

SAMe (*S-Adenosyl L-Methionine*)

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S-Adenosyl-L-methionine (SAMe): from the bench to the bedside--molecular basis of a pleiotropic molecule.

Bottiglieri T.

S-Adenosyl-L-methionine (SAMe), a metabolite present in all living cells, plays a central role in cellular biochemistry as a precursor to methylation, aminopropylation, and transsulfuration pathways. As such, SAMe has been studied extensively since its chemical structure was first described in 1952. Decades of research on the biochemical and molecular roles of SAMe in cellular metabolism have provided an extensive foundation for its use in clinical studies, including those on depression, dementia, vacuolar myelopathy, liver disease, and osteoarthritis. This article provides an overview of the biochemical, molecular, and therapeutic effects of this pleiotropic molecule.

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Role of S-adenosyl-L-methionine in the treatment of depression: a review of the evidence.

Mischoulon D, Fava M.

Major depression remains difficult to treat, despite the wide array of registered antidepressants available. In recent years there has been a surge in the popularity of natural or alternative medications. Despite this growing popularity, there is limited evidence for the effectiveness of many of these natural treatments. S-adenosyl-L-methionine (SAMe) is one of the better studied of the natural remedies. SAMe is a methyl donor and is involved in the synthesis of various neurotransmitters in the brain. Derived from the amino acid L-methionine through a metabolic pathway called the one-carbon cycle, SAMe has been postulated to have antidepressant properties. A small number of clinical trials with parenteral or oral SAMe have shown that, at doses of 200-1600 mg/d, SAMe is superior to placebo and is as effective as tricyclic antidepressants in alleviating depression, although some individuals may require higher doses. SAMe may have a faster onset of action than do conventional antidepressants and may potentiate the effect of tricyclic antidepressants. SAMe may also protect against the deleterious effects of Alzheimer disease. SAMe is well tolerated and relatively free of adverse effects, although some cases of mania have been reported in bipolar patients. Overall, SAMe appears to be safe and effective in the treatment of depression, but more research is needed to determine optimal doses. Head-to-head comparisons with newer antidepressants should help to clarify SAMe's place in the psychopharmacologic armamentarium.

J Fam Pract 2002 May;51(5):425-30

Safety and efficacy of S-adenosylmethionine (SAMe) for osteoarthritis.

Soeken KL, Lee WL, Bausell RB, Agelli M, Berman BM.

OBJECTIVE: We assessed the efficacy of S-adenosylmethionine (SAMe), a dietary supplement now available in the United States, compared with that of placebo or nonsteroidal anti-inflammatory drugs (NSAIDs) in the treatment of osteoarthritis (OA). **STUDY DESIGN:** This was a meta-analysis of randomized controlled trials. **DATA SOURCES:** We identified randomized controlled trials of SAMe versus placebo or NSAIDs for the treatment of OA through computerized database searches and reference lists. **OUTCOMES MEASURED:** The outcomes considered were pain, functional limitation, and adverse effects. **RESULTS:** Eleven studies that met the inclusion criteria were weighted on the basis of precision and were combined for each outcome variable. When compared with placebo, SAMe is more effective in reducing functional limitation in patients with OA (effect size [ES] = .31; 95% confidence interval [CI], .099-.520), but not in reducing pain (ES = .22; 95% CI, -.247 to .693). This result, however, is based on only 2 studies. SAMe seems to be comparable with NSAIDs (pain: ES = .12; 95% CI, -.029 to .273; functional limitation: ES = .025; 95% CI, -.127 to .176). However, those treated with SAMe were less likely to report adverse effects than those receiving NSAIDs. **CONCLUSIONS:** SAMe appears to be as effective as NSAIDs in reducing pain and improving functional limitation in patients with OA without the adverse effects often associated with NSAID therapies.

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S-adenosyl-L-methionine: its role in the treatment of liver disorders.

Lieber CS.

S-Adenosyl-L-methionine (S-AdoMet) exerts many key functions in the liver, including serving as a precursor for cysteine, 1 of 3 amino acids of glutathione--the major physiologic defense mechanism against oxidative stress. S-AdoMet is particularly important in opposing the toxicity of free oxygen radicals generated by various pathogens, including alcohol, which cause oxidative stress largely by the induction of cytochrome P4502E1 (CYP2E1) and by its metabolite acetaldehyde. S-AdoMet also acts as the main methylating agent in the liver. The precursor of S-AdoMet is methionine, one of the essential amino acids, which is activated by S-AdoMet-synthetase (EC 2.5.1.6). Unfortunately, the activity of this enzyme is significantly decreased as a consequence of liver disease. Because of decreased utilization, methionine accumulates and, simultaneously, there is a decrease in S-AdoMet that acquires the status of an essential nutrient and therefore must be provided exogenously as a supernutrient to compensate for its deficiency. Administration of this innocuous supernutrient results in many beneficial effects in various tissues, mainly in the liver, and especially in the mitochondria. This was shown in alcohol-fed baboons and in other experimental models of liver injury and in clinical trials, some of which are reviewed in other articles in this issue.

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Efficacy and tolerability of oral and intramuscular S-adenosyl-L-methionine 1,4-butanedisulfonate (S-AdoMet) in the treatment of major depression: comparison with imipramine in 2 multicenter studies.

Delle Chiaie R, Pancheri P, Scapicchio P.

BACKGROUND: S-Adenosyl-L-methionine (S-AdoMet), a natural compound, is the most important methyl donor in the central nervous system. In several clinical trials, S-AdoMet showed antidepressant activity. **OBJECTIVE:** Two multicenter studies were conducted in patients with a diagnosis of major depressive episode [baseline score on the 21-item Hamilton Depression Rating Scale (HAM-D) ≥ 18] to confirm the efficacy and safety of S-AdoMet in the treatment of major depression. In the first study (MC3), 1600 mg S-AdoMet/d was given orally; whereas, in the second study (MC4), 400 mg S-AdoMet/d was given intramuscularly. In both studies, the effects of S-AdoMet were compared with those of 150 mg imipramine/d given orally in a double-blind design. **DESIGN:** In MC3, 143 patients received oral S-AdoMet and 138 patients received imipramine for 6 wk. In MC4, 147 patients received S-AdoMet intramuscularly and 148 patients received imipramine for 4 wk. In both studies the 2 main efficacy measures were the final HAM-D score and the percentage of responders to Clinical Global Impression at the endpoint. Secondary efficacy measures were the endpoint Montgomery-Asberg Depression Rating Scale scores and the percentage of responders, responders being those patients showing a decrease in HAM-D score of $\geq 50\%$ from baseline. **RESULTS:** In both studies, the results of S-AdoMet and imipramine treatment did not differ significantly for any efficacy measure. However, significantly fewer adverse events were observed in the patients treated with S-AdoMet. **CONCLUSIONS:** The antidepressive efficacy of 1600 mg S-AdoMet/d orally and 400 mg S-AdoMet/d intramuscularly is comparable with that of 150 mg imipramine/d orally, but S-AdoMet is significantly better tolerated.

Am J Clin Nutr 2002 Nov;76(5):1148S-50S

S-Adenosylmethionine: molecular, biological, and clinical aspects--an introduction.

Lieber CS, Packer L.

In clinical research, a novel approach has emerged: some of the essential nutrients are being used to treat pathologic conditions. Many of these nutrients, including methionine, must first be activated in the liver or in other tissues before they can exert their key functions. However, this activating process is impaired in disease states and, as a consequence, nutritional requirements change. For instance, for methionine to act as the main cellular methyl donor, it must first be activated to S-adenosylmethionine (S-AdoMet; also known as ademetionine). S-AdoMet is required and is of fundamental importance for the metabolism of nucleic acids and polyamines, the structure and function of membranes, and as a precursor of glutathione. These processes are often seriously altered in various pathologic states addressed in this symposium, but they cannot be restored by simply administering methionine. For instance, in liver disease associated with impairment of the enzyme that activates methionine to S-AdoMet, supplementation with methionine is useless and may even become toxic as it accumulates because it is not used. Accordingly, one must correct the lack of S-AdoMet by bypassing the deficiency in enzyme activation; this is done by providing the product of the defective reaction, namely S-AdoMet. Under these pathologic conditions, S-AdoMet becomes crucial for the functioning of the cell. Thus S-AdoMet, which is found in all living organisms, becomes the essential nutrient instead of methionine. This symposium reviewed the biological and corresponding molecular aspects of S-AdoMet metabolism and the clinical consequences of its deficiency or supplementation in various tissues.

Alcohol 2002 Jul;27(3):179-83

S-Adenosyl-L-methionine and mitochondrial reduced glutathione depletion in alcoholic liver disease.

Fernandez-Checa JC, Colell A, Garcia-Ruiz C.

