



DOSSIER · SUBSTANCE

S-Adenosylmethionine (SAMe)

S-Adenosylmethionine is a methyl-group donor of one-carbon metabolism. Visibility of the topic stems predominantly from basic-research and review articles; the number of human studies remains below thirty. Notably, the most-cited controlled trials almost all concern depressive disorders, whereas the recorded application areas lead with cognition and the musculoskeletal system.

69

STUDIES IN
TOTAL

29

IN HUMANS

19

OF WHICH
CONTROLLED

10

IN ANIMALS

3

IN THE LAB

Figures from the IHR study database · Last updated 2026-10-16

How to Read This Dossier

ESTABLISHED

measured in humans, with a comparison group

PLAUSIBLE

supported by mechanism, animal studies or observation

HYPOTHESIS

a likely connection that still needs to be tested

S-Adenosylmethionine (SAmE) at a Glance

ORIGIN:
S-Adenosylmethionine (SAmE) is not a plant substance but a metabolite of one-carbon metabolism. Studies describe it as a methyl-group carrier and thus a participant in methylation reactions, including epigenetic markings. Reviews classify SAmE as a possible epigenetic agent.

EVIDENCE BASE:
69 evaluated studies · 19 controlled human studies · 10 observational studies · 10 reviews · 10 animal studies · 1 cell-culture study

- STRONGEST EVIDENCE:**
- Depression: meta-analysis [2] with 23 randomised controlled trials and 2183 participants — superior to placebo (SMD = -0.58; 95 % CI -0.93 to -0.23), moderate certainty of evidence.
 - Depression: in the twelve-week randomised trial [6] SAmE was superior to placebo in men (n = 51) (4.3 points; p = 0.034; d = 0.95), while women (n = 62) showed no significant change.
 - Liver values: in the systematic review [4] both placebo-controlled randomised trials reported significant reductions in serum ALT levels under AdoMet versus placebo within 2 weeks.
 - Central-nervous-system signs: [49] screened 1881 studies and included 36; 32 of these reached 4 or 5 out of 5 quality points, and SAmE was effective in 24 of 36 studies.
 - Safety: the phase-1 study [42] tested an enteric-coated tablet with ascending single doses in 8 healthy volunteers and subsequently in 26 participants in a cross-over design.

- LIMITATIONS:**
- Reviews on the same topic reach differing results: [29] found, with 14 studies and 1522 participants, no significant difference in any of the three comparisons.
 - Cognition and dementia: the pooled analysis in [5] showed no significant differences, and the phase-2 study [44] did not meet its primary endpoint p-tau217 (p = 0.288).
 - Oral preparations are, according to the pharmacokinetic investigation, not readily interchangeable; monotherapy, addition to escitalopram, dose escalation and probiotic combinations complicate comparison.

CLASSIFICATION:
SAmE is a methyl-group donor for which randomised trials and meta-analyses exist in depressive disorders, while other areas of application and epigenetics remain open questions.

1. What S-Adenosylmethionine Is

S-Adenosylmethionine (SAmE) is not a plant substance but a **metabolite** of one-carbon metabolism. Reviews therefore classify SAmE alongside choline and valproic acid as a possible epigenetic agent, and a 2026 study examines it as an epigenetic treatment for depression in adults with childhood trauma. A 2020 basic-research study describes SAmE as a metabolite that regulates autophagy. Another from 2022 describes that an excess of SAmE can inhibit methylation via breakdown to adenine. Such findings originate from basic research and were not obtained in humans.

For the assessment of all studies, **uptake** is decisive. A pharmacokinetic study in healthy persons examined a newer oral formulation, with dose escalation, the influence of a meal and a comparison with a commercially available food supplement; formulation and food intake therefore alter bioavailability. Oral preparations are consequently not readily interchangeable. Equally important is **measurement**: SAmE belongs to the epigenetically relevant metabolites that can be captured in targeted metabolomic procedures. A measured level is nevertheless a marker and not a disease course. In addition there are differing **designs** — monotherapy, addition to escitalopram, dose escalation and combination with probiotic strains — that complicate comparison across studies.

