

S-Adenosylmethionine (Ademetionine) in Psychiatric Disorders

Historical Perspective and Current Status

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Summary

S-Adenosylmethionine (SAME; ademetionine) is a naturally occurring compound that is found in virtually all living organisms. It serves as a major source of methyl groups in the brain, donating these groups to molecules such as hormones, neurotransmitters, nucleic acids, proteins and phospholipids, and is of fundamental importance in a number of intracellular metabolic pathways.

The most commonly reported effect of SAME is mood elevation in depressed patients. A few, relatively small clinical studies have shown that parenteral SAME is superior to placebo and at least as effective as standard antidepressants, perhaps with a relatively rapid onset of action. Furthermore, the addition of SAME to standard antidepressants may shorten the time to treatment response compared with the use of antidepressants alone. There are also additional reports suggesting the usefulness of the compound in dementia. SAME appears to be remarkably well tolerated and free of severe adverse effects.

Further studies are needed to clearly establish the role that SAME may play in the treatment of depressive disorders and dementia.

Over the past few decades, researchers have focused their attention on the development of new drug treatments for psychiatric disorders. Additionally, there has been an increased interest in the possible use of natural substances in the treatment of medical and psychiatric disorders. One of the most promising compounds is S-adenosylmethionine (SAME; ademetionine), a naturally occurring metabolite with psychotropic effects. This article reviews the evidence for the neuropharmacological effects of this compound.

1. Biochemical and Neuropharmacological Aspects of Methylation

1.1 General Overview

1.1.1 Tissue Distribution

SAME is present in virtually all living organisms.^[1] In humans, it is distributed in numerous body tissues and fluids, including the brain and CSF. Besides the liver and adrenal glands, the high-

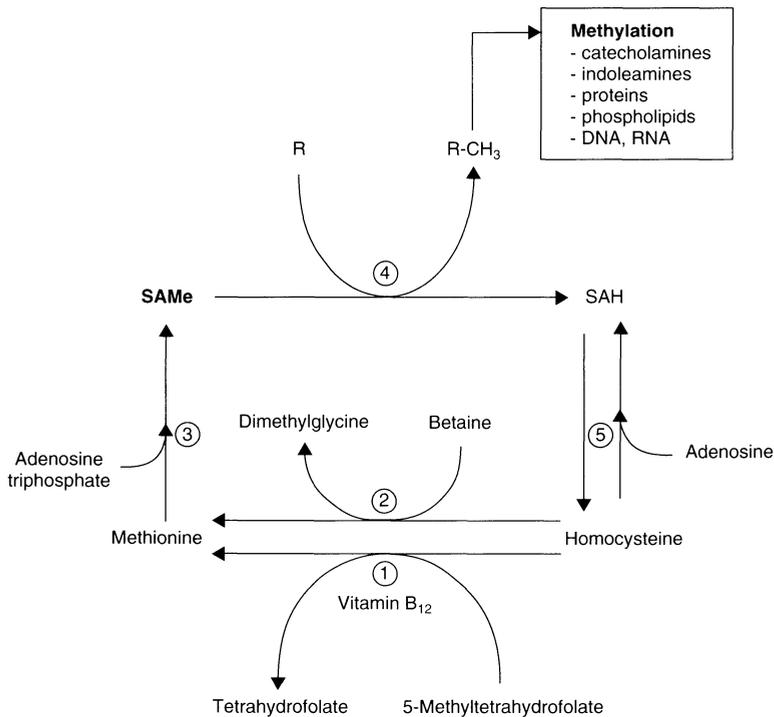


Fig. 1. Schematic diagram of the one-carbon cycle, showing the synthesis of *S*-adenosylmethionine (SAME; ademetionine). Key: 1 = methionine synthetase; 2 = betaine:homocysteine methyltransferase; 3 = methionine adenosyltransferase; 4 = *R*-methyltransferase; 5 = *S*-adenosylhomocysteine (SAH) hydrolase.

est levels of SAME are found in the pineal gland, where it is utilised for melatonin synthesis.^[2,3]

1.1.2 Physiological Role

Physiologically, SAME serves as a major source of methyl groups^[4] and is of fundamental importance in a number of intracellular metabolic pathways. The high transfer potential of the methyl group in SAME enables it to be donated to a wide variety of acceptors such as catecholamines and other biogenic amines, phospholipids, proteins and nucleic acids.^[2,5]

1.1.3 Synthesis

SAME is synthesised by the transfer of an adenosyl group from adenosine triphosphate (ATP) to the sulphur atom of methionine, in a reaction catalysed by methionine adenosyltransferase (MAT).^[5,6] In the process of methylation, SAME is converted to *S*-adenosylhomocysteine (SAH), a

competitive inhibitor for methylation reactions in which SAME is involved (see fig. 1).^[7] Thus, trans-methylation is a self-limiting process.