The pathogenesis of alcohol-induced liver disease is not well understood, and many factors have been described to contribute to the progressive loss of liver functions, including the overgeneration of reactive oxygen species. Mitochondria are specific targets of the toxic effects of ethanol, reflected in the loss of phosphorylative oxidation and defective ATP generation, which underlie one of the hallmarks of the hepatic alterations induced by chronic alcohol intake. Mitochondrial reduced glutathione (GSH), whose primary function is to maintain a competitive functional organelle, becomes depleted by alcohol intake. Furthermore, GSH depletion in hepatocyte mitochondria has been revealed as an important mechanism in the sensitization of liver to alcohol-induced injury. This depletion of the mitochondrial GSH level is determined by an impaired transport of GSH from the cytosol into the mitochondrial matrix owing to a partial inactivation of mitochondrial GSH carrier. The loss of function of this specific mitochondrial transporter is due to the alterations in the physicochemical properties of the inner mitochondrial membrane caused by alcohol. Because of the primary defect in the transport of cytosolic GSH into mitochondria, GSH precursors are inefficient in replenishing the levels of mitochondrial GSH despite significant increase in cytosolic GSH. Supplementation of S-adenosyl-L-methionine (SAM) to rats fed alcohol chronically has been shown to replete the mitochondrial GSH levels because of normalization of the microviscosity of the mitochondrial inner membrane. Because of the instrumental role of GSH in mitochondria in hepatocyte survival against inflammatory cytokines, its repletion by SAM feeding may underlie the potential therapeutic use of this hepatoprotective agent in the treatment of alcohol-induced liver injury.

Alcohol 2002 Jul;27(3):173-7

S-Adenosyl-L-methionine and alcoholic liver disease in animal models: implications for early intervention in human beings.

Lieber CS.

In patients with severe alcoholic liver disease (i.e., cirrhosis), a deficiency of S-adenosylmethionine (S-AdoMet) develops as a result of decreased S-AdoMet synthetase activity. Whether a sizeable S-AdoMet depletion occurs already at earlier stages of alcoholic liver disease has been the subject of debate. To address this issue, rats were fed alcohol (or isocaloric carbohydrate) in Lieber-DeCarli liquid diets containing adequate amounts of protein, vitamins, and lipotropic factors, including methionine. Alcohol feeding resulted in hepatic steatosis (without fibrosis) and unchanged S-AdoMet synthetase activity, yet S-AdoMet concentration was already greatly decreased. This most likely resulted from oxidative stress associated with the metabolism of alcohol and the induction of cytochrome P4502E1 (CYP2E1), which generates free radicals. Indeed, the decrease in hepatic S-AdoMet correlated with parameters of oxidative stress, such as increased 4-hydroxynonenal (measured by gas chromatography-mass spectrometry) and diminished glutathione (GSH). Decreased GSH, occurring as a result of excessive GSH consumption caused by the oxidative stress, probably generated by enhanced utilization of S-AdoMet, a precursor of GSH, thereby explaining the depletion of S-AdoMet. In view of the known differences between rodents and primates in the metabolism of lipotropes, my colleagues and I have also studied the interaction between alcohol and S-AdoMet in baboons and found again that, at early stages preceding the development of cirrhosis, there was already a significant lowering of hepatic S-AdoMet concentration, associated with a striking oxidative stress documented by decreased levels and accelerated turnover of GSH. This was associated with increased lipid peroxidation and damage to cellular membranes, including those of the mitochondria, assessed by electron microscopy. Oral administration of S-AdoMet resulted in its hepatic repletion with a corresponding attenuation of the ethanol-induced oxidative stress and liver injury, with significantly less GSH depletion, less increases in plasma aspartate aminotransferase (AST) levels, less leakage of mitochondrial glutamic dehydrogenase into the plasma, and fewer megamitochondria. In conclusion, (1) both in rodents and in non-human primates, significant S-AdoMet depletion occurs already at early stages of alcoholic liver disease, despite the consumption of adequate diets; (2) the decreased hepatic S-AdoMet concentration and the associated liver lesions, including mitochondrial injury, can be corrected with S-AdoMet supplementation; and (3) accordingly, therapeutic administration of S-AdoMet should be the subject of a comprehensive clinical trial to assess its capacity to attenuate early stages of alcoholic liver injury in human beings.

Alcohol 2002 Jul;27(3):163-7

S-Adenosylmethionine revisited: its essential role in the regulation of liver function.

Avila MA, Garcia-Trevijano ER, Martinez-Chantar ML, Latasa MU, Perez-Mato I, Martinez-Cruz LA, del Pino MM, Corrales FJ, Mato JM.

Dietary methionine is mainly metabolized in the liver where it is converted into S-adenosylmethionine (AdoMet), the main biologic methyl donor. This reaction is catalyzed by methionine adenosyltransferase I/III (MAT I/III), the product of MAT1A gene, which is exclusively expressed in this organ. It was first observed that serum methionine levels were elevated in experimental models of liver damage and in liver cirrhosis in human beings. Results of further studies showed that this pathological alteration was due to reduced MAT1A gene expression and MAT I/III enzyme inactivation associated with liver

injury. Synthesis of AdoMet is essential to all cells in the organism, but it is in the liver where most of the methylation reactions take place. The central role played by AdoMet in cellular function, together with the observation that AdoMet administration reduces liver damage caused by different agents and improves survival of alcohol-dependent patients with cirrhosis, led us to propose that alterations in methionine metabolism could play a role in the onset of liver disease and not just be a consequence of it. In the present work, we review the recent findings that support this hypothesis and highlight the mechanisms behind the hepatoprotective role of AdoMet.

Alcohol 2002 Jul;27(3):151-4

Role of S-adenosyl-L-methionine in the treatment of alcoholic liver disease: introduction and summary of the symposium.

Purohit V, Russo D.

The National Institute on Alcohol Abuse and Alcoholism and the Office of Dietary Supplements, National Institutes of Health, sponsored a symposium on "Role of S-Adenosyl-L-Methionine (SAME) in the Treatment of Alcoholic Liver Disease" in Bethesda, Maryland, September 2001. Alcoholic liver disease (ALD) is a major cause of illness and death in the United States. Oxidant stress plays a key role in pathogenesis of liver disease. S-Adenosyl-L-methionine, a dietary supplement, is the methyl donor for biochemical methylation reactions and a precursor of glutathione, the main hepatocellular antioxidant. S-Adenosyl-L-methionine has been shown to attenuate liver injury caused by alcohol and other hepatotoxins in some animal models. Understanding the mechanisms by which SAME attenuates liver injury caused by alcohol may provide useful information for full-scale human clinical trials. For this symposium, seven speakers were invited to address the following issues: (1) impaired methionine metabolism in alcoholic liver injury; (2) regulation of liver function by SAME; (3) folate deficiency, methionine metabolism, and alcoholic liver injury; (4) attenuating effect of SAME on ALD in experimental animals; (5) SAME and mitochondrial glutathione depletion in ALD; (6) SAME and cytokine production in liver injury; and (7) role of SAME in the prevention of hepatocarcinogenesis. The presentations of this symposium support the suggestion that SAME may have potential to treat ALD by (1) acting as a precursor of antioxidant glutathione, (2) repairing mitochondrial glutathione transport system, (3) attenuating toxic effects of proinflammatory cytokines, and (4) increasing DNA methylation. Further studies are required to evaluate the safety and effectiveness of SAME treatment.

Crit Rev Clin Lab Sci 2000 Dec;37(6):551-84

Hepatic, metabolic, and nutritional disorders of alcoholism: from pathogenesis to therapy.

Lieber CS.

Much progress has been made in the understanding of the pathogenesis of alcoholic liver disease, resulting in an improvement in treatment. Nutritional deficiencies should be corrected when present but, because of the alcohol-induced disease process, some of the nutritional requirements change. For instance, methionine, one of the essential amino acids for humans, must be activated to S-adenosylmethionine (SAME), but, in severe liver disease, the activity of the corresponding enzyme is depressed. Therefore, the resulting deficiencies and associated pathology can be attenuated by the administration of SAME, but not by methionine. Similarly, phosphatidylethanolamine methyltransferase (PEMT) activity, which is important for hepatic phosphatidylcholine (PC) synthesis, is also depressed in alcoholic liver disease, therefore calling for the administration of the products of the reaction. Inasmuch as free radical generation by the ethanol-induced CYP2E1 plays a key role in the oxidative stress, inhibitors of this enzyme have great promise and PPC, which is presently being evaluated clinically, is particularly interesting because of its innocuity. In view of the striking negative interaction between alcoholic liver injury and hepatitis C, an antiviral agent is eagerly awaited that, unlike Interferon, is not contraindicated in the alcoholic. Antiinflammatory agents may also be useful. In addition to steroids, down-regulators of cytokines and endotoxin are being considered. Finally, anticraving agents such as naltrexone or acamprosate should be incorporated into any contemplated therapeutic cocktail.