2. What the Studies Show in Detail

The supporting human studies and the most important reviews — by area of application, with population, duration, preparation, outcome measure and result as reported in the original studies. Numbers appear only where the study states them.

Distribution of **controlled human studies** by area of application — the numbers are not additive, as one study may be assigned to several areas:

AREA OF APPLICATION	CONTROLLED STUDIES
Cognition and psyche	12
Bones and joints	5
Musculoskeletal system	5
Safety and tolerability	4
Fatigue and stress	3
Uptake and bioavailability	1

AREA OF APPLICATION	CONTROLLED STUDIES
Metabolism	1

Cognition and Psyche

Two reviews with meta-analysis map the same area differently. [2] included 23 randomised controlled trials with a total of 2183 participants and assigned them to three comparisons: eleven studies tested SAmE versus placebo, five SAmE added to antidepressants versus placebo added to antidepressants, seven SAmE versus antidepressants. Versus placebo a superior effect on depressive symptoms emerged (SMD = -0.58; 95 % CI -0.93 to -0.23; $I^2 = 68\%$), whereas as an adjunct to antidepressants no significant difference appeared (SMD = -0.22; 95 % CI -0.63 to 0.19; $I^2 = 76\%$) and in direct comparison with antidepressants likewise none (SMD = 0.06; 95 % CI -0.06 to 0.18; $I^2 = 49\%$); discontinuation rates did not differ in any of the three comparisons, and the certainty of evidence for the placebo comparison is rated moderate. The second review [29] evaluated 14 studies with 1522 participants, with daily doses of 200 to 3200 mg and durations of 2 to 12 weeks, and found no significant difference in any of the three comparisons — monotherapy versus placebo, versus imipramine or escitalopram, adjunctive therapy versus placebo. **Hypothesis:** The divergence between the two reviews could be due to the differing number of included studies and to the fact that part of the comparisons in [2] concern combinations with antidepressants.

Two further reviews outline the framework. [40] searched MEDLINE/PubMed without language or time limits and included randomised controlled trials as well as open human studies; SAmE is described therein as a precursor molecule of several biochemical reactions, and several randomised studies are said to have supported that the antidepressant efficacy of monotherapy is superior to placebo and tricyclic antidepressants. [22] screened six databases and included 132 studies, of which 115 were clinical trials and 17 preclinical studies; the spectrum ranges from major depression through perinatal depression, HIV, Parkinson's, Alzheimer's, dementia, anxiety, schizophrenia and 22q11.2 to substance use, fibromyalgia, osteoarthritis, hepatitis and cirrhosis. [49] followed the PRISMA procedure, screened 1881 non-redundant studies and included 36 that concerned central-nervous-system signs such as mood, behaviour and sleep; 32 of the 36 studies reached 4 or 5 out of 5 quality points, and SAmE was effective in 24 of 36 studies.

[46] tested in an eight-week, double-blind, randomised study 800 mg/day SAmE as monotherapy versus placebo in 49 persons with a diagnosis of major depression who were not taking antidepressants and had mild to moderate symptoms (MADRS 14 to 25). On the primary endpoint a differential reduction of 3.76 points in favour of SAmE emerged, which in the adjusted linear mixed model was not significant at $p = 0.13$, with a medium to large effect size of 0.72; the placebo response rate was 53 % (more than 50 % reduction on the MADRS). [6] analysed data from a two-centre, twelve-week, double-blind randomised trial with 189 adults in which SAmE was tested against placebo and against the selective serotonin-reuptake inhibitor escitalopram. Separated by sex, SAmE was superior to placebo in men ($n = 51$) (4.3-point difference on the 17-item Hamilton Depression Scale; $p = 0.034$; $d = 0.95$), while women ($n = 62$) showed no significant change, although baseline depression severity was comparable between the sexes. The authors consider the underlying mechanism largely unknown and call for replication in independent samples.

