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SAMe: A dietary tonic for mind and body? Is it the long awaited wonder cure?

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Introduction

Although SAME, pronounced "Sammy", was made available in the U.S. only a year ago, it has already become the fourth most popular individual supplement in drugstore chains and retail stores. General Nutrition Centers (GNC), a major U.S. supplier of dietary supplements, reports that SAME is surpassing even popular supplements such as St. John's wort in sales (1). Despite its novelty in the U.S., SAME has been used as a prescription medicine for over 20 years in Europe to treat depression and arthritis. In the early 1970's, an Italian pharmaceutical company developed the means for producing SAME in vitro, however, FDA regulations posed a tough obstacle for distributing the compound in the U.S.

Last March, General Nutrition Centers and Pharmavite along with other U.S. drug companies began marketing SAME as an over-the-counter dietary supplement rather than as a pharmaceutical (2). Under the Dietary Supplement and Health Education Act of 1994, dietary supplements can be sold without virtually any regulation by the FDA as long as explicit therapeutic claims are avoided (3); SAME is being sold as a supplement to promote "joint health and emotional well being." The unregulated marketing of SAME and the limited number of research studies into the nature of this compound, considering the stringent conditions required by the FDA for drug approval, create concerns regarding the safety and efficacy of the supplement. Dr. Gilbert Ross of the American Council on Science and Health, a watchdog group, cautions consumers and asserts that drug companies are attempting to "flimflam the public into using untested remedies instead of FDA-approved pharmaceuticals.(2)"

Nevertheless, some U.S. physicians including Dr. Richard Brown, an associate professor of clinical psychiatry at Columbia University, have already begun recommending SAME to their patients. When interviewed by ABC News, Dr. Brown stated: "It's the best antidepressant I've ever prescribed...I've only seen benefits." "By and large, SAME is faster, better, and has hardly any side effects [compared to prescription anti-depressants]...In fact, it does a lot of good things in the body [like easing joint pain and producing an antioxidant that's helpful to the liver] (4). SAME has become so popular that Internet web sites, devoted solely to disseminating information on the supplement, have already been developed. "Sam-e-Support", a web site created by a user of SAME, contains a brief summary of current knowledge on the compound and various links to articles and Internet sites relating to SAME (5). Moreover, during the short period of time since SAME's release in the U.S., several books, written by authoritative figures, have been released. *Stop Depression Now*, co-authored by Dr. Brown and Dr. Teodoro Bottiglieri, a renowned Baylor University neuro-pharmacologist, cites the various research studies performed to support the beneficial effects attributed to SAME (6).

Although no exact figures are yet available due to its recent nature, it appears that SAME has established a lucrative industry not only for pharmaceutical companies but also popular health-book publishers.

SAME's Biochemical role in the body

SAME, known scientifically as S-adenosylmethionine, is not a hormone or an herb but an endogenous molecule formed from methionine (found in protein rich foods) and ATP. SAME's biological role has been associated with the essential process of methylation, a phenomenon that occurs thousands of times a second throughout the body. Methylation, a reaction that affects a wide a range of processes from fetal development to brain function, causes conformational changes in the shape of the methylated species and regulates gene expression, maintains cellular membranes, and modulates the action of various hormones and neurotransmitters, including serotonin, melatonin, dopamine and adrenaline. Despite many methyl donors having been identified to date, S-adenosylmethionine remains the most potent methyl donor ever discovered (7).