Mov Disord 2000 Nov;15(6):1225-9

S-Adenosyl-Methionine improves depression in patients with Parkinson's disease in an open-label clinical trial.

Di Rocco A, Rogers JD, Brown R, Werner P, Bottiglieri T.

We report a pilot study of S-adenosyl-methionine (SAM) in 13 depressed patients with Parkinson's disease. All patients had been previously treated with other antidepressant agents and had no significant benefit or had intolerable side effects. SAM was administered in doses of 800 to 3600 mg per day for a period of 10 weeks. Eleven patients completed the study, and 10 had at least a 50% improvement on the 17-point Hamilton Depression Scale (HDS). One patient did not improve. Two patients prematurely terminated participation in the study because of increased anxiety. One patient experienced mild nausea,

and another two patients developed mild diarrhea, which resolved spontaneously. The mean HDS score before treatment was 27.09 +/- 6.04 (mean +/- standard deviation) and was 9.55 +/- 7.29 after SAM treatment ($p < 0.0001$). Although uncontrolled and preliminary, this study suggests that SAM is well tolerated and may be a safe and effective alternative to the antidepressant agents currently used in patients with Parkinson's disease.

Semin Thromb Hemost 2000;26(3):219-25

Pathways and regulation of homocysteine metabolism in mammals.

Finkelstein JD.

Two intersecting pathways, the methionine cycle and the transsulfuration sequence, compose the mechanisms for homocysteine metabolism in mammals. The methionine cycle occurs in all tissues and provides for the remethylation of homocysteine, which conserves methionine. In addition, the cycle is essential for the recycling of methyltetrahydrofolate. The synthesis of cystathionine is the first reaction in the irreversible pathway for the catabolism of homocysteine by means of the sequential conversion to cysteine and sulfate. This pathway has a limited distribution and is found primarily in the liver, kidney, small intestine and pancreas. Regulation of homocysteine metabolism is achieved by changes in the quantity of homocysteine distributed between the two competing pathways. Two mechanisms are basic to the regulatory process. Changes in tissue content of the relevant enzymes are the response to sustained perturbations. The inherent kinetic properties of the enzymes provide an immediate response to alterations in the tissue concentrations of substrates and other metabolic effectors. S-adenosylmethionine, S-adenosylhomocysteine, and methyltetrahydrofolate are of particular importance in that context.

Am Fam Phys 2000 Sep 1;62(5):1051-60

Alternative therapies: Part I. Depression, diabetes, obesity.

Morelli V, Zoorob RJ.

Natural supplements are widely used in the United States and, while claims of their therapeutic effects abound, medical research does not always support their effectiveness. St. John's wort acts as a weak selective serotonin reuptake inhibitor with fewer side effects. S-Adenosylmethionine (SAME) has enough of an antidepressant effect to warrant further research. More human studies are needed before garlic, bitter melon, soy and fenugreek supplements can be recommended for the management of diabetes, although chromium may be a promising treatment in some cases. Alpha lipoic acid is used in the treatment of diabetic neuropathy. The effects of ma huang/guarana combinations in obesity have not been well studied. These combinations may have potentially serious side effects but may also offer some benefit. The combination of hydroxycitric acid and garcinia has proved no more effective than placebo.

Int J Biochem Cell Biol 2000 Apr;32(4):391-5

S-Adenosylmethionine.

Lu SC.

S-Adenosyl-L-methionine (SAM) is an important molecule in normal cell function and survival. SAM is utilized by three key metabolic pathways: transmethylation; transsulfuration; and polyamine synthesis. In transmethylation reactions, the methyl group of SAM is donated to a large variety of acceptor substrates including DNA, phospholipids and proteins. Thus, interference of these reactions can affect a wide spectrum of processes ranging from gene expression to membrane fluidity. In transsulfuration, the sulfur atom of the SAM is converted via a series of enzymatic steps to cysteine, a precursor of taurine and glutathione, a major cellular anti-oxidant. Polyamines are required for normal cell growth. Given the importance of SAM in tissue function, it is not surprising that this molecule is being investigated as a possible therapeutic agent for the treatment of various clinical disorders.

J Hepatol 2000;32(1 Suppl):113-28

Alcoholic liver disease: new insights in pathogenesis lead to new treatments.

Lieber CS.

Much progress has been made in the understanding of the pathogenesis of alcoholic liver disease, resulting in improvement of prevention and therapy, with promising prospects for even more effective treatments. The most successful approaches that one can expect to evolve are those that deal with the fundamental cellular disturbances resulting from excessive alcohol consumption. Two pathologic concepts are emerging as particularly useful therapeutically. Whereas it continues to be

important to replenish nutritional deficiencies, when present, it is crucial to recognize that because of the alcohol-induced disease process, some of the nutritional requirements change. This is exemplified by methionine, which normally is one of the essential amino acids for humans, but needs to be activated to S-adenosylmethionine (SAME), a process impaired by the disease. Thus, SAME rather than methionine is the compound that must be supplemented in the presence of significant liver disease. Indeed, SAME was found to attenuate mitochondrial lesions in baboons, replenish glutathione, and significantly reduce mortality in patients with Child A or B cirrhosis. Similarly, polyenylphosphatidylcholine (PPC) corrects the ethanol-induced hepatic phospholipid depletion as well as the decreased phosphatidylethanolamine methyltransferase activity and opposes oxidative stress. It also deactivates hepatic stellate cells, whereas its dilinoleoyl species (DLPC) increases collagenase activity, resulting in prevention of ethanol-induced septal fibrosis and cirrhosis in the baboon. Clinical trials with PPC are ongoing in patients with alcoholic liver disease. Furthermore, enzymes useful for detoxification, such as CYP2E1, when excessively induced, become harmful and should be downregulated. PPC is one of the substances with anti-CYP2E1 properties that is now emerging. Another important aspect is the association of alcoholic liver disease with hepatitis C: a quarter of all patients with alcoholic liver disease also have markers of HCV infection, with an even higher incidence in some urban areas but, at present, no specific therapy is available since interferon is contraindicated in that population. However, in addition to antiviral medications, agents that oppose oxidative stress and fibrosis should also be tested for hepatitis C treatment since these two processes contribute much to the pathology and mortality associated with the virus. In addition to antioxidants (such as PPC, silymarin, alpha-tocopherol and selenium), anti-inflammatory medications (corticosteroids, colchicine, anticytokines) are also being tested as antifibrotics. Transplantation is now accepted treatment in alcoholics who have brought their alcoholism under control and who benefit from adequate social support but organ availability is still the major limiting factor and should be expanded more aggressively. Finally, abstinence from excessive drinking is always indicated; it is difficult to achieve but agents that oppose alcohol craving are becoming available and they should be used more extensively.

Clin Hemorheol Microcirc 2000;22(3):215-21

Blood viscosity and red cell morphology in subjects suffering from cirrhosis before and after treatment with S-adenosyl-L-methionine (SAM).

Turchetti V, Bellini MA, Leoncini F, Petri F, Trabalzini L, Guerrini M, Forconi S.

Alterations of fluidity of the hepatocytic membrane and of the transport related systems are the basis of the cholestatic syndrome and favour the tissue accumulation of cytotoxic metabolites. S-Adenosyl-L-Methionine (SAM) is a natural molecule which acts as a giver of methyl groups and as an enzymatic activator in several enzymatic actions of transmethylation and of transsulphuration and plays a key role in biochemical processes of hepatic cell. The aim of our study was to evaluate the effects of SAM on the restoration of the membrane fluidity and on the hepatic function in general. In studying the fluidity of the cell membrane we evaluated some hemorheological parameters (total blood viscosity and red cell morphology). Fluidity of the red cell membrane is one of the most important elements of red cell rheology. We studied 15 patients (Group A) suffering from micro- and macro-nodular cirrhosis verified through hepatic biopsy, with alcoholic or post-viral causes. We evaluated the values of: blood viscosity (with a cone-plate rheometer by Carri-med), haematocrit, plasma fibrinogen and the erythrocytic morphology at the optical microscope with the Zipursky-Forconi method before and after 7 days of therapy with SAM i.v.. Data were compared with those of a similar group (Group B) treated with traditional therapy only (hyposodic and hypoprotein diet supplemented with multivitamin preparations, vitamin K in particular, if necessary, and potassium sparing diuretics). We also measured biliary salts, alkaline phosphatase, transaminase and gamma-GT. In the first group we observed a statistically significant reduction of blood viscosity, haematocrit didn't change significantly; biliary salts reduced in a statistically significant way. Evaluation of red cell morphology showed in all cases a pathological percentage (>15%) of echinocytes and knizocytes which reduced to a mean of 5% after SAM therapy. We observed no further modifications of the other hemorheological parameters. Results demonstrate that SAM has a positive action on the fluidity of the membrane, as indicated by the improvement of haemorheological parameters and by the significant decrease of biliary salts, indicating the presence of cholesteasis.

