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Permalink

<https://escholarship.org/uc/item/7m99k1dp>

Journal

The Journal of Clinical Psychiatry, 78(6)

ISSN

0160-6689

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Publication Date

2017-06-28

DOI

10.4088/jcp.16r11113

Peer reviewed



Published in final edited form as:

J Clin Psychiatry. 2017 June ; 78(6): e656–e667. doi:10.4088/JCP.16r11113.

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

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Abstract

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Disclosures: Anup Sharma: Dr. Sharma reports no competing interests. He is member of the American Psychiatric Association (APA) Council on Research and Quality.

Patricia Gerbarg: Dr. Gerbarg receives royalties from two books that include information about SAME. She serves as a consultant for NCCAM Award #8T007483: The Treatment of Depression with Yoga and Walking.

Teodoro Bottiglieri: Dr. Bottiglieri reports having been the chairman of the advisory board for Methylation Sciences Inc., holding stock options in Methylation Sciences Inc., Scientific Advisor to Gnosis S.p.A. Nestle Health Sciences and PamLab Inc. and having received research funding from Nestle Health Sciences, PamLab Inc., distributor of B vitamins as a medical food.

Lila Massoumi: Dr. Massoumi reports no competing interests.

Linda L. Carpenter: Dr. Carpenter reports consulting income from Magstim Ltd. and research support from the National Institutes of Health and through clinical trial contracts between Butler Hospital and Neuronetics, Inc., NeoSync, and Cervel. She is member of the American Psychiatric Association (APA) Council on Research and Quality.

Helen Lavretsky: Dr. Lavretsky reports no competing interests. She reports grant support from the NIMH, NCCIH, Forest Research Institute, Alzheimer's Research and Prevention foundation (APRF)

Philip R. Muskin: Dr. Muskin reports no competing interests.

Richard P. Brown: Dr. Brown serves as a consultant to Humanetics and holds a patent on the use of 7-keto DHEA for PTSD. He receives royalties from two books that include information about SAME and receives honoraria for lectures on CAIM that may include information on SAME.

David Mischoulon: Dr Mischoulon has received research support from the FisherWallace, Nordic Naturals, Methylation Sciences, Inc. (MSI), and PharmRx Therapeutics. He has received honoraria from the Massachusetts General Hospital Psychiatry Academy. He has received royalties from Lippincott Williams & Wilkins for published book "Natural Medications for Psychiatric Disorders: Considering the Alternatives."

As Work Group of the American Psychiatric Association Council on Research

Objective—A systematic review on S-adenosylmethionine (SAMe) for treatment of neuropsychiatric conditions and co-morbid medical conditions.

Data Sources—Searches were conducted between 7/15/2015 and 9/28/2016 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 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 of 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 in order 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 the use of SAMe 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 co-morbid medical conditions.

Conclusions—SAMe 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 co-morbid medical illnesses.

Introduction

Complementary, alternative, and integrative medicine (CAIM) includes a wide range of biological, psychological and mind-body treatments being used to enhance standard medical practices and improve patient outcomes. Integrative Psychiatry (IP), a form of CAIM, “seeks to enrich mainstream mental health care with valuable treatments from global healing traditions as well as from modern laboratories in related fields.” (1,2). CAIM 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 CAIM 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 co-substrate 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 B12, necessary co-factors in the synthesis of SAmE, may account for decreased SAmE levels, especially in patients with depression and dementia. Studies have shown that with either oral or parenteral treatment, SAmE crosses the blood-brain barrier and increases CSF levels, including in patients with neuropsychiatric conditions (14,15). As a CAIM therapy, SAmE has been utilized for treatment of psychiatric and medical conditions in 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 (DSHEA).

This review summarizes clinical trials of SAmE for treatment of neuropsychiatric disorders and co-morbid 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 literature encompassing samples of patients with a wide variety of neuropsychological symptoms for whom decisions about psychiatric treatments may take into account co-existing 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 7/15/2015 and 9/28/2016 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

SAmE is the universal methyl donor in more than 100 methyltransferase reactions, which regulate essential metabolic pathways (see review, by 6,16). Methylation involves the transfer of a methyl group (CH₃) 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 post-

translational 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 for disease prevention, to delay disease progression, and to enhance therapeutic outcomes (16,19).

