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## REPORT

## A New Era for SAME



The results are officially in: S-adenosyl-methionine (SAME) is potentially one of the safest and most effective treatments for depression, arthritis, liver disorders and a host of other diseases prevalent in advancing age.

While the United States is often at the forefront of pharmaceutical innovation, it frequently lags behind European nations in its understanding of the therapeutic impact of nutritional supplements. To sufferers of depression, joint and liver disease one such governmental lapse has been in recognizing the multiple benefits of SAME.

After years of being touted by European physicians and researchers-as well as the Life Extension Foundation itself - the U.S. Department of Health and Human Services has completed a meticulous examination of previous research studies and clinical trials. The official proclamation is that SAME has demonstrated proven efficacy in the treatment of several common disorders and is virtually free from side effects.<sup>1</sup>

In this article we discuss the therapeutic properties of SAME being investigated by researchers that may lead to a new era in the treatment of age-related diseases in the U.S. We begin with a brief discussion of the history and biochemical influence of this remarkable natural compound.

SAME is a biological compound that is found in virtually every living cell of the human body, affecting their function, stability and activity. Originally discovered by researchers in Italy in 1952 and later identified as a metabolite of the amino acid methionine, SAME acts as a co-factor in a number of critical biochemical reactions necessary for sustaining life.<sup>2</sup>

Typical adults produce anywhere from 6 to 8 grams of SAME daily, with most of it being made in the liver where it works to detoxify the body of poisons such as drugs, alcohol, heavy metals, pesticides and solvents. Beyond its function in liver detoxification, SAME is a critical component in cartilage production, an important factor in brain chemistry and a key element in methylation, one of the most crucial biochemical actions.<sup>3</sup>

Because of its widespread benefits to biological function, SAME has recently generated a great deal of interest for its potential therapeutic properties. Indeed, numerous research studies have found that raising the level of SAME in the body reduces the age-related biological processes that result in diseases such as depression, osteoarthritis and liver disorders.

#### Depression: limitations of conventional therapy

Depression is a modern-day epidemic. Worldwide, it is a leading public health problem with as many as one in six people suffering from the disorder and as many as 20% developing a case serious enough to warrant professional treatment.<sup>6</sup>



While drug therapy for depression can be effective, research has shown that as many as 30% of depressed people fail to respond favorably to even the newest pharmaceuticals available. To make matters worse, anti-depressants can provoke a host of side effects such as heart palpitation, hallucination, confusion, anxiety, insomnia, disorientation and loss of libido. In addition, many anti-depressive drugs are dangerous for patients with Parkinson's disease, heart problems, glaucoma, high blood pressure and liver problems, thereby placing them off limits to many older sufferers.<sup>7</sup>

Considering the potential for failure, usage limitations with respect to concurrent diseases, and potential side effects, anti-depressive drugs are not always a preferred course of treatment. As such, identifying alternative methods for combating depression is paramount. One of the most promising substitutes is SAME.

#### Clinical studies supporting efficacy of SAME

Research into SAME's anti-depressant value was first cited in Italy in 1973 when scientists examining its effect on schizophrenic patients noticed that many of the test subjects were becoming less depressed. These unexpected results triggered a surge of clinical trials whose aim was to verify and understand this enigmatic result.<sup>8</sup>

Years of research followed, with an overwhelming number of studies concluding that SAME is at least as effective at treating depression as its pharmaceutical counterparts - with some trials showing that it outperforms conventional medications. Furthermore, these studies also found that SAME has surprisingly few side effects, works in as quickly as a few days and is remarkably well tolerated in elderly patients.<sup>9</sup>

A study performed by the Clinical Psychopharmacology Unit in Boston confirmed these findings in an open trial of 20 outpatients suffering from major depression who had not previously responded to conventional anti-depressant drugs. Impressively, upon receiving oral supplementation of SAME, the group as a whole reported significant improvement, and seven out of 11 patients experienced a full anti-depressant response. In addition, only minimal and transient side effects resulted, further suggesting that SAME is well tolerated.<sup>10</sup>

