


S-Adenosyl-L-Methionine (SAMe)

**DESCRIPTION**

S-adenosyl-L-methionine (SAMe) is a natural substance present in the cells of the body. It is a direct metabolite of the essential amino acid L-methionine. It is variously known as ademetionine, S-adenosylmethionine, SAM, SAMe and SAM-e. It is represented structurally as:

\[
\text{S-Adenosylmethionine}
\]

SAMe is used as a drug in Europe for the treatment of depression, liver disorders, osteoarthritis and fibromyalgia. Recently, SAMe has been introduced into the United States as a dietary supplement for the support of bone and joint health, as well as mood and emotional well being.

**ACTIONS AND PHARMACOLOGY**

**ACTIONS**

SAMe plays a crucial biochemical role in the body by donating a one-carbon methyl group in a process called transmethylation. SAMe, formed from the reaction of L-methionine and adenosine triphosphate catalyzed by the enzyme S-adenosylmethionine synthetase, is the methyl group donor in the biosynthesis of both DNA and RNA nucleic acids, phospholipids, proteins, epinephrine, melatonin, creatine and other molecules.

Supplemental SAMe may have antidepressant and hepatoprotective activities.

**MECHANISM OF ACTION**

The mechanism of action of supplemental SAMe is unclear. Much is known, however, of the mechanism of action of endogenous SAMe.

Methylation of DNA is critical in the biological phenomenon known as gene silencing. Gene silencing helps suppress genes that may give rise to cancer or those that may carry information for endogenous retroviruses. Methylation of RNA, particularly transfer RNA, is similarly important in safeguarding the form and function of these molecules in protein synthesis.

SAMe is the methyl donor to phosphatidylethanolamine in the formation of phosphatidylethanolamine (PC). PC is a major component of cell membranes and is vital for maintenance of cellular membrane fluidity, important in sustaining the bioenergetics and information-processing functions of cells.

SAMe is also involved in the methylation of histones, major elements in chromosomal structure. This methylation is believed to play a key role in the regulation of DNA transcription, the process by which RNA is formed. The carbon and nitrogen atoms of L-carnitine are derived from methylated lysine residues, which are formed by methylating certain proteins with SAMe’s methyl group.

SAMe’s importance in the body is further emphasized by the fact that it is also the methyl donor for the synthesis of epinephrine (adrenaline), creatine, melatonin, glutathione, the polyamines spermine and spermidine, and the amino acids L-cysteine and taurine, all of which play vital roles in human health.
PHARMACOKINETICS
SAMe is absorbed from the small intestine following oral intake. Absorption is better on an empty stomach, and enteric-coated tablets are better absorbed than non-enteric-coated varieties. Peak plasma concentrations obtained with enteric-coated tablet formulations are dose related, with a peak concentration of 0.5 to 1 mg/L achieved three to five hours after single doses in the range of 400 to 1,000 milligrams.

Limited trials in healthy volunteers show low bioavailability following oral intake of SAMe. This indicates significant first-pass metabolism in the liver. SAMe is mainly metabolized in the liver (about 50%).

SAMe is metabolized to S-adenosylhomocysteine, which in turn is metabolized to homocysteine. Homocysteine can either be metabolized to cystathionine and then cysteine or to methionine. The cofactor in the metabolism of homocysteine to cysteine is vitamin B₆. Cofactors for the metabolism of homocysteine to methionine are folic acid, vitamin B₁₂ and trimethylglycine (betaine).

Orally administered SAMe follows the same metabolic pathways as the natural compound found in cells. SAMe crosses the blood-brain barrier with slow accumulation in the cerebrovascular fluid. It can also get into joint synovial fluid.

One study showed that 15% of a 200 milligram-dose of SAMe was excreted in urine within 48 hours and that an additional 23% was eliminated in feces within 72 hours. The remainder was believed to be incorporated in stable metabolic pools (phosphatidylethanolamine, DNA, RNA, proteins and creatine, among others).

The pharmacokinetics of SAMe are similar whether in healthy individuals or in those with chronic liver disease.

INDICATIONS AND USAGE
SAMe may be indicated for the promotion and support of mood and emotional well-being. It is being used by some for the treatment of depression. There is some indication it may be helpful in Alzheimer’s disease. It may also be indicated for the support of joint health, mobility and joint comfort. It is used for the treatment of osteoarthritis; there is, as yet, little convincing evidence that it is useful in any other form of arthritis. It is also used in some liver conditions, including various forms of cirrhosis and cholestasis, and there is a very preliminary indication that it might be useful in lowering lipids.

RESEARCH SUMMARY
A number of studies have now demonstrated an association between various neuropsychiatric disorders and deficient SAMe metabolism. SAMe’s possible influence on monoamine neurotransmitter metabolism, in particular, has focused attention on its possible role in depression. This has resulted in a series of small studies using oral and parenteral SAMe to treat depression. The results are preliminary but promising.