SAMe 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 beta-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 beta-amyloid protein (31). SAMe affects site-specific methylation of DNA-promoter regions that regulate gene function, and carboxymethylation of proteins that can regulate b-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 evaluated SAMe in the treatment of depressive disorders: 17 open-label trials with 708 patients (supplemental table, ST1); 19 double-blind, randomized placebo-controlled trials (RPCTs) of SAMe including 878 patients (Table 1); and 21 controlled trials comparing SAMe with other antidepressants with a total of 1591 patients (Table 2). Observations of SAMe-induced hypomania or mania in early studies (45,65,69,70,71) limited subsequent prospective clinical trials to unipolar major depressive episodes, though formal diagnostic criteria were not consistently used in early trials.

SAMe Compared with Placebo: SAMe has been compared to placebo for depressive symptoms in 19 RCTs (Table 1). Five out of six controlled studies conducted between 1976 and 1988 reported that intravenous (200-400mg/day) or intramuscular (45-50mg/day) SAMe was more effective than placebo for depression (37,41,43,62,72). Starting in the 1990's,

adequate oral doses (800-1600mg) of enteric-coated, stabilized SAME could be utilized in clinical studies. Overall, twelve of the nineteen RPCTs showed the antidepressant effect of SAME to be significantly greater than placebo for depressive syndromes ($p < 0.05$, Table 1), though many of these used samples in which diagnostic criteria for MDD were not required or MDD was not a primary diagnosis. In one of two 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, both SAME and escitalopram failed to outperform placebo (see below) (52).

A seminal 2002 meta-analysis by Hardy et al. (73), commissioned by the Agency for Healthcare Research and Quality (AHRQ), including 28 of 47 depression RCTs through the year 2000, remains the only SAME meta-analysis published in the past fifteen years. This fairly exhaustive meta-analysis, excluded 2 potentially informative studies comparing SAME against TCAs (50,67) due to insufficient statistical description, and one (64) because the authors were unable to obtain the paper. 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 papers. Hardy and colleagues 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 samples, 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 depression symptoms with an overall 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 (HAM-D) 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 HAM-D with different numbers of items (e.g. 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, randomized controlled trials (RCTs) compared SAME to other antidepressants: tricyclic antidepressants (TCAs), nomifensine, minaprine and escitalopram (Table 2). Early RCTs showed parenteral SAME (150-400mg/day) to be as effective or superior to TCAs (clomipramine, amitriptyline, imipramine) with fewer side effects (43,54,56,58,60). Subsequently, two larger studies ($n=295$, $n=293$) found intramuscular SAME (400mg/day) to be as efficacious as oral imipramine (150mg/day) in treating MDD for 4 weeks (67,68). Additionally, two large studies by Di Padova and colleagues comparing SAME against imipramine (74) suggested equivalency (effect size = 0.13 , 95% CI -0.10 to 0.36), though these reports were not published in peer reviewed journals. Four RCTs, including one large study ($n=281$) (67) and three smaller studies ($n = 30$) (64,65,66) found oral SAME (1600mg/day) to be as efficacious as oral desipramine (250mg/day) and oral imipramine (140-150mg/day). Overall, in 18

controlled trials, SAME was as effective as chlorimipramine (CMI) (54,55,56,60,61), imipramine (43,53,62,67,68) and nomifensine (59).

One recent multi-center RCT (n=189) comparing SAME, escitalopram and placebo failed to identify significant differences among the three arms at 12 weeks (52), perhaps due to an abnormally high placebo response rate. Re-analysis of the data from subjects enrolled at one of two sites (n=144) found that improvements in depression with SAME were equivalent to improvements with escitalopram and significantly greater than with placebo (75). A second re-analysis of the same trial identified an inter-site 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 gender-specific difference in antidepressant response requires validation by future studies.