According to the U.S Agency for Healthcare Research and Quality's recent review of clinical trials, SAME is associated with an improvement of approximately six points in the score of the 17-point Hamilton Rating Scale for Depression when measured at three weeks. Furthermore, this improvement rating is at least equal to the results achieved with conventional pharmacology. Hence, this degree of improvement is considered both statistically and clinically significant and is equivalent to verification of SAME's beneficial effect on depression.<sup>1</sup>

#### SAME and osteoarthritis

Osteoarthritis is a natural and unfortunate consequence of aging joints. It occurs when the cartilage cushion that lines the joints becomes stiff, resulting in bone overgrowth in the affected area. This overgrowth subsequently causes inflammation and progressively decreased mobility, eventually resulting in the complete loss of function and possibly disfigurement.<sup>11</sup>

Currently, researchers estimate that as many as 24.3 million Americans ages 35 to 65 suffer from some degree of osteoarthritis.<sup>12</sup> Additionally, studies have



**Methylation:**  
A key reaction in biological function

If for no other reason, SAME's key role in methylation makes it absolutely essential for healthy functioning. Methylation is a biochemical process whereby a methyl group (CH<sub>3</sub>) is passed from one molecule to another. Biologically, methylation acts as an "on-off" switch that activates more than a hundred different processes in the body - from producing neurotransmitters (such as serotonin), to preserving joint health, and even protecting against heart disease.<sup>4</sup>

Methylation activity declines with aging, resulting in a gradual slowdown in these processes, causing many researchers to theorize that this methylation decline contributes to the aging process itself as well as the many diseases associated with it.<sup>5</sup>

found that the prevalence of osteoarthritis skyrockets to as much as 90% for people over 75 years of age.<sup>13</sup> At present, the primary treatment options available through conventional medicine are limited - aspirin, steroids, COX-2 inhibitors and nonsteroidal anti-inflammatory (NSAIDs) drugs. While these medications effectively ease pain, they do not reverse the joint cartilage damage. Furthermore, NSAIDs and even the newer COX-2 inhibitors are commonly associated with serious side effects such as intestinal disorders and ulcers.<sup>14</sup> Clearly, more effective treatment options are sorely needed.



How SAME fights arthritis

A study published in Italy first investigated the effect of SAME on osteoarthritis in 1975. In

their open trial carried out on 90 patients with severe degenerative arthropathies, they found that 30 mg of SAME administered intravenously twice a day for two weeks resulted in marked anti-inflammatory effects with no side effects. In a subsequent "double crossover" investigation, SAME was next compared to the effects of intramuscular injections of the analgesic indomethacin. The results showed that the therapeutic responses of the two were exactly alike, whereas the side effects following the indomethacin were not present after SAME.<sup>15</sup>

A study performed at the Konig Institute of General Medicine in Germany tested the effectiveness of SAME in 108 patients with osteoarthritis of the knee, hip and spine. During the 24-month study, patients received 600 mg of SAME daily for the first two weeks, followed by 400 mg daily thereafter until the conclusion. According to researchers, improvement of clinical symptoms were reported after only two weeks of treatment, and continued throughout the trial. Minor, non-specific side effects such as nausea occurred in only 20 of the patients, most of which disappeared during the trial.<sup>16</sup>

Even more compelling, according to the latest report issued by the U.S. Department of Health and Human Services, SAME has shown to be 80% more effective in relieving the pain associated with osteoarthritis when compared with placebo. Furthermore, their report also found that when compared to treatment with NSAID drugs, SAME was at least equally effective. The significance of this finding is that NSAID drugs are known to induce serious side effects, whereas SAME can provide identical results with no ill effects.<sup>1</sup>

