ВНУТРЕННИЕ БОЛЕЗНИ

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S-adenosylmethionine therapy in rheumatic and related autoimmune diseases*

J. F. de Carvalho[1], L. P. Churilov[2,3], A. Lerner[4,5], P. A. Sobolevskaia[2], A. A. Basina[2], N. Yu. Gavrilova[2,6]

[1] Núcleo de Pesquisa em Doenças Crônicas não Transmissíveis (NUPEN), Rua Augusto Viana, Palácio da Reitoria, Canela, Salvador, 40110-909, Brazil
[2] St. Petersburg State University, 7–9, Universitetskaya nab., St. Petersburg, 199034, Russian Federation
[3] St. Petersburg Research Institute of Phthisiopulmonology, 2–4, Ligovskiy pr., St. Petersburg, 191036, Russian Federation
[4] The Zabludowicz Research Center for Autoimmune Diseases, 2, Derech Sheba, Ramat Gan, 52621, Israel
[5] Ariel University, 65, ul. Ramat HaGolan, Ariel, 40700, Israel
[6] St. Petersburg University's N. I. Pirogov Clinic of High Medical Technologies, 154, nab. r. Fontanki, St. Petersburg, 190103, Russian Federation

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S-adenosylmethionine has been used to treat neuropsychiatric diseases, including those accompanied with depression. These entities often are comorbid with rheumatic and thyroid pathology, and in the COVID-19 pandemic and post-pandemic periods, there was a growing number of such cases. That's why the article evaluates the experience and perspectives of S-adenosylmethionine therapy in osteoarthritis and a few rheumatic and comorbid thyroid diseases (fibromyalgia, systemic sclerosis, gout and autoimmune thyroiditis). PubMed/MEDLINE, EMBASE, elibrary.ru and Scielo databases were searched for targeted topic between 1966 and 2023. 15 articles were depicted to fulfill the inclusion criteria, 13 in Latin and 2 in Cyrillic scripts, including 1,499 patients (1,383 in osteoarthritis and 116 in other rheumatic diseases). The dosage varied from 200 mg to 1,200 mg/day. The follow-up ranged from 3 weeks to 24 months. Almost all studies (13/15) showed at least one benefit after S-adenosylmethionine

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therapy supplementation, including 2 papers documented positive effect in vitro achieved upon the cells taken from patients. Most side effects were mild, one study showed borderline moderate/severe adverse effects. Only pre-clinical/experimental studies of S-adenosylmethionine therapy effects on thyroid regulation were revealed. S-adenosylmethionine is a promising and safe element of complex therapy for some rheumatic diseases.

Keywords: S-adenosylmethionine, SAMe, methylation, rheumatic diseases, rheumatoid arthritis, systemic sclerosis, osteoarthritis, fibromyalgia, thyroid gland.

Introduction

S-adenosylmethionine (SAMe) was discovered in 1952, and it is an amino acid metabolite and enzyme co-substrate involved in multiple biochemical pathways, including the neurotransmitters and hormones production [1]. Deficiencies of vitamin B12 and folic acid, which are important co-factors for SAMe synthesis, may account for decreased SAMe levels. In addition, reduction of SAMe levels in cerebrospinal fluid has been also observed in patients with rare inherited defects in folate and methionine metabolism [2], and in more common diseases such as depressive disorders, Alzheimer's disease, and Parkinson's disease [3].

SAMe has been used in psychiatric and medical disorders in Europe. The supplement has been reported to exert clinically significant anti-inflammatory and analgesic effects [4]. In Russia there is some experience of its successful application in liver diseases and in experimental hepatic encephalopathy [5, 6]. While the mechanism remains unclear, SAMe does not appear to alter the eicosanoid system like non-steroidal anti-inflammatory drugs (NSAID) but may enhance proteoglycan biosynthesis and secretion [7]. Recently it has been shown that it may regulate the process of autophagy, thus influencing autoimmunity and inflammation. An additional mechanism may be regulation of gene methylation/activity [8, 9]. Systemic blood concentration of SAMe is regarded as an indicator of enhanced global transmethylation [10]. In several randomized controlled studies, including many patients, SAMe was as effective as NSAIDs in relieving pain in osteoarthritis (OA) [11–19].

Therefore, it is reasonable to systematically review the articles that evaluate SAMe therapy in various rheumatic diseases and co-morbid autoimmune pathology.