Once it donates its methyl group to the target molecule, SAME turns into S-adenosyl-homocysteine (SAH) which is rapidly metabolized to homocysteine, a compound entirely produced from the methylation cycle as it is absent from dietary sources. When homocysteine concentration increases, the above reaction shifts toward SAH, a potent competitive inhibitor of most methylation reactions (8). However, with the aid of several B vitamins (B6, B12, and folic acid), homocysteine can be converted to glutathione (Figure 1, pathway 2), an important antioxidant with neuro-protective properties (9). Alternatively, homocysteine can

be remethylated in the presence of B vitamins to regenerate S-adenosylmethionine (SAMe) (Figure 1, pathway 2). In other words, when B vitamins are present at sufficient concentrations, the byproduct of SAMe methyl transfer can be detoxified and SAMe molecules recycled. Homocysteine, at high intracellular levels, acts as a powerful pro-oxidant (toxin) and has been implicated in myocardial infarction and cerebral vascular accidents (strokes) as well as spina bifida in the fetus during pregnancy. Interestingly, abnormally high concentrations of homocysteine have also been associated with depression (8).

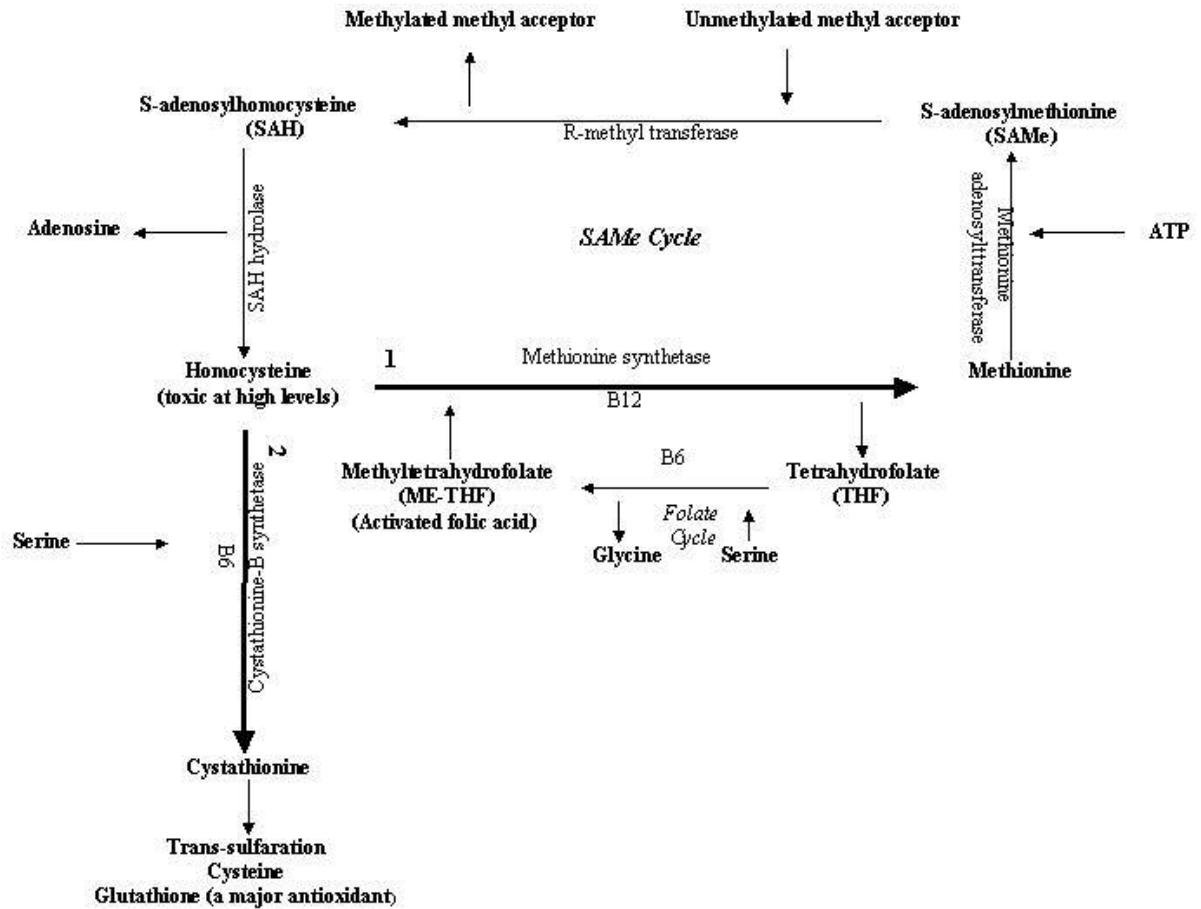


Figure 1. S-adenosylmethionine metabolic pathway. (Adapted from Bottiglieri and Hyland)