### Protecting the liver

The liver is the primary organ involved in removing toxic substances from the human body.<sup>19</sup> One way the liver achieves this is to produce glutathione, a powerful antioxidant composed of three amino acids, cysteine, glutamic acid and glycine. When glutathione encounters a toxin, such as a pesticide or drug, it immediately attaches to it, making the substance become more water-soluble. Once it is in this water-soluble state, the toxin can then be excreted safely via the urine without causing any damage.<sup>20</sup>

Because of the liver's continuous battle against toxins, adequate concentrations of glutathione are crucial to survival. Damage occurs when the liver is so overwhelmed by toxins that it cannot produce enough glutathione. Part of that concentration burden falls to SAME, which is a necessary component of glutathione's creation. Not coincidentally, the concentration of SAME in the liver is one of the highest in the body.

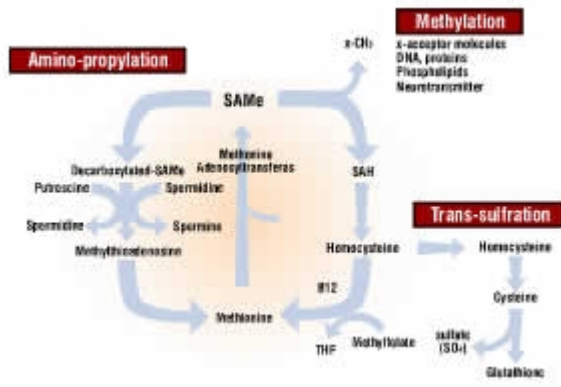
The interrelationship between SAME and glutathione production is of such critical importance to the removal of toxins and general liver health that it is considered by many researchers to be a liver super-nutrient. Nothing comes close to providing the spectrum of health benefits that SAME provides for the liver.

Based on published clinical trials, elevating SAME levels can have a beneficial effect on many conditions. As a preventive agent, SAME is so powerful that it can reverse the effects of chemicals and alcohol as they occur.<sup>23</sup> Studies also show that low SAME levels create a toxic environment that can increase liver cancer risk.<sup>24</sup> SAME can prevent these conditions from occurring. In short, anyone concerned about the effects of drugs, chemicals, alcohol and aging on their liver should consider adding SAME to the supplemental regimen.

### How Glutathione is created from SAME

SAME is the precursor for the sulfur amino acids cysteine and taurine, as well as the tri-peptide glutathione. SAME is first transformed into S-adenosylhomocysteine, which is then converted into cysteine and taurine. Sulfur compounds are so important that under conditions of absolute deficiency of sulfur, there is no living material. Every cell in the body contains sulfur compounds.<sup>21</sup>

In the test tube, SAME increases the number of chondrocytes (cartilage cells) and proteoglycans (structural proteins). This suggests that SAME treatment may reverse the underlying process of osteoarthritis by stimulating cartilage to grow.<sup>17</sup> As discussed earlier, cartilage acts like a spongy cushion where bone meets bone at the joint. In osteoarthritis, this cushion gradually disintegrates. Another major component of the joint is synovial fluid, a lubricant that allows for smooth motion. A pro-inflammatory cytokine called tumor necrosis factor-alpha (TNF-a) has been found in the synovial fluid of people with rheumatoid arthritis. TNF-a plays a role in bone and cartilage destruction. According to an article published in the British Journal of Rheumatology, researchers demonstrated that SAME reverses the damage caused by TNF-a when added to cells at the same time.<sup>18</sup>



Glutathione is the most important substance in the liver. The liver's principle function is to break down damaging substance the body encounters. These may be drugs, or the body's own products. Liver malfunction, whether caused by alcohol, viral infection or acetaminophne overdose is invariably accompanied by glutathione depletion. When glutathione is depleted, the liver simply can't work effectively.<sup>22</sup>