Methods

A systematic search of articles published in PubMed/MEDLINE, EMBASE, elibrary.ru and Scielo from 1966 to March 2023 using the following MeSH entry terms: "SAMe" OR "S-adenosylmethionine" and "rheumatic" OR "rheumatologic" OR "systemic lupus erythematosus" OR "lupus" OR "fibromyalgia" OR "rheumatoid arthritis" OR "spondyloarthritis" OR "Sjögren's syndrome" OR "myositis" OR "systemic sclerosis" OR "vasculitis" OR "Takayasu disease" OR "Wegener's disease" OR "granulomatosis with polyangiitis" OR "Kawasaki's disease" OR "polyarteritis nodosa" OR "Livedoid vasculitis" OR Churg-Strauss" OR "eosinophilic granulomatosis with polyangiitis" OR "osteoarthritis" OR "gout" OR "thyroid". The search had no language restrictions. The reference lists of the selected articles were analyzed to identify additional publications.

Three authors (JFC, AL and LPC) initially performed the literature search and independently selected the study abstracts. Then, in the second stage, the same reviewers

independently read the full-text articles selected by abstracts. Again, the authors followed PRISMA guidelines [20]. Finally, a standardized form was designed to extract the information from relevant articles, including authors, year of publication, number of patients studied, demographic data, disease duration, study follow-up, SAMe posology, outcomes, and side effects. The same work for Cyrillic script sources was performed by Russian part of the team (PAS, AAB, NYG and LPC).

Results

Table 1 summarizes the search results on SAMe treatment in OA. There are 8 articles in this field, including 1,383 patients. The countries that produced those articles were Germany (n = 3), Italy (n = 3), Argentina (n = 1), Korea (n = 1), and the United States (n = 1). Most studies performed a double-blind clinical trial as a study design (n = 8), and only one was an open trial. Age varied from 40 to 64.37 years old, and female gender ranged from 22.2 to 84 %. Disease duration went from 4.5 to 11.7 years. The SAMe dosage varied from 600 mg to 1,200 mg/day. The study time follow-up ranged from 3 weeks to 24 months.

All articles demonstrated improvements in diverse OA parameters. Pain intensity, patient's and physician's global assessments of response to therapy, and WOMAC index scores compared to placebo improved. When SAMe was compared to NSAID, no difference was observed, attesting to the fact that the supplement is as good as the pharmaceutical therapy of NSAID. No significant side effect was detected; however, mild gastrointestinal symptoms were the most common.

Table 2 shows the search results for the other rheumatic diseases [21–25]: three trials in fibromyalgia, 1 in systemic sclerosis, and 1 in gout with 110 patients. Concerning study design, most of them were double-blinded trials (n = 3), followed by case series (n = 1) and case report (n = 1). Italy was ahead by the number of studies (n = 2), followed by Denmark (n = 1), Germany (n = 1), and Malaysia (n = 1). In those studies, females predominated (from 20 to 82 %); age varied from 5.6 to 49 years old, and disease duration from 3.6 to 11 years. The study follow-up ranged from 3 weeks to 1 year. The SAMe dosage varied from 200 to 800 mg/day.

Regarding outcome, 4 out of 5 studies showed the benefits of SAMe in rheumatic diseases. The patients observed improved pain, functional parameters, fatigue, mood, and sleep. On the contrary, only one fibromyalgia study did not follow changes after supplementation. However, a trend was observed regarding pain, stiffness, and fatigue [21]. The other two studies verified improved systemic sclerosis parameters [25], and the patients with Lesch-Nyhan and gout get better neurological conditions [24]. Furthermore, in 4/5 of the studies, no side effects were observed, while in one study, moderate to severe reactions were seen, such as an anaphylactic reaction [21] (Table 2).

Two Russian language articles revealed both were biomedical and dedicated to preclinical SAMe use in rheumatoid arthritis (RA) [26, 27]. Using synovial cells from 6 patients with active RA, Russian authors have demonstrated that SAMe in vitro significantly increased the methylation of DNA in these target cells, also the production of pro-inflammatory cytokines in vitro by these cells could be noticeably decreased by SAMe in all cases. SAMe also decreased in vitro osteoprotegrin biosynthesis and migration/invasiveness of RA synovial cells.

Table 1. **Studies of SAMe in osteoarthritis**

Author, reference	Study design	Country	No.	Age (years old), gender	Disease duration	SAMe dose	Follow-up	Outcome	Side effects
Kim et al., 2009 [11]	Multicenter, Randomized, Double-Blind, Double-Dummy, Phase IV Study	Korea	134	63.9 ± 8.2, 84 % females	7.9 ± 6.3 years	400 mg TID	weeks	After 8 weeks, SAMe improved compared to baseline: — pain intensity; — although SAMe and ibuprofen were similar. Physician and patient's global assessment of response to therapy and WOMAC index scores did not differ	SAMe: 35.8 % vs. nabumetone 31.3 %, p = NS
Najm et al., 2004 [12]	Randomized double-blind cross-over trial; 20 weeks	The United States	61	53, 70 % females	11.7 ± 10.1 years	1,200 mg	16 weeks	In the first month of Phase 1, celecoxib showed significantly more reduction in pain than SAMe (p = 0.024). By the second month of Phase 1, both groups had no significant difference (p < 0.01)	Gastrointestinal and psychiatric mild side effects were the most common
Caruso & Pietrogrande, 1987 [13]	Double-Blind Multicenter	Italy	734	58.4 (27–75), 74 % females	6.1 years	1,200 mg	4 weeks	After 30 days, SAMe improved compared to the placebo: — standing up from a seat; — walking on a plane; — going upstairs; — diurnal pain; — functional limitation; — although SAMe and naproxen were similar	SAME had fewer side effects than naproxen, and they were equal to the placebo
Muller-Fassbender, 1987 [14]	Double-Blind Clinical Trial	Germany	36	54 (37–70), 22.2 % females	55 months	1,200 mg	4 weeks	SAMe improved compared to baseline: global clinical score; — total score of knee OA; — total score of hip OA; — total score of spine OA. Although SAMe and ibuprofen were similar	Well tolerated

