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Research Overview

# S-Adenosyl Methionine in the Therapy of Depression and Other Psychiatric Disorders

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**ABSTRACT** S-adenosyl methionine (SAM) is a major methyl donor and as such exerts its influence on CNS function through methylation reactions, such as methylation of several catecholamine moiety-containing neurotransmitters, epigenetic changes through methylation of DNA, RNA, RNA-binding proteins and histones, and phospholipid methylation. Based on available evidence, SAM is currently recommended as a next-step (second-line) treatment option following inadequate treatment response to a first-line antidepressant. It shows significant promise in the treatment of pediatric and perinatal depression, as well as Alzheimer's disease, but to make this a recommendation further clinical trials are needed. SAM is safe to use in most patients, but is contraindicated in those with bipolar disorder. Concerns considering the possible increase of homocysteine levels (and cardiovascular complications) due to long-term SAM therapy need to be further addressed in clinical trials taking into account individual's ability to metabolize homocysteine and his/her folate status. Drug Dev Res 77 : 336–346, 2016. 

**Key words:** S-adenosyl methionine; depression; Alzheimer's disease; schizophrenia; bipolar disorder

## INTRODUCTION

S-adenosyl methionine (SAM) was discovered in 1953 by Giulio Cantoni and was described as the methyl donor formed from methionine and the adenosine moiety of ATP in a reaction catalyzed by methionine adenosyltransferase (MAT). As a major methyl donor SAM is involved in variety of biochemical reactions, making it the second most frequently used enzyme substrate (the first being ATP). Approximately 95% of SAM in the body is used for methylation and the remainder for the polyamine synthesis [Loenen, 2006]. SAM biosynthesis and metabolism is depicted in Figure 1. Therapeutic use of SAM has increased in the United States after the Dietary Supplement Health and Education Act was passed in 1994, which allowed the marketing of SAM as a dietary supplement. SAM is also sold as dietary supplement in India, but is classified as a prescription drug in Europe and Russia under several different brand names. As a dietary supplement it has been used for numerous indications, however, as a prescription drug it is only indicated in the treatment of depression, osteoarthritis and liver disease [AHRQ, 2002].

The first indication that folates and metabolically related compounds might have an influence on CNS and psychiatric status came from the coincidental observation that symptoms of depression and psychosis were more frequent in epileptic patients on anticonvulsant therapy than in general population.

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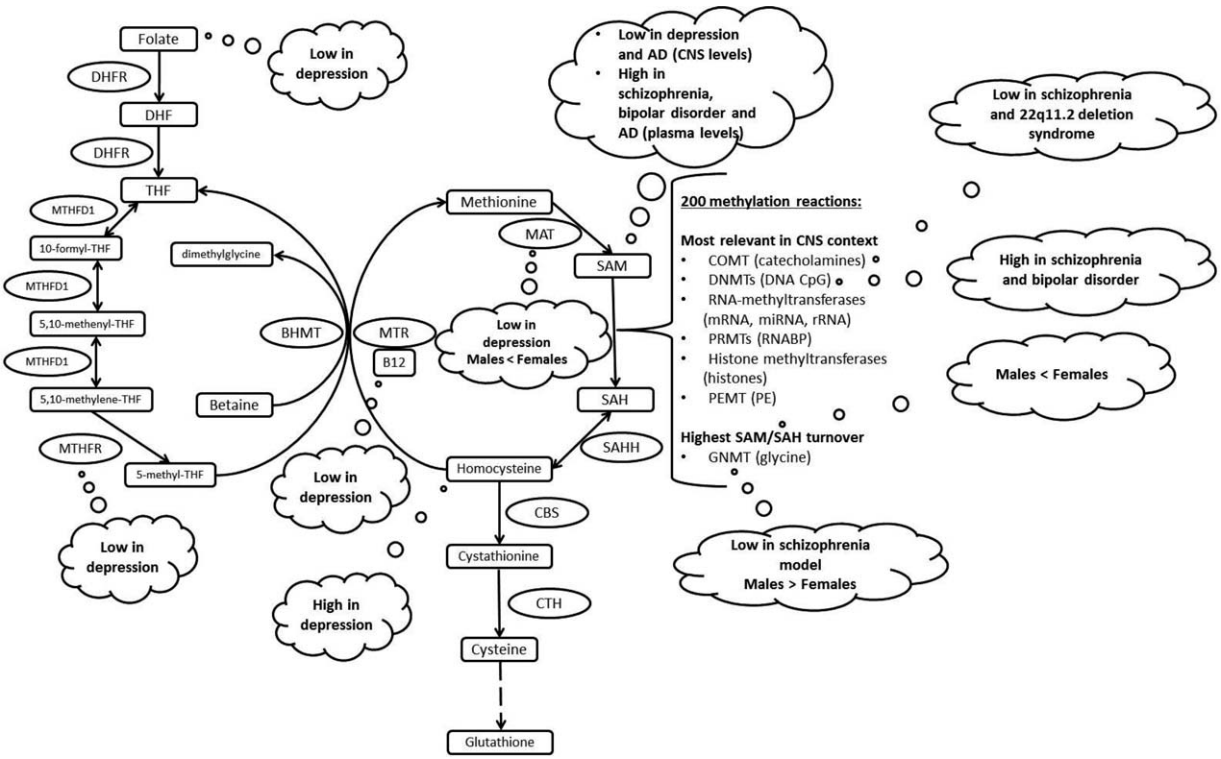