SAMe and Depression

Clinical Trials

A meta-analysis (analysis of pooled results) of a dozen placebo-controlled trials involving just under 500 patients has found SAMe to be "superior to that of placebo and comparable with that of standard tricyclic antidepressants [such as imipramine and nortriptyline]. (10)" Furthermore, a double blind trial comparing the effect of SAMe with desipramine (a tricyclic antidepressant) has shown that SAMe decreased extent of depression (based on depression rating scale scores) as well as if not more than desipramine. Interestingly, both SAMe and desipramine were found to have increased plasma concentrations of SAMe in patients who responded to either drug (11). Moreover, a multicenter study involving 195 patients has demonstrated that not only did SAMe administration perform similar to tricyclic antidepressants but it also worked with a more rapid onset of action (12). Whereas conventional antidepressants may take up to six weeks to show results, parenteral and oral SAMe can show their effect in less than a week (13).

Side Effects

In addition to its prompt action, SAME is being publicized for its remarkable safety profile. To date, the incidence of adverse effects with SAME has been similar to that with placebo. Studies have only reported a few cases of vomiting, nausea, diarrhea, headache and anxiety. On the other hand, conventional antidepressants including Prozac, tricyclics and MAO inhibitors have long been known to be associated with headaches, diarrhea, insomnia and sexual dysfunction. Although certain classic antidepressants can be harmful and even fatal in combination with other medications, no adverse interactions between SAME and other drugs have been found (14). However, use of SAME by patients who are prone to manic behavior such as those with bipolar disease is contraindicated as amelioration of depression can exacerbate mania in these patients (13).

Biochemical Explanation for Observed Effects

The biochemical basis for the mood enhancing effects of SAME remains poorly understood. It is known that monoamine neurotransmitters (serotonin, norepinephrine, and dopamine) play an important modulatory role in affect. Standard antidepressants exert their action by increasing synaptic transmission via these neurotransmitters in the CNS by increasing neurotransmitter release or by inhibiting neurotransmitter reuptake into the presynaptic neuron. Indeed, SAME has also been linked to the monoamine neurotransmitter metabolic pathway. This methyl donor can activate tyrosine hydroxylase, the enzyme essential for catecholamine (norepinephrine, epinephrine, and dopamine) synthesis. Moreover, studies of the rat brain have demonstrated increased turnover rate of monoamine neurotransmitters by SAME administration. Other studies have even indicated SAME's ability to inhibit monoamine reuptake and to regulate monoamine oxidase (MAO, a monoamine deactivating enzyme) (7). However, studies of depression associated with Parkinson's disease in rat models have found that SAME actually reduces tyrosine hydroxylase activity in the frontal cortex accompanied with tremor and hypokinesia (15). The contradiction observed in SAME's effect on tyrosine hydroxylase activity suggests that its biochemical role is site specific in the CNS; SAME can have excitatory or inhibitory effects on monoamine synthetic pathways. It is becoming clear, though, that the SAME-mediated methylation reactions are in fact involved in monoamine metabolism. Inhibitors of MAO have been shown to increase SAME levels in the CNS. (16)

In addition to controlling monoamine neurotransmitter metabolism, SAME is believed to have the ability to regulate neurotransmitter receptor density. It has been hypothesized that by methylating the phospholipids of the plasma membrane, SAME can increase membrane fluidity, a process which allows the receptors to move and change freely in response to chemical signals. The reduction in muscarinic receptors in the striatum and hippocampus of aged rats was remediated following administration of SAME (7).