In a meta-analysis of the most significant clinical studies, SAMe’s efficacy was shown to exceed that of placebo and to equal or slightly better that of tricyclic antidepressants. (There is no reliable data comparing SAMe with the selective serotonin reuptake inhibitors.) Parenteral administration was only slightly more effective than oral.

SAMe, unlike traditional antidepressants, has few side effects and a rapid onset of action (usually within one or two weeks compared with three to four weeks or longer for standard antidepressants). SAMe rarely produces the side effects common to many other antidepressants, such as insomnia, nervousness, nausea and sexual dysfunction. SAMe should only be used in bipolar disorder under strict medical supervision, if at all.

SAMe’s possible role in ameliorating a number of other neurological disorders is suggested by some early research but is far from proved. These disorders include Alzheimer’s dementia and other clinical dementia syndromes. SAMe has been shown to have some positive effect on mood and depression associated with Parkinson’s disease and chronic epileptic seizures.

A recent paper suggested that SAMe might not be appropriate for Parkinson’s disease since some mouse studies demonstrated adverse reactions. The same authors stated that these same adverse reactions might not occur in humans but that caution is advised, pending further research. Some others have worried that SAMe might also interfere with the activity of levodopa, often used in the treatment of Parkinson’s. Fear has also been expressed that SAMe might potentiate the manic phase of bipolar disorder; use in subjects with this disorder may thus be contraindicated.

Some recent in vitro and animal studies have shown that SAMe supplementation may have the potential to favorably mediate glutathione S-transferase (GST) activity. Alzheimer’s disease has been associated with reduced GST activity, diminished levels of S-adenosylmethionine (SAM) and increased S-adenosylhomocysteine (SAH). Diminished GST has been shown to result in increased oxidative species within brain tissues. Mice in some of these studies have shown reduced levels of SAM and increased levels of SAH, which, in turn, further inhibits SAM. Supplemeting diet with SAMe has helped to correct these imbalances and might therefore, it has been postulated, be beneficial in those with Alzheimer’s. Some dated studies suggested some benefit in mood and cognitive improvement among some early stage Alzheimer’s patients taking SAMe. Much more recently,
another study found that a "nutraceutical cocktail" containing vitamins and SAMe delayed cognitive decline and improved mood, again in early stage Alzheimer's subjects. This same cocktail was said to improve reaction time and cognitive performance among adults and elderly without dementia. These preliminary findings need follow-up.

SAMe is depleted in liver disease, and its replenishment through supplementation has been demonstrated in several studies. Its methylating properties promote the fluidity of liver lipid membranes. SAMe has been shown to improve functions measured by standard liver and liver-function tests, to increase hepatic glutathione levels in patients with both alcohol and non-alcoholic cirrhosis, to restore normal hepatic function in various forms of cholestasis and prevent or reverse hepatic toxicity induced by drugs, alcohol and various chemicals.

Some dated studies indicated that SAMe is as effective as standard anti-inflammatory drugs in the treatment of osteoarthritis. More recently, a double-blind study pitted SAMe against celecoxib, a nonsteroidal anti-inflammatory drug. The latter produced more rapid effects, but SAMe seemed to match these effects over time. Lack of placebo control made results somewhat indefinite. More research is needed and warranted.

Again, some dated studies found SAMe helpful in cases of fibromyalgia. Most of these studies, however, used injectable SAMe. In one study using oral SAMe, 44 subjects with fibromyalgia were randomized to receive either 800 mg of SAMe daily or placebo for 8 weeks. By several measures—including mood, fatigue, and morning stiffness—the SAMe-supplemented subjects were judged to have enjoyed significant improvement, compared with placebo subjects, in whom no significant improvement was noted.

SAMe is used as a cytoprotective agent against liver toxicity and there hope that it might one day be used as a chemopreventive agent against liver tumors. Some animal experiments suggest the possibility that it could be useful for that purpose through its apparent ability to inhibit the expression of some oncogene functions.

There is a single study, apparently without follow-up, showing that SAMe might be an effective agent for lowering lipids in humans.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS
Known hypersensitivity to a SAMe-containing product.

PRECAUTIONS
Sufferers of bipolar disorder (manic-depressive illness) should not use SAMe unless under medical supervision. Those who are taking antidepressant medications should confer with their physicians before taking SAMe in place of or in addition to those medications. They should continue to be monitored by their physician. SAMe is not recommended for use in children. It should only be used by pregnant women with a physician's approval and under a physician's supervision. Nursing mothers should avoid SAMe supplementation.

There is no evidence that SAMe is either mutagenic or carcinogenic. But since nucleic acid methylation patterns may change in those with cancer, the use of SAMe by cancer patients should be discussed with their physicians. SAMe may one day be shown to be effective in preventing and possibly even treating some forms of cancer but, in the meantime, because it is an active methylating agent, some caution is advised in those who have cancer.