End of the table 1

Author, reference	Study design	Country	No.	Age (years old), gender	Disease duration	SAMe dose	Follow-up	Outcome	Side effects
Konig, 1987 [15]	Long-term multicenter, open trial	Germany	108	62 ± 9, 55 % females	70 ± 61 months	600 mg for 2 weeks later supporting 40 mg	24 months	90 % of the physicians and > 85% of the patients assessed the efficacy of SAMe as being "very good" or "good". 18/97 became asymptomatic. The complaint score dropped from 20.3 to 4.5. Score of the mental state rating (feelings) dropped from 31.7 to 16.1	None
Macagno et al., 1987 [16]	Double-Blind Clinical Trial	Argentina	48	64.36 t 1.6; 68 % females	Not available	1,200 mg	12 weeks	Both SAMe and piroxicam improved: total pain score after 28 days of treatment; morning stiffness; the distance walked before the onset of pain, and active and passive motility improved about day 58 in both groups	4 patients in SAMe and 9 in the piroxicam group reported side effects. The adverse effects were mainly related to gastric intolerance
Vetter, 1987 [17]	Double-Blind Comparative Clinical Trial	Germany	36	64 ± 37 56 % females	73 ± 5.9 months	1,200 mg	4 weeks	SAMe improved compared to baseline: — global clinical score; — total score of knee OA; — total score of hip OA; — total score of spine OA. Although SAMe and indomethacin were similar	2 patients in the SAMe group had slight náusea. 11 % in SAMe vs. 3 % in the indomethacin group
Montrone et al., 1985 [18]	Double-Blind Clinical Trial	Italy	76	Not available	Not available	1,200 mg	3 weeks	SAMe improved compared to placebo: nigh pain, loading pain, pain poll, going upstairs and downstairs, standing up from a chair. Getting out of bed. "Difficulty in specific activity" pool	Gastrointestinal side effects were experienced in 3 patients receiving SAMe and in 6 of the placebo
Glorioso et al. 1985 [19]	Double-blind multicentre	Italy	150	Not available	Not available	400 mg thrice daily	30 days	SAMe exhibited a slightly more marked activity than the reference drug in managing the various painful manifestations	Minor side-effects: in 5 patients (SAMe) and 16 (ibuprofen)

Table 2. **Studies in SAMe use in fibromyalgia, gout, and systemic sclerosis**

Author, reference	Study design	Country	No., age, gender	Rheumatic disease	Disease duration	SAMe dose (mg/day)	Follow-up	Outcome	Side effects
Volkmann et al., 1997 [21]	Prospective, randomized, double-blind, cross-over, placebo-controlled	Germany	34, 49 ± 10, not available	Fibromyalgia	11 (2–42) years	600 mg i.v. or placebo daily for 10 days in a cross-over trial	30 days	No significant difference in improvement in tender point Count. There was a tendency towards statistical significance in favor of SAMe on the subjective perception of pain at rest (p=0.08), pain on movement (p=0.11), and overall well-being (p=0.17), and slight improvement only on fatigue, quality of sleep, morning stiffness, and on the Fibromyalgia Impact Questionnaire for pain	4 patients (SAMe) withdrew: 2 severe nausea/vomiting and diarrhea; 1 anaphylactic reaction. Most patients had mild effects equal to a placebo
Jacobsen et al., 1991 [22]	Double-Blind Clinical Trial	Denmark	44, 49.8, 82 % females	Fibromyalgia	4.5 years	800 mg	16 weeks	SAMe improved: — clinical disease activity; — pain experienced during the last week; — fatigue; — morning stiffness; — mood evaluated by Face Scale	Equal to a placebo