**Fig. 1.** SAM-related metabolic pathways. Enzymes are depicted by ovals and their substrates, products, and cofactors by rectangles. DHFR, Dihydrofolate reductase; THF, Tetrahydrofolate; MTHFD1, Methylenetetrahydrofolate dehydrogenase 1; MTHFR, 5,10- Methylene tetrahydrofolate reductase; BHMT, Betaine-homocysteine S-methyltransferase; MTR, Methionine synthase; B12, Vitamin B12; MAT, Methionine adenosyltransferase; SAM, S-adenosyl methionine; SAH, S-adenosyl homocysteine; SAHH, S-adenosyl-L-homocysteine hydrolase; CBS, Cystathionine-beta-synthase; CTH, Cystathionine gamma-lyase; COMT, Catechol-O-methyltransferase; DNMTs, DNA-methyl transferases; PRMTs, Protein arginine methyltransferases; RNABP, RNA-binding proteins; PEMT, Phosphatidylethanolamine *N*-methyltransferase; PE, Phosphatidylethanolamine; GNMT, Glycine *N*-methyltransferase; AD, Alzheimer's disease.

Further investigation revealed that anticonvulsants were associated low levels of serum folate [Maxwell et al., 1972) which was presumed to be responsible for the psychiatric disturbances. Between 1967 and 1990 numerous studies of depression, bipolar disorder and schizophrenia confirmed the connection between low folate status and those psychiatric diseases. Since the folate cycle is tightly interconnected with methionine recycling and SAM biosynthesis (Fig. 1), and due to its universal metabolic role as major methyl donor, SAM was also intensively investigated as a potential psychiatric drug beginning in 1970. Its efficiency as psychotropic agent was confirmed in numerous clinical trials and some mechanistic studies [Bottiglieri, 2013]. Although the influence of SAM on the CNS was demonstrated by several studies, the mechanism is still somewhat unclear, probably due to its complex nature. Studies indicate that the most probable mechanism of SAM's influence on CNS and its pathological states is through methylation reactions, the three most relevant being: (i) deactivation by methylation of several catecholamine moiety-containing neurotransmitters, which is catalyzed by catechol-O-methyltransferase (COMT); (ii) epigenetic changes through methylation of DNA, RNA, RNA-binding proteins (RNABP) and histones, catalyzed by DNA-(DNMTs) and RNA-methyltransferases, protein arginine methyltransferases (PRMTs) and other histone methyltransferases, respectively; and (iii) phospholipid methylation.

