Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer’s Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

S-Adenosylmethionine (SAM or SAMe) Evidence Summary

Evidence Summary
There is little evidence that SAM would be beneficial for aging or Alzheimer’s disease.

**Neuroprotective Benefit:** In post-mortem Alzheimer’s tissue there is DNA hypomethylation, so theoretically SAM administration may improve methylation status. However, the effect on Alzheimer’s pathology or cognition is unknown.

**Aging and related health concerns:** Multiple biomarkers studies implicate altered one-carbon metabolism in cardiovascular disease (CVD) and lifespan, though no intervention studies suggest that SAM may be beneficial.

**Safety:** SAM is generally safe, though there are case studies that it can induce mania in certain individuals. Long-term studies have not been conducted.
**What is it?**

S-adenosylmethionine (SAM) is a methyl donor involved in the metabolism of methionine to homocysteine (see image below). This is also called one-carbon metabolism.

There are more than 50 SAM-dependent methyltransferases that methylate a broad spectrum of molecules including DNA, histones, phospholipids, and other small molecules. This can lead to changes in epigenetic regulation, lipid metabolism, or protein function. All SAM-dependent methyltransferase reactions release the by-product S-adenosylhomocysteine (SAH), which can then be metabolized to adenosine or homocysteine. SAH itself is a potent inhibitor of most SAM-dependent methyltransferases.

Homocysteine is reported to be a marker of vascular disease. However, SAH may be a more sensitive marker of vascular diseases, and, although folate and B vitamins reduce levels of homocysteine, they do not reduce levels of SAH (Xiao et al, 2015; Kerins et al, 2001).

In healthy individuals, plasma SAH levels increase linearly with plasma homocysteine levels (r=0.73), but there is no correlation between homocysteine and SAM. SAH effects are intracellular, and plasma SAH
may be due to the leakage of cellular SAH. Indeed, plasma SAH correlated with intracellular lymphocyte concentrations of SAH (r=0.81) and lymphocyte DNA hypomethylation (r=0.74) (Yi et al, 2000).

**Neuroprotective Benefit:** In post-mortem Alzheimer’s tissue there is DNA hypomethylation, so theoretically SAM administration may improve methylation status. However, the effect on Alzheimer’s pathology or cognition is unknown.

**Types of evidence:**
- One clinical study suggesting that SAM crosses the blood-brain barrier
- Three pilot studies in Alzheimer’s patients
- Eight biomarker studies suggested altered one-carbon metabolism in Alzheimer’s disease with mixed results
- Multiple preclinical studies

**Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?**

In an open label trial in four patients, Cohen et al (1988) reported that 14-day treatment with SAM (400mg IV) increased the fluidity of platelet cell membranes. Bottiglieri et al (1990) reported that oral treatment of Alzheimer’s patients with 1200mg/day (400mg 3x day) SAM nearly doubled levels of CSF SAM (suggesting it crosses the blood-brain barrier).

**Human research to suggest benefits to patients with dementia:**

Small open-label pilot studies have suggested possible cognitive benefits in some patients with Alzheimer’s disease, though there are no randomized controlled trials (Bottiglieri et al, 1994; Rudolph et al, 2011).

Post-mortem studies suggest that SAM and SAH levels are decreased in multiple brain regions of Alzheimer’s patients (by 60-80%) (Morrison et al, 1996). Additionally, post-mortem studies suggest greater methylation was associated with less amyloid in Alzheimer’s patients (Do Carmo et al, 2016). Theoretically, SAM may increase DNA methylation in Alzheimer’s patients, though it is unclear what effect this would have on Alzheimer’s pathology or cognition.
Other biomarker results are mixed. Dayon et al (2017) reported that plasma and CSF levels of SAH increased with cognitive impairment (CI) (CSF levels for SAH were 16.1nmol/l in patients with CI and 13.5nmol/l cognitively normal (CN) patients) and were correlated with CSF p-tau levels. There was no change in SAM levels, however (CSF for SAM = 179.4nmol/l vs. 188.2nmol/l, not significant, in CI and CN, respectively). Other studies (Obeid et al, 2007; Popp et al, 2009) also reported that aging and CSF p-tau correlated with CSF levels of SAH and a lower SAM:SAH ratio in patients with Alzheimer’s disease or various neurological conditions.