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## REPORT

### A New Era for SAMe

#### SAMe and liver cirrhosis

The liver is Grand Central Station for molecules that chaperone lipids around the body. It is the site where very low-density lipoproteins (VLDL) and cholesterol are synthesized. Despite the general misconception that cholesterol is inherently bad, it is actually a very important substance that functions as the precursor for important steroid hormones such as estrogen, DHEA, androgens and the glucocorticoids. It also is part of bile, which acts as a natural detergent against dietary fat.<sup>24</sup>

Cirrhosis of the liver is a chronic, diffuse degenerative disease (most commonly induced by alcohol abuse) in which the lobules are infiltrated with fat and structurally altered, resulting in a localized loss of function and an increased resistance to blood flow through the damaged area. Although about a third of all cases are compensated, meaning that there are no clinical symptoms, severe cases of cirrhosis can lead to ammonia toxicity, hepatic coma, gastrointestinal hemorrhage, kidney failure and eventually death.<sup>25</sup>

Research has shown that SAMe can prevent and, if discovered early enough, even reverse this condition. In a rodent study published in *Toxicology and Applied Pharmacology*, SAMe completely prevented fatty liver when given at the same time as alcohol.<sup>26</sup> Not only does SAMe prevent fat from accumulating in the liver, it prevents cirrhosis-related lipid elevation outside of the liver. Studies have found that the blood cells in people with cirrhosis have a high cholesterol-to-phospholipid ratio, a factor that causes problems with the way liver cells function.<sup>27</sup> A group in England recently showed that SAMe dramatically reduces cholesterol and re-establishes healthy levels. That study found that the cholesterol-to-phospholipid ratio decreased substantially in the erythrocytes of people with liver disease two weeks after they were treated orally with 1,600 mg of SAMe.<sup>28</sup>

#### The cancer connection

It has long been thought that alterations in the liver caused by alcohol, toxins and diseases can eventually lead to cancer. The proof behind this theory began to appear in 1988, when a team of Spanish researchers studying cirrhosis discovered that it is directly related to deficiencies of S-adenosylmethionine synthetase and phospholipid methyltransferase, two important enzymes that convert methionine to SAMe and form phospholipids.<sup>29</sup> Later studies by researchers at the University of Southern California further revealed that liver cancer cells are totally lacking in liver-specific SAMe synthetase; the genes for this enzyme are completely turned off in liver cancer patients.<sup>30</sup> A group at the Institute of Biomedical Investigation in Spain further elucidated the relationship between SAMe synthetase and cancer. Their study found that the immune substance interleukin-2 (IL-2) turns on the SAMe synthetase gene in T-cells. IL-2 is necessary for the growth of immune cells that fight viruses and cancer.<sup>31</sup> Many of the chemicals used to induce cancer in lab animals work by inhibiting SAMe. SAMe's role as a methyl donor (a methyl group is a biochemical entity that catalyzes important biochemical reactions in the body) is critical in preventing cancer. The liver appears to be particularly sensitive to under-methylation.<sup>32</sup>

It is well established that methyl deficiency produces liver cancer in rodents. Methyl deficiency causes a reduction in SAMe levels and a subsequent elevation in S-adenosylmethionine homocysteine (SAH).<sup>33</sup> SAH is what remains after SAMe donates a methyl group for biochemical reactions. An enzyme, SAH hydrolase, turns SAH into homocysteine. Homocysteine can be toxic if it builds up within the body, but is typically converted into cysteine (and eventually glutathione) when enough SAMe is present. If, however, SAMe levels are extremely low, nothing gets converted and SAH and homocysteine levels rise. This is when cancer gets its foothold. A low SAMe-to-SAH ratio is step number one in the development of liver cancer. However, re-establishing adequate SAMe levels can reverse the early changes in the process.<sup>34</sup>

Finally, cancer suppressor genes also are adversely affected by under-methylation. Researchers at the FDA's National Center for Toxicological Research have conducted research showing how under-methylation affects the p53 tumor suppressor gene. They have found that rats fed a diet deficient in SAMe precursors (methionine, choline and folic acid) accumulate DNA strand breaks in certain areas of the p53 gene within days. DNA strand breaks translate into a defective or non-functioning p53 protein. Without p53 to stop them, some types of cancer cells will run wild.<sup>35</sup>

