S-Adenosylmethionine (SAMe) for Neuropsychiatric Disorders: A Clinician-Oriented Review of Research

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ABSTRACT

Objective: A systematic review on *S*-adenosylmethionine (SAMe) for treatment of neuropsychiatric conditions and comorbid medical conditions.

Data Sources: Searches were conducted in PubMed, EMBASE, PsycINFO, Cochrane Library, CINAHL, and Google Scholar databases between July 15, 2015, and September 28, 2016, by combining search terms for SAMe (*s-adenosyl methionine* or *s-adenosyl-l-methionine*) with terms for relevant disease states (*major depressive disorder*, *MDD*, *depression*, *perinatal depression*, *human immunodeficiency virus*, *HIV*, *Parkinson's*, *Alzheimer's*, *dementia*, *anxiety*, *schizophrenia*, *psychotic*, *22q11.2*, *substance abuse*, *fibromyalgia*, *osteoarthritis*, *hepatitis*, or *cirrhosis*). Additional studies were identified from prior literature. Ongoing clinical trials were identified through clinical trial registries.

Study Selection: Of the 174 records retrieved, 21 were excluded, as they were not original investigations. An additional 21 records were excluded for falling outside the scope of this review. Of the 132 studies included in this review, 115 were clinical trials and 17 were preclinical studies.

Data Extraction: A wide range of studies was included in this review to capture information that would be of interest to psychiatrists in clinical practice.

Results: This review of SAMe in the treatment of major depressive disorder found promising but limited evidence of efficacy and safety to support its use as a monotherapy and as an augmentation for other antidepressants. Additionally, preliminary evidence suggests that SAMe may ameliorate symptoms in certain neurocognitive, substance use, and psychotic disorders and comorbid medical conditions.

Conclusions: *S*-adenosylmethionine holds promise as a treatment for multiple neuropsychiatric conditions, but the body of evidence has limitations. The encouraging findings support further study of SAMe in both psychiatric and comorbid medical illnesses.

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Complementary, alternative, and integrative medicine includes a wide range of biological, psychological, and mind-body treatments being used to enhance standard medical practices and improve patient outcomes. Integrative psychiatry, a form of complementary, alternative, and integrative medicine, "seeks to enrich mainstream mental health care with valuable treatments from global healing traditions as well as from modern laboratories in related fields."[1(p xiv),2] Complementary, alternative, and integrative medicine interventions include nutraceuticals, classified by the US Food and Drug Administration (FDA) as "dietary supplements," defined as products intended for ingestion that contain ingredients such as vitamins, minerals, amino acids, herbs or other botanicals and nutrient concentrates, metabolites, or constituents. Many patients with mental health disorders utilize these modalities, often without physician supervision.[3,4] Understanding the growing evidence supporting the efficacy of certain complementary, alternative, and integrative medicine therapies will prepare clinicians to better advise patients when discussing integrative treatments.

S-adenosylmethionine (SAMe) was discovered in 1952 by the late Italian scientist and former National Institutes of Health biochemistry director Giulio Cantoni.[5,6] It is an endogenous, intracellular amino acid metabolite and enzyme cosubstrate involved in multiple crucial biochemical pathways, including biosynthesis of hormones and neurotransmitters.[7–9] SAMe concentrations have been measured in blood and cerebrospinal fluid (CSF), with ranges established in normal[10,11] and disease states. SAMe deficiency in CSF has been reported in patients with rare inherited defects in folate and methionine metabolism[12,13] as well as in more common diseases such as depressive disorders, Alzheimer's dementia, Parkinson's disease, and HIV infection.[14,15] Deficiencies of folate and vitamin B_{12}, necessary cofactors in the synthesis of SAMe, may account for decreased SAMe levels, especially in patients with depression and dementia. Studies[14,15] have shown that with either oral or parenteral treatment, SAMe crosses the blood-brain barrier and increases CSF levels, including those in patients with neuropsychiatric conditions. As a complementary, alternative, and integrative medicine therapy, SAMe has been utilized for treatment of psychiatric and medical conditions in

Clinical Points

- *S*-adenosylmethionine (SAMe) is a viable treatment in major depressive disorder, and early evidence suggests that it holds promise for a number of neuropsychiatric conditions.
- Clinical opportunities for the use of SAMe may include multiple neuropsychiatric disorders and comorbid medical conditions.
- Additional research is needed to strengthen the body of evidence.

Europe for over 30 years. In the United States, it became better known after 1999 as an over-the-counter dietary supplement under the Dietary Supplement Health and Education Act.[2]

This review summarizes clinical trials of SAMe for treatment of neuropsychiatric disorders and comorbid conditions encountered by psychiatrists in practice. To provide information that will assist clinicians considering treatment options in a broad range of complex clinical situations, we discuss the literature encompassing samples of patients with a wide variety of neuropsychological symptoms for whom decisions about psychiatric treatments may take into account coexisting medical conditions and medication interactions. In addition to preclinical research, we include results from controlled trials, open studies, and case reports on SAMe monotherapy and augmentation therapy. SAMe safety, contraindications, and medication interactions are addressed. This review also highlights limitations of the current literature and suggests future potential areas for research.

METHODS

A literature search conducted between July 15, 2015, and September 28, 2016, utilized electronic databases including PubMed, EMBASE, PsycINFO, Cochrane Library, CINAHL, and Google Scholar by combining search terms for SAMe (*s-adenosyl methionine* or *s-adenosyl-l-methionine*) with terms for relevant disease states, including *major depressive disorder*, *MDD*, *depression*, *perinatal depression*, *human immunodeficiency virus*, *HIV*, *Parkinson's*, *Alzheimer's*, *dementia*, *anxiety*, *schizophrenia*, *psychotic*, *22q11.2*, *substance abuse*, *fibromyalgia*, *osteoarthritis*, *hepatitis*, or *cirrhosis*. Additional studies were identified using previous literature reviews, meta-analyses, books, and book chapters (Figure 1 [PRISMA flowchart]). Ongoing clinical trials were identified through ClinicalTrials.gov and the WHO (World Health Organization) International Clinical Trials Registry Platform.