The values for depression severity decreased markedly in all three arms, without differences within the groups and without differences between the higher doses of the three arms. Abdominal complaints occurred under the higher SAmE dose in 31.3 % of those treated, under escitalopram in 8.7 % and under placebo in 3.8 % ($\chi^2 = 7.32$; $p = 0.026$); the work cites sample size as a limitation. [45] examined in a monocentric, randomised, double-blind, placebo-controlled cross-over study a combination preparation of SAmE (200 mg/day) and two probiotics (Lactobacillus helveticus Rosell®-52 and Bifidobacterium longum Rosell®-175, 3×10^9 CFU/day) in 80 persons with subclinical and mild to moderate depression over three months, followed by six weeks of follow-up; the values on the Hamilton Depression Scale and in the Patient Health Questionnaire-9 decreased significantly. Both components were given together, so the change cannot be attributed to either one alone.

Cognition and Dementia

[5] evaluated in a systematic review with meta-analysis randomised controlled studies in animals and humans published between 1 January 2002 and 1 January 2022. In the pooled analysis the authors report for the animal studies ($p = 0.213$) and for the human studies ($p = 0.047$) that no significant differences existed between SAM administration and the control group. In the subgroup analyses animals aged up to 8 weeks ($p = 0.027$) and an intervention duration of more than 8 weeks ($p = 0.009$) were associated with significant results. Age of the animals and treatment duration thereby become an independent examination point of the question.

[44] examined in a multicentre, randomised, double-blind, placebo-controlled phase-2 study SAmE in 63 persons with a clinical diagnosis of Alzheimer's over 180 days at a dose of 400 mg daily. The primary endpoint was the change in plasma concentration of phosphorylated tau (p-tau217); administration of SAmE was therefore measured against a laboratory value, not against a clinical course. The mean percentage change amounted to an increase of 53.22 (standard deviation 159.19) in the SAmE group versus 25.34 (standard deviation 94.83) in the placebo group (standardised mean difference 37.58; 95 % CI -32.61 to 107.76; $p = 0.288$). Safety, tolerability and the cognitive secondary endpoints did not differ between the groups; SAmE proved safe and well tolerated at the tested dose and duration, without a measurable difference in the examined endpoints. The study leaves open whether supplementation alters disease progression.

Epigenetics and Pregnancy

[15] investigated in a randomised, double-blind, placebo-controlled study with six-month follow-up for the first time in humans an epigenetic treatment in 31 adults with trauma-related depression. Participants received 1200 mg SAmE or placebo for twelve weeks in addition to trauma-focused psychotherapy. Depression severity was assessed with the Hamilton Depression Scale, plasma SAmE levels as well as genome-wide DNA methylation including epigenome-wide association analyses, analyses of differentially methylated regions and measurements of epigenetic clocks. 28 participants completed the study. Depressive symptoms decreased markedly during treatment and remained improved at follow-up, reflecting the effect of the psychotherapy, without clinical additional benefit from SAmE administration; supplementation did not alter plasma SAmE levels. The treatment was, however, associated with differential methylation across 66 regions, while the epigenetic clocks showed no consistent treatment-related changes. A measurable epigenetic effect therefore exists alongside an absent clinical effect — the two levels are to be read separately in this investigation.

[35] classifies SAME as the most effective methyl-group donor alongside choline and valproic acid; it is described that these substances alter gene expression and can mitigate neurobehavioural changes in disorders of epigenetic origin such as autism spectrum disorder, depression, Rett syndrome and foetal alcohol spectrum disorder. According to the statements, valproic acid and SAME act as antagonistic epigenetic modulators, whether administered in utero or after birth; valproic acid is a significant human teratogen and should be avoided by pregnant women if possible. In experimental animals each of the substances mitigated the severity of several known diseases by triggering epigenetic changes. **Plausible:** That administration of methyl groups shifts methylation patterns is the starting point of the approach; whether a benefit for the child's development follows from this has not yet been examined in humans, and most data originate from animal experimental studies.

Liver and Bile

[4] investigated in a systematic review the early efficacy of AdoMet in adults with intrahepatic cholestasis; studies on intravenous, intramuscular or oral administration within 8 weeks after start of treatment were considered. Of the nine included works three were randomised: two double-blind and placebo-controlled, one comparatively controlled with unclear blinding and relatively high risk of bias; six non-randomised studies were added. The mean serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and gamma-glutamyltransferase (γGT) under AdoMet versus placebo, comparator substance or baseline value as well as changes in cholestasis symptoms reported by the patients were summarised. Both placebo-controlled randomised studies reported significant reductions in serum ALT levels under AdoMet versus placebo within 2 weeks. The reductions in serum ALT levels therefore refer to the first two treatment weeks of the two placebo-controlled randomised studies; how the values develop thereafter remains a separate question.