Meta-analyses concluded that SAME and TCAs were equally efficacious in treating depression (73,77). The Hardy et al. meta-analysis (73) 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 of add-on parenteral SAME (250mg/day) vs. placebo injections in patients receiving either CMI or mianserin showed improved clinical symptoms by day 10 in the group receiving parenteral SAME compared to placebo (78). In an open-label trial, patients with MDD (n=30) who had not fully responded to a selective serotonin reuptake inhibitor (SSRI) or venlafaxine were treated with oral SAME (800mg/day) for 2 weeks, followed by oral SAME (1600mg/day) for an additional 4 weeks (79). At 6 weeks, 50% of patients achieved clinical response and 43% clinical remission. Reduction in depressive symptoms reached statistical significance at week 1 and remained significant through week 6 (p<0.001). In another open-label study, MDD patients (n=33) who failed to respond to at least 8 weeks of treatment with two adequate and stable doses of antidepressants were treated with a fixed dose of adjunctive SAME (800mg/day) (80). At 8 weeks, clinical response was achieved in 60% of patients and remission in 36% based on HAM-D. Changes from baseline were significant by week 1 and remained significant by week 8 (p<0.001). In a RCT, outpatients with MDD (n=73) who were non-responders or partial responders to SSRI or serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressants were randomized to receive adjunctive SAME (up to 1600mg/day) or placebo for 6 weeks (51). Both response rates (SAME: 36.1% vs. placebo: 17.6%) and remission rates (SAME: 25.8% vs. placebo 11.7%) were significantly higher for patients receiving SAME (p<0.05). A recent meta-analysis examining adjunctive nutraceuticals for depression demonstrated positive results for SAME (81).

A multi-center, double-blind RPCT add-on study of 800mg SAME (MSI-195, a novel SAME formulation with improved bioavailability) for patients with MDD with inadequate responses to antidepressant treatment was completed in 2015 (82). Results are not yet published, but a press release from the sponsor stated that MSI-195 did not demonstrate efficacy over placebo, though post-hoc analysis identified a responsive sub-group of 143 subjects (74 on MSI-195 and 69 on placebo) after patients with obesity and/or unstable symptom profiles were excluded. In this subanalysis using last observation carried forward (LOCF), the MSI-195 produced a significant reduction in the Montgomery–Asberg Depression Rating Scale (MADRS) of -3.41 ($p=0.031$) relative to placebo, with an effect size of 0.36. (83).

SAME in Depression with Co-morbid Medical Conditions

Depression and HIV: Relatively low concentrations of SAME have been reported in the CSF from patients with depression or Human Immunodeficiency Virus (HIV) infection (14,15). An 8 week, open-label study assessed 20 HIV seropositive individuals with MDD treated with SAME (800-1600mg/day) supplemented with vitamin B12 (1,000mcg/day) and folic acid (800mcg) (84). Intent-to-treat (ITT) analysis demonstrated significant reduction in Beck Depression Inventory (BDI) scores from baseline (Mean=33.5, SD=11.1) to week 8 (Mean=6.6, SD= 6.1, $p<0.001$). Similarly, 17-item HAM-D scores significantly decreased from baseline (Mean=26.5, SD=6.8) to week 8 (Mean=7.7, SD=10.1, $p<0.001$). Between baseline and week 1, there was evidence for a rapid therapeutic effect on BDI and HAM-D ($p<0.01$). At 8 weeks, the remission rate (17-item HAM-D of 7) was 79% for ITT analysis and 93% for the 15 subjects who completed the study. Two patients reported transient nausea and one 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 PD 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 (PD), can limit use of prescription antidepressants (86). SAME has been proposed to protect dopaminergic neurons from L-dopa induced neurotoxicity (87). In PD, chronic treatment with Levodopa (L-dopa) depletes blood levels of SAME (88). L-dopa is methylated to 3-O-methyl-dopa by catechol-O-methyltransferase (COMT). Since SAME is the methyl donor in this reaction, its levels become depleted with L-dopa treatment. Pre-clinical studies show that acute treatment with L-dopa markedly depletes SAME levels in liver and brain tissue (25). In PD, 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 three small trials in patients with PD and MDD ($n=13$, $n=21$, $n=32$), SAME (1600 – 4000 mg/day) significantly reduced depression scores on HAM-D ($p<0.05$) (44, 91,92). A 10 week, open-label study involving patients with co-morbid treatment-resistant MDD and PD ($n=13$) showed significant improvement in HAM-D depression scores following administration of SAME monotherapy (800-3600mg/daily) (91). Mean HAM-D dropped from a baseline of 27.09 (SD= 6.04) to 9.55 (SD= 7.29, $p<0.002$) after 10 weeks. Out of eleven completers, ten had 50% or more improvement on HAM-D. 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 PD and depression (n=32), both SAME and escitalopram groups had significantly improved depression scores compared to placebo (p<0.05) (92). In two out of three clinical trials, SAME improved PD motor symptoms (91,92). Larger controlled studies are needed to follow-up these preliminary findings in PD (93).