#### Other liver disorders respond to SAMe

It seems that almost any liver disease may be improved with SAMe therapy. Cholestasis, for example, is a common condition of insufficient bile. While this problem may not generate as much awe and public scrutiny as cancer, nonetheless it can be a serious condition resulting in anything from painful gallstones to death.<sup>36</sup>

Among the usual causes of cholestasis are estrogen-replacement therapy, birth control pills, certain drugs (including antidepressants) and pregnancy. Studies into the effects of SAMe on cholestasis have found that it protects against this disorder at oral doses of between 600 mg and 800 mg per day.<sup>1</sup> These findings were further supported by the recent U.S. government study, which concluded that SAMe is an effective treatment of cholestasis during pregnancy.

The prevention of liver disease is just as important as the prevention of heart disease and cancer. Like these two killers, liver diseases can be prevented by simple yet very effective dietary means. No person escapes liver damage. Chemicals in air and water, drugs, radiation, pesticides, hormones and drugs in meat, fungicides on grains, bacteria, parasites and other entities constantly assault us. The liver must deal with all of them on a daily basis. It generates a massive amount of free radicals during detoxification. Helping the liver is one of the simplest and most important steps persons can do for their health. It is very likely that many diseases in other organs begin when the liver can't do its job.

#### The future of SAMe

Obviously, SAMe's importance to maintaining biological stability cannot be overstated. Clear evidence exists showing that SAMe is an effective treatment for many age-related disorders including depression, arthritis and liver disease. But researchers aren't stopping there. Currently, studies are underway examining the relationship between SAMe deficiency and numerous other diseases associated with advanced age, such as cancer, Parkinson's disease, Alzheimer's disease, heart disease, Addison's disease, senile dementia and sleep disorders. Considering the far-reaching effects already discovered about this extraordinary compound, undoubtedly it will soon become a major focus of supplemental medicine.

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## REPORT


### Exclusive Interview With Leading SAME Researcher

SAME is a naturally occurring compound found in all living cells. Its production is vital in cellular metabolism and has been associated with a host of therapeutic properties that for years have gone largely unnoticed by the medical community.

To uncover the hidden value of SAME, Life Extension spoke with Dr. Richard Brown, a clinical psychiatrist at Columbia University, SAME researcher and author of the bestselling book *Stop Depression Now*.

**Life Extension Foundation:** Who should take SAME?

**Dr. Richard Brown:** That's a broad question. In a nutshell, people with mild depression, liver damage and mild to moderate arthritis will find SAME highly effective. With depression, SAME works for about 70% of the people who take it. That's at least equal to, and possibly better than, the results achieved by other antidepressants. Anyone with liver disease, such as that caused by alcohol abuse, can definitely benefit from taking SAME. Some very well-done studies have found that SAME is very effective at treating liver damage. In fact, SAME is really the only good product for treating liver problems.



For arthritis sufferers, many studies have found that it is very effective at relieving pain and in higher doses, it is very good for repairing joint damage. Because of its effectiveness, it is used as a treatment for arthritis throughout Europe and in fact, the head of the Olympic program in Germany has made it standard practice to have all of their athletes on SAME to prevent against developing arthritis.

**LEF:** How much SAME should someone with arthritis take? What about for depression?

**Brown:** For mild to moderate arthritis, I would suggest taking about 600 mg to 800 mg/day. At this dose, patients should achieve about the same pain-relieving results as they would with NSAIDs. However, what SAME does that NSAIDs do not is regenerate cartilage. For more advanced problems, such as severe joint damage, patients typically need higher doses of about 1200 mg/day.