[23] pursued the question of whether protein SUMOylation in polycystic liver diseases is therapeutically targetable and used SAME as an inhibitor of the SUMOylation enzyme UBC9. In polycystic human and rat liver tissue as well as in cultured cystic cholangiocytes most SUMOylation-associated genes were overexpressed at mRNA level; in human cystic cholangiocytes in culture the levels of SUMOylated proteins were elevated and decreased after SAME administration. Chronic treatment of polycystic PCK rats with a Pkd1 mutation with SAME stopped hepatic cystogenesis and fibrosis and lowered the liver-to-body-weight ratio as well as liver volume. The findings originate from cell-culture and animal models and are therefore preclinical; whether the approach can be transferred to patients is an open question that requires separate studies in humans.

Safety and Tolerability

[42] reports on a phase-1 study of a new, gastro-resistant coated tablet with high bioavailability (MSI-195). The investigation was two-stage: first, safety of MSI-195 was examined in an exploratory design with ascending single dose in 8 healthy male volunteers; this was followed by a single-dose evaluation in 26 male and female volunteers with fixed doses of MSI-195 and a commercial comparator preparation (SAM-e Complete™) in cross-over design, supplemented by an examination of the influence of food on the pharmacokinetic profile. Planned were determination of the safety of single doses, testing of dose proportionality at 400, 800 and 1600 mg, comparison of pharmacokinetics with the reference preparation over 24 hours and the effect of a meal. A validated HPLC method with MS/MS detection served as the analytical method; evaluation of absorption and distribution parameters was performed non-compartmentally with log-linear assumption of the terminal phase and statistics via an ANOVA model or t-tests.

Regarding tolerability the controlled works provide individual details: In [13] 31.3 % of persons with the higher SAME dose reported abdominal complaints versus 8.7 % under escitalopram and 3.8 % under placebo ($\chi^2 = 7.32$; $p = 0.026$). In [44] SAME over 180 days at a dose of 400 mg daily proved safe and well tolerated, without differences versus placebo in safety and secondary endpoints. [49] summarises that the observed adverse effects were predominantly mild and transient and affected the gastrointestinal tract. The documented complaints are therefore mainly gastrointestinal; they were systematically recorded with dedicated instruments in only a portion of the studies, and how longer intake over months affects tolerability remains open.

Oncology and Analytics

[55] investigated in a multicentre pilot study in a case-control design the associations between circulating SAM, S-adenosylhomocysteine (SAH) and the SAM/SAH ratio on the one hand and hepatocellular carcinoma in metabolically induced fatty-liver disease (MASLD) on the other. Included were 69 MASLD-HCC cases and 136 cancer-free MASLD controls; SAM and SAH were quantified in plasma by liquid chromatography-tandem mass spectrometry and the values were divided on the basis of the distribution in the controls into those above and below the median; logistic regression took account of age, sex, body-mass index, smoking status and type-2 diabetes. The cases exhibited higher plasma SAM levels (mean 121 vs. 96 nmol/L; $p = 0.001$) and a higher SAM/SAH ratio (2.09 vs. 1.48; $p = 6.42 \times 10^{-7}$); in the multivariably adjusted model a SAM value above the median was associated with an odds ratio of 2.76. Endogenous levels were measured; whether SAME intake shifts these levels and whether an influence on development or course results from this is not answered by this design.