Depression and Osteoarthritis or Fibromyalgia: SAME 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 NSAIDs, but may enhance proteoglycan synthesis and secretion (33,94). In several RCTs including more than 22,000 patients, SAME was as effective as nonsteroidal anti-inflammatory drugs (NSAIDs) in relieving pain in osteoarthritis (99-106). An AHRQ meta-analysis of eight 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, 0.35]) (73). In three out of four small RCTs with fibromyalgia patients, SAME (200-800mg) significantly reduced pain symptom primary outcomes including the VAS (p<0.05) (107-110) compared to placebo. Concurrently, SAME improved symptoms of depression (HAM-D or BDI, p<0.05). These results warrant further investigation into SAME treatment for patients with MDD and rheumatologic co-morbidities.

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 (described in detail above) of SAME augmentation in SSRI/SNRI non-responders examined whether adjunctive SAME was associated with greater improvement in sexual functioning than adjunctive placebo (112). Relative to those who got placebo, men treated with adjunctive SAME demonstrated significantly lower arousal dysfunction (p=0.0012) and degree of erectile dysfunction (p=0.01) at study endpoint, 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 re-analyses of previously published studies.

Neurocognitive Disorders and Cognitive Function—

MDD is commonly associated with cognitive impairment. Preclinical and early clinical trials provide some support for beneficial effects of SAME alone or in combination with other nutraceuticals, on cognitive function (17, 113-115). A secondary analysis of data from a RCT on adjunctive SAME for MDD (n=46) demonstrated that oral SAME (1600mg/day), as compared to placebo, improved two memory-related cognitive functions (recall, p=0.04 and word-finding, p=0.09), but not five other cognitive domains (116). 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 found that CSF levels of SAME in patients with Alzheimer's Disease were significantly reduced compared to controls (28). A one year, open-label study that treated early-stage Alzheimer's Disease patients (n=14) with a nutraceutical formulation (NF) containing SAME (400mg) in addition to other vitamins (folic acid, 400µg; vitamin B12, 6µg) and nutraceuticals (alpha-tocopherol, 30 IU; N-acetyl cysteine, 600mg; acetyl-L-carnitine, 500mg) demonstrated improvement in cognitive symptoms as assessed by the Dementia Rating Scale (DRS) and clock-drawing tests (117). Family caregivers also reported improvement in multiple domains of the Neuropsychiatric Inventory (NPI). In another pilot study in moderate-to-late stage Alzheimer's disease (n=12), treatment with a similar NF containing SAME did not show statistical separation between active and placebo groups, but there were some suggestive signals 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 NF (118). Recently, a larger, multi-site, phase II RCT was conducted in AD patients (n=106) randomized to receive either a NF containing SAME (400mg) or placebo for 3 to 6 months (119). Relative to the placebo group, within 3 months, the NF cohort demonstrated improved cognitive performance on the Clox-1 (p=0.0083, CI [0.4481, 2.9343]) and the age and education-adjusted Dementia Rating Scale (DRS; p=0.0266, CI [0.1722, 2.7171]). Notably, in the NF group, there was significant improvement in the DRS memory domain scores from baseline to 3 month endpoint (p<0.0001, CI [1.2348, 3.2283]). Across all studies evaluating the cognitive effects of NF containing SAME, the treatment was well tolerated. Interpretation of the results of these trials with regard to effect of SAME is limited because SAME comprised one of multiple ingredients in the NF. Future studies in AD may include clinical trial designs that isolate the contribution of SAME to cognitive improvement.