SAME and Arthritis

If there was ever a drug whose alleged beneficial effects were too good to be true, SAME would make a strong candidate for one. This dietary supplement has not only been reported to act as a potent antidepressant, but it has also been used as an anti-inflammatory and as a pain medication by patients suffering from arthritis. Out of the few clinical trials undertaken to evaluate the relationship between SAME and palliation of arthritis-associated complications, a double blind study published over 10 years ago with over 700 subjects has shown that over a period of 30 days, SAME was as effective as naproxen (a standard anti-inflammatory, pain medication), and both medications were significantly more effective than the placebo. In addition, SAME and the placebo had fewer side effects than naproxen (gastrointestinal tract damage) (17).

Another study, released that same year, has demonstrated that SAME may actually aid in slowing the progression of osteoarthritis (characterized by degeneration of joint cartilage) by increasing the synthesis of proteoglycans, extracellular matrix components that are needed for cartilage repair. As noted previously, once SAME donates its methyl group to a substrate, homocysteine is generated. Homocysteine which can be toxic is removed via two different pathways. One of these pathways which forms glutathione (Figure 1, pathway 2), also produces sulfate groups that participate in proteoglycan synthesis (18). Thus, the believers

of SAME's therapeutic effects in arthritis hold that SAME diminishes the pain and inflammation and even helps restore joint health and yet doesn't trigger the severe side effects caused by non-steroidal anti-inflammatory drugs such as aspirin.

What's Next: Challenges To Be Overcome and Uncertainties To Be Resolved

Although the few studies published indicate promising results (therapeutic effect at low doses, 100-200 mg daily, with minimal side effects) for treatment of depression by SAME, their findings can only be considered preliminary at best. The clinical trials have been too small in sample size and too short in duration of study relative to standards required by the FDA for drug approval. Ideally clinical trials of antidepressant drugs should be at least 6 weeks long, since it can take several weeks for the medication to produce results and sustained effectiveness cannot be adequately evaluated at shorter durations (14). Statistically, as the size of the clinical trials increases, the potential adverse side effects of SAME are more likely to surface. Therefore, the antidepressant effects of SAME may not prove to be as encouraging as currently thought.

The major studies on the efficacy of SAME as a therapeutic agent for arthritis, have been short-term and small in sample size (13). The increasing popularity of SAME among the American population has urged the Arthritis Foundation to make a full statement clarifying its current position on the issue: "The Arthritis Foundation believes that SAME is an unproven remedy, but one that is an interesting and promising substance... [However] Arthritis Foundation medical experts feel there is sufficient information to support the claim that SAME provides pain relief...[But] the Foundation has no scientific evidence to support the company's claims that the supplement contributes to 'joint health'(19)". Thus, future clinical trials with larger sample sizes and longer durations, in addition to basic science research studies are necessary to make solid and conclusive statements regarding SAME.

Furthermore, there is increased concern that patients currently under prescription medication for severe depression with suicidal inclinations may start to substitute their medication with SAME or cause dangerous drug interactions by making various SAME-medication combinations. Also, reports indicate that formulas for SAME synthesis are not standardized. The two formulas available in the U.S. exhibit variable stability and reliability. The heterogeneity of the product as well as uncertainty regarding the optimal dosage, make unregulated use of SAME by the public even more disturbing (13). To prevent potential disasters, the FDA needs to take a more active part in overseeing use of SAME and other dietary supplements.

In the meantime, many American consumers will find the reported beneficial effects of SAME on joint health and mental wellbeing sufficiently appealing for use despite the absence of concrete and rigorous scientific data on its efficacy and safety. Although, SAME may prove to be a powerful tool against depression and arthritis, its therapeutic profile can be ethically explored only if the consumers are adequately informed about the potential dangers of using SAME. Healthcare professionals will undoubtedly play an important role in educating the public about SAME and other new dietary supplements whose marketing is loosely regulated by the FDA, and counseling patients on the possible risks and benefits associated with innovative yet experimental therapies.

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