RESULTS

Preclinical Studies

S-adenosylmethionine is the universal methyl donor in more than 100 methyltransferase reactions that regulate

Figure 1. PRISMA Flowchart of Studies Included in the Systematic Review

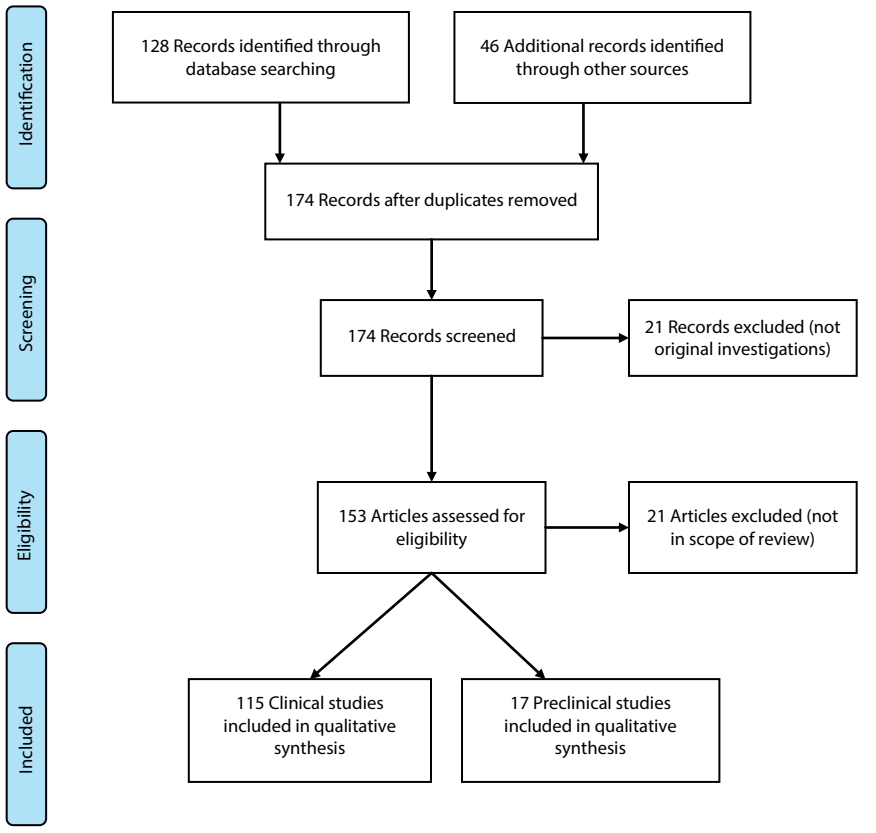
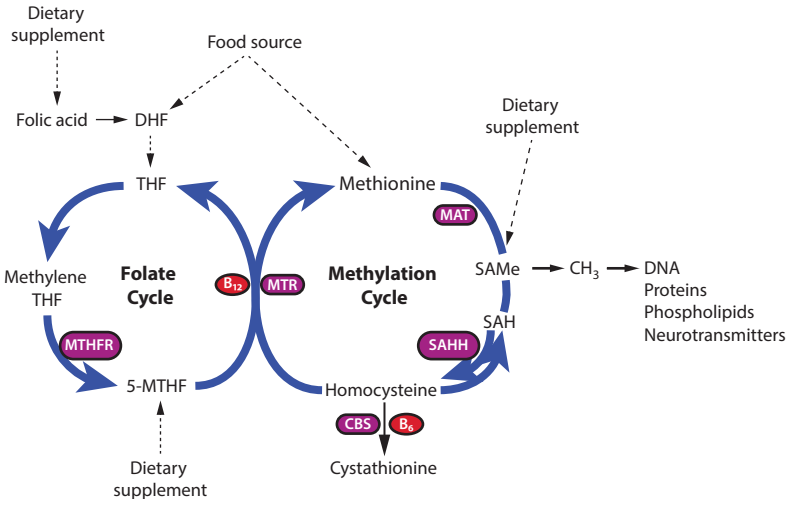


Figure 2. *S*-Adenosylmethionine in the Methylation Cycle[a]



[a]Reproduced with permission from Psychiatric Clinics of North America.[17]
Abbreviations: CBS = cystathionine β-synthase, DHF = dihydrofolate, 5-MTHF = 5-methyltetrahydrofolate, MAT = methionine adenosyltransferase, MTHFR = methylenetetrahydrofolate reductase, MTR = methionine synthase, SAH = *S*-adenosylhomocysteine, SAHH = *S*-adenosylhomocysteine hydrolase, SAMe = *S*-adenosylmethionine, THF = tetrahydrofolate.

essential metabolic pathways (see reviews by Cantoni[6] and Bottiglieri[16]). Methylation involves the transfer of a methyl group (CH_3) to an acceptor molecule (Figure 2), including DNA bases, proteins, phospholipids, free amino acids, and neurotransmitters. DNA methylation can turn gene transcription "on" or "off." Similarly, methylation of proteins results in posttranslational modifications that can regulate enzyme activity. Methylation of phospholipids is necessary for cell-membrane integrity and optimal function of receptors in the lipid membrane bilayer. Aberrant methylation has been implicated as a pathogenic mechanism in central nervous system (CNS) disorders, including depression and dementia.[16,18] Methyl group donation is a target mechanism to prevent disease, to delay disease progression, and to enhance therapeutic outcomes.[16,19]

S-adenosylmethionine has been studied in animal models of depression.[20,21] In rodents, SAMe dose dependently decreases immobility time in the forced swimming test[22] and increases concentrations of CNS monoamine neurotransmitters serotonin and norepinephrine.[23] Animal studies show that chronic SAMe administration increases dopaminergic tone in brain regions, including rat striatum,[24] and increases CNS β-adrenergic receptor density and activity.[25,26] Thus, studies of central monoaminergic neurotransmitters support proposed mechanisms for SAMe antidepressant effects. SAMe may also have modulatory effects on cell-signaling pathways in the CNS. In rats, chronic treatment with SAMe resulted in a marked increase in calcium/calmodulin dependent protein kinase II (CaMKII) in synaptic vesicles from the hippocampus, as well as a marked increase of synapsin I in the synaptic cytosol of the hippocampus and frontal cortex.[27] Typical antidepressants have been shown to activate CaMKII and synapsin I, which suggests that SAMe may share a similar modulatory action on neurotransmitter release.