Those undergoing gene therapy should avoid supplemental SAMe.

ADVERSE REACTIONS
Although classified and sold as a drug in Europe, SAMe is marketed in the United States as a dietary supplement. There are so far no reports of serious adverse events in those taking this supplement in doses up to 1,600 mg per day over long periods of time. Side effects that have been reported include mild gastrointestinal upset (such as stomach pain, nausea, diarrhea and flatulence), anxiety, hyperactive muscle movement, insomnia and hypomania. When these side effects occur they often diminish with time or resolve with lower doses or cessation of use. There are no documented cases of allergies to SAMe.

INTERACTIONS
There are so far no reported adverse interactions with SAMe and other drugs, dietary supplements or foods.

OVERDOSAGE
No overdose reported.

DOSAGE AND ADMINISTRATION
SAMe is highly unstable at temperatures above 0 degree C. Since the 1970s, certain salts of SAMe have become available that are stable at higher temperatures. These forms, which are clearly more desirable, include SAMe paratoluene sulfonates (SAMe tosyls). These more stable forms have been used in many of the SAMe studies, but they are not always the forms that are found in the supplement marketplace. Another temperature-stable form is SAMe 1,4 butanedisulfonate. Even these temperature-stable forms must be kept very dry since moisture can cause hydrolysis. Stable, enteric-coated tablets are recommended.

SAMe is most frequently available in 200 mg tablets. The usual oral dose for use in depression has been in the range of 400 to 1,600 milligrams daily in divided doses. For liver
problems, usual doses reported are up to 1,600 mg daily in divided doses. For bone and joint health, the daily dose is typically 200 to 1,200 milligrams in divided doses. SAMe should always be taken on an empty stomach, i.e., one hour before meals or two hours after meals. It is often reported in the literature that these doses can usually be cut in half when a positive effect is achieved. Effects, if any, are usually evident within two weeks of starting supplementation.

It is advisable to take SAMe with supplemental B6, B12, folic acid and possibly trimethylglycine (particularly in those with elevated homocysteine levels). Some SAMe supplements come with B6, B12 and folic acid. These other nutrients help metabolize homocysteine which, at elevated levels, increases the risk of cardiovascular disease and some other disorders.

**LITERATURE**


### Secoisolariciresinol Diglycoside (SDG)

**DESCRIPTION**

Secoisolariciresinol diglycoside, or SDG, is a plant lignan most notably found in flaxseed (linseed). SDG is classified as a phytoestrogen since it is a plant-derived, nonsteroid compound that possesses estrogen-like activity. SDG has weak estrogenic activity. The level of SDG in flaxseed typically varies between 0.6% and 1.8%.

Lignans are one of the two major classes of phytoestrogens; the other class is the isoflavones. Plant lignans are polyphenolic substances derived from phenylalanine via dimerization of substituted cinnamic alcohols. Mammalian lignans are lignans derived from plant lignans. For example, following ingestion, SDG is converted to the aglycone secoisolariciresinol, which is then metabolized to the mammalian lignans enterolactone and enterodiol. Most of the effects of oral SDG are mediated by enterolactone and enterodiol.

The molecular formula of SDG is C$_{32}$H$_{46}$O$_{16}$, and its molecular weight is 686.71 daltons. The aglycone of SDG is also known as 2, 3-bis (3-methoxy-4-hydroxybenzyl) butan-1, 4-diol. Enterolactone is also known as trans-2, 3-bis [(3-hydroxyphenyl) methyl]-butyrolactone. It is represented by the following structural formula:

![Secoisolariciresinol diglycoside](image)

See also Flaxseed Lignans.

### ACTIONS AND PHARMACOLOGY

#### ACTIONS

SDG has estrogenic and antioxidant activities. It may also have antiestrogenic, anticarcinogenic, antiatherogenic and antidiabetic activities.

#### MECHANISM OF ACTION

SDG, as well as its mammalian lignan metabolites, enterolactone (EL) and enterodiol (ED), have weak estrogenic activity as measured in in vivo and in vitro assays.

SDG, EL and ED have a number of antioxidant activities, including inhibition of lipid peroxidation and scavenging of hydroxy radicals. SDG also has anti-platelet-activation factor (PAF) activity. PAF can induce the release of reactive oxygen species from neutrophils. SDG, via its metabolite EL, has been found to inhibit estrogen synthase (aromatase) and to stimulate the synthesis of sex hormone binding globulin (SHBG). Both of these actions could account for the possible anti-estrogen activity of SDG.

The possible anticarcinogenic, antiatherogenic and antidiabetic activities of SDG are thought to be due, in large part, to the antioxidant activities of its metabolites EL and ED.

#### PHARMACOKINETICS

SDG, following ingestion, is transported to the large intestine, where it is hydrolyzed by bacteria to the aglycone...