1.1.4 Methionine – the Precursor Amino Acid

Methionine is an essential amino acid that is required for protein synthesis as well as for synthesis of choline, cysteine, glutathione and taurine by the trans-sulphuration pathway.^[7] Since the daily nutritional supply of methionine is not sufficient to grant the total amount needed for SAME synthesis, endogenous methionine synthesis is necessary (see fig. 1).^[8] The additional methionine biosynthesis involves the transfer of a methyl group from 5-methyltetrahydrofolate to homocysteine. This reaction is catalysed by methionine synthetase, a vitamin B₁₂ (cyanocobalamin)-dependent enzyme. Alternatively, homocysteine can be methylated to methionine by donors such as betaine, a

vitamin B₁₂-independent methyl donor, in a reaction catalysed by betaine:homocysteine methyltransferase.

1.2 S-Adenosylmethionine (SAME) in the CNS

There is increasing evidence that SAME plays an important role in numerous metabolic pathways in the CNS.

1.2.1 Distribution

SAME appears to be widely and equally distributed throughout the CNS. Studies of regional brain levels of SAME in rats showed no significant differences between those of the basal ganglia, brain stem, cerebral cortex and cerebellum.^[3]

1.2.2 Role of Methylation in the CNS

On a cellular basis, one of the most important transmethylation reactions is the methylation of phospholipids that regulate essential cell membrane functions, including cell membrane fluidity and β -adrenergic and dopaminergic receptor characteristics.^[1,2,9] Thus, methylation might facilitate neurotransmission by increasing the density and activity of available receptors or increasing the efficiency of receptor-effector coupling.^[9]

Furthermore, animal studies have shown that in rats the administration of SAME was highly correlated with an increase in the level of monoamines and the serotonin (5-hydroxytryptamine; 5-HT) metabolite 5-hydroxyindoleacetic acid (5-HIAA), as well as an increase in turnover of monoamines in some regions of the brain.^[10-12]

1.2.3 SAME Synthesis

Betaine:homocysteine methyltransferase, the enzyme catalysing the vitamin B₁₂-independent synthesis of methionine, is absent from human brain tissue.^[13] Therefore, the CNS synthesis of SAME is highly dependent on both folic acid and vitamin B₁₂ metabolism. A deficiency of either of these vitamins may cause a decrease in the brain level in SAME and perhaps lead to neurological and psychiatric features, such as dementia, peripheral neuropathy and depression.^[14,15]

1.2.4 Methods for Measurement of CNS Methylation

Studies of the CSF level of SAME in patients with congenital metabolic defects suggest that this may be a good indicator of the overall degree of methyl group metabolism in the CNS.^[16] SAME appears to influence the turnover of monoamines,^[10-12] with several studies in humans finding that administration of SAME led to an increase in CSF levels of 5-HIAA and the dopamine metabolite homovanillic acid.^[17,18]

1.3 Neuropharmacological Role of SAME

Given the physiological actions of SAME, investigators have evaluated the efficacy of this substance in the treatment of various diseases or conditions. Indeed, there is some evidence to suggest a role for SAME in the treatment of liver diseases, including cirrhosis and cholestasis,^[1,7] and rheumatological diseases,^[19] and neuropsychiatric disorders (see section 2). The neuropharmacological actions of SAME on catecholamines and other biogenic amines are of great interest, as dysregulations in the metabolism of these neurotransmitters are strongly related to different neurological and psychiatric disturbances.^[20-22]

However, the ability of the compound to produce physiological actions when given as an exogenous agent is uncertain. For example, there is evidence that *in vivo*, SAME levels are normally in excess of those required for methyltransferase reactions.^[23-25] Also, while SAME levels in various tissues, including brain and liver, can be increased by loading doses of exogenous L-methionine, this does not seem to increase the production of some methylated products, including potentially psychotogenic methylated indoleamines.^[24] Furthermore, although there have been some anecdotal, unpublished case reports suggesting the usefulness of methionine as an antidepressant, there are no published studies on this topic.