Psychotic Disorders—Aggression in schizophrenia (SCZ) has been linked to a genetic variant of the catechol-O-methyltransferase (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 SCZ patients. In one RCT, 18 patients with chronic SCZ and the low-activity, COMT polymorphism (codon 158 polymorphism) were randomly assigned to either SAME (800mg/day) or placebo for 8 weeks (122). There was a significant decrease in the primary outcome measure of aggression (Overt Aggression Scale) from baseline to 8 week endpoint in only the SAME group (p=0.016), resulting in a significant group by time interaction (p=0.032). While there were no significant group differences in side effects, the study was terminated because worsening irritability in two subjects who received SAME.

The 22q11.2 deletion syndrome (22q11.2DS) is a genetic disorder associated with high rates of psychiatric co-morbidity including psychosis, depression and attention-deficit/hyperactivity disorder (ADHD) (123). Individuals with this syndrome are missing one 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, cross-over, placebo-control study assessed feasibility and safety of SAME (1600mg/day) in 22q11.2DS patients (n=12) (124). There were no significant group differences found for the randomized population in the

primary outcome measure (Clinical Global Impression 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 (CDRS-R) 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, Cholestasis—SAME 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 (e.g. 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 conducted a RCT with n=123 patients with alcoholic liver cirrhosis. The primary outcome, measured as the overall all-cause mortality or liver transplantation at 2 year study endpoint was 30% in the placebo group and 16% in the SAME group, although the difference was not statistically significant (p=0.077). 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=0.025) (131).

Use in Pregnancy, Risks and Medication Interactions

The need for safer treatments for depression in women during pregnancy and post-partum 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 (UDCA) (135,136). UDCA is a natural bile acid commonly used to reverse impaired bile formation (137). A systematic review and meta-analysis of ten RCTs (n= 727 pregnant women with intrahepatic cholestasis of pregnancy) found that a combination of ursodeoxycholic acid (UDCA) and SAME significantly (p<0.05) reduced rates of Caesarian sections, preterm birth, and fetal asphyxia (138). The mean endogenous CSF concentration of SAME in normal infants and youth may be greater than in adults, though 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, less frequently, diarrhea, abdominal discomfort, or vomiting. 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, particularly important in 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).

SAMe 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 (CMI) while on SAMe was reported (140). Her symptoms developed 48-72 hours after the dose of CMI was increased three-fold (25mg/day to 75mg/day), while the dose of SAMe was kept constant. It is likely that her symptoms developed from the rapid dose escalation of CMI. 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 LFTs, SAMe reduced or normalized liver functions (141). The theoretical possibility that SAMe could induce hyper-homocysteinemia has never been substantiated, nor has any confirmed case been reported. A small study of adults given a high dose of oral SAMe (1600mg for 5 days) showed no change in serum homocysteine levels (142).

Discussion

This review of the role of S-adenosylmethionine in the treatment of Major Depressive Disorder found encouraging evidence of efficacy and safety of SAMe as a monotherapy and as an augmentation for other antidepressants. Since the US FDA Agency for Healthcare Research and Quality (AHRQ) review (73), additional studies have generally supported SAMe as efficacious for treatment of MDD and comparable to several prescription antidepressants, though 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 co-morbid 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 co-morbid 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 meta-analysis, which, while generally positive, were cautious and acknowledged the limitations of the body of work, such as small samples, different doses and delivery systems, and concerns about publication biases (73).

Careful consideration of pursuing 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 (two 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, MD, Record Nos. 7176, 7177). 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 (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 co-morbid medical conditions. Notably, encouraging evidence is found for the safety and efficacy of SAME as a monotherapy and as an adjunctive agent for Major Depressive Disorder, though 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 co-morbid medical illnesses. Exploration of the full range of potential benefits of SAME through controlled clinical studies is much needed and is advised.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We appreciate the helpful review and input from American Psychiatric Association Council on Research.