Linnebank et al (2009) reported that in 120 individuals, Alzheimer’s patients had lower CSF levels of SAM (193nmol/l vs. 207nmol/l) and higher levels of SAH (26.9nmol/l vs. 24.3nmol/l). SAH levels were no longer significant after adjusting for age and sex. SAM levels were no longer significant after adjusting for ApoE status. They further reported that CSF SAM levels were lower in ApoE4 patients. Therefore, it is not clear whether ApoE4 status, per se, or Alzheimer’s disease resulted in lower CSF SAM levels.

Contrary to the previous studies, Arlt et al (2012) reported that in 149 patients there was no significant difference in CSF SAM or SAH levels (though the results were numerically in the same direction as the previous studies), and a smaller study of 58 patients reported no difference in CSF SAM, SAH, or SAM:SAH ratio in individuals with probable Alzheimer’s (Mulder et al, 2005). Therefore, the relationship between SAM, SAH, and Alzheimer’s disease is unclear.

In cognitively healthy subjects, increased CSF AB42 and APP levels were associated with increased CSF SAH levels, suggesting increased production of amyloid (as opposed to Alzheimer’s patients where CSF AB42 decreases likely due to incorporation of AB42 into amyloid plaques) (Oikonomidi et al, 2016).

**Mechanisms of action for neuroprotection identified from laboratory and clinical research:**

In 36 aged dogs, 8 weeks of SAM supplementation (18mg/kg of SAM tosylate) improved activity (57% vs 9% of dogs in SAM and placebo group, respectively) and awareness (60% vs. 21% of dogs in SAM and placebo group, respectively). Additionally, the aggregate mental impairment score was reduced by more than 50% in 41% and 16% of the dogs treated with SAM or placebo, respectively (Reme et al, 2008).

In a meta-analysis of three Alzheimer’s mouse studies, Montgomery et al (2014) reported that SAM supplementation improved cognition in transgenic mouse models in the context of a folate-deficient diet. Lee et al, 2012 reported that SAM supplementation reduced amyloid plaques and p-tau levels in an Alzheimer’s model. These results were stronger when animals were treated at a younger age.
Hooijmans et al (2009) reported that SAM and SAH levels do not differ between Alzheimer’s and (wild type) WT mice at 8 months, but SAM levels drop with age in WT mice and SAH levels fall with age in both Alzheimer’s and WT mice. Do Como et al (2016) reported that there is DNA hypomethylation in the brain in an Alzheimer’s animal model, and low doses of chronic SAM administration improved DNA methylation, improved cognition, and reduced amyloid levels.

APOE4
Linnebank et al (2009) reported that in 120 individuals, Alzheimer’s patients had lower CSF levels of SAM (193nmol/l vs. 207nmol/l) and higher levels of SAH (26.9nmol/l vs. 24.3nmol/l). SAH levels were no longer significant after adjusting for age and sex. SAM levels were no longer significant after adjusting for ApoE status. They further reported that CSF SAM levels were lower in ApoE4 patients. Therefore, it is not clear whether ApoE4 status, per se, or Alzheimer’s disease results in lower CSF SAM levels.

Aging and related health concerns: Multiple biomarker studies implicate altered one-carbon metabolism in CVD and lifespan, though no intervention studies suggest that SAM may be beneficial.

Types of evidence:
• Four preclinical studies on lifespan
• One biomarkers study on aging
• One clinical study for homocysteine levels
• Eight biomarkers studies for CVD
• Two meta-analyses for osteoarthritis

Lifespan
Ogawa et al (2016) reported that stimulating the production of SAM in yeast extended lifespan in an AMPK-dependent manner. Importantly, this may not be due to production of SAM, per se, but could be due to consumption of methionine, as methionine restriction is reported to increase lifespan in model organisms. Evidence for this comes from a studies by Obata and Miura(2015), where increasing SAM catabolism (and possibly increasing methionine consumption) increased lifespan in flies and by Brown-Borg et al, 2009 where long-lived Ames mice had increased expression of genes related to SAM metabolism in the liver. Hansen et al, 2005 reported that inhibition of SAM synthetase (involved in the production of SAM) in worms increased lifespan, questioning whether increasing SAM levels would truly extend lifespan.
A cross-sectional study reported an increase in plasma SAM levels in women, but not men, with age in a Chinese population (Inoue-Choi et al, 2012).

