The Therapeutic benefits of S-adynosylmethionine for Depression, Osteoarthritis and Longevity: A Literature Review

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A senior research project submitted in partial requirement

for the degree Doctor of Chiropractic

August 11, 2011

Abstract

Objective: This article provides a summary of the current literature associated with S-adenosylmethionine (SAMe) as well as providing an explanation of how SAMe is used effectively for certain ailments such as longevity, osteoarthritis, and depression. The Emphasis of this literature review discusses the biochemistry of SAM-e as well as comparing supplementation of SAM-e to traditional allopathic treatments for depression. Finally, recommendations for usage and benefits will be made based upon review of the documented information.

Data Collection: A computer search of PubMed, Google Scholar, and the Logan College of Chiropractic Library, amongst other sources, for articles containing relevant information on SAMe and its effects on longevity, osteoarthritis and depression. Information was sought concerning usage for these ailments individually and concurrently where available. Literature was included which was associated with the analysis of the effectiveness of the usage and outcomes. Referenced sources were identified from the individual searches and from accumulated review of related literature. PubMed and Google Scholar searches were restricted to sources from the past ten years and generated over 40,000 articles on the topic of SAMe on its own, but fewer than 1,500 when paired with any ailment.

Conclusion: A consensus of thousands of articles consisting of clinical trials, controlled studies, retrospective analyses, and literature reviews supports the use SAM-e for ailments such as Alzheimer's Disease, osteoarthritis and depression. Emerging evidence suggests promise in the efficacy of SAM-e for treating mild to moderate depression as well as reducing the symptoms associated with osteoarthritis and even retarding accelerated aging. However, ongoing research on the use of SAM-e for bodily function and the subsequent alleviation of particular ailments and pathology is needed.

Key Indexing Terms: S-adenosylmethionine, Methlyation, Transmethlyation, depression, osteoarthritis, Alzheimer's disease, Serotonin, Norepinephrine, Vitamin B, Folate

INTRODUCTION

The use of complementary and alternative medicine has become increasingly popular among the general public over recent decades throughout the industrialized world, including the United States. Physicians from all allied health professions, therefore, must begin to appreciate the potential benefits as well as understand the evidence-based research, which may support the use of a non-pharmaceutical therapy. One such therapy, which has gained popularity in recent years, has been S-adenosylmethionine also known as SAM-e (1).

SAM-e is a naturally occurring molecule present in all living cells. It is used within the human body as a major methyl group donor. (2) The methyl group attached to methionine within SAM-e is chemically reactive. This allows donation of this group to an acceptor substrate in a process known as transmethylation. Transmethylation is an organic chemical reaction in which a methyl group is transferred to another compound (3). In order to sustain sufficient reaction rates during metabolic stress, there needs to be a recovery of methionine from homocysteine. This reaction requires adequate levels of vitamin B12 and folic acid. Methyl tetrahydrofolate delivers methyl groups to form the active methyl form of vitamin B12, which is required for this conversion (2). Other important biochemical reactions that require methylation include the metabolism of lipids and DNA (2).

In the United States and Canada, SAM-e is sold as a nutritional supplement. It is also marketed under the Gumbaral, Samyr, Adomet, Heptral and Admethionine brand names as prescription drug approved in Russia, Italy and Germany. Research suggests that methylation declines with age, and therefore, supplementation may prove beneficial (8). Other research has indicated that taking SAM-e on a regular basis may help fight depression and osteoarthritis and may even provide anti-aging benefits (5). Despite the wide variety of anti-depressants available for the treatment of major depressive disorder and bone density enhancing pharmaceuticals, these allopathic therapies do not always work for everyone and are often accompanied by side effects. The interest in nutritional supplementation and alternative treatment is creating a need for more research to evaluate the effectiveness of these therapies.