## INFLUENCE OF SAM ON THE CNS: COMT

COMT catalyzes the first step in a degradation pathway of the catecholamine neurotransmitters, dopamine (DA), noradrenaline and adrenaline. SAM is the enzyme cofactor and donates the methyl group to catechol. Besides catechol and SAM, the active site of the enzyme must also bind divalent magnesium for the reaction to be completed [Tsao et al., 2011]. The COMT gene is located on Chromosome 22q11, with the most common variant $Val^{158}Met$

(rs4680) in which single base G to A substitution results in a valine (Val) to methionine (Met) change at codon 158. This substitution reduces COMT activity, causing Met carriers to have higher DA levels in prefrontal cortex (PFC), a region critical for affect, decision making and several psychiatric disorders [He et al., 2012]. Actually, in the setting of stressful life events, carriers of Met allele had higher risk of poor decision making, which is the hallmark of depression, schizophrenia, and addiction disorders [He et al., 2012]. Furthermore, there is a decreased caudate volume in depressed carriers of Met alleles compared to healthy individuals with the same genotype. This effect was not observed in wild-type (Val/Val) individuals [Watanabe et al., 2015]. These changes in caudate volume may be due to the increased DA levels in PFC, which is the consequence of decreased COMT activity (caused by the presence of Met allele). Finally, serotonin can also act as an COMT inhibitor, due to the structural similarity of serotonin indole ring to the adenosine motif of SAM [Tsao et al., 2012]. Computational modeling, and in vitro testing showed that binding of serotonin to the COMT catalytic site inhibits SAM access thus preventing the methylation of COMT substrates [Tsao et al., 2012]. This could explain the synergy between the action of SAM and serotonin reuptake inhibitors (SSRIs) noted in some clinical trials of depression treatment, since both high intracellular levels of SAM (due to SAM administration) and low intracellular levels of serotonin (due to SSRI action) prevent binding of serotonin to COMT and its consequent inhibition.

## INFLUENCE OF SAM ON CNS: EPIGENETIC REGULATION

Another possible mechanism of SAM in the CNS may be involve epigenesis, as SAM is a crucial for methylation of key molecules involved in gene expression. The most obvious is DNA-methylation of CpG islands located in promoter and regulatory regions of numerous genes, thus controlling their transcription. Another SAM-regulated epigenetic process is RNA methylation. SAM depletion leads to mRNA hypomethylation and consequently low translation rates and disrupted splicing patterns. Also, hypomethylation of rRNA in the nucleus inhibits its cytoplasmic export, thus further inhibiting mRNA processing. Arginine methylation of RNABPs at arginine flanked by glycine (RGG) domains influences the processing of mRNA associated with specific RNABPs. This type of methylation is catalyzed by PRMTs, the activity of which is dependent on SAM levels [Trivedi and Deth, 2012]. Finally, SAM is also involved in the methylation of histone lysine residues, which can cause both repression and activation of gene expression depending on which lysine residue is involved [Boks et al., 2012]. Interestingly, several traditional psychiatric drugs can alter the epigenome and experimental compounds with epigenetic targets have been investigated as potential psychiatric drugs. For example, the antidepressants, amitriptyline and esciatlopram and the mood stabilizer, valproate can inhibit DNA methylation through the inhibition and/or down regulation of DNMTs. The SSRI fluoxetine inhibits histone methylation, while the antipsychotic, clozapine increases expression of histone methyltransferase Mll1 [Boks et al., 2012]. This indicates that concurrent administration of SAM or methionine rich foods might influence conventional pharmacotherapy of mental disorders through common epigenetic pathways. Therefore, SAM might be a good candidate for adjunctive or main therapeutic drug in the management of psychiatric disease [Peedicayil, 2012].

There is evidence that SAM epigenetically modulates the expression of genes coding for inflammatory mediators, for example, TNFα, IL-10, CCL2 and CCR2 [Pfalzer et al., 2014], and SAM has been reported to have anti-inflammatory effects via reduction of the expression of the pro-inflammatory cytokine TNFα through histone [Gobejishvili et al., 2011] and DNA methylation [Pfalzer et al., 2014] and of the chemo-attractant CCL2 and its receptor CCR2 through DNA methylation [Pfalzer et al., 2014]. Conversely, SAM increases expression of the anti-inflammatory cytokine, IL-10 through the DNA methylation [Pfalzer et al., 2014]. SAM's anti-inflammatory action might be important in the treatment of depression, as inflammation might play a role in its initiation and progression [Pace and Miller, 2009].