A growing literature linking relative hypomethylation to disease pathophysiology in dementia includes reports of decreased SAMe concentrations in CSF in patients with Alzheimer's disease,[28] hypomethylation of proteins that regulate levels of CNS phosphorylated tau,[29,30] and hypomethylation of genes that affect expression of β-amyloid protein.[31] SAMe affects site-specific methylation of DNA promoter regions that regulate gene function, and carboxymethylation of proteins that can regulate β-amyloid and tau proteins, neuropathological hallmarks of Alzheimer's disease.[18]

Clinical Trials

Depressive disorders. The antidepressant effects of SAMe were first described in 1970s.[32] Early clinical studies used parenteral formulations until an oral preparation became available in the 1980s.[33] More than 50 clinical trials in the United States and Europe have evaluated SAMe in the treatment of depressive disorders: 17 open-label trials with 708 patients (see Supplementary eTable 1); 19 double-blind, randomized placebo-controlled trials of SAMe including 878 patients (Table 1); and 21 controlled trials comparing SAMe with other antidepressants with a total of 1,591 patients (Table 2). Observations of SAMe-induced hypomania or mania in early studies[45,65,69–71] limited subsequent prospective clinical trials to unipolar major depressive episodes, although formal diagnostic criteria were not consistently used in early trials.

SAMe compared with placebo. *S*-adenosylmethionine has been compared to placebo for depressive symptoms in 19 randomized controlled trials (RCTs) (Table 1). Six of 9 controlled studies conducted between 1976 and 1988

Table 1. Controlled Trials of SAMe Versus Placebo for Depression

Trial	Year	Patients Enrolled (randomized)			Experimental Design	Study Duration, d	SAMe Dose, mg/d	Route	Primary Outcome Measure	Primary Outcome (SAMe vs placebo), *P* Value	
		Total, N	SAMe, n	Placebo, n						Positive	Negative
Fazio et al[34]	1973	19	14	5	Double-blind	8	45	IV	HDRS	< .01	
Agnoli et al[35]	1976	30	20	10	Double-blind	15	45	IM	HDRS	*P* value for comparison not provided	
Barberi and Puscateri[36,a]	1978	40	20	20	Crossover	10	200	IV	HDRS	< .05	
Muscettola et al[37]	1982	20	10	10	Double-blind	15	150	IM	HDRS	< .01	
Caruso et al[38]	1984	49	25	24	Double-blind	21	200	IM	HDRS	< .001	
Carney et al[39]	1986	32	15	17	Double-blind	14	200	IV	HDRS	NS[b]	
Caruso et al[40]	1987	59	30	29	Double-blind	21	200	IM	HDRS	< .01	
De Leo[41]	1987	40	20	20	Double-blind	30	200	IM	ZSDS	< .05	
Thomas et al[42]	1987	20	9	11	Double-blind	14	200	IV	HDRS	NS[b]	
Janicak et al[43,c]	1988	15	7	5	Double-dummy	15	400	IV	HDRS	< .02	
Carrieri et al[44]	1990	21	11	10	Crossover	15	1,000	PO	HDRS	< .05	
Kagan et al[45,a]	1990	18	9	9	Double-blind	21	1,600	PO	HDRS	< .05	
Fava et al[46,d]	1992	43	11	21	Double-blind	42	1,600	PO	HDRS		NS[e,f,g]
Ancarani et al[47,h]	1993	53	41	10	Double-blind	21	400[i]	IV	IPAT-DS	NS[j]	
Salmaggi et al[48,a]	1993	80	40	40	Double-blind	30	1,600	PO	HDRS total	< .01	
Cerutti et al[49,a,k]	1993	60	30	30	Double-blind	30	1,600	PO	KSQ		NS[l]
Delle Chiaie and Boissard[50]	1997	75	40	35	Double-blind	21	800	IV	MADRS	< .05	
Papakostas et al[51]	2010	73	39	34	Double-blind/ augmentation	45	1,600	PO	HDRS, % response	< .05	
Mischoulon et al[52,m]	2014	189	64	60	Double-blind; escitalopram was third treatment group	84	1,600–3,200	PO	HDRS total		NS[e,f]

[a]SAMe-treated groups only. Significant ($P < .05$) improvement by day 10.
[b]SAMe response rate greater than placebo, results not statistically significant.
[c]Total N = 15 includes 3 additional subjects treated in an imipramine arm.
[d]Total N = 43 includes 11 subjects who did not complete the study.
[e]SAMe response rate equivalent to placebo.
[f]Considered failed trial (see text).
[g]Describes a post hoc analysis of thyrotropin-releasing hormone as a predictor of response to SAMe in 32 outpatients from a placebo-controlled trial (n = 43). Both the larger trial and this subset produced negative results.
[h]Total N = 53 includes 2 subjects who did not complete the study.
[i]SAMe dose was 400 mg IV given every other day at the end of a dialysis session.
[j]*P* value for comparison not present in text, but graphed figure indicates no group difference.
[k]Diagnosis was puerperal psychological distress.
[l]SAMe > placebo at 10-day assessment ($P < .05$); no significant differences at study end point.
[m]Total N = 189 includes 65 subjects treated in an escitalopram arm.
Abbreviations: HDRS = Hamilton Depression Rating Scale, IM= intramuscular, IV = intravenour, IPAT-DS = Institute for Personality and Ability Testing-Depression Scale, KSQ = Kellner Symptom Questionnaire, MADRS = Montgomery-Asberg Depression Rating Scale, NS = not statistically significant, PO = by mouth, SAMe = *S*-adenosylmethionine, ZSDS = Zung Self-Rating Depression Scale.

reported that intravenous (200–400 mg/d) or intramuscular (45–200 mg/d) SAMe was more effective than placebo for depression.[37,41,43,62,72] Starting in the 1990s, adequate oral doses (800–1,600 mg) of enteric-coated, stabilized SAMe could be utilized in clinical studies. Overall, 12 of the 19 randomized, placebo-controlled trials showed the antidepressant effect of SAMe to be significantly greater than placebo for depressive syndromes ($P < .05$, Table 1), although many of these studies used samples in which diagnostic criteria for major depressive disorder (MDD) were not required or MDD was not a primary diagnosis. In 1 of 2 studies that failed to find a significant difference compared to placebo, an older, less stable oral form of SAMe was used, in which the tablets were degraded due to excess exposure to air.[46] In the other study,[52] both SAMe and escitalopram failed to outperform placebo.