DISCUSSION

S-Adenosylmethionine is a co-substrate involved in methyl group transfers. G.L Cantoni first discovered SAM-e in Italy in 1952. This organic compound is made from adenosine triphosphate, more popularly known as ATP, as well as methionine by methionine adensoyltransferase. Transmethylation, transsulfuration, and aminoproylation are the metabolic pathways that use SAMe (10). Methylation protects our DNA and repairs damaged DNA. It also switches DNA on and off at the right time to maintain health. Methylation is necessary for the production and removal of neurotransmitters including dopamine, serotonin and norepinephrine to maintain neurologic homeostasis (12). Although these anabolic reactions occur throughout the body, most SAMe is produced and consumed in the liver (8).

The methyl group attached to the methionine sulfur atom in SAMe is chemically reactive. This allows for the donation of this group to an acceptor substrate in transmethylation reactions. More than forty metabolic reactions involve the transfer of a methyl group from SAMe to various substrates such as nucleic acids, proteins and lipids (3). These reactions that produce, consume and regenerate SAMe are called the SAMe Cycle. In the first step of this cycle, the SAMe dependant methylases use SAMe as a substrate to produce S-adenosyl homocysteine. This is hydrolyzed to homocysteine and adenosine by adenosylhomocysteine hydrolase and the homocysteine is recycled back to methionine through the transfer of a methyl group from 5-methyletrahydrofolate, by one of the two classes of methionine synthases. This methionine can then be converted back to SAMe completing the cycle (2).

As stated previously, SAMe is required for cellular growth and repair. It is also involved in the bioysnthesis of several hormones and neurotransmitters that affect mood, such as dopamine and serotonin. Methyltransferases are also responsible for the addition of methyl groups to the 2-hydroxls of the first and second nucleotides next to the messenger RNA. Once SAMe donates its methyl group to choline, in the formation of creatine, carnitine, DNA, tRNA, norepinephrine, and other compounds, it is transformed into S-adenosylhomocysteine (2). Under normal

circumstances, homocysteine, in the presence of vitamin B6, vitamin B12 and folic acid, which are SAMe's main co-factors, will eventually be converted back into methionine, SAMe, cysteine, glutathione, and other useful substances (20). However, if adequate amounts of these vitamins are not present, SAMe may not break down properly. As a consequence, the full benefits of SAMe will not be obtained, and homocysteine may increase to unsafe levels. Small studies have not shown a consistent effect of SAMe on homocysteine levels, but more research is needed.

High levels of homocysteine have been associated with atherosclerosis, as well as an increased risk of heart attacks, strokes, liver damage, and possibly Alzheimer's disease. Therefore, Vitamin B supplements are often taken along with SAMe. These vitamins help metabolize the homocysteine into other useful compounds (4). Therapeutic uses of SAMe have increased as dietary supplements have gained in popularity, especially after the Dietary Supplement Health and Education Act was passed in 1994. This law allowed the distribution of SAMe as a dietary supplement, and therefore allowed it to bypass the regulatory requirements for drugs of the Food and Drug Administration (11).

Although SAMe has shown to be helpful to many biological systems, there are some side effects. Some of these effects include gastrointestinal disorder, dyspepsia, anxiety, headache, psychiatric, insomnia, allergy and rashes. Long-term effects are unknown. SAMe is a weak DNA-alkyling agent, and may act as a weak carcinogen. Other possible side effects include insomnia, meaning this should be taken in the morning. Other mild side effects include lack of appetite, constipation, nausea, dry mouth, sweating, and anxiety/nervousness. Some users report increased anxiety with as little as 50 mg/day. Special precautions should also be taken when using SAMe with dextromethorphan, meperidine, pentazocine,cyclobenzaprine, or tramadol. (19)

Depression: More than 20 million Americans suffer from depression. The use of antidepressants has tripled in the last decade. In 2006, expenditures on antidepressants soared to over $1.9 billion (15). Antidepressants work to normalize brain chemicals called neurotransmitters, most notably serotonin and norepinephrine while others target another neurotransmitter called dopamine (22). Research behind these three neurotransmitters suggests

that they are important for mood regulation but admittedly the scientific researchers say that they are unaware as to how they work (22). Medications alter biochemistry in a way that no other naturally occurring material that is ingested does. Medications have side effects and the ways in which antidepressants affect an individual are varied.