[54] classifies the analytics: SAM and SAH are central intermediates of one-carbon metabolism and key regulators of cellular methylation capacity; their concentrations and ratio are increasingly investigated as biomarkers in metabolic, cardiovascular, neurological and cancer-related diseases. Liquid chromatography with tandem mass spectrometry (LC-MS/MS) is regarded as the gold standard in clinic and research; the review compares it with alternative procedures such as immunoassays with regard to sensitivity, specificity, matrix effects and clinical relevance, addresses pre-analytical variables such as choice of biological matrix, sample handling and storage and names current limits of standardisation between laboratories. [58] describes the development of a targeted metabolomic method that simultaneously captures 42 epigenetically relevant metabolites without chemical derivatisation, including SAM and acetyl-coenzyme A, and links the analytics with stable isotope labelling for tracking biosynthesis. Extraction is performed in two phases with phosphoric acid (15 %) and methyl-tert-butyl ether; the organic fraction is analysed by GC-MS/MS, the aqueous fraction by LC-MS/MS on a zwitterionic HILIC column. Comparably measured target variables are the prerequisite for findings from different SAME studies to be pooled at all.

Overall Picture

Across the fields depression research carries the broadest base: two reviews with meta-analysis over 23 studies with 2183 participants and over 14 studies with 1522 participants, randomised controlled studies of 49 to 189 persons, daily doses of 200 to 3200 mg and treatment durations of 2 to 12 weeks. The results diverge: one review shows an advantage versus placebo, the other none, and adjunctive administration to antidepressants was not superior in either.

In cognition research in animals and humans the pooled results were not significant, and the phase-2 study in Alzheimer’s found under 400 mg daily over 180 days no disease-modifying effect with good tolerability. Among the best-documented adverse effects are gastrointestinal complaints, which were predominantly mild and transient. In the liver the early ALT reductions within 2 weeks are the most clearly reported laboratory finding.

Open questions arising from the works themselves: follow-ups beyond the mostly short treatment periods are rare, the gender observation from [6] originates from a post-hoc analysis and requires independent replication, administration of SAmE did not alter its own plasma levels in [15], the combination with probiotics in [45] permits no conclusion about SAmE alone, and the analytics of SAM and SAH are not yet standardised between laboratories ([54]). The clinical-psychiatric review [22] names fibromyalgia, osteoarthritis, HIV, hepatitis and cirrhosis as examined fields; for exhaustion and stress, for bones and joints, for viral infections and for oxidative stress a separate, individually evaluable examination of SAmE is still outstanding. Next to be clarified would be which dose, which treatment duration and which patient group actually benefit in a sufficiently large, independent study.

Methodology of the Evidence Base

The controlled works in humans are predominantly randomised, double-blind, placebo-controlled studies; in addition there are a post-hoc analysis of existing study data, a phase-1 pharmacokinetic study with ascending single dose and cross-over comparison and a phase-2 study over 180 days; the case-control study on biomarkers belongs to the observational studies. Systematic reviews and meta-analyses as well as preclinical cell and animal works are added. Treatment duration lies mostly between 2 and 12 weeks, at 180 days in the Alzheimer study and at 12 weeks with 6 months of follow-up in the epigenetic study. Typical endpoints are observer- and self-rating scales such as HAM-D, MADRS and PHQ-9, laboratory values such as ALT, AST, ALP and γGT, phosphorylated tau in plasma as well as genome-wide DNA methylation and the analytics of SAM and SAH. Systematically lacking are blinded follow-ups over months, independent replications of individual findings and laboratory-uniform measurement of SAM and SAH.

The most-cited works are not studies in humans

A glance at the ranking reveals a confusion. The most-cited works on SAmE are basic-science works on methylation and autophagy; the most-cited review with clinical reference stands below them. Whoever reads the citation numbers as a measure of examination in humans overestimates the clinical base. The mechanism literature is rich, the number of controlled works in humans remains under thirty. Both have their value, yet they answer different questions.

One of the most-cited controlled works is at the same time the most difficult for attribution. It examined in persons with subclinical and mild to moderate depression a supplement of SAmE and probiotic strains in randomised design. From such a mixture no statement about SAmE alone can be derived. The work contributes to the question of whether this combination preparation changes something in this group, not to the question of what share SAmE has in it. Whether a study with SAmE alone shows the same is open.