## INFLUENCE OF SAM ON CNS: PHOSPHOLIPID METHYLATION

Methylation of membrane-bound phosphatidylethanolamine by SAM increases cell membrane fluidity. This might alter the organization of lipid rafts and consequently modulate the function of numerous membrane-bound receptors and transporters [Papakostas et al., 2003].

## SAM IN THE THERAPY OF DEPRESSION

Major depressive disorder (MDD) is adisabling and prevalent condition, which influences the work and social performance of an individual. Only 30–40% of depressed individuals reach symptomatic

**TABLE 1. Selected Clinical Trials of SAM Efficiency in the Therapy of Depression, Comparing SAM Versus Placebo**

| Study | Number of enrolled patients | Study duration in days | SAM dose in mg/day | SAM application route | Efficiency |
|---|---|---|---|---|---|
| SAM versus placebo: | | | | | |
| [Agnoli et al., 1976] | 30 | 15 | 45 | IM | SAM > placebo |
| [Barberi and Pusateri, 1978] | 40 | 10 | 200 | IV | SAM > placebo |
| [Muscettola et al., 1982] | 20 | 15 | 150 | IM | SAM = placebo |
| [Caruso et al., 1984] | 49 | 21 | 200 | IM | SAM > placebo |
| [Carney et al., 1986] | 32 | 14 | 200 | IV | SAM = placebo |
| [Caruso et al., 1987] | 59 | 21 | 200 | IM | SAM > placebo |
| [Thomas et al., 1987] | 20 | 14 | 200 | IV | SAM = placebo |
| [De Leo et al., 1987] | 40 | 28 | 200 | IM | SAM > placebo |
| [Janicak et al., 1988] | 12 | 15 | 400 | IV | SAM > placebo |
| [Kagan et al., 1990] | 18 | 21 | 1,600 | PO | SAM > placebo |
| [Salmaggi et al., 1993] | 80 | 30 | 1,600 | PO | SAM > placebo |
| [Fava et al., 1992] | 55 | 42 | 1,600 | PO | SAM = placebo |
| [Mischoulon et al., 2014] (two site study): | 189 | 84 | 1,600 | PO | SAM = placebo |
| • [Sarris et al., 2014], Site 1 (59% males) | 144 | 84 | 1,600 | PO | SAM > placebo |
| • Site 2 (31% males) | 45 | 84 | 1,600 | PO | SAM = placebo |

Overall, SAM was found to be superior to placebo. However, some earlier studies found no benefit of SAM over placebo. All of these studies used low doses of IM or IV SAM (150–200 mg/day), with the exception of one that used 1,600 mg/day PO. The trials indicated that the minimum SAM therapeutic dose is 400 mg/day, which means that most of the early trials used suboptimal doses. Another reason for negative results in the earlier studies may reflect unstable formulations of SAM, which might contained no active ingredient. Finally, earlier studies enrolled small numbers of patients (less than 100), which decreased statistical power and might lead to ambiguous results.
IM, intramuscular; IV, intravenous; PO, per os.

remission after treatment with first-line antidepressants but many individuals experience residual symptoms, including cognitive impairment across multiple domains: attention, working memory, learning, processing speed, and executive functions. Thus, there is an increased awareness of the fact that cognitive remission might be the key element of functional recovery in MDD. Unfortunately, conventional antidepressants do not affect cognitive outcome. Therefore, the search for alternative adjunctive therapies of MDD is ongoing. One of the promising candidates is SAM, which exhibited cognitive improvement in MDD clinical trials [Bortolato et al., 2016].

SAM has been implicated in the pathogenesis of depression. Depressed patients have lower SAM levels in serum and cerebrospinal fluid than healthy controls. They also have lower MAT activity and higher incidence of activity lowering 677C > T variant in the 5,10-methylenetetrahydrofolate reductase (MTHFR) gene [Papakostas et al., 2003]. Both MAT and MTHFR are key enzymes in the biosynthesis of SAM. Furthermore, depressed elderly patients had increased levels of homocysteine and decreased levels of folate and vitamin B12 [Tiemeier et al., 2002] (Fig. 1).