Annu Rev Nutr 2000;20:395-430

ALCOHOL: its metabolism and interaction with nutrients.

Lieber CS.

In the past, alcoholic liver disease was attributed exclusively to dietary deficiencies, but experimental and judicious clinical studies have now established alcohol's hepatotoxicity. Despite an adequate diet, it can contribute to the entire spectrum of liver diseases, mainly by generating oxidative stress through its microsomal metabolism via cytochrome P4502E1 (CYP2E1). It also interferes with nutrient activation, resulting in changes in nutritional requirements. This is exemplified by methionine, one of the essential amino acids for humans, which needs to be activated to S-adenosylmethionine (SAME), a process impaired by liver disease. Thus, SAME rather than methionine is the compound that must be supplemented in the presence of significant liver disease. In baboons, SAME attenuated mitochondrial lesions and replenished glutathione; it also significantly reduced mortality in patients with Child A or B cirrhosis. Similarly, decreased phosphatidylethanolamine methyltransferase activity is

associated with alcoholic liver disease, resulting in phosphatidylcholine depletion and serious consequences for the integrity of membranes. This can be offset by polyenylphosphatidylcholine (PPC), a mixture of polyunsaturated phosphatidylcholines comprising dilinoleoylphosphatidylcholine (DLPC), which has high bioavailability. PPC (and DLPC) opposes major toxic effects of alcohol, with down-regulation of CYP2E1 and reduction of oxidative stress, deactivation of hepatic stellate cells, and increased collagenase activity, which in baboons, results in prevention of ethanol-induced septal fibrosis and cirrhosis. Corresponding clinical trials are ongoing.

Biochem J 1999 Aug 15;342 (Pt 1):21-5

S-adenosylmethionine attenuates the lipopolysaccharide-induced expression of the gene for tumour necrosis factor alpha.

Watson WH, Zhao Y, Chawla RK.

Intracellular deficiency of S-adenosylmethionine (AdoMet) and elevated serum concentrations of tumour necrosis factor alpha (TNF) are hallmarks of toxin-induced liver injury. In these models, the administration of either exogenous AdoMet or antibody/soluble receptor for TNF attenuates the injury. We have demonstrated previously that the administration of exogenous AdoMet to AdoMet-deficient rats attenuated lipopolysaccharide (LPS)-induced liver injury and serum TNF concentrations. Here we report that AdoMet lowered the amount of TNF secreted by LPS-stimulated murine macrophage cells (RAW 264.7) in a dose-dependent manner. The inhibition of TNF release was correlated with changes in the steady-state TNF mRNA concentrations. Changes in TNF mRNA were not due to its altered stability and might have been due to an attenuation of the transcription rate of the TNF gene. The inhibition of TNF release in RAW cells was not mediated by GSH because treatment with AdoMet did not increase intracellular GSH. In addition, N-acetylcysteine, whereas it did increase GSH concentration, had no effect on LPS-stimulated TNF release in these cells. Exogenous AdoMet also attenuated LPS-induced serum TNF levels in normal rats sensitized with lead. Thus AdoMet administration might exert its hepatoprotective effects at least in part by its inhibitory effect on expression of the gene for TNF.

Med Hypotheses 1999 Oct;53(4):350-60

Niacinamide therapy for osteoarthritis--does it inhibit nitric oxide synthase induction by interleukin 1 in chondrocytes?

McCarty MF, Russell AL.

Fifty years ago, Kaufman reported that high-dose niacinamide was beneficial in osteoarthritis (OA) and rheumatoid arthritis. A recent double-blind study confirms the efficacy of niacinamide in OA. It may be feasible to interpret this finding in the context of evidence that synovium-generated interleukin-1 (IL-1), by inducing nitric oxide (NO) synthase and thereby inhibiting chondrocyte synthesis of aggrecan and type II collagen, is crucial to the pathogenesis of OA. Niacinamide and other inhibitors of ADP-ribosylation have been shown to suppress cytokine-mediated induction of NO synthase in a number of types of cells; it is therefore reasonable to speculate that niacinamide will have a comparable effect in IL-1-exposed chondrocytes, blunting the anti-anabolic impact of IL-1. The chondroprotective antibiotic doxycycline may have a similar mechanism of action. Other nutrients reported to be useful in OA may likewise intervene in the activity or synthesis of IL-1. Supplemental glucosamine can be expected to stimulate synovial synthesis of hyaluronic acid; hyaluronic acid suppresses the anti-catabolic effect of IL-1 in chondrocyte cell cultures, and has documented therapeutic efficacy when injected intra-articularly. S-adenosylmethionine (SAM), another proven therapy for OA, upregulates the proteoglycan synthesis of chondrocytes, perhaps because it functions physiologically as a signal of sulfur availability. IL-1 is likely to decrease SAM levels in chondrocytes; supplemental SAM may compensate for this deficit. Adequate selenium nutrition may down-regulate cytokine signaling, and ample intakes of fish oil can be expected to decrease synovial IL-1 production; these nutrients should receive further evaluation in OA. These considerations suggest that non-toxic nutritional regimens, by intervening at multiple points in the signal transduction pathways that promote the synthesis and mediate the activity of IL-1, may provide a substantially superior alternative to NSAIDs (merely palliative and often dangerously toxic) in the treatment and perhaps prevention of OA.

Altern Med Rev 1999 Oct;4(5):330-41

Natural treatments for osteoarthritis.

Gaby AR.

Osteoarthritis (OA) is the most common form of joint disease. Although OA was previously thought to be a progressive, degenerative disorder, it is now known that spontaneous arrest or reversal of the disease can occur. Conventional medications are often effective for symptom relief, but they can also cause significant side effects and do not slow the progression of the

disease. Several natural substances have been shown to be at least as effective as nonsteroidal anti-inflammatory drugs at relieving the symptoms of OA, and preliminary evidence suggests some of these compounds may exert a favorable influence on the course of the disease.

J Hepatol 1999 Jun;30(6):1081-9

S-adenosylmethionine in alcoholic liver cirrhosis: a randomized, placebo-controlled, double-blind, multicenter clinical trial.

Mato JM, Camara J, Fernandez de Paz J, Caballeria L, Coll S, Caballero A, Garcia-Buey L, Beltran J, Benita V, Caballeria J, Sola R, Moreno-Otero R, Barrao F, Martin-Duce A, Correa JA, Pares A, Barrao E, Garcia-Magaz I, Puerta JL, Moreno J, Boissard G, Ortiz P, Rodes J.

BACKGROUND/AIM: The efficacy of S-adenosylmethionine (AdoMet) in the treatment of liver cell injury has been demonstrated in several experimental models. The aim of this study was to investigate the effects of AdoMet treatment in human alcoholic liver cirrhosis. **METHODS:** A randomized, double-blind trial was performed in 123 patients treated with AdoMet (1200 mg/day, orally) or placebo for 2 years. All patients had alcoholic cirrhosis, and histologic confirmation of the diagnosis was available in 84% of the cases. Seventy-five patients were in Child class A, 40 in class B, and 8 in class C. Sixty-two patients received AdoMet and 61 received placebo. **RESULTS:** At inclusion into the trial no significant differences were observed between the two groups with respect to sex, age, previous episodes of major complications of cirrhosis, Child classification and liver function tests. The overall mortality/liver transplantation at the end of the trial decreased from 30% in the placebo group to 16% in the AdoMet group, although the difference was not statistically significant ($p = 0.077$). When patients in Child C class were excluded from the analysis, the overall mortality/liver transplantation was significantly greater in the placebo group than in the AdoMet group (29% vs. 12%, $p = 0.025$), and differences between the two groups in the 2-year survival curves (defined as the time to death or liver transplantation) were also statistically significant ($p = 0.046$). **CONCLUSIONS:** The present results indicate that long-term treatment with AdoMet may improve survival or delay liver transplantation in patients with alcoholic liver cirrhosis, especially in those with less advanced liver disease.

J Pharmacol Exp Ther 1997 Aug;282(2):845-50

Influence of oral S-adenosylmethionine on plasma 5-methyltetrahydrofolate, S-adenosylhomocysteine, homocysteine and methionine in healthy humans.

Loehrer FM, Schwab R, Angst CP, Haefeli WE, Fowler B.