A seminal 2002 meta-analysis by Hardy et al,[73] commissioned by the Agency for Healthcare Research and Quality (AHRQ), including 28 of 47 RCTs on depression through the year 2000, remains the only SAMe meta-analysis published in the past 15 years. This fairly exhaustive meta-analysis excluded 2 potentially informative studies[50,67] comparing SAMe against tricyclic antidepressants (TCAs) due to insufficient statistical description and 1 study[64] because the authors were unable to obtain the article. Regarding placebo comparisons, Cerutti et al[49] was excluded because it covered postpartum depression. Fazio et al[32] and Agnoli et al[35] were excluded because their data were covered in other articles. Hardy and colleagues[73] examined effect size and risk ratio of response in these studies. Only 3 studies were evaluable in the risk-ratio analysis, which all favored SAMe. However, the authors could not draw definitive conclusions because overall power was modest due to small sample sizes, differences between groups were nonsignificant, and studies had methodological limitations. The effect-size analysis included 11 studies. The authors found no escalating dose-response effect, perhaps due to the mixture of studies using oral versus intramuscular SAMe. Nonetheless, the authors found that SAMe monotherapy was more effective than placebo in treating depressive symptoms, with an overall

Table 2. Controlled Trials of SAMe Versus Other Antidepressants

Trial	Year	Patients Enrolled: Total, N	SAMe, n	Other, n	Experimental Design	Duration, d	SAMe Dose, mg/d	Route	Other Antidepressant	Other Dose, mg/d	Route	Primary Outcome Measure	Relative Efficacy (SAMe vs other)
Mantero et al[53]	1975	31	16	15	Double-blind	21	75	IM	Imipramine	75	IM	HDRS	SAMe = other
Miccoli et al[54]	1978	86	45	41	Double-blind	21	200	IV	Clomipramine or amitryptyline	100	IV	HDRS	SAMe = other
Barberi and Puscateri[36]	1978	20	10	10	Double-blind	20	200	IV	Amitriptyline	100	IV	HDRS	*P* value for comparison not provided[a]
Del Vecchio et al[55]	1978	28	14	14	Double-blind	21	150	IV	Clomipramine	100	IV	HDRS	SAMe = other
Scarzella and Appiotti[56,b]	1978	20	10	10	Double-blind	15	250	IV	Clomipramine	100	IV	HDRS	SAMe = other
Calandra et al[57]	1979	24	12	12	No blind	15	150	IV	Clomipramine	100	IV	HDRS	SAMe = other
Monaco and Quattrocchi[58]	1979	20	11	9	Double-blind	15	200	IV	Amitriptyline	100	IV	HDRS	SAMe = other
Scaggion et al[59]	1982	40	22	18	Double-dummy	15	300	IV	Nomifensine	200	PO	HDRS	SAMe = other
Küfferle and Grüberger[60]	1982	20	10	10	Double-blind	18	150	IV	Clomipramine	50	IV	HDRS	SAMe = other
Ubago et al[61]	1984	30	15	15	Double-blind	30	100	IV	Clomipramine	50	PO	HDRS	SAMe = other
Bell et al[62,b]	1988	22	11	11	Double-dummy	14	400	IV	Imipramine	150	PO	HDRS	SAMe > other[c]
Janicak et al[43,d]	1988	15	7	3	Double-dummy	14	400	IV	Imipramine	150	PO	HDRS	SAMe = other
Cerutti et al[63]	1989	20	20	20	Crossover	21	800	PO	Minaprine	200	PO	HDRS	SAMe > other[c]
Bell et al[64]	1990	28	14	14	Double-blind	28	1,600	PO	Desipramine	250	PO	HDRS	SAMe = other
De Vanna and Rigamonti[65,b]	1992	30	15	15	Double-blind	42	1,600	PO	Imipramine	140	PO	MADRS	*P* value for comparison not provided[a]
Bell et al[66]	1994	17	11	6	Double-blind	28	1,600	PO	Desipramine	250	PO	HDRS	*P* value for comparison not provided[a]
Delle Chiaie and Boissard[50]	1997	122	57	65	Double-blind	21	800	IV	Clomipramine	100	IV	HDRS	Other > SAMe[e]
Delle Chiaie et al[67]	2002	281	143	138	Double-blind	42	1,600	PO	Imipramine	150	PO	HDRS	SAMe = other
Delle Chiaie et al[67]	2002	295	147	148	Double-blind, dummy	28	400	IM	Imipramine	150	PO	HDRS	SAMe = other
Pancheri et al[68]	2002	293	146	147	Double-blind	28	400	IM	Imipramine	150	PO	HDRS	SAMe = other
Mischoulon et al[52,f]	2014	189	64	65	Double-blind, crossover	84	1,600–3,200	PO	Escitalopram	10–20	PO	HDRS	SAMe = other

[a]Both groups demonstrated significant ($P < .05$) improvements on primary outcome measure. *P* value for between-group comparison not provided.
[b]SAMe-treated groups only. Significant ($P < .05$) improvement by day 10.
[c]SAMe group demonstrated significant ($P < .05$) improvement compared to other antidepressant group on primary outcome measure.
[d]Total N = 15 includes 5 additional subjects treated in a placebo arm.
[e]Other antidepressant demonstrated significant ($P < .05$) improvement compared to SAMe on primary outcome measure.
[f]Total N = 189 includes 60 subjects treated in a placebo arm.
Abbreviations: HDRS = Hamilton Depression Rating Scale, IM = intramuscular, IV = intravenous, MADRS = Montgomery-Asberg Depression Rating Scale, PO = by mouth, SAMe = *S*-adenosylmethionine.

effect size of −0.65 (95% CI, −1.05 to −0.25).[73] This corresponds to an improvement in the 17-item Hamilton Depression Rating Scale (HDRS) of 5–6 points. While this is often considered clinically significant in a single trial, because the studies were based on different editions of the HDRS with different numbers of items (eg, 17 vs 21), the authors considered 10 points to represent clinically significant change. Thus, although SAMe demonstrated an advantage over placebo, the clinical significance is to be considered with caution.