End of the table 2

Author, reference	Study design	Country	No., age, gender	Rheumatic disease	Disease duration	SAMe dose (mg/day)	Follow-up	Outcome	Side effects
Tavoni et al., 1987 [23]	Ddouble-blind crossover trial	Italy	17, 44.5, not available	Fibromyalgia	7 years	200 mg or placebo for 21 days by intramuscular administration and then, after a 2 weeks wash-out period, therapy was switched to the agent	3 weeks	SAMe caused a significant decrease in pain, evaluated as the number of trigger points plus painful anatomic sites. Hamilton and the SAD (Scala di Autovalutazione per la Depression) scales decreased significantly after	Apart from the abscesses at the injection sites, no significant side effects were noted during the study
Chen et al., 2014 [24]	Case series	Malaysia	5, 5.6, 80 % males	Gout secondary to Lesch-Nyhan disease	3.6 years	21 to 38 mg/kg/day	1 year	Dramatic reductions of self-injury and aggressive behavior, as well as a milder reduction of dystonia was observed in all 5 patients. No description of uric acid evolution	Not available
Oriente et al., 1985 [25]	Case report	Italy	10, not available, 100 % females	Systemic sclerosis (6 systemic sclerosis, 3 morphea, and 1 sclerodactyly)	Not available	600 mg daily i.v. in the first two months, subsequently 400 mg 3 times daily per os	6 months	After 4 months: 5 patients (3 with PSS, 2 with morphea) exhibited significant improvement in their indurative skin. 5 other patients (3 PSS, 1 morphea, 1 sclerodactyly) did not present any significant increase in cutaneous elasticity after 6 months' medication	None

No clinical papers on SAMe use in autoimmune thyroid disease was found. Although few pre-clinical and experimental biomedical findings allowing to relate SAMe and pathogenesis of these diseases exist. Thus, SAMe increased affinity of thyrotropin receptor to its ligand in vitro [28]. Anti-thyroid inhibitor thiouracil increases the SAMe level [29].

Discussion

This is the first study to systematically review the therapeutic effects of SAMe in many rheumatic and related autoimmune diseases.

In a biochemical basis, SAMe is involved in three main metabolic routes: 1) methylation, it is the main font of methyl groups in the human body; 2) trans-sulfuration, while SAMe forms S-adenosylhomocysteine and then homocysteine which can be converted to cystathionine then to cysteine and the sulfate that is available to other metabolic routes; 3) aminopropylation, while SAMe participates in the synthesis of polyamines which can eventually recycle as methionine [30, 31].

The specific mechanism of action of SAMe in reducing pain in OA patients needs to be discover. There is hypothesis that SAMe may be a COX-2 inhibitor. Furthermore, *in vitro* studies in chondrocytes have demonstrated increased levels of proteoglycan production and proliferation rates [32, 33]. In addition, SAMe may reduce inflammatory mediators, including tumor necrosis factor (TNF)-alpha and fibronectin [34]. In turn, SAMe-dependent polyamines also may render some anti-inflammatory effects [35].

Regarding SAMe in OA, the benefits of this supplementation in this degenerative disorder are evident. Almost all articles demonstrated efficacy similar to NSAIDs with minor side effects. Concerning SAMe mechanism of action in OA, studies in animals and *in vitro* suggested that SAMe reduces inflammation and induces proteoglycan synthesis [34].

Randomized, double-blind clinical trials have been conducted evaluating SAMe, and most of them compared SAMe to NSAIDs [11–16, 36, 37]. The studies revealed similar effects on pain reduction and function improvement when SAMe was comapred with NSAIDs. Although, SAMe groups had much less adverse events.

Interestingly, two meta-analyses concluded that the pain and functional improvements caused by SAMe were similar to those of NSAIDs [36, 37].

This review has some strengths that are: 1) the inclusion of studies with patients fulfilling the international criteria for rheumatic diseases; 2) the inclusion of all kinds of study designs using SAMe in rheumatic diseases, except reviews, animal studies, and *in vitro* studies. Applying the inclusion criteria, it is assumed that all published articles of SAMe in rheumatic patients were collected. Not only Latin script written, but also Cyrillic script written sources were covered.

Some limitations were seen in this study. No comparison between classical pharmacological therapies commonly used in rheumatic diseases was available for conditions other than OA. In addition, with the exception of OA studies, the number of participants was low, and the follow-up was short for the investigated diseases. Therefore, new studies should include larger patient samples with a more long-term observation, enabling a better understanding of SAMe therapy in rheumatic conditions.

