S-Adenosyl-L-methionine (SAMe)

Common Indications

- Neurological protection – depression, schizophrenia, Parkinson's disease
- Inflammatory conditions – osteoarthritis, fibromyalgia
- Hepatic disease

General Comments

SAMe is a naturally occurring molecule that is synthesized in the cytosol of every cell and is derived from two acids, methionine and adenosine triphosphate (ATP). Up to half of the daily methionine is converted to SAMe in the liver and it is metabolized to S-adenosylhomocysteine (SAH) and then homocysteine. It is linked with other methyl donors like betaine (choline), which is important for cell membranes, neurotransmission, cell signaling, and lipid metabolism[1]. It is a cofactor in three important biochemical pathways, including DNA, RNA, and proteins[2]. It is also involved in the synthesis of creatinine, acetylcholine, melatonin, glutathione (GSH), phospholipids, and adrenaline[3].

Benefits & Mechanism of Action

Antidepressant

- Since SAMe is a methyl donor it is involved in the metabolism and synthesis of CNS neurotransmitters, like noradrenaline, dopamine and serotonin[4,5,8]. It can increase serotonin, dopamine, and phosphatidylserine and improve these neurotransmitters binding to their receptors, therefore increasing the activity[7].
- At a dose of 800 mg/day for 2 weeks, there was significantly increased concentrations of 5-hydroxyindoleacetic acid in the cerebrospinal fluid, which means there is increased serotonin in the brain[5].
- Involved in the formation of phosphatidylcholine, which may be related to one of the mechanisms of action for depression[6].

Anti-inflammatory

- A 2002 meta-analysis reported that it appeared to be as effective as NSAIDs in reducing pain and improving functional limitation in patients with OA[14]. Side effects were also minimal compared to NSAIDs.

- Mechanism is unclear but is not thought to be mediated by prostaglandins
- Stimulates synthesis of proteoglycans through articular chondrocytes and produces a chondroprotective effect[9,10,12].
- In animal models, it has been shown to reduce TNF-alpha and fibronectin RNA expression[11].
- Animal models also suggest that serotonin-induced pain hypersensitivity is reduced, showing a potential analgesic mechanism[15].
- Showed reduced number of trigger points and areas of pain, improved mood, and reduced fatigue in patients with fibromyalgia[13].

Hepatoprotective

- Indirectly reduces oxidative stress in the liver since it serves as a precursor for GSH, which reduces the toxic effects of free radical molecules
- Decreased hepatic SAMe concentrations and associated liver lesions, like mitochondrial injury, can be corrected with SAMe supplementation[18].
- An animal study showed that it prevents damage associated with paracetamol toxicity[16].
- Found to minimize hepatic fibrogenesis by modulating nuclear factor-kappaB (NF-kB) signaling and inhibiting collagen processing[19].
- Critical role in progression of liver regeneration though enhancing GSH and polyamine synthesis, which is needed for cell proliferation and differentiation, and can help the recovery process after liver injury[17].
- Trials have shown benefit for various forms of liver disease including alcoholic cirrhosis, intrahepatic cholestasis of pregnancy and chemotherapy-induced NASH[20].

Anticancer

- Proapoptotic in hepatic carcinoma cells[21,23].
- Enhance hypomethylation of DNA and block mitogenic signaling in colon cancer cells in vitro[22].

Antioxidant

- Binds iron molecules in an inert form, which blocks iron-dependent interaction with molecular oxygen to generate reactive oxygen species (ROS) rather than by free radical scavenging[24].

Dose:

- Depression: 1200-3200 mg/day in divided doses

- Sometime started as 200 mg twice daily then increased to 400 mg twice daily on day 2 and then again to 400 mg three time a day on day 10 until taking it four times a day by day 20

- Osteoarthritis: 1200 mg/day in divided doses similar to titration schedule for depression but having a reduced dose of 400 mg/day for maintenance when a response occurs
- Fibromyalgia: 600-800 mg/day in divided doses
- Liver disease: 400-1200 mg/day in divided doses
- Parkinson's disease: 800-3600 mg/day in divided doses
- Migraine: 400-800 mg/day in divided doses
- Reducing aggression in schizophrenia: 800 mg/day (*under supervision*)

Administration

- Better absorbed when taken at least 20 minutes before breakfast and 20 minutes before lunch
- It can disturb sleep if taken after 4 pm[5]

Cautions & Side Effects:

- Generally well tolerated but the following adverse effects have been reported[28].
  - Nausea
  - Anxiety
  - Headache
  - Urinary frequency
  - Dizziness
  - Nervousness
  - Sweating
  - Pruritis

- Some interactions are suspected but not confirmed since there are no clinical studies available.
  - Levodopa
    - Could potentially reduce effectiveness of levodopa, which is typically used in Parkinson's disease
  - Thyroxine
    - Caution and monitoring needed
  - Betaine
    - Increases SAMe with a three-fold elevation of the activity of methionine adenosyltransferase
  - Monitoring homocysteine levels may be needed if using for long-term supplementation

- Avoid in patients with bipolar disease during the depressive phase since it has the potential to cause agitation and mania[25,26] as well as in patients with schizophrenia or schizoaffective disorder[27].

References:

Mechanism of action

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Antioxidant

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Adverse Effects

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