SAMe compared with other antidepressants. Several double-blind RCTs compared SAMe to other antidepressants: TCAs, nomifensine, minaprine, and escitalopram (Table 2). Early RCTs[43,54,56,58,60] showed parenteral SAMe (150–400 mg/d) to be as effective or superior to TCAs (clomipramine, amitriptyline, imipramine), with fewer side effects. Subsequently, 2 larger studies[67,68] (n = 295, n = 293) found intramuscular SAMe (400 mg/d) to be as efficacious as oral imipramine (150 mg/d) in treating MDD for 4 weeks. Additionally, 2 large studies by Di Padova and colleagues[74] comparing SAMe against imipramine suggested equivalency (effect size = 0.13; 95% CI, −0.10 to 0.36), although these reports were not published in peer-reviewed journals. Four RCTs, including 1 large study (n = 281)[67] and 3 smaller studies (n ≤ 30),[64–66] found oral SAMe (1,600 mg/d) to be as efficacious as oral desipramine (250 mg/d) and oral imipramine (140–150 mg/d). Overall, in 18 controlled trials, SAMe was as effective as clomipramine,[54–56,60,61] imipramine,[43,53,62,67,68] and nomifensine.[59]

One recent multicenter RCT (n = 189)[52] comparing SAMe, escitalopram, and placebo failed to identify significant differences among the 3 arms at 12 weeks, perhaps due to an abnormally high placebo response rate. Reanalysis of the data from subjects enrolled at 1 of 2 sites (n = 144) found that improvements in depression with SAMe were equivalent to improvements with escitalopram and significantly greater than that with placebo.[75] A second reanalysis of the same trial identified an intersite difference in the proportion of women to men and analyzed the outcomes separately for men and women[76] using the full sample from both sites. SAMe was found to be superior to placebo among males (n = 51) but not females (n = 62). Whether there is a significant sex-specific difference in antidepressant response requires validation by future studies.

Meta-analyses[73,77] concluded that SAMe and TCAs were equally efficacious in treating depression. The Hardy et al[73] meta-analysis examined studies of SAMe versus TCAs. Eleven studies included in the risk analysis for response collectively produced risk ratios of approximately 1, which supported equality between SAMe and the comparison antidepressant drugs. The corresponding effect-size analysis of 14 studies also found a nonsignificant difference between SAMe and its comparators, suggesting equivalent efficacy. However, most of these studies were limited by the lack of an inactive placebo comparator arm.

SAMe in combination with other antidepressants. A number of studies support the use of SAMe as an adjunctive treatment for MDD. An RCT[78] of add-on parenteral SAMe (250 mg/d) versus placebo injections in patients receiving either clomipramine or mianserin showed improved clinical symptoms by day 10 in the group receiving parenteral SAMe compared to placebo. In an open-label trial,[79] patients with MDD (n = 30) who had not fully responded to a selective serotonin reuptake inhibitor (SSRI) or venlafaxine were treated with oral SAMe (800 mg/d) for 2 weeks, followed by oral SAMe (1,600 mg/d) for an additional 4 weeks. At 6 weeks, 50% of patients achieved clinical response and 43% achieved clinical remission. Reduction in depressive symptoms reached statistical significance at week 1 and remained significant through week 6 ($P < .001$). In another open-label study,[80] MDD patients (n = 33) who failed to respond to at least 8 weeks of treatment with 2 adequate and stable doses of antidepressants were treated with a fixed dose of adjunctive SAMe (800 mg/d). At 8 weeks, clinical response was achieved in 60% of patients and remission in 36% based on HDRS. Changes from baseline were significant by week 1 and remained significant by week 8 ($P < .001$). In an RCT,[51] outpatients with MDD (n = 73) who were nonresponders or partial responders to SSRI or serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressants were randomized to receive adjunctive SAMe (up to 1,600 mg/d) or placebo for 6 weeks. Both response rates (SAMe, 36.1% vs placebo, 17.6%) and remission rates (SAMe, 25.8% vs placebo, 11.7%) were significantly higher in patients receiving SAMe ($P < .05$). A recent meta-analysis[81] examining adjunctive nutraceuticals for depression demonstrated positive results for SAMe.

A multicenter randomized, double-blind, placebo-controlled add-on study[82] of 800 mg SAMe (MSI-195, a novel SAMe formulation with improved bioavailability) for patients with MDD with inadequate responses to antidepressant treatment was completed in 2015. Results are not yet published, but a press release[83] from the sponsor stated that MSI-195 did not demonstrate efficacy over placebo, although post hoc analysis identified a responsive subgroup of 143 subjects (74 on MSI-195 and 69 on placebo) after patients with obesity, unstable symptom profiles, or both were excluded. In this subanalysis using last observation carried forward, the MSI-195 produced a significant reduction in the Montgomery-Asberg Depression Rating Scale of −3.41 ($P = .031$) relative to placebo, with an effect size of 0.36.[83]

SAMe in depression with comorbid medical conditions. Depression and HIV. Relatively low concentrations of SAMe have been reported in the CSF from patients with depression or HIV infection.[14,15] An 8-week, open-label study assessed 20 HIV seropositive individuals with MDD treated with SAMe (800–1,600 mg/d) supplemented with vitamin B_{12} (1,000 μg/d) and folic acid (800 μg).[84] Intent-to-treat (ITT) analysis demonstrated significant reduction in Beck Depression Inventory (BDI) mean (SD) scores from baseline (33.5 [11.1]) to week 8 (6.6 [6.1], $P < .001$). Similarly, 17-item HDRS scores significantly decreased from baseline (26.5 [6.8]) to week 8 (7.7 [10.1], $P < .001$). Between baseline and week 1, there was evidence for a rapid therapeutic effect on BDI and HDRS ($P < .01$). At 8 weeks, the remission rate (17-item HDRS of ≤ 7) was 79% for ITT analysis and 93% for the 15 subjects who completed the study. Two patients reported transient nausea, and 1 reported transient diarrhea. No patients ended participation due to side effects. This encouraging result warrants further SAMe research in this population.