There have been numerous studies comparing the efficiency of SAM versus placebo and/or conventional antidepressants in treatment of depression (Table 1) [Bressa, 1994; Bottiglieri, 2013]. Overall, the SAM was found to be more efficient as a therapeutic than placebo as assessed in a meta-analysis of early trials [Bressa, 1994]. However, a recent study that included larger number of patients than any of the previous studies, using 1,600 mg/day of SAM PO [Mischoulon et al., 2014] found no difference in the antidepressant activity between SAM and placebo. Reanalysis of data from two different sites, showed that at one of the two, SAM was more effective than placebo [Sarris et al., 2014]. Further analysis revealed that at this site the proportion of male patients was almost two times that at the other site, leading to a conclusion that SAM therapy of depression is more efficient in males than females, which was confirmed by statistical comparisons between sexes at both collection sites [Sarris et al., 2015]. This finding is intriguing, but not surprising in light of the results of healthy population study that males have a significantly lower SAM/SAH ratio, suggesting that SAM therapy might have a greater impact on men [King et al., 2012]. The reason for lower methylation potential in males is unclear, but there is some indication from animal studies that this could be due to the lower MAT [Oscarsson et al., 2001] and higher glycine *N*-methyltransferase (GNMT) [McMullen et al., 2002] activity in males (Fig. 1).

In studies comparing the antidepressant activity of SAM with that of other conventional

**TABLE 2. Selected Clinical Trials of SAM Efficiency in the Therapy of Depression, Comparing SAM Versus Other Anti-Depressant or SAM in Combination with Several SSRIs Versus Placebo in Combination with SSRIs**

| Study | Number of enrolled patients | Study duration in days | SAM dose in mg/day | SAM application route | Efficiency |
|---|---|---|---|---|---|
| SAM versus antidepressant | | | | | |
| [Miccoli et al., 1978], SAM versus Chlorimipramine or Amitryptyline | 86 | 21 | 200 | IV | SAM = antidepressant |
| [Scarzella and Appiotti, 1978], SAM versus Chlorimipramine | 20 | 15 | 250 | IV | SAM = antidepressant |
| [Monaco and Quattrocchi, 1979], SAM versus Amitryptyline | 20 | 15 | 200 | IV | SAM = antidepressant |
| [Bell et al., 1988], SAM versus Imipramine | 22 | 14 | 400 | IV | SAM > antidepressant |
| [Janicak et al., 1988], SAM versus Imipramine | 10 | 15 | 400 | IV | SAM = antidepressant |
| [Bell et al., 1990], SAM versus Desipramine | 28 | 28 | 1,600 | PO | SAM = antidepressant |
| [De Vanna and Rigamonti, 1992], SAM versus Imipramine | 30 | 42 | 1,600 | PO | SAM = antidepressant |
| [Delle Chiaie et al., 2002], SAM versus Imipramine (multicenter study)[a]: | 571 | 28/42 | 400/1,600 | IM/PO | SAM = antidepressant |
| • MC3 | 278 | 42 | 1,600 | PO | SAM = antidepressant |
| • MC4 | 293 | 28 | 400 | IM | SAM = antidepressant |
| [Mischoulon et al., 2014], SAM versus Escitalopram (two site study) | 189 | 42 | 1,600 | PO | SAM = antidepressant |
| • [Sarris et al., 2014], Site 1 (59% males) | 144 | 42 | 1,600 | PO | SAM > antidepressant |
| • Site 2 (31% males) | 45 | 42 | 1,600 | PO | not studied |
| SAM±SSRI[b] versus Placebo±SSRI[b] | | | | | |
| [Papakostas et al., 2010] | 73 | 42 | 1,600 | PO | SAM+SSRIs > Placebo+SSRI |
| [Levkovitz et al., 2012] | 46 | 42 | 1,600 | PO | SAM+SSRIs > Placebo+SSRI |

[a]MC3 and MC4 are being treated as separate studies, as they have different protocols and their results are reported separately in the same paper.

[b]Fluoxetine, Sertraline, Paroxetine, Citalopram, Escitalopram, Venlafaxine, or Duloxetine.