Careful consideration of pursuing treatment with SAMe, as opposed to a registered NSAID or antidepressant, is required by the clinician and the patient. Clinicians

recommending SAMe must inform their patients that this compound has not been tested as rigorously as its counterparts approved by Federal Drug Administration (FDA) or analogous national services of other countries. As such, its relative efficacy cannot be guaranteed. However, the risks of SAMe are still generally speaking lower when compared with the NSAIDs (with their gastrointestinal bleeding, renal failure, etc.) and antidepressants, particularly in SAMe in which sexual dysfunction or weight gain, are not seen. No cases of death by SAMe overdose have been reported. In a mouse study, a lethal oral dose of SAMe was equivalent to over 400,000 mg in a 70 kg man (National Library of Medicine, 1999 RTECS (Registry of Toxic Effects of Chemical Substances), Bethesda, MD, Record Nos. 7176, 7177). At the same time, various comorbidities and specifics of individual anamnesis should always be taken into account when SAMe treatment is considered. Thus, it is known that fibromyalgia, rheumatic and related autoimmunity conditions may be provoked in many individuals by COVID-19 [38]. SAMe, although therapeutically effective in these disorders, at the same time was shown to be positively related to COVID-19 lung involvement severity, because transmethylation is essential for SARS-CoV-2 replication [10, 39]. It means that SAMe therapy is possible for such patients only after elimination of acute viral infection, in appropriate patterns of post-COVID syndrome, but in virus-negative state.

Although the cost of SAMe is not covered by insurance companies, compared with the high co-payments on many prescriptions, it may be a reasonable expense. Patients should be discouraged from self-medicating their diseases and encouraged to seek professional evaluation before starting any treatment.

Conclusion

A few articles evaluated the effects of SAMe in rheumatological diseases, and only four conditions (OA, fibromyalgia, scleroderma, and Lesch-Nyhan) were addressed in the literature. Nevertheless, almost all analyzed studies demonstrated that SAMe use is efficacious in treating rheumatic diseases, with rare and mild side effects. Therefore, it can be concluded that SAMe emerges as an exciting option to be explored in rheumatological conditions.

Highlight key points:

1. S-adenosylmethionine (SAMe) has been used to treat some rheumatic disorders.
2. This article systematically reviews the use of SAMe in osteoarthritis (OA), fibromyalgia, systemic sclerosis, and gout.
3. Almost all studies demonstrated at least one benefit after SAMe supplementation: pain intensity, fatigue, and functional parameters.
4. Most side effects were mild or absent.

References

1. Bottiglieri T., Laundy M., Martin R., Carney M. W., Nissenbaum H., Toone B. K., Johnson A. L., Reynolds E. H. S-adenosylmethionine influences monoamine metabolism. *The Lancet,* 1984, vol. 324, p. 224.
2. Surtees R., Leonard J., Austin S. Association of demyelination with deficiency of cerebrospinal-fluid s-adenosylmethionine in inborn errors of methyl-transfer pathway. *Lancet,* 1991, vol. 338, pp. 1550–1554.