Funding/Support: None

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Clinical Points

- Clinical opportunities for using S-adenosylmethionine (S-AMe) may include multiple neuropsychiatric disorders and co-morbid medical conditions.
- S-adenosylmethionine (S-AMe) is a viable treatment in MDD, and early evidence suggests that it holds promise for a number of neuropsychiatric conditions.
- Additional research is needed to strengthen the body of evidence.

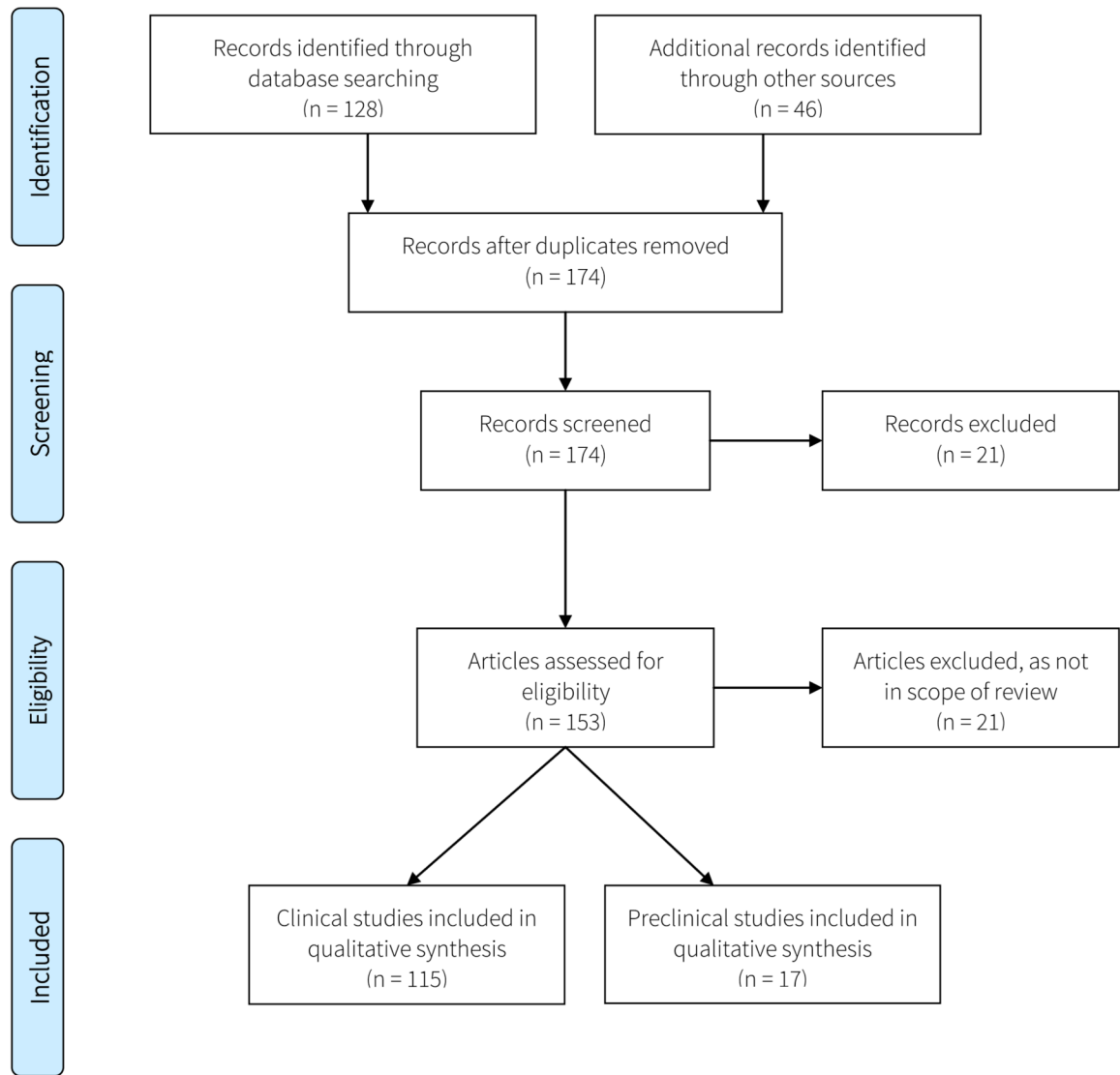


Figure 1. Flowchart of Studies Included in the Systematic Review

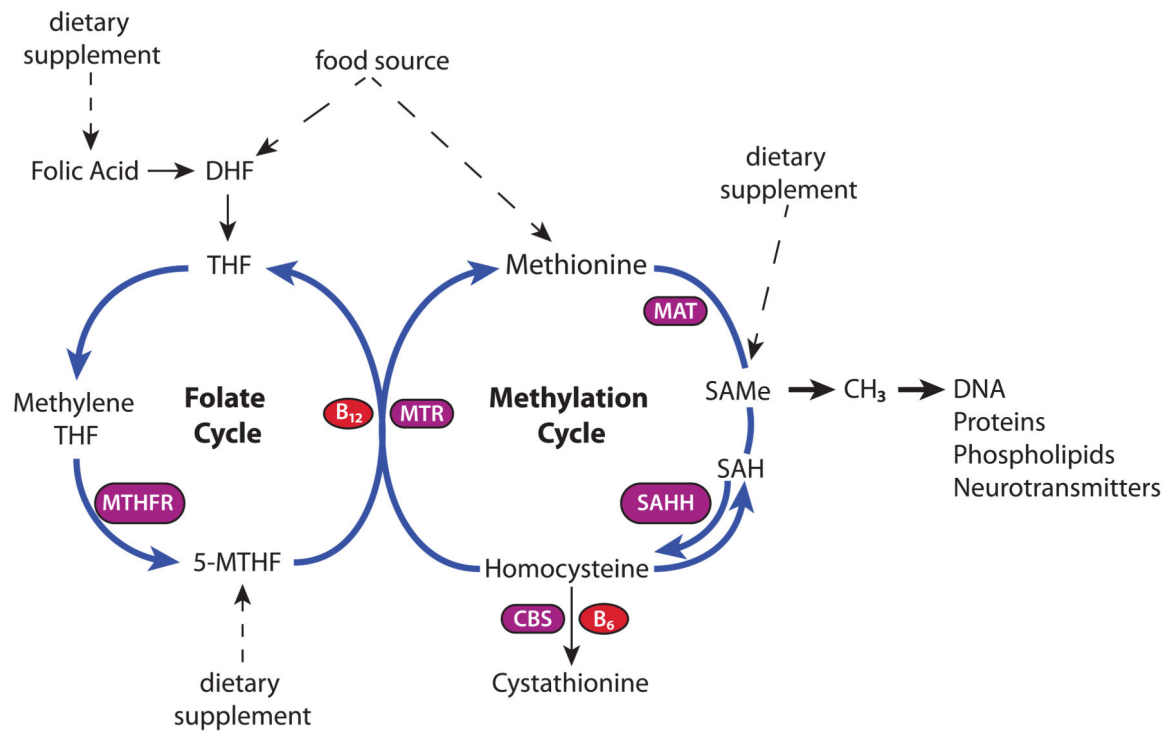


Figure 2. S-adenosylmethionine in the Methylation Cycle

DHF, dihydrofolate; THF, tetrahydrofolate; 5-MTHF, 5-methyltetrahydrofolate; S-AMe, S-adenosylmethionine; SAH, S-adenosylhomocysteine; MTHFR, methylenetetrahydrofolate reductase; MTR, methionine synthase; MAT, methionine adenosyltransferase; SAHH, S-adenosylhomocysteine hydrolase.