Overall, SAM was comparable to other antidepressants in a therapy of depression. In two trials SAM was slightly more effective than imipramine and escitalopram. However, these findings might be unreliable, as the first study enrolled very small number of patients ($N = 10$) and the second had a large proportion of males, which are presumed to have better response to SAM. Two trials demonstrated that SAM enhances the efficacy of SSRIs. Both found that the combination of SAM and SSRI was more effective than placebo and SSRI in the antidepressant nonresponders with MDD, with most prominent improvement in cognitive outcome.

IM, intramuscular; IV, intravenous; PO, per os.

antidepressants, including a large multicenter study with more than 500 patients [Delle Chiaie et al., 2002] (Table 2), SAM was at least equally efficient at treating depression as chlorimipramine, amitryptyline, imipramine, desipramine, and escitalopram.

Two recent studies investigated the efficiency of SAM as an adjunctive therapy to SSRIs in the treatment of MDD resistant to conventional antidepressants and demonstrated that SAM enhanced the therapeutic activity of SSRIs (Table 2). A meta-analysis comparing the efficiency of several add-on treatments in antidepressant nonresponders, found SAM equi-effective to antidepressants, and quetiapine-XR, but more effective than lithium [Turner et al., 2014]. A recent meta-analysis showed that SAM increases the efficiency of conventional antidepressants when used together in the treatment of nonresponsive MDD patients [Sarris et al., 2016]. One study demonstrated that the combination of SAM and betaine as an add-on therapy in depressed patients, who did not respond to conventional antidepressants, was more effective than SAM alone [Di Pierro et al., 2015]. Betaine is an alternative methyl group donor in re-methylation of methionine (a SAM precursor) from

homocysteine (Fig. 1). Thus, addition of betaine to SAM further increases SAM levels and decreases those of homocysteine. This finding is important, as there have been some concerns about SAMs safety, as its administration might lead to increased homocysteine levels.

Due to its favorable safety profile, SAM may be especially suitable for the treatment of depression in children, adolescents, pregnant women and nursing mothers. Only one small study has examined the effectiveness of SAM in pediatric depression. This included three adolescents (8–16 years) receiving SAM (400–1,200 mg/day) which improved the depressive symptoms in all participants and was well tolerated [Schaller et al., 2004]. Although these results were promising, no further studies in the pediatric population have been conducted as there is little scientific support for SAM use in pediatric depression and further studies are required. As for antenatal depression, no studies have evaluated the efficiency of SAM in its treatment. Five trials investigated the use of SAM in cholestasis of pregnancy and reported a good safety profile. In one placebo-controlled trial for postnatal depression SAM was superior to placebo in reducing symptoms [Deligiannidis and Freeman, 2014]. Further studies are needed before using SAM in the perinatal period.

SAM is currently not recommended as first-line monotherapy treatment for MDD but is recommended as a second-line treatment option following and inadequate treatment response to a first-line antidepressant [Cleare et al., 2015].

## SAM IN THE THERAPY OF SCHIZOPHRENIA AND BIPOLAR DISORDER

SAM levels are increased in the brain of schizophrenic (SCZ) and bipolar (BPD) patients, but not MDD patients. In fact, concomitant increases in SAM levels and overexpression of DNMT1 led to DNA hypermethylation, leading to decreased expression of critical genes associated with SCZ, for example, *RELN*, coding for reelin [Guidotti et al., 2007]. Reelin is glycoprotein that controls neural cell migration during embryogenesis and synapse structure and function in adults. Its levels are decreased in SCZ and BPD [Guidotti et al., 2016]. Increased SAM levels may reflect either increased transport of its precursor, methionine, through the blood-brain barrier or decreased activity of the methyltransferases involved in its degradation [Guidotti et al., 2007]. In the latter context, GNMT knock-out mice are used as a murine model of SCZ. GNMT has the highest SAM to SAH turnover rate among all known methyltransferases and is thus very important in controlling SAM levels [Yang et al., 2012]. It can be assumed that SAM treatment would exacerbate the symptoms of SCZ and BPD and that it only be safe in patients with decreased COMT activity which is typical in SCZ. Two studies of SAM therapy in SCZ and BPD are described in Table 3.