3. Bottiglieri T., Godfrey P., Flynn T., Carney M. W., Toone B. K., Reynolds E. H. Cerebrospinal fluid s-adenosylmethionine in depression and dementia: Effects of treatment with parenteral and oral s-adenosylmethionine. *J. Neurol. Neurosurg. Psychiatry*, 1990, vol. 53, pp. 1096–1098.
4. Hardy M. L., Coulter I. D., Favreau J. T., Morton S. C., Venuturupalli S. R., Chiapelli F., Rossi F., Orshansky G., Jungvig L. K., Roth E. A., Suttorp M. J., Shekelle P. S-adenosyl-L-methionine for treatment of depression, osteoarthritis, and liver disease. *Evid. Rep. Technol. Assess. (Summ.),* 2003, vol. 64, pp. 1–3.
5. Baranovskij A. Yu., Rajhel'son K. L., Marchenko N. V. The use of s-adenosylmethionine (heptral®) in the treatment of patients with non-alcoholic steatohepatitis. *Klinicheskie perspektivy gastroenterologii, gepatologii,* 2010, vol. 1, pp. 3–10. (In Russian)
6. Lukivskaya O. Ya., Belonovskaya E. B., Naruta E. E., Kuz'mickaya I. A., Kirko S. N., Buko V. U. S-adenosylmethionine for the correction of experimental hepatic encephalopathy. *Hepatology and gastroenterology,* 2019, vol. 3, no. 2, pp. 166–171. (In Russian)
7. di Padova C. S-adenosylmethionine in the treatment of osteoarthritis. Review of the clinical studies. *Am. J. Med.,* 1987, vol. 83, pp. 60–65.
8. Ouyang Y., Wu Q., Li J., Sun S., Sun S. S-adenosylmethionine: A metabolite critical to the regulation of autophagy. *Cell Prolif.,* 2020, vol. 53, no. 11, e12891. https://doi.org/10.1111/cpr.12891
9. Pascale R. M., Simile M. M., Calvisi D. F., Feo C. F., Feo F. S-Adenosylmethionine: From the Discovery of Its Inhibition of Tumorigenesis to Its Use as a Therapeutic Agent. *Cells,* 2022, vol. 11, no. 3, p. 409. https://doi.org/10.3390/cells11030409
10. Kryukov E. V., Ivanov A. V., Karpov V. O., Aleksandrin V. V., Dygai A. M., Kruglova M. P., Kostiuchenko G. I., Kazakov S. P., Kubatiev A. A. Plasma S-Adenosylmethionine Is Associated with Lung Injury in COVID-19. *Dis. Markers,* 2021, vol. 2021, e7686374.
11. Kim J., Lee E. Y., Koh E. M., Cha H. S., Yoo B., Lee C. K., Lee Y. J., Ryu H., Lee K. H., Song Y. W. Comparative clinical trial of S-adenosylmethionine versus nabumetone for the treatment of knee osteoarthritis: an 8-week, multicenter, randomized, double-blind, double-dummy, Phase IV study in Korean patients. *Clin. Ther.,* 2009, vol. 31, no. 12, pp. 2860–2872.
12. Najm W. I., Reinsch S., Hoehler F., Tobis J. S., Harvey P. W. S-adenosyl methionine (SAMe) versus celecoxib for the treatment of osteoarthritis symptoms: a double-blind cross-over trial. [ISRCTN36233495]. *BMC Musculoskelet Disord.,* 2004, vol. 5, p. 6.
13. Caruso I., Pietrogrande V. Italian double-blind multicenter study comparing S-adenosylmethionine, naproxen, and placebo in the treatment of degenerative joint disease. *Am. J. Med.,* 1987, vol. 83, no. 5ª, pp. 66–71.
14. Müller-Fassbender H. Double-blind clinical trial of S-adenosylmethionine versus ibuprofen in the treatment of osteoarthritis. *Am. J. Med.,* 1987, vol. 83, no. 5ª, pp. 81–83.
15. König B. A long-term (two years) clinical trial with S-adenosylmethionine for the treatment of osteoarthritis. *Am. J. Med.*, 1987, vol. 83, no. 5ª, pp. 89–94.
16. Maccagno A., Di Giorgio E. E., Caston O. L., Sagasta C. L. Double-blind controlled clinical trial of oral S-adenosylmethionine versus piroxicam in knee osteoarthritis. *Am. J. Med.,* 1987, vol. 83, no. 5ª, pp. 72–77.
17. Vetter G. Double-blind comparative clinical trial with S-adenosylmethionine and indomethacin in the treatment of osteoarthritis. *Am. J. Med.*, 1987, vol. 83, no. 5ª, pp. 78–80.
18. Montrone F., Fumagalli M., Sarzi Puttini P., Boccassini L., Santandrea S., Volpato R., Locati M., Caruso I. Double-blind study of S-adenosyl-methionine versus placebo in hip and knee arthrosis. *Clin. Rheumatol.,* 1985, vol. 4, no. 4, pp. 484–485.
19. Glorioso S., Todesco S., Mazzi A., Marcolongo R., Giordano M., Colombo B., Cherie-Ligniere G., Mattara L., Leardini G., Passeri M. Double-blind multicentre study of the activity of S-adenosylmethionine in hip and knee osteoarthritis. *Int. J. Clin. Pharmacol. Res.,* 1985, vol. 5, no. 1, pp. 39–49.
20. Page M. J., McKenzie J. E., Bossuyt P. M., Boutron I., Hoffmann T. C., Mulrow C. D., Shamseer L., Tetzlaff J. M., Akl E. A., Brennan S. E., Chou R., Glanville J., Grimshaw J. M., Hróbjartsson A., Lalu M. M., Li T., Loder E. W., Mayo-Wilson E., McDonald S., McGuinness L. A., Stewart L. A., Thomas J., Tricco A. C., Welch V. A., Whiting P., Moher D. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*, 2021, vol. 372, p. 71.
21. Volkmann H., Nørregaard J., Jacobsen S., Danneskiold-Samsøe B., Knoke G., Nehrdich D. Double-blind, placebo-controlled cross-over study of intravenous S-adenosyl-L-methionine in patients with fibromyalgia. *Scand. J. Rheumatol.*, 1997, vol. 26, no. 3, pp. 206–211.