There isn't an individual who ever lived that has not suffered emotional pain. The amount of pain endured varies widely between individuals and is guided by society and perception. The underlying motivator behind every human action is the pursuit of happiness and when that happiness is disturbed or disrupted suffering ensues. Quickly, the human mind creates strategies to absolve their suffering and return to the preferred uplifted state. Drug companies throughout the 20th century have created a powerfully lucrative business that attempts to reverse the symptoms of depression. Selective serotonin reuptake inhibitors (SSRI's), serotonin and norepinephrine re-uptake inhibitors (SNRIs), tricyclics and monoamine oxidase inhibitors (MAOIs) are among the most popular classifications of antidepressants. Lately there has been a growing trend toward prescribing two antidepressants which, in some studies, have shown an increase effectiveness than when taking only one prescription. The National Institute of Mental Health (NIMH) – funded research has shown that patients who did not get well after taking a first medication increased their chances of becoming symptom-free after they switched to a different medication or added another medication to their existing one (22).The NIMH goes on to say within the same article, quite interestingly that “Some individuals, such as those with chronic or recurrent depression, may need to stay on the medication indefinitely (22). Most patients who take antidepressants either do not respond or have only a partial response to the medication (9). Some studies which were conducted by the Food and Drug Administration (FDA) revealed that the risk of suicide among children and adolescents who were prescribed antidepressant medication increased two-fold as compared to those taking a placebo (22). This information prompted the FDA, in 2005, to adopt a “black box” warning-label on all antidepressant medications to alert the public about the potential increased risk of suicidal thinking or attempts in children and adolescents taking antidepressants. This level of warning is the most serious type of warning on

prescription drug labeling (22). It is tragically ironic that one of the most common symptoms of taking an antidepressant is a worsening of depression and suicidal thinking and behavior. Commercials and advertisements are no longer bashful about hiding these facts either and yet the pharmaceutical sales keep soaring exponentially. Fortunately, viable alternative options are available.

Many studies have been done with the effectiveness of SAMe on depression. In 1994, Dr. Bressa from Italy concluded that, "The efficacy of SAMe in treating depressive syndromes and disorders is superior to that of placebo and comparable to that of standard tricyclic antidepressants. Since it is a naturally occurring compound with relatively few side-effects, it is a potentially important treatment for depression." (16) It was also tested in the United States at Irvine Medical Center, where after a four-week trial 62% of the patients who were treated with SAMe significantly improved. In accordance, only 50% of the patients who were treated with Desipramine showed any improvement. Another study done at Massachusetts General Hospital showed that with six-weeks of SAMe, 43% of patients had complete remission of their symptoms and 50% of them saw their symptoms improve when Prozac, Paxil, and Zoloft showed no improvement at all (16).

Depression has often been linked to a decrease in the amount of serotonin or norepintephrine in the brain. With SAMe being a key factor in the creation of these neurotransmitters, being deficient would likely be a cause for the decrease in concentrations. As stated earlier, SAMe acts as a methylation donor and works in conjunction with vitamin B6, B12 and the folic acid pathways for a multitude of cellular processes. There is an unremarkable amount of evidence that links low folate, B12, and B6 levels to depression and mood disorders (15). One study in the American Journal of Psychiatry found that 27 percent of severely depressed woman over the age of 65 were B12 deficient. This was found not by blood levels of B12, but by the functional indicator of B12, methymalonic acid. (17). An overwhelming amount of evidence suggests that ingesting vitamins and nutrients associated with the transmethylation processes of

the body have a significant impact on maintaining neurobiological homeostasis, thereby creating an environment conducive to normal cognitive function.

Osteoarthritis: SAMe helps support the incorporation of sulfate groups into proteoglycans, which help maintain cartilage and protect joints (21). Some studies have suggested that SAMe possesses anti-inflammatory and tissue-healing properties that may help protect the health of joints, and perhaps may lessen pain. It is quite possible that it may be useful for some people with arthritis. A deficiency of SAMe in the joint space can cause a decrease in the cartilage, which can lead to osteoarthritis. A study done in Germany reported that SAMe is capable producing improvements in the structure and function of cartilage in joints affected by osteoarthritis (4). Another study shows that in comparison to cyclyooxygenase-2 (COX-2) inhibitors for pain control after the second month there was no significant difference in pain reduction (21).