Depression and Parkinson's disease. Estimated rates of depression in patients with Parkinson's disease range from 30% to 50%.[85] Significant side effects and potential interactions with selegiline, a monoamine oxidase inhibitor (MAOI) used to treat Parkinson's disease, can limit use of prescription antidepressants.[86] SAMe has been proposed to protect dopaminergic neurons from levodopa (L-dopa)-induced neurotoxicity.[87] In Parkinson's disease, chronic treatment with L-dopa depletes blood levels of SAMe.[88] L-Dopa is methylated to 3-O-methyldopa by catechol-*O*-methyltransferase (COMT). Since SAMe is the methyl donor in this reaction, its levels become depleted with L-dopa treatment. Preclinical studies show that acute treatment with L-dopa markedly depletes SAMe levels in liver and brain tissue.[25] In Parkinson's disease, L-dopa treatment is associated with increased levels of total homocysteine in plasma[89] and CSF[90] as a by-product of increased COMT methylation of L-dopa.

In 3 small trials[44,91,92] in patients with Parkinson's disease and MDD (n = 13, n = 21, n = 32), SAMe (1,600–4,000 mg/d) significantly reduced depression scores on HDRS ($P < .05$). A 10 week, open-label study[91] involving patients with comorbid

treatment-resistant MDD and Parkinson's disease (n = 13) showed significant improvement in HDRS depression scores following administration of SAMe monotherapy (800–3,600 mg/daily). Mean (SD) HDRS scores dropped from a baseline of 27.09 (6.04) to 9.55 (7.29) ($P < .002$) after 10 weeks. Of 11 completers, 10 had 50% or more improvement on the HDRS. Two patients dropped out due to increased anxiety; other side effects included nausea (n = 1) and diarrhea (n = 2). In another 12-week double-blind, placebo-controlled RCT in patients with Parkinson's disease and depression (n = 32), both SAMe and escitalopram groups had significantly improved depression scores compared to placebo ($P < .05$).[92] In 2 of 3 clinical trials, SAMe improved Parkinson's disease motor symptoms.[91,92] Larger controlled studies are needed to follow-up these preliminary findings in Parkinson's disease.[93]

Depression and osteoarthritis or fibromyalgia. *S*-adenosylmethionine has been reported to exert clinically significant anti-inflammatory and analgesic effects.[73,94–98] While the mechanism remains to be elucidated, SAMe does not appear to alter the eicosanoid system in the same manner as nonsteroidal anti-inflammatory drugs (NSAIDs), but it may enhance proteoglycan synthesis and secretion.[33,94] In several RCTs[99–106] including more than 22,000 patients, SAMe was as effective as NSAIDs in relieving pain in osteoarthritis. An AHRQ meta-analysis[73] of 8 studies comparing SAMe to NSAIDs found equivalent efficacy on the primary outcome measure of pain symptoms (visual analog scale [VAS], comparative effect size = 0.11; 95% CI, −0.56 to 0.35). In 3 of 4 small RCTs[107–110] in patients with fibromyalgia, SAMe (200–800 mg) significantly reduced pain symptom primary outcomes including the VAS ($P < .05$) compared to placebo. Concurrently, SAMe improved symptoms of depression (HDRS or BDI, $P < .05$). These results warrant further investigation into SAMe treatment for patients with MDD and rheumatologic comorbidities.

Sexual dysfunction secondary to depression or antidepressant medication. Sexual dysfunction is commonly associated with MDD as well as with chronic use of most standard antidepressant treatment, leading to interest in agents that specifically treat or reduce the emergence of antidepressant-induced sexual dysfunction.[111] One single-site RCT[112] (described in detail in "SAMe in combination with other antidepressants" section[51]) of SAMe augmentation in SSRI/SNRI nonresponders examined whether adjunctive SAMe was associated with greater improvement in sexual functioning than adjunctive placebo. Relative to those who got placebo, men treated with adjunctive SAMe demonstrated significantly lower arousal dysfunction ($P = .0012$) and degree of erectile dysfunction ($P = .01$) at study end point independent of treatment-associated change in depression severity. Whether SAMe may benefit male arousal and erectile dysfunction in MDD can be further assessed in prospective trials as well as in reanalyses of previously published studies.

Neurocognitive disorders and cognitive function. Major depressive disorder is commonly associated with cognitive impairment. Preclinical and early clinical trials[17,113–115] provide some support for beneficial effects of SAMe alone or in combination with other nutraceuticals on cognitive function. A secondary analysis[116] of data from an RCT on adjunctive SAMe for MDD (n = 46) demonstrated that oral SAMe (1,600 mg/d), as compared to placebo, improved 2 memory-related cognitive functions (recall, $P = .04$, and word-finding, $P = .09$) but not 5 other cognitive domains. These preliminary findings suggest that SAMe may have beneficial effects on memory-related cognition in MDD. Further studies are needed to evaluate whether this effect is independent of improvement in depressive symptoms.

Linnebank and colleagues[28] found that CSF levels of SAMe in patients with Alzheimer's disease were significantly reduced compared to controls. A 1-year, open-label study[117] that treated early stage Alzheimer's disease patients (n = 14) with a nutraceutical formulation containing SAMe (400 mg) in addition to other vitamins (folic acid, 400 µg; vitamin B_{12}, 6 µg) and nutraceuticals (α-tocopherol, 30 IU; *N*-acetylcysteine, 600 mg; acetyl-L-carnitine, 500 mg) demonstrated improvement in cognitive symptoms as assessed by the Dementia Rating Scale (DRS) and clock-drawing tests. Family caregivers also reported improvement in multiple domains of the Neuropsychiatric Inventory. In another pilot study[118] in moderate- to late-stage Alzheimer's disease (n = 12), treatment with a similar nutraceutical formulation containing SAMe did not show statistical separation between active and placebo groups, but some suggestive signals were observed in post hoc data analyses, including greater delay in cognitive decline as measured by the DRS and clock-drawing tests among those who got active nutraceutical formulation. Recently, a larger, multisite, phase 2 RCT[119] was conducted in patients with Alzheimer's disease (n = 106) randomized to receive either a nutraceutical formulation containing SAMe (400 mg) or placebo for 3 to 6 months. Relative to the placebo group, within 3 months, the nutraceutical-formulation cohort demonstrated improved cognitive performance on the CLOX 1 ($P = .0083$; 95% CI, 0.4481 to 2.9343) and the age- and education-adjusted DRS ($P = .0266$; 95% CI, 0.1722 to 2.7171). Notably, in the nutraceutical formulation group, there was significant improvement in the DRS memory domain scores from baseline to 3-month end point ($P < .0001$; 95% CI, 1.2348 to 3.2283). Across all studies evaluating the cognitive effects of nutraceutical formulation containing SAMe, the treatment was well tolerated. Interpretation of the results of these trials with regard to effect of SAMe is limited because SAMe was 1 of multiple ingredients in the nutraceutical formulation. Future studies in Alzheimer's disease may include clinical trial designs that isolate the contribution of SAMe to cognitive improvement.