3. How Robust the Research Is

Research on SAmE is distributed across two levels. In humans, controlled studies stand alongside observational work; the application areas recorded are cognition, bone, musculoskeletal system, safety, exhaustion, bioavailability and metabolism. A separate point on depression does not appear in this list, although the most frequently cited controlled studies almost invariably concern depressive disorders — from treatment-resistant bipolar depression through subclinical to moderate severity, as monotherapy and as adjunctive therapy, plus several systematic reviews and meta-analyses. Opposite this stands a large block of basic and mechanistic studies that leads the citation landscape. The number of studies in humans remains below thirty.

The field is methodologically divided in two. For depressive disorders, double-blind randomised controlled trials as well as current systematic reviews and meta-analyses are available; this is the strongest form of evidence in the field. For cognition, a meta-analysis exists that combines animal and human studies; application in humans remains the subject of further work there. The methodological limits lie in heterogeneity: monotherapy and adjunctive therapy, different oral preparations and different patient groups complicate comparison. One frequently cited study did not test SAmE alone, but a supplement containing SAmE and probiotic strains; a study with SAmE alone would be the next test that decides this question.

4. What Is Frequently Claimed — and What the Data Provide

STATEMENT	STUDY SITUATION
SAmE is well established as an antidepressant	For depressive disorders, double-blind randomised studies, systematic reviews and meta-analyses are available — the strongest evidence in the field. Preparation
SAmE improves cognition and drive	A meta-analysis of randomised controlled trials combines animal and human studies on cognition. In humans the number of studies remains small, and exhaustion
Long-term data are available on safety	Safety is recorded as a separate application area with several controlled studies. They cover the respective groups and periods studied, not long-term use.

STATEMENT	STUDY SITUATION
Oral SAmE preparations are interchangeable	A pharmacokinetic study in healthy subjects examined dose escalation, the influence of a meal and the comparison with a commercially available product. F

5. Profile: Molecule and Charge

S-Adenosylmethionine (SAmE) is not a single molecule, but a **mixture** — there is no molecular formula and no fixed molecular mass. What can be described are functional groups, charge behaviour and redox properties; that is exactly what the next section addresses.

6. Charge, Electrons, Radicals

None of the evaluated studies measures charge, cation exchange or electron transfer of S-adenosylmethionine.

Nothing has been measured in humans on this. This leaves open whether SAM itself acts as an electron donor or acceptor, whether its metabolites shift the cellular redox balance and whether this can be demonstrated in blood or tissue of humans. The first question to clarify would be which electrochemical quantity is meant — charge of the sulfonium centre, cation exchange at membranes or radical formation — and with which method it could be measured in humans. This is followed by the question of whether such a measurement correlates with SAM metabolism.

7. Interactions with Other Substances

With which other substances on the platform this substance has been **jointly** investigated or discussed in human studies and reviews — combination, comparison or shared mechanism of action. The number indicates studies in which both appear.

SUBSTANCE	SHARED STUDIES	OF WHICH CONTROLLED IN HUMANS
Chronic inflammation	115	10
Acupuncture	112	70
Osteopathy and manual therapy	111	52
Virtual-reality therapy	105	75
Stress, cortisol and inflammation	98	14
Light therapy	97	66
Gut microbiome	96	10
Vitamin D	83	16
Acupressure	65	52
Hyperthermia	61	20

In an observation in humans SAmE was effective in 24 of 36 studies; adverse events were predominantly mild, transient gastrointestinal complaints¹⁴. As epigenetic modulators valproic acid and SAmE act antagonistically, both prenatally and after birth¹⁷. In cell culture SAmE together with decitabine enhanced inhibition of growth and metastasis of breast cancer¹⁸. The finding is classified as preclinical and described as a basis for clinical trials^{18 18}.

Absorption: In a controlled human study the relative bioavailability of one preparation, measured as the AUC ratio, was approximately 2.8-fold higher than that of a comparator preparation; exposure was approximately dose-proportional¹⁰. Alcohol strengthens the interaction of MATα1 with PIN1, thereby blocking mitochondrial targeting of MATα1; the amount of mitochondrial MATα1 decreases, partly via upregulation of cytochrome P450 2E1¹⁶. Alcohol activates CK2, which phosphorylates MATα1 at Ser114 and thereby facilitates binding to PIN1¹⁹. In animal experiments MATα1-K48 gene-edited mice were protected against ethanol-induced fat accumulation and liver damage¹⁶.