Against placebos in eleven different studies SAMe proved to be more effective in the reduction of pain with osteoarthritis. Also, it proved to be just as effective as NSAIDs but with less side effects (21). Though these are good results, SAMe may prove to be effective not because it is helping the pain, but decreasing the depressive symptoms associated with the pain (18). There has not been enough research done with SAMe and osteoarthritis to be certain how it actually works in the reduction of joint pain, but it is proving to be a very new and effective method (18). In addition to this effect, SAMe has also demonstrated some mild pain-relieving and anti-inflammatory effects in animal studies. All of these effects combine to produce exceptional clinical benefits.

One study has suggested that sublingual ingestion of SAMe achieves peak plasma concentrations 3 to 5 hours after ingestion of an enteric-coated tablet (400–1000 mg). The half-life is about 100 minutes. It may require up to one month for it to reach full effectiveness in treating osteoarthritis (4).

Longevity: Since the dawn of time, humans have been on a quest to find something that will enhance their vitality and prolong their life. One very important aspect of maintaining a vital, long and enriched life is maintaining clear cognitive function. Some studies have suggested that SAMe has anti-aging properties that help to retard the on-set of mental illness such as Alzheimer's disease (9). The idea that psychiatric or neurological diseases like depression, anxiety and Alzheimer's can be effectively treated, not by administering psychoactive medication, but by altering dietary and lifestyle influences and repairing the body's systems, which affect the entire Body-Mind system in which the brain functions, is resisted by conventional psychiatry and neurology (15).

Initially, a line of evidence suggested that abnormally low levels of endogenous SAMe may play an important role in the development of Alzheimer's disease and that SAMe may therefore have therapeutic potential in the treatment of Alzheimer's disease. However, further research has indicated this effect is likely due to vitamin B12 deficiencies, which cause neurologic defects through one-carbon transfers with folate (10). Severely low levels of SAMe have been found in the cerebrospinal fluid and in all brain regions of Alzheimer's disease patients examined (10). Preliminary research suggests SAMe may have therapeutic potential in treating Alzheimer's disease patients and a recent study using a mouse model of AD found that supplementary SAMe prevented oxidative damage and cognitive impairment.

Most elderly people are at a high risk for being deficient in vitamin B12 and folate, which is due to low hydrochloric acid production. This allows for the re-methylation of homocysteine to form methionine, which is subsequently converted to SAMe. An increasing amount of evidence supports a role for folate in improving cognitive function and reducing the incidence of Alzheimer's disease (20). Several studies have shown associations between low folate levels and corresponding elevated levels of homocysteine concentrations and cognitive dysfunction. "It is suspected that the mechanism by which folate is associated with mental illness involves its' role in the synthesis of SAMe which is used for adequate methylation of neurotransmitters, phopholipids or myelin in

brain tissue, or the potential ability of elevated homocysteine to cause vascular disease that may result in brain ischemia" (20).

Conclusion:

After review of many articles, the effects of SAMe are clear. SAMe is a natural co-factor that helps with methlyation processes (2). These processes are very important to the human body because without these, there are consequences. These consequences can be Alzheimer's disease or depression just to name a few. Interestingly, current neurological research suggests that depression decreases cortical thickness in the brain and dramatically increases the chances of Alzheimer's disease. Research has shown that supplementing with SAMe can help reduce the incidence of these two rampant diseases. Research also suggests that vitamin deficiencies associated within trans methylation processes can also lead to a decrease in the amount of SAMe, which would have the same negative effects on the body (20). With vitamin B12 and folate being two of the main co-factors in the production of SAMe, it is very important that people are getting enough of these supplements as well.

Depression may be a very complex diagnosis, but with the help of SAMe, the solution may be very simple. Ongoing and continued research is necessary to further support SAMe as an efficacious supplement in response to a nation in a depressive epidemic. SAMe may prove to be one answer for those who struggle daily and may also enhance the quality of life to those who are already attempting to live well.

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