Elevated plasma homocysteine concentration is an independent risk factor for vascular disease in humans. In addition to nutritional and genetic factors, an interruption of the coordinate regulatory function of S-adenosylmethionine has been proposed to be involved in the occurrence of hyperhomocysteinemia. The effect of oral S-adenosylmethionine on homocysteine metabolism in humans is unknown. We investigated the effect of oral S-adenosylmethionine (400 mg) on plasma levels of 5-methyltetrahydrofolate, which is the active form of folate in the remethylation of homocysteine to methionine, S-adenosylhomocysteine, the demethylated product of S-adenosylmethionine, homocysteine and methionine over 24 hr in 14 healthy subjects. After oral administration, S-adenosylmethionine increased from 38.0 \pm 13.4 to 361.8 \pm 66.4 nmol/liter (mean \pm S.E., $P < .001$) and returned to base-line values with a half-life of 1.7 \pm 0.3 hr. Both S-adenosylhomocysteine and 5-methyltetrahydrofolate showed a significant transient increase (from 29.9 \pm 3.7 to 51.7 \pm 7.1 nmol/liter, and from 25.1 \pm 2.5 to 36.2 \pm 3.5 nmol/liter, respectively, $P < .001$), although homocysteine and methionine did not change over the time of measurement. These changes were not found in subjects without previous S-adenosylmethionine administration. The observed metabolic changes suggest that S-adenosylmethionine, at least in concentrations obtained in this study, does not inhibit 5,10-methylenetetrahydrofolate reductase, the 5-methyltetrahydrofolate forming enzyme. Rather they indicate a positive effect on 5-methyltetrahydrofolate, a key cofactor in homocysteine metabolism, which should be considered in homocysteine lowering strategies for the prevention of vascular disease.

Arterioscler Thromb Vasc Biol 1996 Jun;16(6):727-33

Low whole-blood S-adenosylmethionine and correlation between 5-methyltetrahydrofolate and homocysteine in coronary artery disease.

Loehrer FM, Angst CP, Haefeli WE, Jordan PP, Ritz R, Fowler B.

Mild elevation of plasma homocysteine is an independent risk factor for vascular disease. We studied the role of 5-methyltetrahydrofolate (5-MTHF), the folate form directly involved in homocysteine metabolism, in contrast to previous studies, which used total folate measurements, in 70 coronary artery disease (CAD) patients and control subjects. We also measured S-adenosylmethionine (SAM), which controls the activity of critical enzymes of homocysteine metabolism. Fasting

plasma total homocysteine was elevated (> 12.4 $\mu\text{mol/L}$ for women, > 13.3 $\mu\text{mol/L}$ for men) in 17% of patients, in accordance with earlier studies. These patients showed lower 5-MTHF (12.4 ± 1.0 $\mu\text{mol/L}$, mean \pm SD) than control subjects (24.2 ± 15.0 , $P < .001$), and there was a clear correlation (multiple linear regression analysis: $P = .002$) of this relevant form of folate with homocysteine. However, 37% of the normohomocysteinemic patients also revealed similarly low 5-MTHF levels, suggesting that a decrease of 5-MTHF does not necessarily cause hyperhomocysteinemia. SAM was significantly decreased in patients (1.4 ± 0.4 $\mu\text{mol/L}$) compared with control subjects (1.8 ± 0.3 , $P < .001$) but was not correlated to homocysteine or 5-MTHF. The correlation between homocysteine and 5-MTHF that was found in CAD patients but not in control subjects confirms the direct relationship between these compounds in vivo. The new finding of low SAM in patients demands further studies, since it might indicate that low levels pose risk and that SAM might be a protective factor against the development of CAD.

Psychiatry Res 1995 Apr 28;56(3):295-7

Rapidity of onset of the antidepressant effect of parenteral S-adenosyl-L-methionine.

Fava M, Giannelli A, Rapisarda V, Patralia A, Guaraldi GP.

A possible method of reducing the delay in antidepressant response is to use S-adenosyl-L-methionine (SAME), a naturally occurring compound that appears to have a rapid onset of effect in the treatment of depression. In this open, multicenter study, 195 patients were given 400 mg of SAME, administered parenterally, for 15 days. Depressive symptoms remitted after both 7 and 15 days of treatment with SAME, and no serious adverse events were reported. Further studies with a double-blind design are needed to confirm this preliminary indication that SAME is a relatively safe and fast-acting antidepressant.

Alcohol Alcohol 1994 Sep;29(5):597-604

Effect of S-adenosyl-L-methionine administration on red blood cell cysteine and glutathione levels in alcoholic patients with and without liver disease.

Loguercio C, Nardi G, Argenzio F, Aurilio C, Petrone E, Grella A, Del Vecchio Blanco C, Coltorti M.

We measured glutathione and cysteine concentrations in erythrocytes of chronic alcohol misusers with (20 subjects) and without liver cirrhosis (20 subjects). Glutathione levels were decreased, whereas those of cysteine were increased in all patients. Parenteral treatment with S-adenosylmethionine (SAME); (2 g daily in 250 ml 0.15 M NaCl for 15 days) corrected the erythrocyte thiol alterations. We conclude that parenteral treatment with SAME affects the metabolism of SH compounds in erythrocytes of alcoholic patients.

J Rheumatol 1994 May;21(5):905-11

A randomized, double blind, placebo controlled trial of intravenous loading with S-adenosylmethionine (SAM) followed by oral SAM therapy in patients with knee osteoarthritis.

Bradley JD, Flusser D, Katz BP, Schumacher HR, Brandt KD, Chambers MA, Zonay LJ.

OBJECTIVE. We evaluated the effectiveness and rapidity of onset of S-adenosylmethionine (SAM), administered as daily intravenous boluses of 400 mg for 5 days, followed by oral tablets, 200 mg thrice daily for 23 days, versus a matching placebo regimen, in the treatment of 81 patients with symptomatic knee osteoarthritis (OA). **METHODS.** The study was bicentric, double blinded, and placebo controlled. Patients underwent a 7-day washout of arthritis medications prior to initiation of this study treatment. Major outcome measures were the Stanford Health Assessment Questionnaire disability and pain scales, and supplemental visual analog scales for rest and walking pain. **RESULTS.** At one site, patients had milder OA, the baseline characteristics of the treatment groups were well matched, and the SAM treated group showed significantly greater reduction in overall pain and rest pain ($p < 0.05$) than the placebo treated group. At the other site, the patients had more severe OA, randomization yielded markedly different treatment groups, and the response to treatment did not differ between groups. Onset of SAM effect was seen as early as 14 days after the start of treatment. **CONCLUSION.** SAM may be an effective treatment for some patients with symptomatic knee OA, and merits further study. Intravenous loading before oral maintenance therapy may be advantageous.

Drugs 1994 Aug;48(2):137-52

The clinical potential of ademetionine (S-adenosylmethionine) in neurological disorders.

Bottiglieri T, Hyland K, Reynolds EH.

This review focuses on the biochemical and clinical aspects of methylation in neuropsychiatric disorders and the clinical potential of their treatment with ademetionine (S-adenosylmethionine; S-AdoMet). S-AdoMet is required in numerous transmethylation reactions involving nucleic acids, proteins, phospholipids, amines and other neurotransmitters. The synthesis of S-AdoMet is intimately linked with folate and vitamin B12 (cyanocobalamin) metabolism, and deficiencies of both these vitamins have been found to reduce CNS S-AdoMet concentrations. Both folate and vitamin B12 deficiency may cause similar neurological and psychiatric disturbances including depression, dementia, myelopathy and peripheral neuropathy. S-AdoMet has a variety of pharmacological effects in the CNS, especially on monoamine neurotransmitter metabolism and receptor systems. S-AdoMet has antidepressant properties, and preliminary studies indicate that it may improve cognitive function in patients with dementia. Treatment with methyl donors (betaine, methionine and S-AdoMet) is associated with remyelination in patients with inborn errors of folate and C-1 (one-carbon) metabolism. These studies support a current theory that impaired methylation may occur by different mechanisms in several neurological and psychiatric disorders.

Acta Neurol Scand Suppl 1994;154:7-14

S-adenosyl-l-methionine (S-AdoMet) as antidepressant: meta-analysis of clinical studies.

Bressa GM.

INTRODUCTION--S-adenosyl-l-methionine (S-AdoMet) is a naturally-occurring substance which is a major source of methyl groups in the brain. **MATERIAL AND METHODS**—We conducted a meta-analysis of the studies on S-AdoMet to assess the efficacy of this compound in the treatment of depression compared with placebo and standard tricyclic antidepressants. **RESULTS**--Our meta-analysis showed a greater response rate with S-AdoMet when compared with placebo, with a global effect size ranging from 17% to 38% depending on the definition of response, and an antidepressant effect comparable with that of standard tricyclic antidepressants. **CONCLUSION**--The efficacy of S-AdoMet in treating depressive syndromes and disorders is superior with that of placebo and comparable to that of standard tricyclic antidepressants. Since S-AdoMet is a naturally occurring compound with relatively few side-effects, it is a potentially important treatment for depression.

Acta Neurol Scand Suppl 1994;154:15-8

S-adenosylmethionine blood levels in major depression: changes with drug treatment.

Bell KM, Potkin SG, Carreon D, Plon L.