1.3.1 CNS Levels of SAME

SAME levels in the CSF of humans have been shown to increase significantly with daily intravenous injections of SAME 200mg for 14 days,^[17] as

well as with oral administration of SAmE 1200 mg/day for 4 to 8 months.^[26] This indicates that the compound crosses the blood-brain barrier.^[26,27]

Low CSF SAmE levels have been reported in varied disorders such as depression,^[26] subacute combined degeneration of the spinal cord (a demyelination disorder),^[28] and HIV infection.^[29] CSF SAmE levels were particularly low in patients with Alzheimer's dementia.^[26,30] This evidence contributes to the hypothesis of a possible disturbance of methylation in such patients.

1.3.2 Plasma Levels of SAmE

Plasma SAmE levels can be increased by both oral and parenteral administration of the compound.^[1,31,32] Recently, a significant positive correlation between increases in plasma SAmE level and the degree of clinical improvement was found in both depressed patients treated with SAmE and those treated with imipramine. Interestingly, an increase in plasma SAmE level occurred regardless of the type of treatment.^[33] Given the relatively small sample size in this study, its findings need replication in larger cohorts. In addition, the relationship between plasma and CNS SAmE levels is poorly understood, and the change in SAmE metabolism may simply reflect clinical recovery. Furthermore, these results contrast with previous trials that measured plasma SAmE levels, in which the degree of clinical improvement was not consistently found to correlate with changes in SAmE level.^[16,33]

1.3.3 Erythrocyte Methionine Adenosyltransferase Function

The activity of MAT, the enzyme that catalyses the formation of SAmE (see section 1.1.3), has been found to be decreased in patients with major depression and schizophrenia and increased in manic patients relative to healthy individuals.^[18,34,35] These reports also show a normalisation of MAT function after the administration of psychotropic medications,^[18,34,35] suggesting that SAmE may play an important role in regulating mood. Specifically, it is possible that CNS SAmE levels are decreased in depression and increased in mania.

1.3.4 SAmE and Folic Acid

There is neuropharmacological evidence for a relationship between SAmE and folic acid from experimental work in animals, and it has long been recognised that folic acid may have an important role in regulating mood.^[36-38] Rats maintained on a diet deficient in folic acid showed reduced brain SAmE levels, whereas supplementation of the deficient diet with folic acid restores SAmE levels to nondeficient control values.^[39]

2. Possible Clinical Utility of SAmE in Psychiatric Disorders

2.1 Schizophrenia

In 1952, Harley-Manson postulated that schizophrenia is due to a specific disorder of the adrenal glands, and that disturbances in transmethylation of normally occurring biogenic amines and the production of a mescaline-like compound might be involved in the pathophysiology of schizophrenia (see review by Osmond and Smythies^[40]). This idea led to investigations of adrenaline (epinephrine) metabolism in schizophrenia, which showed no differences in adrenaline metabolism between patients with schizophrenia and unaffected individuals.^[41]

A few years later, Smythies^[42,43] formulated the transmethylation and one-carbon cycle hypothesis of schizophrenia, which postulates that the 'biochemical fault ... might lie in the biochemical mechanism itself of transmethylation: namely the one-carbon cycle, in which methionine, *S*-adenosylmethionine (SAmE) and folic acid are involved – rather than any abnormally methylated products'.

Cohen et al.^[44] reviewed the results of 10 investigations based on this hypothesis and found that about 30% of patients with chronic schizophrenia developed a psychotic exacerbation after oral administration of methionine in combination with a monoamine oxidase inhibitor (MAOI). The rationale for using the MAOI was to slow the metabolic degradation of biogenic amines that might be formed as a result of transmethylation with methionine. It was felt that such slowing would increase

Table I. Summary of the double-blind studies of S-adenosylmethionine (SAME; ademetionine) in the treatment of depression