22. Jacobsen S., Danneskiold-Samsøe B., Andersen R. B. Oral S-adenosylmethionine in primary fibromyalgia. Double-blind clinical evaluation. *Scand. J. Rheumatol.,* 1991, vol. 20, no. 4, pp. 294–302.
23. Tavoni A., Vitali C., Bombardieri S., Pasero G. Evaluation of S-adenosylmethionine in primary fibromyalgia. A double-blind crossover study. *Am. J. Med.,* 1987, vol. 83, no. 5[a], pp. 107–110.
24. Chen B. C., Balasubramaniam S., McGown I. N., O'Neill J. P., Chng G. S., Keng W. T., Ngu L. H., Duley J. A. Treatment of Lesch-Nyhan disease with S-adenosylmethionine: Experience with five young Malaysians, including a girl. *Brain Dev.*, 2014, vol. 36, no. 7, pp. 593–600.
25. Oriente P., Scarpa R., Biondi C., Riccio A., Farinaro C., Del Puente A. Progressive systemic sclerosis and S-adenosylmethionine. *Clin. Rheumatol.*, 1985, vol. 4, no. 3, pp. 360–361.
26. Shnajder M. A., Kalinovskaya N. Yu. Pleiotropic effect of DNA methylation modulators on synovial fibroblasts of patients with rheumatoid arthritis in vitro. *Russian Journal of Immunology,* 2019, vol. 13, no. 2-1 (22), pp. 663–635. (In Russian)
27. Shnajder M. A., Shirinskij V. S., Kalinovskaya N. Yu., Shirinskij I. V. Effect of DNA methylation modulators on osteoprotegerin production by rheumatoid fibroblast-like synoviocytes in vitro, their migration and invasion. *Bulletin of Siberian Medicine,* 2019, vol. 18, no. 3, pp. 116–124. (In Russian)
28. Shishiba Y., Ozawa Y. The effect of S-adenosyl methionine on the TSH receptor function in human thyroid tissue: increase in binding of TSH and decrease in adenylate cyclase coupling. *Endocrinol. Jpn.,* 1982, vol. 29, no. 5, pp. 589–592. https://doi.org/10.1507/endocrj1954.29.589
29. Keating J. N., Kusano G., Stokstad E. L. Effect of thiouracil in modifying folate function in severe vitamin B12 deficiency. *Arch. Biochem. Biophys.*, 1988, vol. 267, no. 1, pp. 119–124. https://doi.org/10.1016/0003-9861(88)90015-x
30. Friedel H. A., Goa K. L., Benfield P. S-adenosyl-L-methionine. A review of its pharmacological properties and therapeutic potential in liver dysfunction and affective disorders concerning its physiological role in cell metabolism. *Drugs,* 1989, vol. 38, pp. 389–416.
31. Bottiglieri T. S-Adenosyl-L-methionine (SAMe): From the bench to the bedside- molecular basis of a pleiotropic molecule. *Am. J. Clin. Nutr.,* 2002, vol. 76, 1151S-7S.
32. Harmand M. F., Vilamitjana J., Maloche E., Duphil R., Ducassou D. Effects of S-adenosylmethionine on human articular chondrocyte differentiation. An in vitro study. *Am. J. Med.,* 1987, vol. 83, pp. 48–54.
33. Barcelo H. A., Wiemeyer J. C., Sagasta C. L., Macias M., Barreira J. C. Effect of S-adenosylmethionine on experimental osteoarthritis in rabbits. *Am. J. Med.,* 1987, vol. 83, pp. 55–59.
34. Gutierrez S., Palacios I., Sanchez-Pernaute O., Gutierrez S., Palacios I., Sánchez-Pernaute O., Hernández P., Moreno J., Egido J., Herrero-Beaumont G. SAMe restores the changes in the proliferation and the synthesis of fibronectin and proteoglycans induced by tumor necrosis factor-alpha on cultured rabbit synovial cells. *Br. J. Rheumatol.,* 1997, vol. 36, pp. 27–31.
35. Colombatto S., Fasulo L., Grillo M. A. Polyamines in rat liver during experimental inflammation. *Agents Actions,* 1988, vol. 24, no. 3–4, pp. 326–330.
36. Soeken K. L., Lee W. L., Bausell R. B., Agelli M., Berman B. M. Safety and efficacy of S-adenosylmethionine (SAMe) for osteoarthritis. *J. Fam. Pract.*, 2002, vol. 51, no. 5, pp. 425–430.
37. Witte S., Lasek R., Victor N. Wirksamkeit von Ademetionin und Oxaceprol für die Behandlung von Arthrosen Eine Metaanalyse. *Orthopade,* 2002, vol. 31, pp. 1058–1065.
38. Ehrenfeld M., Tincani A., Andreoli L., Cattalini M., Greenbaum A., Kanduc D., Alijotas-Reig J., Zinserling V., Semenova N., Amital H., Shoenfeld Y. COVID-19 and autoimmunity. *Autoimmun Rev.,* 2020, vol. 19, no. 8, e102597.
39. Kottur J., White K. M., Rodriguez M. L., Rechkoblit O., Quintana-Feliciano R., Nayar A., García-Sastre A., Aggarwal A. K. Structures of SARS-CoV-2 N7-methyltransferase with DOT1L and PRMT7 inhibitors provide a platform for new antivirals. *PLoS Pathog.,* 2023, vol. 19, no. 7, e1011546.