Psychotic disorders. Aggression in schizophrenia has been linked to a genetic variant of the *COMT* gene associated with low activity of an enzyme critical for neurotransmission.[120] As SAMe increases COMT enzymatic activity,[121] researchers investigated its utility in managing aggression in a subset of patients with schizophrenia. In 1 RCT,[122] 18 patients with chronic schizophrenia and the low-activity COMT

polymorphism (codon 158 polymorphism) were randomly assigned to either SAMe (800 mg/d) or placebo for 8 weeks. There was a significant decrease in the primary outcome measure of aggression (Overt Aggression Scale) from baseline to 8-week end point in only the SAMe group ($P = .016$), resulting in a significant group-by-time interaction ($P = .032$). While there were no significant group differences in side effects, the study was terminated because of worsening irritability in 2 subjects who received SAMe.

The 22q11.2 deletion syndrome (22q11.2DS) is a genetic disorder associated with high rates of psychiatric comorbidity including psychosis, depression, and attention-deficit/hyperactivity disorder.[123] Individuals with this syndrome are missing 1 copy of the *COMT* gene. The ability of SAMe to increase COMT enzymatic activity has been proposed as a potential therapeutic mechanism for alleviating psychiatric symptoms in this patient population. A 12-week randomized, double-blind, crossover, placebo-control study[124] assessed feasibility and safety of SAMe (1,600 mg/d) in 12 patients with 22q11.2DS. No significant group differences were found for the randomized population in the primary outcome measure (Clinical Global Impressions Scale).[125] The subset with 22q11.2DS and comorbid depression (n = 5) who received oral SAMe demonstrated numerically greater improvement in Children's Depression Rating Scale-Revised scores compared to those who received placebo. Future studies may include larger samples of subjects with greater symptom severity.

Liver disease associated with substance use disorders, infections, and cholestasis. *S*-adenosylmethionine may have a role in treating depression in patients who develop hepatitis or cirrhosis due to comorbid alcohol dependence[126] or intravenous drug use,[127] as it does not exacerbate hepatic dysfunction. Preclinical and clinical studies suggest that SAMe can improve liver function (eg, decreased transaminase levels) or liver disease outcomes in hepatitis, alcoholic and viral liver cirrhosis, and cholestasis.[73,128–133] In the largest study in this group, Mato and colleagues[131] conducted an RCT with 123 patients with alcoholic liver cirrhosis. The primary outcome, measured as the overall all-cause mortality or liver transplantation at 2-year study end point, was 30% in the placebo group and 16% in the SAMe group, although the difference was not statistically significant ($P = .077$). As part of the post hoc analysis, when patients in child C class (least favorable prognostic group) were excluded (n = 8), overall mortality or liver transplantation was significantly greater in the placebo group compared to the SAMe group (29% vs 12%, $P = .025$).

Use in Pregnancy, Risks, and Medication Interactions

The need for safer treatments for depression in women during pregnancy and postpartum is urgent, particularly in light of evidence that untreated maternal MDD may adversely affect fetal and neonatal development. The use of certain prescription antidepressants has been associated with increased risk of birth defects.[134] SAMe has been evaluated in intrahepatic cholestasis of pregnancy in conjunction with the bile acid ursodeoxycholic acid,[135,136] which is a natural bile acid commonly used to reverse impaired bile formation.[137] A systematic review and meta-analysis[138] of 10 RCTs (n = 727 pregnant women with intrahepatic cholestasis of pregnancy) found that a combination of ursodeoxycholic acid and SAMe significantly ($P < .05$) reduced rates of cesarian sections, preterm birth, and fetal asphyxia. The mean endogenous CSF concentration of SAMe in healthy infants and youth may be greater than that in adults, although rigorous studies of age-related changes in levels of SAMe are needed.[139] Trials of SAMe during pregnancy and breast-feeding with long-term monitoring of child development would be worthwhile.

The most common side effect of SAMe is nausea, and diarrhea, abdominal discomfort, or vomiting occurs less frequently. Occasionally, agitation, anxiety, or insomnia can occur in patients sensitive to activating effects of SAMe. As with other antidepressants, SAMe can trigger hypomanic or manic symptoms in patients with bipolar disorder. Overall, SAMe has a favorable side-effect profile in that it does not cause sexual dysfunction or weight gain. Another advantage is that SAMe does not cause cognitive or memory dysfunction, which is particularly important to patients with dementia, age-related cognitive or memory decline, and traumatic brain injury. SAMe is well tolerated in geriatric patients as indicated in open trials showing improved recall and word-finding scores.[115]

S-adenosylmethionine has few known adverse interactions with other drugs. One case of serotonin syndrome in a 71-year-old woman treated with escalating doses of clomipramine while taking SAMe was reported.[140] Her symptoms developed 48–72 hours after the dose of clomipramine was increased 3-fold (25 mg/d to 75 mg/d), while the dose of SAMe was kept constant. It is likely that her symptoms developed from the rapid dose escalation of clomipramine. No other cases of serotonin syndrome attributable to SAMe have been reported, including in trials where SAMe was used to augment SSRIs and TCAs. Furthermore, in an open trial that included 60 depressed patients taking MAOIs, augmentation with SAMe was beneficial and caused no adverse effects.[141] In patients with medication-induced elevated liver function tests, SAMe reduced or normalized liver functions.[141] The theoretical possibility that SAMe could induce hyperhomocysteinemia has never been substantiated nor has any confirmed case been reported. A small study of adults given a high dose of oral SAMe (1,600 mg for 5 days) showed no change in serum homocysteine levels.[142]

DISCUSSION

This review of the role of SAMe in the treatment of MDD found encouraging evidence of its efficacy and safety as a monotherapy and as an augmentation for other antidepressants. Since the FDA AHRQ review,[73] additional studies have generally supported SAMe as efficacious for treatment of MDD and comparable to several prescription antidepressants, although comparisons against newer-generation antidepressants are needed. In addition to

depression, this review found supportive early evidence for SAMe in certain neurocognitive, substance abuse, and psychotic disorders. Studies of SAMe in primary anxiety disorders were not identified. Additional clinical studies are needed to further delineate the role of SAMe in neuropsychiatric conditions.

