers provide SAME at more reasonable prices. As competition and the number of manufacturers of SAME increase, the price of SAME will probably decrease over the next few years.

CONCLUSIONS AND RECOMMENDATIONS

Fairly strong evidence exists that oral and parenteral SAME are effective for the treatment of major depression. Some studies

have suggested a faster onset of action for SAME than for conventional antidepressants. SAME may be used alone or in combination with other agents and may even accelerate the effect of conventional antidepressants. SAME appears to be well tolerated and has relatively benign side effects. Thus, SAME may be especially useful in patients who experience side effects from conventional antidepressants. The use of SAME has not been shown to have toxic side effects; however, as mentioned earlier, there have been reports that SAME may cause increased anxiety and mania in patients with bipolar depression. Recommended doses range from 400 to 1600 mg/d, although some persons may require doses > 3000 mg/d to alleviate depression.

In summary, on the basis of previously published evidence, the best candidates for SAME or other natural antidepressants may be mildly symptomatic patients for whom a delay in adequate treatment would not be devastating. At the other end of the spectrum, patients who have failed multiple trials with conventional remedies or who are highly intolerant of side effects may also be good candidates. The use of SAME in conjunction with conventional antidepressants also appears to be a viable application in patients who achieve only a partial response to conventional antidepressants alone. However, clinicians must be careful about recommending the use of SAME to patients who take other medications, because its interactions with other drugs are not well elucidated. More research is needed to determine optimal doses, and head-to-head comparisons with newer antidepressants should help to clarify SAME's place in the psychopharmacologic armamentarium. 

REFERENCES

1. Pincus HA, Pettit AR. The societal costs of chronic major depression. *J Clin Psychiatry* 2001;62(suppl):5–9.
2. Kendler KS, Thornton LM, Prescott CA. Gender differences in the rates of exposure to stressful life events and sensitivity to their depressive effects. *Am J Psychiatry* 2001;158:587–93.
3. Fava M, Davidson KG. Definition and epidemiology of treatment-resistant depression. *Psychiatr Clin North Am* 1996;19:179–200.
4. Fava M, Kaji K. Continuation and maintenance treatments of major depressive disorder. *Psychiatr Ann* 1994;24:281–90.
5. Eisenberg DM, Kessler RC, Foster C, Norlock FE, Calkins DR, Delbanco TL. Unconventional medicine in the United States: prevalence, costs, and patterns of use. *N Engl J Med* 1993;328:246–52.
6. Mischoulon D, Rosenbaum JF. The use of natural medications in psychiatry. A commentary. *Harv Rev Psychiatry* 1999;6:279–83.
7. Krippner S. A cross cultural comparison of four healing models. *Altern Ther Health Med* 1995;1:21–9.
8. National Institutes of Health, Office of Alternative Medicine, Practice and Policy Guidelines Panel. Clinical practice guidelines in complementary and alternative medicine. An analysis of opportunities and obstacles. *Arch Fam Med* 1997;6:149–54.
9. Ernst E. Harmless herbs? A review of the recent literature. *Am J Med* 1998;104:170–8.
10. Spillmann M, Fava M. S-adenosyl-methionine (ademethionine) in psychiatric disorders. *CNS Drugs* 1996;6:416–25.
11. Alpert JE, Mischoulon D. One-carbon metabolism and the treatment of depression: roles of S-adenosyl methionine (SAME) and folic acid. In: Mischoulon D, Rosenbaum J, eds. *Natural medications for psychiatric disorders: considering the alternatives*. Philadelphia: Lippincott Williams & Wilkins, 2002:44.
12. Alpert JE, Mischoulon D, Nierenberg AA, Fava M. Nutrition and depression: focus on folate. *Nutrition* 2000;16:544–6.