For depression, there is a wide range of possible doses - it really depends on how severe the case is. The starting dose for patients with mild-to-moderate depression is 400 mg daily. For cases of severe depression is, the dosage is much higher, about 1600 mg/day. Patients need to evaluate their level of depression before establishing a proper dosage. In my book *Stop*

*Depression Now* there is a self-assessment test that helps people to determine the severity of their depression.

**LEF:** How long does it take for patients to see the effects of SAME?

**Brown:** Typically for depression, it takes about two weeks to start seeing results. That's faster than what most patients experience with conventional tricyclic antidepressants which often take three or four weeks before patients start seeing results. Of course there are always late bloomers who take a little longer to respond to its effects; these values tend to vary with the person. Also, you can use SAME in conjunction with the tricyclics to get better results. In this type of scenario, the doses for each are typically cut in half.

For joint problems, SAME is a little slower than conventional medication, often about three or four weeks. But SAME is known to regenerate cartilage which other medications can not.

**LEF:** Are there any side effects associated with taking SAME?

**Brown:** All medication has risks. But there have been numerous studies that have shown that patients develop fewer side effects on SAME than they do on other medications. Rarely, some users experience mild headaches after they first begin taking SAME, but those usually disappear after the first week or two. Because SAME makes patients more energetic, some users may also experience minimal bouts of insomnia when first beginning their SAME treatment. This, too, usually vanishes after a week or so. SAME should be taken early in the day so that peak brain energizing effects occur during the most productive hours and not at night.

What you don't see with SAME are weight gain, anxiety attacks and gastrointestinal distress, the common side effects of conventional medications.

**LEF:** SAME sounds relatively safe, but are there people who should not take it?

**Brown:** Anyone who suffers from bipolar disorder (commonly called a "manic/depressive") should not take SAME, as this can actually make them "manic." In addition, patients who are suicidal should not just start taking SAME. They need to be monitored by a trained physician so their dosage can be reviewed and adjusted accordingly. However, this fact is not unique to SAME - that's the case when you are dealing with a suicidal patient beginning any medication.

**LEF:** *Is SAME addictive? Can you overdose?*

**Brown:** SAME has not proven to be addictive. While there are no reports of death due to overdosing with SAME, at high doses, say about 1200 mg/day, patients may experience gastrointestinal distress such as loose bowels. However, even this feature can be beneficial. I know of one elderly patient, for example, that has used that side effect to cure her bouts of constipation!

**LEF:** *Do physicians routinely suggest SAME to their patients? If not, why not?*

**Brown:** Unfortunately, no. SAME is still overlooked by much of the medical community. Why? For one, there are no pharmaceutical companies pushing SAME to physicians - no sales reps coming by, taking them out to lunch discussing the wonders of SAME. And since doctors routinely do what the pharmaceutical companies tell them, SAME goes unnoticed.

Also, many doctors just don't take the time to read-up on all of the latest research. There is so much new information always coming out, but because they have so many hassels with billing and insurance companies they don't have any time. I have colleagues that have actually said to me that they "...don't trust SAME because there is no research on it." But there really are a great many studies that prove its effectiveness and safety for treating depression, arthritis and liver damage.

That's what is so terrific about the Life Extension Foundation. They fill in the void and give patients the ability to get the needed information themselves and then present it to their doctor.

**LEF:** *What other supplements would you suggest for SAME users?*

**Brown:** There are many supplements you can take along with SAME, such as folate, glucosamine chondroitin, etc., but SAME works best in conjunction with adequate B vitamins, such as vitamin B12. B vitamins work synergistically with the methylation pathways in the brain and are required for making methionine, essential for the body's production of SAME.

**LEF:** *What suggestions do you have for people who want to start taking SAME?*

**Brown:** One thing that really needs to be addressed is that while many studies confirm SAME's efficacy, not all brands are created equally. There are many organizations out there that just don't offer quality supplements. Consumers really need to research the companies that they buy from. Companies like Life Extension and consumerlabs.com provide much of this information so that consumers can make an informed choice. Personally, I recommend Life Extension's products.

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