INTRODUCTION--The relationship between plasma levels of S-adenosylmethionine (S-AdoMet), an endogenous methyl donor, and clinical response were studied in patients with a DSM-III-R diagnosis of major depression. **MATERIAL AND METHODS**—A double-blind randomized protocol comparing oral S-AdoMet with oral desipramine, involving a total of 26 patients, was employed. **RESULTS**--At the end of the 4-week trial, 62% of the patients treated with S-AdoMet and 50% of the patients treated with desipramine had significantly improved. Regardless of the type of treatment, patients with a 50% decrease in their Hamilton Depression Scale (HAM-D) score showed a significant increase in plasma S-AdoMet concentration. **CONCLUSION**--The significant correlation between plasma S-AdoMet levels and the degree of clinical improvement in depressed patients regardless of the type of treatment suggests that S-AdoMet may play an important role in regulating mood.

Acta Neurol Scand Suppl 1994;154:19-26

S-adenosylmethionine levels in psychiatric and neurological disorders: a review.

Bottiglieri T, Hyland K.

INTRODUCTION--S-adenosylmethionine (S-AdoMet) is an important methyl donor in over 35 methylation reactions involving DNA, proteins, phospholipids and catechol- and indole- amines. **MATERIAL AND METHODS**--This article reviews the studies that have examined brain and blood levels of S-AdoMet in several psychological, neurological and metabolic disorders. **RESULTS**--Although studies have found no consistent changes in whole blood S-AdoMet levels in psychiatric patients, other investigators have found low cerebrospinal fluid (CSF) S-AdoMet levels in patients with neurological disorders such as Alzheimer's dementia, subacute combined degeneration of the spinal cord (SACD), and HIV-related neuropathies, as well as in patients with metabolic disorders such as 5, 10-CH2-H4 folate reductase deficiency. **CONCLUSION**--Intravenous or oral administration of S-AdoMet thus represents a possible treatment for these neurological and metabolic disorders.

Ann Ital Med Int 1993 Oct;8 Suppl:48S-51S

A meta-analysis of therapeutic trials with ademetionine in the treatment of intrahepatic cholestasis.

Frezza M.

S-adenosyl-L-methionine (ademetionine) has been recently proposed as a therapeutic agent for the treatment of intrahepatic cholestasis (IHC), a syndrome that overlaps with many different types of liver diseases. To obtain a global assessment of the results of the therapeutic efficacy of this compound, a meta-analysis of 6 controlled clinical trials with ademetionine in the symptomatic treatment of IHC of liver diseases and pregnancy was carried out. The therapeutic response to ademetionine treatment, for 15 to 30 days, proved to be superior to placebo, as assessed by resolution of pruritus, normalisation or 50% improvement in serum total bilirubin, serum conjugated bilirubin, alanine aminotransferase, gamma-glutamyl transpeptidase and alkaline phosphatase. At present, the therapeutic effect of ademetionine should be regarded as symptomatic, but long term studies on the effect of drug administration on the course of the disease and survival are being performed.

Psychother Psychosom 1993;59(1):34-40

Double-blind, placebo-controlled study of S-adenosyl-L-methionine in depressed postmenopausal women.

Salmaggi P, Bressa GM, Nicchia G, Coniglio M, La Greca P, Le Grazie C.

S-adenosyl-L-methionine (SAME) is a naturally occurring substance which is a major source of methyl groups in the brain and has been found in previous studies to be an effective antidepressant. The aim of this study was to assess the efficacy of oral SAME in the treatment of depressed postmenopausal women in a 30-day double-blind placebo-controlled randomized trial. During the course of the study, 80 women, between the ages of 45 and 59, who were diagnosed as having DSM-III-R major depressive disorder or dysthymia between 6 and 36 months following either natural menopause or hysterectomy, underwent 1 week of single-blind placebo washout, followed by 30 days of double-blind treatment with either SAME 1,600 mg/day or placebo. There was a significantly greater improvement in depressive symptoms in the group treated with SAME compared to the placebo group from day 10 of the study. Side effects were mild and transient.

J Clin Psychiatry 1993 Jan;54(1):13-20

Psychotropic treatment of chronic fatigue syndrome and related disorders.

Goodnick PJ, Sandoval R.

BACKGROUND: Chronic fatigue syndrome (CFS) and fibromyalgia frequently are associated with symptoms of major depression. For this reason, antidepressants have been used in treatment of these disorders; however, little direction has been provided into this application in psychopharmacology. **METHOD:** First, nine studies were reviewed regarding the relationship of the symptoms of fatigue and depression. Next, 23 reports (12 double-blind studies, 7 open studies, and 4 case reports) were reviewed for the effectiveness of therapy as assessed by global response and improvement of both depression and pain. Studies were differentiated by type of controls, as well as by alleged mechanism of action of the pharmacologic agent. **RESULTS:** Disturbances in brain neurochemistry shared by CFS and major depression may serve as a basis for the effectiveness of some antidepressants in CFS. Response to some antidepressants in patients with CFS or fibromyalgia may occur at doses lower than those used in major depression, e.g., amitriptyline 25-75 mg/day. We further found that the more serotonergic treatments (e.g., clomipramine) were more successful in alleviating pain than depression, whereas catecholaminergic agents (e.g., maprotiline, bupropion) seemed particularly effective for symptoms of associated depression. **CONCLUSION:** To maximize response of the physiologic and psychological consequences of the disorder, more investigation is needed to replicate the apparent findings that relate the neurochemical impairment underlying CFS and fibromyalgia to the type of antidepressant mechanism.

Acta Psychiatr Scand 1990 May;81(5):432-6

The antidepressant potential of oral S-adenosyl-L-methionine.

Rosenbaum JF, Fava M, Falk WE, Pollack MH, Cohen LS, Cohen BM, Zubenko GS.

S-adenosyl-L-methionine (SAME), a naturally occurring brain metabolite, has previously been found to be effective and tolerated well in parenteral form as a treatment of major depression. To explore the antidepressant potential of oral SAME, we conducted an open trial in 20 outpatients with major depression, including those with (n = 9) and without (n = 11) prior history of antidepressant nonresponse. The group as a whole significantly improved with oral SAME: 7 of 11 non-treatment-resistant and 2 of 9 treatment-resistant patients experienced full antidepressant response. Side effects were mild and transient.

J Neurol Neurosurg Psychiatry 1990 Dec;53(12):1096-8

Cerebrospinal fluid S-adenosylmethionine in depression and dementia: effects of treatment with parenteral and oral S-adenosylmethionine.

Bottiglieri T, Godfrey P, Flynn T, Carney MW, Toone BK, Reynolds EH.

Cerebrospinal fluid (CSF) S-adenosylmethionine (SAM) levels were significantly lower in severely depressed patients than in a neurological control group. The administration of SAM either intravenously or orally is associated with a significant rise of CSF SAM, indicating that it crosses the blood-brain barrier in humans. These observations provide a rational basis for the antidepressant effect of SAM, which has been confirmed in several countries. CSF SAM levels were low in a group of patients with Alzheimer's dementia suggesting a possible disturbance of methylation in such patients and the need for trials of SAM treatment.

Am J Psychiatry 1990 May;147(5):591-5

Oral S-adenosylmethionine in depression: a randomized, double-blind, placebo-controlled trial.

Kagan BL, Sultzer DL, Rosenlicht N, Gerner RH.

Methylation has been implicated in the etiology of psychiatric illness. Parenteral S-adenosylmethionine, a methyl group donor, has been shown to be an effective antidepressant. The authors studied the antidepressant effect of oral S-adenosylmethionine in a randomized, double-blind, placebo-controlled trial for 15 inpatients with major depression. The results suggest that oral S-adenosylmethionine is a safe, effective antidepressant with few side effects and a rapid onset of action. S-Adenosylmethionine induced mania in a patient with no history of mania. S-Adenosylmethionine may be useful for patients who cannot tolerate tricyclic anti-depressants. These findings support a role for methylation in the pathophysiology of depression.

J Psychiatr Res 1990;24(2):177-84

Neuroendocrine effects of S-adenosyl-L-methionine, a novel putative antidepressant.

Fava M, Rosenbaum JF, MacLaughlin R, Falk WE, Pollack MH, Cohen LS, Jones L, Pill L.

S-adenosyl-L-methionine (SAME), a putative antidepressant, is a naturally occurring substance whose mechanism of action is still a matter of speculation. It has been recently postulated that SAME may increase the dopaminergic tone in depressed patients. Since dopamine inhibits both thyrotropin (TSH) and prolactin secretion, we investigated the effects of treatment with SAME on the TSH and prolactin response to thyrotropin-releasing-hormone (TRH) stimulation in 7 depressed outpatient women (mean age: 46.1 +/- 7.2 years) and 10 depressed outpatient men (mean age: 38.0 +/- 10.0 years) participating in a six-week open study of oral SAME in the treatment of major depression. At the end of the study, there was a significant reduction after treatment with SAME in the response of both prolactin and TSH to TRH stimulation in the group of depressed men compared to pre-treatment values. On the other hand, in the group of depressed women, the posttreatment prolactin response to TRH did not appear to change when compared to pre-treatment and the TSH response to TRH challenge tended even to augment slightly after treatment with SAME. Our results, at least in depressed men, seem to support the hypothesis of a stimulating effect of SAME on the dopaminergic system.