Clinical reviews often exclude studies in patients with comorbid medical illnesses or concurrent prescription medications. Consequently, because of these exclusions, clinical opportunities for using SAMe are often overlooked. Depressed patients present with a broad array of comorbid conditions, concurrent medications, and medication-related side effects. SAMe may ameliorate symptoms associated with medical conditions such as hepatic disease, osteoarthritis, fibromyalgia, and cognitive and memory decline. As is the case with many over-the-counter natural products, the evidence so far suggests that, compared to prescription medications, SAMe may cause fewer and less severe side effects and considerably fewer drug interactions. Moreover, SAMe may prevent or reverse side effects caused by other medications, such as liver or sexual dysfunction. Knowing that evidence generally supports the safety and efficacy of SAMe in both psychiatric and medical illnesses could impact clinical decision making.

Certain limitations in our review should be noted. First, the methodology of studies cited in this review varies due to the inclusion of diverse neuropsychiatric conditions, smaller studies, open trials, and larger RCTs. This heterogeneity limits interpretation on the clinical significance of SAMe in neuropsychiatric disorders. Second, the relatively modest body of research during the past 15 years precluded our undertaking a new meta-analysis. The consensus of this work group was that the relatively limited new material would not significantly change the overall conclusions of the Hardy et al meta-analysis,[73] which, while generally positive, were cautious and acknowledged the limitations of the body of work, such as small sample sizes, different doses and delivery systems, and concerns about publication biases.

Careful consideration over whether to pursue treatment with SAMe as opposed to a registered antidepressant is required on the part of the clinician and the patient. Clinicians who recommend SAMe need to inform their patients that this compound has not been tested as rigorously as its FDA-approved counterparts, and as such, its relative efficacy cannot be guaranteed. However, the risks of SAMe compare quite favorably with prescription antidepressants, particularly in that it does not cause sexual dysfunction or weight gain (2 of the most common causes for antidepressant discontinuation), and it is less likely to be life threatening in patients who are at risk for overdosing during suicide attempts. No cases of death by SAMe overdose have been reported. In a mouse study, 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, Maryland, record nos. 7176, 7177[https://www.cdc.gov/niosh/rtecs/RTECSaccess.html]). Although the cost of SAMe is not covered by insurance companies, compared with the high copayments on many prescriptions, it may be a reasonable expense.[2] Patients should be discouraged from self-medicating their depression and should be encouraged to seek professional evaluation before starting any treatment.

CONCLUSION

This review provides a broad perspective on the role of SAMe in the treatment of depression, neuropsychiatric disorders, and comorbid medical conditions. Notably, encouraging evidence is found for the safety and efficacy of SAMe as a monotherapy and as an adjunctive agent for MDD, although with several caveats in view of the heterogeneity of the studies and methodological concerns as discussed. Preliminary evidence suggests SAMe may hold promise in a number of neuropsychiatric conditions and comorbid medical illnesses. Exploration of the full range of potential benefits of SAMe through controlled clinical studies is much needed and is advised.

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Supplementary material follows this article.

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Supplementary Material

Article Title: *S*-Adenosylmethionine (SAMe) for Neuropsychiatric Disorders: A Clinician-Oriented Review of Research

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List of Supplementary Material for the article

1. **eTable 1** Open Trials of SAMe for Depression

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Supplementary Table

Table S1: Open Trials of SAMe for Depression

Trial	Year	Patients enrolled	Study duration (days)	SAMe dose (mg/day)	Route	Primary Outcome	Baseline to Endpoint *P* Value
Fazio et al.[34]	1973	28	12	45	IV/IM	HAM-D	< 0.01
Fazio et al.[32]	1974	49	8	45	IM	HAM-D	< 0.05
Agnoli et al.[143]	1975	51	15	75	IM	HAM-D	< 0.05
Andreoli et al.[144]	1977	17	15	135	IM	HAM-D	< 0.05
Barberi et al.[36]	1978	20	24	200	IV	HAM-D	< 0.01
Salvadorini et al.[145]	1980	39	21	60	IV	HAM-D	< 0.001
Carney et al.[69]	1983	12	14	350	IV	HAM-D	No *P* value provided
Lipinsky et al.[70]	1984	9	14	150	IV	HAM-D	No *P* value provided
Labriola et al.[146]	1986	50	30	100	IV/IM	HAM-D	< 0.01
Antun et al.[147]	1987	58	15	300	IV	HAM-D	< 0.05
Rosenbaum et al.[148]	1990	20	42	1600	PO	HAM-D	< 0.001
Fava et al.[149]	1990	17	42	1600	PO	HAM-D	< 0.0005
Cerutti et al.[48,a]	1993	40	30	1600	PO	KSQ	< 0.01
Criconia et al.[150]	1994	48	28	400-800	IV/IM	BDI	< 0.01
Fava et al. [151,a]	1995	195	15	400	IM	HAM-D	< 0.01
Alpert et al.[79]	2004	30	42	800-1600	PO	HAM-D	< 0.0001
De Berardis et al.[80]	2013	25	60	800	PO	HAM-D	< 0.001

TABLE S1 LEGEND:

[a] SAMe-treated groups only. Significant ($p<0.05$) improvement by Day 10.

Abbreviations.

HAM-D, Hamilton Rating Scale for Depression

KSQ, Kellner Symptom Questionnaire

BDI, Beck Depression Inventory

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