## SAM IN THE THERAPY OF ALZHEIMER'S DISEASE

The association between Alzheimer's disease (AD) and SAM levels are somewhat unclear. Older studies reported low levels of SAM in CSF [Bottiglieri et al., 1990] and brain [Morrison et al., 1996] of AD patients, while a more recent study found increased plasma SAM levels in AD patients [Selley, 2007]. Increased SAM levels were observed in triple knockdown APP/APLP1/APLP2 cell line, probably a consequence of decreased MAT2A expression [Schrotter et al., 2012]. The authors noted that apparent discrepancies between different studies may be due to SAM levels being regulated by two MAT, which are coded by two different genes: MAT1A and MAT2A that have opposing effects on SAM levels [Schrotter et al., 2012]. Taken together, the murine [Lee et al., 2012] and early human studies [Shea and Chan, 2008] demonstrate that SAM can positively affect hallmarks of AD (presenilin-1 expression, $\beta$- and $\gamma$-secretase activity, amyloid-$\beta$ generation, phospho-tau accumulation and acetylcholine synthesis), as well as its clinical manifestations (depression, cognition, and aggression). Recent clinical trials of AD using SAM as a part of nutritional formulation (NF) are presented in Table 3.

## SAM IN OTHER NEUROLOGIC AND PSYCHIATRIC CONDITIONS

The 22q11.2 deletion or DiGeorge syndrome is associated with high rates of SCZ-like psychosis, depression and attention deficit/hyperactivity disorder, probably due to a missing copy of COMT gene, which is located within the deletion region. SAM showed no improvement in psychiatric symptoms but was well tolerated (Table 3) [Green et al., 2012].

In 2006 a dramatic improvement in self-injurious behavior (SIB) in a patient with Lesch–Nyhan syndrome (LNS) after SAM administration was reported [Glick, 2006]. However, a subsequent study [Dolcetta et al., 2013] gave mixed results (Table 3)

## SAM STABILITY, DOSING, AND SAFETY PROFILE

Although pharmaceutical grade SAM is available in Europe, some brands marketed on internet may contain no or very little active ingredient, since SAM

**TABLE 3. Selected Clinical Trials of SAM Efficiency in the Therapy of Schizophrenia, Bipolar Disorder, Alzheimer's Disease, 22q11.2 Deletion Syndrome, and Lesch–Nyhan Syndrome**

| Study | Number of enrolled patients | Study duration in days | SAM dose in mg/day | Study design | Results |
|---|---|---|---|---|---|
| Schizophrenia: | | | | | |
| [Strous et al., 2009] | 18 | 56 | 800 mg/day | Double-blind Placebo-controlled Randomized | Improvement in aggression levels<br>Irritability in 2/9 patients in SAM group |
| Bipolar disorder: | | | | | |
| [Murphy et al., 2014] | 17 | 28 | 400-800 mg/day | Double-blind Placebo-controlled Randomized | No improvement of symptoms<br>No mania induction |
| Alzheimer's disease: | | | | | |
| [Chan et al., 2010] | 115 (healthy subjects, Phase I study) | 84 (+84) | 800 mg/day | Double-blind Placebo-controlled Randomized (open-label extension) | Improved cognitive performance |
| [Remington et al., 2015] | 106 (AD patients, Phase II study) | 84–168 (+168) | 800 mg/day | Double-blind Placebo-controlled Randomized (open-label extension) | Improved cognitive performance, with specific improvement in memory domain |
| 22q11.2 deletion syndrome: | | | | | |
| [Green et al., 2012] | 12 | 84 | 1,600 mg/day | Double-blind Placebo-controlled Randomized | No improvement of psychiatric symptoms, SAM well tolerated |
| Lesch–Nyhan syndrome: | | | | | |
| [Dolcetta et al., 2013] | 14 | 168 | 400–1,600 mg/day | Open-label Dose-escalation | 4/14 improvement of self-injurious behavior<br>10/14 worsening of self-injurious behavior (did not reach full dose) |