Rev Clin Esp 1990 Jun;187(2):74-8

Experimental osteoarthritis and its course when treated with S-adenosyl-L-methionine.

Barcelo HA, Wiemeyer JC, Sagasta CL, Macias M, Barreira JC.

Degenerative arthropathy was experimentally induced in the right knee of 24 rabbits. The animals were randomly divided in 3 groups of 8 rabbits each. S-Adenosyl-L-Methionine (SAME) was administered intramuscularly to 2 groups. One group received 30 and 60 mg/kg/day i.m. The remaining group was a control and received only a diluent. After 12 weeks of therapy rabbits were sacrificed and tibial and femoral cartilage specimens of both knees were taken. The latter was stained with hematoxylin-eosine, Masson's trichromic and Safranin O stains and was microscopically studied. The thickness and cell density of the lesioned cartilages were significantly greater in both groups treated with SAME than the group control (p less than 0.001). Statistical differences (p less than 0.05) were found within 60 and 30 mg/kg/day of SAME. A greater concentration of proteoglycans in the cartilage matrix was found in animals treated with SAME, as a severe reduction was found in controls. The severity of the lesions, based on the histologic-histochemical analysis, was significantly lower in rabbits receiving SAME (p less than 0.0005). These differences were correlated with the administration of SAME and the possible mechanisms of action are discussed.

Drugs 1989 May;37(5):713-38

Antidepressants. A comparative review of the clinical pharmacology and therapeutic use of the 'newer' versus the 'older' drugs.

Rudorfer MV, Potter WZ.

Supplementing but not supplanting the original series of tricyclic and monoamine oxidase (MAO) inhibitor compounds, a new generation of antidepressant medications has been developed and marketed throughout the past decade. Constituting a more diverse group of drugs than the standard agents, the newer drugs in general have more selective acute biochemical actions (reuptake blockade of a single neurotransmitter, inhibition of 1 subtype of MAO), enabling more precise targeting of symptoms and avoiding common antidepressant-associated side effects, especially anticholinergic and cardiovascular effects. Moreover, a number of recent additions to this group, such as bupropion and ademetionine (S-adenosyl-methionine), incorporate novel mechanisms of action, challenging previous concepts of how antidepressants work, and offering opportunities for research into the pathophysiology of mood disorders. Caution in prescribing the newer antidepressants must be applied, however, as recent experience, e.g. with nomifensine, suggests that unforeseen toxicities may not appear until a medication has been in use for several years.

Trends Neurosci 1989 Sep;12(9):319-24

Affective disorders and S-adenosylmethionine: a new hypothesis.

Cantoni GL, Mudd SH, Andreoli V.

S-Adenosyl-L-methionine (AdoMet) is a safe and probably effective antidepressant agent in certain forms of clinical depression. This article presents a new hypothesis to account for the mechanism of action of S-adenosylmethionine in such illnesses, based upon the known biochemistry of this compound, and upon current knowledge of clinical and genetic aspects of affective disorders. Giulio Cantoni, S. Harvey Mudd and V. Andreoli postulate that at least some major mood disorders are due to abnormalities affecting the AdoMet-dependent methylation of a substance in the CNS. For convenience and without prejudging the chemical structure of this substance, they call it 'barinine'. The model requires that barinine be subject to AdoMet-dependent methylation and that methylbarinine be subject to metabolic demethylation to regenerate the original barinine. Methylbarinine should be mood elevating, whereas barinine itself should not be. Depression is a result of abnormalities lowering the normal steady-state concentration of methylbarinine, whereas mania results from an abnormal elevation of methylbarinine.

Scand J Gastroenterol 1989 May;24(4):407-15

Effects of oral S-adenosyl-L-methionine on hepatic glutathione in patients with liver disease.

Vendemiale G, Altomare E, Trizio T, Le Grazie C, Di Padova C, Salerno MT, Carrieri V, Albano O.

S-Adenosyl-L-methionine (SAME) is a physiologic precursor of thiols and sulfurated compounds, which are known to be decreased in patients with liver disease. The effect of its administration on the hepatic glutathione content of liver patients was investigated. Four groups of subjects were selected: a) 9 patients with alcoholic liver disease treated with SAME (1.2 g/day orally for 6 months); b) 7 patients with non-alcoholic liver disease treated as above; c) 8 placebo-treated patients with alcoholic liver disease; and d) 15 normal subjects as a control group. Total and oxidized glutathione were assayed by high-performance liquid chromatography of liver biopsy specimens before and after the treatment period. In all patients pre-treatment hepatic glutathione was significantly decreased as compared with controls. SAME therapy resulted in a significant increase of hepatic glutathione levels both in patients with alcoholic and in those with non-alcoholic liver diseases as compared with placebo-treated patients. SAME may therefore exert an important role in reversing hepatic glutathione depletion in patients with liver disease.

Drugs 1989 Sep;38(3):389-416

S-adenosyl-L-methionine. A review of its pharmacological properties and therapeutic potential in liver dysfunction and affective disorders in relation to its physiological role in cell metabolism.

Friedel HA, Goa KL, Benfield P.

S-Adenosyl-L-methionine (SAME) is a naturally occurring molecule distributed to virtually all body tissues and fluids. It is of fundamental importance in a number of biochemical reactions involving enzymatic transmethylation, contributing to the synthesis, activation and/or metabolism of such compounds as hormones, neurotransmitters, nucleic acids, proteins, phospholipids and certain drugs. The administration of a stable salt of SAME, either orally or parenterally, has been shown to restore normal hepatic function in the presence of various chronic liver diseases (including alcoholic and non-alcoholic cirrhosis, oestrogen-induced and other forms of cholestasis), to prevent or reverse hepatotoxicity due to several drugs and chemicals such as alcohol, paracetamol (acetaminophen), steroids and lead, and to have antidepressant properties. In all of

these studies SAME has been very well tolerated, a finding of great potential benefit given the well-known adverse effects of tricyclic antidepressants with which it has been compared in a few trials. Thus, with its novel mechanisms of action and good tolerability, SAME is an interesting new therapeutic agent in several diverse disease conditions, but its relative value remains to be determined in appropriate comparisons with other treatment modalities in current use.

Am J Psychiatry 1988 Sep;145(9):1110-4

S-adenosylmethionine treatment of depression: a controlled clinical trial.

Bell KM, Plon L, Bunney WE, Potkin SG.

The antidepressant properties of S-adenosylmethionine, an endogenous methyl donor, were studied in inpatients who met the DSM-III criteria for major depression. Nine patients given intravenous S-adenosylmethionine and nine given low oral doses of imipramine were compared in a double-blind design for 14 days. The S-adenosylmethionine produced superior results by the end of the first week of treatment. By the end of the second week, 66% of the S-adenosylmethionine patients had a clinically significant improvement in depressive symptoms, compared to 22% of the imipramine patients. Side effects appeared to be fewer with S-adenosylmethionine than with imipramine during the last 5 days of the study.

Neurosci Biobehav Rev 1988 Summer;12(2):139-41

S-adenosylmethionine in the treatment of depression.

Vahora SA, Malek-Ahmadi P.

The antidepressant property of S-adenosylmethionine (SAME) has been supported by several uncontrolled and controlled studies. Compared to standard antidepressant agents, SAME has fewer side-effects and shorter lag period. Future studies to delineate SAME-responsive depression are warranted.

Am J Med 1987 Nov 20;83(5A):60-5

S-adenosylmethionine in the treatment of osteoarthritis. Review of the clinical studies.

di Padova C.

S-Adenosylmethionine (SAME), a physiologic compound that ranks with ATP as a pivotal molecule in biology, offers physicians an innovative approach to the treatment of osteoarthritis. Experimental investigations suggest that the administration of SAME exerts analgesic and antiphlogistic activities and stimulates the synthesis of proteoglycans by articular chondrocytes with minimal or absent side effects on the gastrointestinal tract and other organs. The results of extensive clinical trials, which have enrolled about 22,000 patients with osteoarthritis in the last five years, support the clinical effectiveness and the optimal tolerability of SAME administration. The intensity of therapeutic activity of SAME against osteoarthritis is similar to that exerted by nonsteroidal anti-inflammatory drugs, but its tolerability is higher. Based on these findings, SAME is proposed as the prototype of a new class of safe drugs for the treatment of osteoarthritis.

Am J Med 1987 Nov 20;83(5A):66-71

Italian double-blind multicenter study comparing S-adenosylmethionine, naproxen, and placebo in the treatment of degenerative joint disease.

Caruso I, Pietrogrande V.