Reference	No. of patients	Duration of treatment (days)	Dosage of SAME (mg/day)	Route of administration of SAME	Results ^a
Placebo-controlled					
Barberi & Pusateri ^[54]	P 20 SAME 20	20	200	IV	SAME > P
Salmaggi et al. ^[55]	P 30 SAME 30	30	1600	PO	SAME > P
Fava et al. ^[56]	P 31 SAME 24	42	1600	PO	SAME ≡ P
Janicack et al. ^[57]	P 5 SAME 7	14	200-400 (days 1-3); 400 (days 4-14)	IV	SAME > P
Agnoli et al. ^[58]	P 10 SAME 20	7	45	IM	SAME > P ^b
Caruso et al. ^[59]	P 24 SAME 25	21	200	IM	SAME > P
Carney et al. ^[60]	P 17 SAME 15	14	200	IV	SAME ≡ P
Kagan et al. ^[61]	P 9 SAME 9	21	1600	PO	SAME > P
Comparisons with tricyclic antidepressants					
Bell et al. ^[62]	D 13 SAME 12	28	1600	PO	SAME ≡ D
De Vanna & Rigamonti ^[63]	IMP 11 SAME 11	42	1600	PO	SAME ≡ IMP
Bell et al. ^[64]	IMP 11 SAME 11	14	400	IV	SAME > IMP
Janiack et al. ^[57]	IMP 3 SAME 7	14	400	IV	SAME ≡ IMP
Mantero et al. ^[65]	IMP 15 SAME 16	21	75	IM	SMAe ≡ IMP
Monaco & Quattrocchi ^[66]	A 9 SAME 11	15	200	IV	SAME ≡ A
Miccoli et al. ^[67]	A or C 41 SAME 45	21	200	IV	SAME ≡ A/C
Scarzella & Appiotti ^[68]	C 10 SAME 10	15	250	IV	SAME ≡ C

a In all studies, efficacy was assessed using the Hamilton Depression Rating Scale.

b For depressed mood.

Abbreviations and symbols: A = amitriptyline; C = clomipramine; D = desipramine; IMP = imipramine; IM = intramuscular; IV = intravenous; P = placebo; PO = oral; > indicates significantly more effective than; ≡ indicates as effective as.

the level (and possibly the clinical effect) of any psychotomimetic that might be formed as a result of abnormal transmethylation.^[44] The authors concluded that, in light of the high frequency of symptoms and signs of organic brain disorder such as dementia and different unspecific neurological symptoms in these patients, the administration of

methionine does not seem to reproduce the symptoms of schizophrenia. However, blood levels of SAME have been reported to be low in patients with acute schizophrenia when compared with patients with chronic schizophrenia or depression, and healthy individuals.^[45] Unfortunately, these studies were conducted using diagnoses based on DSM-

II^[46] criteria for schizophrenia and other psychotic disorders, thereby including symptoms that would be now regarded as DSM-IV^[47] criteria for bipolar disorder.

2.2 Depression and Mania

2.2.1 Efficacy

Since Smythies^[42,43] first postulated abnormalities of the one-carbon cycle as one of the major causes of schizophrenia, evidence has arisen suggesting a causal link between affective disorders and the metabolism of methylation.

In 1973, a clinical trial with SAME first reported beneficial effects of the compound on depressive symptoms.^[48] These findings have since been supported by a number of open, noncomparative and double-blind, placebo-controlled studies that have evaluated the efficacy of SAME in the treatment of depression. Indeed, a recent meta-analysis of all the double-blind studies of parenteral and oral SAME has concluded that this agent is more effective than placebo and as effective as standard antidepressant drugs.^[49]

Several noncomparative trials showed marked improvement or remission of depression in patients given intramuscular or intravenous SAME.^[50-53] In various studies, parenteral SAME was generally equally or more effective when compared with a number of standardised treatments (primarily tricyclic antidepressants) [see table I].^[57,64-70] In addition, studies examining the efficacy of parenteral SAME compared with placebo showed SAME to be generally equal or superior to the effects of placebo (see table I).^[54,58-60,71]

For the past few years, data on the effectiveness of an orally administered stable salt of SAME have also been available. Preliminary open, noncomparative trials have shown the efficacy of this form,^[32,72,73] using dosages up to 1600 mg/day. Double-blind clinical studies found that oral SAME 1600 mg/day was as effective as imipramine 140 mg/day^[63] or desipramine 250 mg/day,^[62] and superior to placebo.^[55,61]

In contrast, we were unable to find any effect of oral SAME in a study that we conducted.^[56] How-

ever, in this study of 36 depressed outpatients, a formulation of SAME containing 400mg of the compound was used that differed from that used in other studies. Soon after completion of this double-blind study, the US Food and Drug Administration (FDA) requested all the US sites of clinical investigations of SAME to discontinue their studies because of technical issues regarding data on the dissolution of the 400mg tablets. We therefore postulated that the failure of oral SAME to produce effects significantly different from those of placebo in our double-blind study might have been due to the instability of the new preparation of this compound. Our suspicions were confirmed by an analysis of the content of the 400mg tablets of SAME by Trapp et al. (unpublished data). This showed the salt to be unstable, and about 50% of SAME had degraded into a material that probably contained the adenine nucleus and methionine.