13. Fava M, Borus JS, Alpert JE, et al. Folate, B12, and homocysteine in major depressive disorder. *Am J Psychiatry* 1997;154:426–8.
14. Bottiglieri T, Godfrey P, Flynn T, Carney MWP, Toone BK, Reynolds EH. Cerebrospinal fluid *S*-adenosylmethionine in depression and dementia: effects of treatment with parenteral and oral *S*-adenosylmethionine. *J Neurol Neurosurg Psychiatry* 1990;53:1096–8.
15. Bell KM, Potkin SG, Carreon D, Plon L. *S*-adenosylmethionine blood levels in major depression: changes with drug treatment. *Acta Neurol Scand Suppl* 1994;154:15–8.
16. Bottiglieri T, Chary TK, Laundry M, et al. Transmethylation in depression. *Ala J Med Sci* 1988;25:296–301.
17. Matthyse S, Baldessarini RJ. *S*-adenosylmethionine and catechol-*O*-methyl-transferase in schizophrenia. *Am J Psychiatry* 1972;128:1310–2.
18. Tolbert LC. MAT kinetics in affective disorders and schizophrenia. An account. *Ala J Med Sci* 1988;25:291–6.
19. Bressa GM. *S*-Adenosyl-*l*-methionine (SAME) as antidepressant: meta-analysis of clinical studies. *Acta Neurol Scand* 1994;154 (suppl):7–14.
20. Mantero M, Pastorino P, Carolei A, Agnoli A. Studio controllato in doppio cieco (SAME-imipramina) nelle sindromi depressive. [Controlled double-blind study (SAME-imipramine) in depressive syndrome.] *Minerva Med* 1975;66:4098–101 (in Italian).
21. Miccoli L, Porro V, Bertolino A. Comparison between the antidepressant activity of *S*-adenosyl-*l*-methionine (SAME) and that of some tricyclic drugs. *Acta Neurol (Napoli)* 1978;33:243–55.
22. Del Vecchio M, Iorio G, Cocorullo M, Vacca L, Amati A. Has SAME (Ado-Met) an antidepressant effect? A preliminary trial versus clomipramine. *Riv Sper Freniatr* 1978;102:344–58.
23. Monaco P, Quattrocchi F. Studio degli effetti antidepressivi di un trasmetilante biologico (*S*-adenosil-metionina—SAME). (Study of the antidepressant effect of a biological transmethylator (*S*-adenosylmethionine—SAME.) *Riv Neurol* 1979;49:417–39 (in Italian).
24. Calandra C, Roxas M, Rapisarda V. Azione antidepressiva della SAME a paragone della clomipramina. Ipotesi interpretative del meccanismo d'azione. (Antidepressant action of SAME compared to that of clomipramine. Interpretive hypothesis of the mechanism of action.) *Minerva Psichiatr* 1979;20:147–52 (in Italian).
25. Kufferle B, Grunberger J. Early clinical double-blind study with *S*-adenosyl-*l*-methionine: a new potential antidepressant. In: Costa E, Racagni G, eds. Typical and atypical antidepressants. New York: Raven Press, 1982:175–80.
26. Bell KM, Plon L, Bunney WE Jr, Potkin SG. *S*-adenosylmethionine treatment of depression: a controlled clinical trial. *Am J Psychiatry* 1988;145:1110–4.
27. Janicak PG, Lipinski J, Davis JM, et al. *S*-Adenosylmethionine in depression: a literature review and preliminary report. *Ala J Med Sci* 1988;25:306–13.
28. Fava M, Giannelli A, Rapisarda V, Patralia A, Guaraldi GP. Rapidity of onset of the antidepressant effect of parenteral *S*-adenosyl-*l*-methionine. *Psychiatry Res* 1995;56:295–7.
29. Alvarez E, Udina C, Guillamat R. Shortening of latency period in depressed patients treated with SAME and other antidepressant drugs. *Cell Biol Rev* 1987;S1:103–10.
30. Berlanga C, Ortega-Soto HA, Ontiveros M, Senties H. Efficacy of *S*-adenosyl-*l*-methionine in speeding the onset of action of imipramine. *Psychiatry Res* 1992;44:257–62.
31. Fontanari D, DiPalma C, Giorgetti G, et al. Effects of *S*-adenosyl-*l*-methionine on cognitive and vigilance functions in elderly. *Curr Ther Res* 1994;55:682–9.
32. Reynolds EH, Carney MWP, Toone BK, et al. Transmethylation and neuropsychiatry. *Cell Biol Rev* 1987;2:93–102.
33. Cerutti R, Scichel MP, Perin M, et al. Psychological distress during puerperium: a novel therapeutic approach using *S*-adenosylmethionine. *Curr Ther Res* 1993;53:707–16.
34. Lo Russo A, Monaco M, Pani A, et al. Efficacy of *S*-adenosyl methionine in relieving psychologic distress associated with detoxification on opiate abusers. *Curr Ther Res* 1994;55:905–13.
35. Agricola R, Dalla Verde G, Urani R, et al. *S*-adenosyl-*l*-methionine in the treatment of major depression complicating chronic alcoholism. *Curr Ther Res* 1994;55:83–92.
36. Di Rocco A, Rogers JD, Brown R, Werner P, Bottiglieri T. *S*-Adenosyl-methionine improves depression in patients with Parkinson's disease in an open-label clinical trial. *Mov Disord* 2000;15:1225–9.
37. Martínez-Chantar ML, García-Trevijano ER, Latasa MU, et al. Importance of a deficiency in *S*-adenosyl-*l*-methionine synthesis in the pathogenesis of liver injury. *Am J Clin Nutr* 2002;76(suppl):1177S–82S.
38. Rosenbaum JF, Fava M, Falk WE, et al. The antidepressant potential of oral *S*-adenosyl-*l*-methionine. *Acta Psychiatr Scand* 1990;81:432–6.
39. Carney MWP, Chary TNK, Bottiglieri T. Switch mechanism in affective illness and oral *S*-adenosylmethionine (SAM). *Br J Psychiatry* 1987;150:724–5.
40. Carney MW, Martin R, Bottiglieri T, et al. Switch mechanism in affective illness and *S*-adenosylmethionine. *Lancet* 1983;1:820–1.