8. Overdosage, Tolerability, Limitations

Controlled human studies consistently report good tolerability of S-adenosylmethionine.

The aim of this work was to determine efficacy, safety and optimal dose in signs of the central nervous system ¹⁴. Upper limits, overdosage and contraindications remain open; what needs to be clarified is from which dose and treatment duration adverse events occur more frequently and for which patient groups S-AMe is not suitable.

9. The Most Robust Studies

Ordered by strength of evidence, not by familiarity: reviews and studies with large numbers of participants first. The complete evaluation comprises considerably more studies; the most robust ones are presented here.

Controlled Human Studies

- ¹ S-Adenosylmethionine (S-AMe) as an adjuvant therapy for patients with depression: An updated systematic review and meta-analysis (2024) — Review, 1,522 participants
- ² Efficacy and acceptability of S-adenosyl-L-methionine (S-AMe) for depressed patients: A systematic review and meta-analysis (2024) — Review, 2,183 participants
- Autologous adipose-derived mesenchymal stromal cell injection for knee osteoarthritis improves pain and function without a clear increase in adverse ... (2026) — Review, 551 participants
- ³ Early treatment efficacy of S-adenosylmethionine in patients with intrahepatic cholestasis: A systematic review (2020) — Review
- ⁴ Effects of S-Adenosylmethionine on Cognition in Animals and Humans: A Systematic Review and Meta-Analysis of Randomized Controlled Trials (2023) — Review
- ⁵ Is S-Adenosyl Methionine (S-AMe) for Depression Only Effective in Males? A Re-Analysis of Data from a Randomized Clinical Trial (2015) — 189 participants
- Functional alignment preserves the native Coronal Plane Alignment of the Knee phenotype while improving early clinical outcomes after ... (2026) — 100 participants
- ⁶ A comprehensive review on the efficacy of S-Adenosyl-L-methionine in Major Depressive Disorder (2016)
- ⁷ Efficacy of a food supplement based on S-adenosyl methionine and probiotic strains in subjects with subthreshold depression and mild-to-moderate ... (2022) — 80 participants
- ⁸ S-Adenosylmethionine (S-AMe) monotherapy for depression: an 8-week double-blind, randomised, controlled trial (2020) — 49 participants
- ⁹ Oral S-AMe in persistent treatment-refractory bipolar depression: a double-blind, randomized clinical trial (2014)
- ¹⁰ Pharmacokinetic study of a novel oral formulation of S-adenosylmethionine (MSI-195) in healthy subjects: dose escalation, food effect and comparison ... (2020)
- ¹¹ Dose increase of S-Adenosyl-Methionine and escitalopram in a randomized clinical trial for major depressive disorder (2020)
- Efficacy of ondansetron and palonosetron in prevention of shivering under spinal anesthesia: A prospective randomized double-blind study in patients ... (2021) — 84 participants
- ¹² S-adenosylmethionine as an epigenetic treatment of depression in adults with childhood trauma (2026) — 31 participants
- Adding microfracture to an SVF-based arthroscopic pathway was associated with greater 24-month improvements in pain, function and MRI cartilage ... (2026)
- Effects of Training with Hybrid Assistive Device on Motor Unit Behavior After Total Knee Arthroplasty: A Randomized Controlled Trial (2026) — 24 participants
- ¹³ A phase 2, randomized, multicenter, double-blind, placebo-controlled trial of S-adenosyl methionine in participants with mild cognitive impairment or ... (2026) — 63 participants
- Methylprednisolone Taper After Total Knee Arthroplasty: A Prospective Single-Blinded Randomized Trial (2026) — 69 participants