2.2.2 Onset of Action

In contrast with most available antidepressants, which have a delayed onset of efficacy, the onset of the therapeutic effect of SAME is relatively rapid, with some patients showing a clinical response within a few days and most within 2 weeks.^[53,64]

A study by Torta et al.^[74] found that SAME, combined with a low dose of tricyclic antidepressants, was associated with an earlier improvement in mood than the tricyclic antidepressants alone. Similar results were found in a double-blind trial of daily administration of intravenous SAME or placebo combined with standardised antidepressant therapy.^[75] Clinical improvement was seen after 10 days in the groups receiving antidepressants and SAME, while it was not observed until 25 days after initiation of treatment in the groups receiving antidepressants and placebo. After 6 weeks, the 2 groups showed the same degree of clinical improvement.^[75]

Another double-blind study reported an earlier improvement in depressive symptoms among patients receiving imipramine and intramuscular SAME as opposed to the group receiving imipramine and placebo.^[76]

Overall, the use of SAME to shorten the onset of action of antidepressants could be of great clinical importance, particularly for severely ill inpatients.

2.2.3 Use in Comorbid Depression

Oral SAME has also been used successfully:

- as a treatment to relieve the symptoms of psychological distress during puerperium^[77]
- to reduce the psychological distress associated with detoxification in opioid-dependent patients^[78]
- to treat major depression complicating chronic alcoholism^[79]
- to reduce depressive symptoms in critically ill medical patients, in whom the use of standard antidepressant agents is relatively contraindicated.^[72]

Further studies are needed to confirm these preliminary observations of the efficacy of SAME in these populations.

2.3 Alzheimer's Disease

Reduced levels of folic acid and vitamin B₁₂ are frequently found among patients with dementia.^[8,80] Since these vitamins are closely involved in the metabolism of SAME and methylation (see fig. 1), it is not surprising that CSF SAME levels have also been shown to be significantly reduced in patients with Alzheimer's disease.^[26]

As several investigations in animals have indicated, continuous treatment with SAME may protect against the reduction in cell membrane fluidity and associated loss of dopaminergic and β -adrenergic binding sites seen with aging.^[2,9] Reduced membrane fluidity has been observed in patients with Alzheimer's disease, and this has been hypothesised to be involved in the pathophysiology of this disorder.^[81]

Clinical improvements were observed in elderly patients with impaired cognition and vigilance functions associated with dementia after 2 months of treatment with SAME.^[82] Other studies have shown that continuous treatment with oral SAME for 3 to 5 months leads to increased plasma and CSF SAME levels and improved mood, measures of cognitive function and the capability of mental

processing in patients with Alzheimer's disease.^[83,84] However, another study in demented patients showed no changes in cognitive function or mood state after 14 days of intravenous SAME.^[81]

3. Adverse Effects of SAME

The administration of SAME to psychiatric patients has been generally very well tolerated and the relative lack of unwanted adverse effects or toxicity is a major advantage in the treatment of affective disorders. However, there have been cases reported of increased anxiety,^[60] and SAME may precipitate mood transitions into a state of mania or hypomania in a few patients with bipolar depression,^[32,85] which could be a possible clinical concern with the use of the compound as an antidepressant. Furthermore, the occurrence of a manic episode was observed in a patient with no prior history of mania or hypomania after 19 days of oral therapy with SAME (1600 mg/day).^[61]

Most other known adverse events (i.e. insomnia, nervousness, lack of appetite, constipation, headaches, heart palpitations, nausea, dry mouth, sweating and dizziness) are reported to be mild and transient.^[1,8,53] SAME does not appear to have any hepatotoxic or anticholinergic effects.^[1]

4. Conclusions

SAME is a naturally occurring compound that has antidepressant effects (as supported by a number of double-blind studies), particularly as an parental form. The mixed results obtained with oral preparations have raised concerns about stability and perhaps bioavailability of this compound. Encouraging results from studies of the use of SAME in patients with Alzheimer's disease have suggested its usefulness in this population. SAME appears to have relatively few adverse effects and perhaps a relatively rapid onset of action.

Further investigations of the compound are required both in depression and dementia and should be highly encouraged to more firmly define the full clinical potential of SAME in psychiatric disorders.

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