**Cardiovascular disease**

Cross-sectional studies indicate that altered one-carbon metabolism may be an indicator of cardiovascular disease. Kerins et al (2001) reported that SAH was a more sensitive marker of cardiovascular disease (n=30 CVD; n=29 controls) than homocysteine. SAM levels were also greater in patients with CVD. The slight increase in homocysteine was non-significant, suggesting that although homocysteine may indicate CVD in large population studies, it may not be a valuable marker on an individual patient level. Plasma SAH concentrations are about 1/500\textsuperscript{th} that of homocysteine, and since homocysteine is a metabolite of SAH, a small change in homocysteine levels indicate large changes in SAH levels. Increased plasma SAH and a decrease in SAM/SAH ratio (but not plasma SAM) were reported in patients with atherosclerosis (n=32) (Castro et al, 2003) and in patients with a greater extent of coronary arterial stenosis (Huang et al, 2017). SAH levels were also correlated with leukocyte hypomethylation (Castro et al, 2003). Additionally, SAH levels were correlated with subclinical atherosclerosis in healthy patients (n=420) (Zawada et al, 2014).

SAH was associated with an increased risk of cardiovascular events in a prospective study over three years. In 1003 patients undergoing coronary angiography, increase plasma SAH (top quartile vs. bottom quartile) was associated with increased risk of a cardiovascular event after adjusting for covariates and plasma homocysteine levels (HR = 2.76; 95%CI 1.34-5.70). Homocysteine levels were not significant after adjusting for SAH (again suggesting that SAH is a better predictor of CVD than homocysteine). SAM levels were not associated with increased risk of CVD (Xiao et al, 2013).

Spijkerman et al (2005) reported that increased plasma levels of SAM were associated with increased endothelium-dependent flow-mediated dilation in 608 elderly individuals, even after adjusting for cardiovascular risk factors and homocysteine levels. Becker et al (2003) reported that increased levels of SAM in erythrocytes was associated with a decreased intima-media thickness in non-diabetic individuals but not in diabetic individuals, suggesting that higher levels of SAM were not indicative of protection in diabetic individuals.

Although biomarker evidence suggests an imbalance in one-carbon metabolism may increase the risk of CVD, there is no evidence that SAM supplementation can reduce levels of homocysteine. In 52 healthy
subject, Thompson et al (2009) reported that 800mg/day of SAM did not alter homocysteine levels; however, the effect on patients with high homocysteine levels is unclear.

**Preclinical studies for CVD**
Kim et al (2013) reported that SAM supplementation prevented endothelial dysfunction in high fat diet-fed rats and decreased apoptosis and endoplasmic reticulum stress in cultured human aortic endothelial cells.

**Osteoarthritis**
In a meta-analysis of 4 clinical trials, Rutjes et al (2009) reported small, non-significant benefits for pain reduction and no change for function in osteoarthritis patients taking SAM. However, the authors note that the trials were not large and the quality of reporting low. On the other hand, another meta-analysis (Soeken et al, 2002) reported that SAM is effective for function in osteoarthritis patients but not pain. The paper suggests the effects are comparable with NSAIDs.

**Safety:** **SAM is generally safe, though there are case studies that it can induce mania in certain individuals. Long-term studies have not been conducted.**

**Types of evidence:**
- 2 meta-analyses of RCTs

Meta-analyses of RCTs suggest that there are few, if any, side effects with SAM, though most of the studies were short in duration (Rutjes et al, 2009; Guo et al, 2015). Drus.com lists common side effects such as headache, dizziness, anxiety, gastrointestinal problems, and insomnia. SAM is reported to induce mania in some patients and should not be taken by individuals with bipolar disorders or a family history of bipolar disorders.

**Drug interactions:**
Drugs.com states that you should not use SAM if you are taking dextromethorphan (found in cough medicines), levodopa, or narcotic medicines such as meperidine. SAM can increase serotonin, so drugs that affect the serotonin system (such as antidepressants or MAO inhibitors) should not be taken with SAM, nor should drugs that may cause serotonin syndrome (such as tramadol).
Sources and dosing:
SAM is available as a supplement, and in clinical trials has been taken in divided doses of 800-1200mg/day. An enteric-coated supplement should be bought so it is released at the appropriate time in the GI tract.

Research underway:
No clinical trials for dementia. Some clinical trials are underway for other indications, primarily liver function.

Search terms:
Pubmed:
S-adenosylmethionine + alzheimer, cardiovascular, aging, osteoarthritis, lifespan, orthostatic, cancer [clinical trial]

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If you have suggestions for drugs, drugs-in-development, supplements, nutraceuticals, or food/drink with neuroprotective properties that warrant in-depth reviews by ADDF’s Aging and Alzheimer's Prevention Program, please contact INFO@alzdiscovery.org. To view our official ratings, visit Cognitive Vitality’s Rating page.