One study explored the use of SAM as treatment for aggressive behavior in schizophrenia in COMT deficient patients. Although there was some improvement in aggression levels, two of the nine patients had to discontinue SAM treatment due to irritability and the study had to be terminated early in the interest of patient safety. Although mania is a known side effect of SAM treatment, a randomized clinical trial on SAM use in refractory bipolar disorder was conducted, although with low doses of SAM. SAM was well tolerated, but there was no difference in the improvement of clinical symptoms between SAM and placebo group. More recent clinical trials of AD used SAM as a part of nutritional formulation (NF), consisting of 400 μg folic acid, 6 μg B12, 30 I.U.α-tocopherol, 400 mg SAM, 600 mg *N*-acetyl cysteine, and 500 mg acetyl-L-carnitine. NF was more effective for individuals at earlier than late stages of AD, which highlights the importance of early nutritional intervention. The treatment of 24 22q11.2 deletion and LNS patients with SAM was ineffective or partially effective, respectively. Since the response to SAM in LNS is unpredictable, very careful administration with monitoring over a 2 months period is recommended.

**TABLE 4. Selected Clinical Trials of SAM Safety Considering Elevation of Homocysteine Levels**

| Study | Number of enrolled individuals | Study duration in days | SAM dose in mg/day | Study design | Results | Other noted side effects |
|---|---|---|---|---|---|---|
| [Goren et al., 2004] | 15 (healthy individuals) | 28 | 1,600 mg/day | Open-label Single arm | No increase of homocysteine levels during and after SAM treatment | Mild gastrointestinal symptoms<br>One individual with family history of bipolar disorder had manic reaction |
| [Thompson et al., 2009] | 52 (healthy individuals) | 28 | 800 mg/day | Double-blind Placebo-controlled Randomized | No increase of homocysteine levels during and after SAM treatment | Small increase in ALT at week 2 in SAM group<br>Small decrease in total cholesterol at week 4 in SAM group |
| [Mischoulon et al., 2012] | 35 (MDD patients, who were SSRI non-responders) | 42 | 800–1,600 mg/day | Double-blind Placebo-controlled Randomized | No increase of homocysteine levels during and after SAM + SSRI treatment | Increase of SAH levels after SAM + SSRI treatment |

Two studies on healthy individuals and one on MDD patients found no increase of homocysteine levels during and after SAM therapy. Trial on MDD patients noted the significant increase of SAH in the SAM + SSRI arm.
ALT, alanine aminotransferase.

is rapidly oxidized when exposed to air. Therefore, tablet quality is very important, as is their storage (in individual blister packs) to achieve adequate efficiency. The absorption is optimal when SAM is taken 20 min before the meal. It should not be taken after 4:00 PM, as it can cause sleep disturbance [Bottiglieri, 2013].

The usual starting dose of SAM is 400 mg/day with increases every 5–7 days to a maximum of 1,600 mg/day (given in two doses). Improvement is usually seen within 10 days, but may take several weeks [Bottiglieri, 2013].

The most common side effects of SAM therapy are gastrointestinal and include nausea, diarrhea, and, rarely vomiting. Because it can induce mania, SAM is contraindicated in patients with BPD [Bottiglieri, 2013]. There was one case-report describing the suicide attempt by self-burning in a depressed patient 4 days after SAM initiation, although in this case there were several other potential risk factors present besides the SAM administration [Chitiva et al., 2012]. One of the greatest concerns regarding safety of SAM therapy is the possible increase in homocysteine levels (Fig. 1), which is associated with higher risk of cardiovascular disease. SAM safety studies considering homocysteine levels are presented in Table 4. Since little is known about the safety of S-adenosyl-homocysteine (SAH), and because neither of these studies included individuals with baseline increased homocysteine levels, further safety studies of SAM that take into account folate status are warranted. Namely, individuals with deficient trans-sulfuration and/or re-methylation pathways, as well as folate and/or vitamin B12 deficiency might not be able to eliminate excessive homocysteine and might be at risk of cardiovascular events when taking SAM for longer periods of time.

## CONCLUSION

SAM is a universal methyl donor, available either as a prescription drug or nutritional supplement, showing promise in the treatment of MMD and AD. For the treatment of MDD in adults it is recommended as a second-line therapy in first-line antidepressant nonresponders, while its potential use in perinatal and pediatric depression and AD therapy requires further study. SAM has a good safety profile, but is contraindicated in patients with BPD. Further studies to assess its influence on the cardiovascular system in the setting of genetic or nutritional SAM deficiency are also needed.

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