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Authors' information:

Jozélio Freire de Carvalho — MD, Professor; jotafc@gmail.com jotafc@gmail.com
Leonid P. Churilov — MD, PhD in Medicine, Associate Professor; l.churilov@spbu.ru, elpach@mail.ru
Aaron Lerner — MD, Professor, Senior Scientist; aaronlerner1948@gmail.com
Polina A. Sobolevskaya — Researcher; dr.polinasobolevskaia@bk.ru
Alena A. Basina — Student; a.a.lamova@mail.ru
Natalia Yu. Gavrilova — MD, PhD in Medicine; fromrussiawithlove_nb@mail.ru

Лечение ревматических и связанных с ними аутоиммунных заболеваний с применением S-аденозилметионина*

Ж. Ф. де Карвальо[1], Л. П. Чурилов[2,3], А. Лернер[4,5], П. А. Соболевская[2], А. А. Басина[2], Н. Ю. Гаврилова[2,6]

[1] Научный центр хронических неинфекционных заболеваний (NUPEN), Бразилия, 40110-909, Сальвадор, Канела, Паласио да Рейтория, Руа Аугусто Виана
[2] Санкт-Петербургский государственный университет, Российская Федерация, 199034, Санкт-Петербург, Университетская наб., 7–9
[3] Санкт-Петербургский научно-исследовательский институт фтизиопульмонологии, Российская Федерация, 191036, Санкт-Петербург, Лиговский пр., 2–4
[4] Исследовательский центр аутоиммунных заболеваний им. П. Заблудовича, Израиль, 52621, Рамат Ган, Дерех Шиба, 2
[5] Ариэльский университет, Израиль, 40700, Ариэль, ул. Рамат ха-Голан, 65
[6] Клиника высоких медицинских технологий им. Н. И. Пирогова Санкт-Петербургского государственного университета, Российская Федерация, 190103, Санкт-Петербург, наб. реки Фонтанки, 154

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S-аденозилметионин (SAMe) использовался для лечения нервных и психиатрических заболеваний, включая сопровождаемые депрессией. Эти нарушения нередко сочетаются с ревматологической и тиреоидной патологией, причем данные коморбидные поражения в период и после пандемии COVID-19 наблюдаются все чаще, в связи с чем была произведена оценка применения S-аденозилметионина для лечения ревматологических заболеваний и сопутствующих тиреопатий. Был проведен систематический обзор использования S-аденозилметионина для ревматических заболеваний, таких как остеоартрит, фибромиалгия, системная склеродермия и подагра; изучен описанный в специализированных источниках опыт применения S-аденозилметионина при лечении аутоиммунных заболеваний щитовидной железы, часто сочетающихся с ревматическими. В наукометрических базах данных PubMed/MEDLINE, EMBASE, elibrary.ru и Scielo был произведен поиск статей о применении S-аденозилметионина при ревматических заболеваниях и сопутствующей патологии щитовидной железы в период с 1966 по март 2023 г. 15 статей соответствовали критериям включения, 13 из них написаны на латинице, 2 — на кириллице, суммарно они содержали сведения о 1499 пациентах. Дозировка S-аденозилметионина варьировала от 200 до 1200 мг в сутки. Период наблюдения составлял от 3 недель до 24 месяцев. Почти все исследования (13/15) показали по крайней мере одно преимущество после приема добавок S-аденозилметионина: снижение интенсивности боли, утомляемости и улучшение функциональных параметров, включая две работы, в которых был задокументирован положительный эффект in vitro с клетками, взятыми у пациентов с ревматоидным артритом. Хотя большинство побочных эффектов были умеренными, одно исследование зафиксировало пограничные с тяжелыми побочные эффекты. Клинический опыт применения S-аденозилметионина при аутоиммунных заболеваниях щитовидной железы не описан в литературе, хотя существуют преклинические/экспериментальные

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исследования влияния S-аденозилметионина на регуляцию функций щитовидной железы. Настоящий систематический обзор показывает, что S-аденозилметионин может служить многообещающим и безопасным элементом комплексного лечения при некоторых ревматических заболеваниях. Однако требуется большее количество данных, полученных в более обширных, хорошо спланированных и контролируемых исследованиях.

Ключевые слова: S-аденозилметионин, SAMe, метилирование, ревматические заболевания, ревматоидный артрит, системный склероз, остеоартрит, фибромиалгия, щитовидная железа.

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Контактная информация:

де Карвальо Жозелио Фрейре — д-р мед. наук, проф.; jotafc@gmail.com
Чурилов Леонид Павлович — канд. мед. наук, доц.; elpach@mail.ru
Лернер Аарон — д-р мед. наук, проф.; aaronlerner1948@gmail.com
Соболевская Полина Анатольевна — науч. сотр.; dr.polinasobolevskaia@bk.ru
Басина Алёна Алексеевна — студент; a.a.lamova@mail.ru
Гаврилова Наталия Юрьевна — канд. мед. наук; fromrussiawithlove_nb@mail