In a double-blind study, the efficacy and tolerability of S-adenosylmethionine (SAME) were evaluated in comparison with those of placebo and naproxen in the treatment of osteoarthritis of the hip, knee, spine, and hand. Thirty-three centers, 18 rheumatologic and 15 orthopedic, participated in this study. A total of 734 subjects, including 582 with coxarthrosis (hip osteoarthritis) or gonarthrosis (knee osteoarthritis), were enrolled. SAME administered orally at a dose of 1,200 mg daily was shown to exert the same analgesic activity as naproxen at a dose of 750 mg daily. Both drugs were more effective than placebo (p less than 0.01). Tolerability of SAME was significantly better than that of naproxen, both in terms of physicians' (p less than 0.025) and patients' (p less than 0.01) judgments and in terms of the number of patients with side effects (p less than 0.05). There was no difference between SAME and placebo in the number of side effects. Ten patients in the SAME group and 13 in the placebo group withdrew from the study because of intolerance to the drug.

Am J Med 1987 Nov 20;83(5A):72-7

Double-blind controlled clinical trial of oral S-adenosylmethionine versus piroxicam in knee osteoarthritis.

Maccagno A, Di Giorgio EE, Caston OL, Sagasta CL.

A double-blind, randomized, 84-day controlled clinical trial was carried out to compare orally administered S-adenosylmethionine (SAME) (1,200 mg per day) with oral piroxicam therapy (20 mg per day) in the management of unilateral knee osteoarthritis. The ability of each drug to maintain the results achieved at the end of the treatment period was also evaluated during a 56-day follow-up period. Forty-five patients completed the study, 22 in the SAME group and 23 in the piroxicam group. Both SAME and piroxicam proved effective in inducing a significant improvement in the total pain score after 28 days of treatment. With regard to the other clinical parameters (i.e., morning stiffness, the distance walked before the onset of pain, active and passive motility), improvement started from about Day 56 in both groups. No significant difference was found between the two treatments in terms of efficacy and tolerability. Patients treated with SAME maintained clinical improvement achieved at the end of treatment longer than did patients receiving piroxicam.

Am J Med 1987 Nov 20;83(5A):78-80

Double-blind comparative clinical trial with S-adenosylmethionine and indomethacin in the treatment of osteoarthritis.

Vetter G.

In a randomized double-blind study, 36 patients with osteoarthritis of the knee, hip, and/or spine were treated orally with a daily dose of S-adenosylmethionine (SAME)(1,200 mg) or indomethacin (150 mg) over a period of four weeks. Pretreatment and posttreatment clinical parameters were determined and assessed according to a standard scoring system. SAME therapy significantly improved the total score obtained by the sum of all clinical findings, as compared with pretreatment values. Similar improvement was evident in indomethacin-treated subjects. Two patients in the SAME group reported slight nausea after two weeks of therapy, whereas adverse effects developed in seven patients in the indomethacin group.

Am J Med 1987 Nov 20;83(5A):81-3

Double-blind clinical trial of S-adenosylmethionine versus ibuprofen in the treatment of osteoarthritis.

Muller-Fassbender H.

Thirty-six subjects with osteoarthritis of the knee, the hip, and/or the spine were enrolled in a randomized double-blind study. Patients received a daily oral dose of 1,200 mg of S-adenosylmethionine (SAME) or 1,200 mg of ibuprofen for four weeks. Morning stiffness, pain at rest, pain on motion, crepitus, swelling, and limitation of motion of the affected joints were assessed before and after treatment. The total score obtained by the evaluation of all the individual clinical parameters improved to the same extent in patients treated with SAME or ibuprofen. Both treatments were well tolerated and no patient from either group withdrew from the study.

Am J Med 1987 Nov 20;83(5A):84-8

A new medical approach to the treatment of osteoarthritis. Report of an open phase IV study with ademetionine (Gumbaral).

Berger R, Nowak H.

A non-controlled clinical phase IV trial was carried out involving 20,641 patients with osteoarthritis of the knee, the hip, and the spine and also with osteoarthritic polyarthrititis of the fingers, who were treated with ademetionine tablets given in a fixed dosage schedule for eight weeks. No additional analgesic/antirheumatic treatment was allowed. Nevertheless, concomitant medication for other diseases was permissible. The efficacy was described as "very good" or "good" in 71 percent of cases, as "moderate" in 21 percent, and as "poor" in 9 percent of cases. The tolerance was assessed as very good or good in 87 percent, as moderate in 8 percent, and as poor in 5 percent of cases. The trial therapy was discontinued prematurely because of symptoms of intolerance in 5 percent of the patients and because of a lack of efficacy in 2.3 percent of cases.

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A long-term (two years) clinical trial with S-adenosylmethionine for the treatment of osteoarthritis.
Konig B.

In a long-term multicenter open trial involving 10 general practitioners, the efficacy and tolerance of S-adenosylmethionine (SAME) were studied for 24 months in 108 patients with osteoarthritis of the knee, hip, and spine. At the end of the 24-month observation period, 97 of the patients were still in the study. The patients received 600 mg of SAME daily (equivalent to three tablets of 200 mg each) for the first two weeks and thereafter 400 mg daily (equivalent to two tablets of 200 mg each) until the end of the 24th month of treatment. Separate evaluations were made for osteoarthritis of the knee, hip, cervical spine, and dorsal/lumbar spine. The severity of the clinical symptoms (morning stiffness, pain at rest, and pain on movement) was assessed using scoring before the start of the treatment, at the end of the first and second week of treatment, and then monthly until the end of the 24-month period. SAME administration showed good clinical effectiveness and was well tolerated. The improvement of the clinical symptoms during therapy with SAME was already evident after the first weeks of treatment and continued up to the end of the 24th month. Non-specific side effects occurred in 20 patients, but in no case did therapy have to be discontinued. Most side effects disappeared during the course of therapy. Moreover, during the last six months of treatment, no adverse effect was recorded. Detailed laboratory tests carried out at the start and after six, 12, 18, and 24 months of treatment showed no pathologic changes. SAME administration also improved the depressive feelings often associated with osteoarthritis.

Am J Med 1987 Nov 20;83(5A):104-6

S-adenosylmethionine and affective disorder.

Carney MW, Toone BK, Reynolds EH.

Several open and double-blind studies suggest that SAME may have an anti-depressant effect, and further studies are indicated. SAME may exert a beneficial effect selectively on endogenous rather than neurotic depression. SAME crosses the blood-brain barrier. SAME is involved in several central enzyme pathways relating to transmethylation and folate and monoamine metabolism as well as in membrane function and neuro-transmission. The neuropharmacology of SAME's effect on mood and the switch mechanism has yet to be fully explored. The actions of SAME on the dopaminergic system are as yet unclear. SAME is a physiologic substance that is non-toxic and relatively free of severe side effects (with the exception of mania, which may be a manifestation of the basic mood disorder).

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Evaluation of S-adenosylmethionine in primary fibromyalgia. A double-blind crossover study.

Tavoni A, Vitali C, Bombardieri S, Pasero G.

The effect of S-adenosylmethionine (SAME) and placebo was evaluated in a short-term crossover study of 17 patients with primary fibromyalgia. Eleven of 17 patients had a significant depressive state as assessed by either the Hamilton Depression Rating Scale or the Scala di Autovalutazione per la Depressione (SAD) rating scale. The number of trigger points plus painful anatomic sites decreased after administration of SAME (p less than 0.02) but not after placebo treatment. In addition, scores on both the Hamilton and SAD rating scales improved after SAME administration (p less than 0.05 and p less than 0.005, respectively), whereas they did not significantly change after placebo treatment. In all the patients, there was a good correlation between scores on the Hamilton rating scale and the number of trigger points. Thus, this preliminary study confirms the close relationship between primary fibromyalgia and psychologic disturbances, particularly with regards to a depressive state. SAME treatment, by improving the depressive state and reducing the number of trigger points, seems to be an effective and safe therapy in the management of primary fibromyalgia.

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Cytoprotective effect of S-adenosylmethionine compared with that of misoprostol against ethanol-, aspirin-, and stress-induced gastric damage.

Laudanno OM.

The administration of oral S-adenosylmethionine (SAME) (100 mg/kg body weight) was well tolerated by the rat gastroduodenal tract. Moreover, rats given SAME exhibited a significant increase in non-protein sulfhydryl groups of gastroduodenal mucosa as compared with control animals. The abilities of SAME and misoprostol, a prostaglandin E1 analogue, to protect the gastric mucosa against necrosis induced by various noxious stimuli (ethanol, aspirin, stress) were also compared in standardized, experimental rat models. Pretreatment with SAME or misoprostol significantly and to the same extent reduced gastric mucosal injury. The experiments described herein indicate that SAME, a molecule used for the treatment of osteoarthritis, can exert a gastric cytoprotective effect in animals. As preliminary data have shown that this effect may also be reproduced in humans, SAME seems to provide a therapeutic advantage, in contrast to currently available nonsteroidal anti-inflammatory agents.