Observational Studies in Humans

- ¹⁴ S-Adenosylmethionine (S-AMe) for Central Nervous System Health: A Systematic Review (2024) — Systematic review, 32 participants
- Association of serum methionine metabolites with non-alcoholic fatty liver disease: a cross-sectional study (2021) — 2,814 participants
- ¹⁵ S-Adenosylmethionine (S-AMe) for Neuropsychiatric Disorders: A Clinician-Oriented Review of Research (2017)
- Targeting UBC9-mediated protein hyper-SUMOylation in cystic cholangiocytes halts polycystic liver disease in experimental models (2021)
- ¹⁶ Sumoylation of methionine adenosyltransferase alpha 1 promotes mitochondrial dysfunction in alcohol-associated liver disease (2024)

10. Summary

Proven initially in the depressive domain: double-blind randomised controlled trials as well as systematic reviews and meta-analyses are available here, the strongest form of evidence in the field. The meta-analysis [2] with 23 studies and 2,183 participants shows a superior effect on depressive symptoms versus placebo (SMD = -0.58; 95 % CI -0.93 to -0.23) at moderate certainty of evidence, while it found no difference as an adjunct to antidepressants and in direct comparison with antidepressants. The review [49] records an effect on central nervous system signs such as mood, behaviour and sleep in 24 of 36 papers. The findings are not consistent throughout: the review [29] with 14 studies and 1,522 participants found no significant difference in any of the three comparisons.

PLAUSIBLE That administration of methyl groups shifts methylation patterns is the starting point of the epigenetic approach; [35] ranks SAmE alongside choline and valproic acid as the most effective methyl-group donor and describes that these substances alter gene expression and can mitigate neurobehavioural changes in disorders of epigenetic origin. This is supported by [15]: in adults with trauma-induced depression, differential methylations across 66 regions occurred under 1,200 mg SAmE over twelve weeks, without clinical added benefit and without change in plasma SAmE levels.

Hypothesis: It could follow that epigenetic markers respond earlier to administration than symptom scales — as a measure for the mechanism, not as a substitute for a clinical endpoint. Whether a benefit for child development arises has not yet been examined in humans.

A study would first have to separate the adjunct question: the frequently cited work [45] tested a combination preparation of SAmE and two probiotic strains, so the change cannot be attributed to either component alone; a study with SAmE alone is the next test that would decide this question. For cognition, [5] names animal age and treatment duration as separate test points. For dementia, [44] measures the laboratory value plasma p-tau217; a disease-modifying effect is not thereby shown, and a study with a clinical endpoint is still outstanding here. The sex-specific finding from [6] requires replication in independent samples; for the liver it remains open how the values develop after the first two treatment weeks, and the preclinical SUMOylation approach from [23] requires its own human studies.

11. What Remains Open

- **Monotherapy or Adjunct:** An eight-week double-blind monotherapy and a dose escalation alongside escitalopram have been examined. Which approach is superior is not clarified by any present work.
- **Methylation in Humans:** A basic-science paper describes that excess SAmE can inhibit methylation via breakdown to adenine. Whether supplementation produces the same effect in humans has not been tested.
- **Combination Preparations:** A frequently cited trial tested SAmE together with probiotic strains. Which share of an observed course is attributable to SAmE would be decided by a study with SAmE alone.

12. Further Paths

Topics, mechanisms and pathways in which this substance occurs — for all who wish to look beyond the substance.

- Interaction Network

Frequently Asked Questions

How should the study evidence on SAmE in depressive disorders be classified?

For depressive disorders the evidence is broadest: double-blind randomised studies on monotherapy, on treatment-resistant bipolar depression and on subclinical presentation, together with systematic reviews and meta-analyses. Different preparations, dosing regimens and groups were examined. One frequently cited study tested a combination preparation of SAmE and probiotic strains, so its result cannot be attributed to the single substance.

What is known about the uptake of oral preparations?

A pharmacokinetic study in healthy persons examined a newer oral formulation with dose escalation, the influence of a meal and a comparison with a commercially available food supplement. Formulation, dosing regimen and food intake therefore affect bioavailability. Oral preparations are consequently not arbitrarily interchangeable, and results from different studies are only comparable to a limited extent.

Are there controlled investigations on tolerability?

Tolerability is recorded as a separate application area with several controlled studies. They refer to the respective examined groups, dosing regimens and observation periods. They do not permit statements on long-term use or on persons with multiple medications; which groups would need to be examined over longer periods remains open.

Sources

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