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Table 1

Controlled Trials of SAME vs. Placebo for Depression

Trial	Year	Patients enrolled (randomized)		Experimental Design	Study duration (days)	SAME dose (mg/day)	Route	Primary Outcome Measure		Primary Outcome (SAME vs. Placebo) P Value
		Total	Placebo					Positive	Negative	
Fazio et al. ³⁴	1973	19	5	double-blind	8	45	IV	HAM-D	<0.01	
Agnoli et al. ³⁵	1976	30	10	double-blind	15	45	IM	HAM-D		<i>P</i> value for comparison not provided
Barberi et al. ^{36,a}	1978	40	20	cross-over	10	200	IV	HAM-D	<0.05	
Muscettola et al. ³⁷	1982	20	10	double-blind	15	150	IM	HAM-D	<0.01	
Caruso et al. ³⁸	1984	49	24	double-blind	21	200	IM	HAM-D	<0.001	
Carney et al. ³⁹	1986	32	17	double-blind	14	200	IV	HAM-D	NS ^b	
Caruso et al. ⁴⁰	1987	59	29	double-blind	21	200	IM	HAM-D	<0.01	
De Leo et al. ⁴¹	1987	40	20	double-blind	30	200	IM	ZSDS	<0.05	
Thomas et al. ⁴²	1987	20	11	double-blind	14	200	IV	HAM-D	NS ^b	
Janicak et al. ⁴³	1988	15	5	double-dummy	15	400	IV	HAM-D	<0.02	
Carriero et al. ⁴⁴	1990	21	10	cross-over	15	1000	PO	HAM-D	<0.05	
Kagan et al. ^{45,a}	1990	18	9	double-blind	21	1600	PO	HAM-D	<0.05	
Fava et al. ⁴⁶	1992	43	31	double-blind	42	1600	PO	HAM-D	NS ^{c,d,e}	
Anacarami et al. ⁴⁷	1993	53	10	double-blind	21	400 ^f	IV	IPAT-DS	NS ^g	
Salmaggi et al. ^{48,a}	1993	80	40	double-blind	30	1600	PO	HAM-D total	<0.01	
Cerutti et al. ^{49,a,h}	1993	60	30	double-blind	30	1600	PO	KSQ	NS ⁱ	

Trial	Year	Patients enrolled (randomized)		Experimental Design	Study duration (days)	SAmE dose (mg/day)	Route	Primary Outcome Measure	Primary Outcome (SAmE vs. Placebo) P Value	
		Total	Placebo						Positive	Negative
Delle Chiaie et al. ³⁰	1997	75	35	double-blind	21	800	IV	MADRS	< 0.05	
Papakostas et al. ⁵¹	2010	73	34	double-blind/augmentation	45	1600	PO	HAM-D % response	< 0.05	
Mischoulon et al. ⁵²	2014	189	60	double-blind; escitalopram was third treatment group	84	1600-3200	PO	HAM-D total		NS ^{c,d}

^aSAmE-treated groups only. Significant ($p < 0.05$) improvement by Day 10.

^bSAmE response rate greater than placebo, results not statistically significant

^cSAmE response rate equivalent to placebo

^dConsidered failed trials (see text).

^eDescribes a post-hoc analysis of TRH as a predictor of response to SAmE in $n=32$ from a placebo-controlled trial ($n=43$). Both the larger trial and this subset produced negative results.

^fSAmE does was 400mg IV given every other day at the end of a dialysis session.

^gp value for comparison not present in text, but graphed figure indicates no group difference.

^hDiagnosis was puerperal psychological distress

ⁱSAmE > placebo at 10 day assessment ($p < 0.05$), no significant differences at study endpoint.

Abbreviations.

HAM-D, Hamilton Rating Scale for Depression

IPAT-DS, Personality and Ability Testing – Depression Scale

KSQ, Kellner Symptom Questionnaire

NS, not statistically significant

ZSDS, Zung Self-Rating Depression Scale

Table 2

Controlled Trials of SAME vs. Other Antidepressants

Trial	Year	Patients enrolled			Experimental Design	Duration (days)	SAME dose (mg/day)	Route	Other Antidepressant	Other dose (mg/day)	Route	Primary Outcome Measure	Relative Efficacy (SAME vs. Other)
		Total	SAME	Other									
Mantero et al. ⁵³	1975	31	16	15	double-blind	21	75	IM	Imipramine	75	IM	HAM-D	SAME = Other
Miccoli et al. ⁵⁴	1978	86	45	41	double-blind	21	200	IV	Chlorimipramine or Amitriptyline	100	IV	HAM-D	SAME = Other
Barberi et al. ⁵⁶	1978	20	10	10	double-blind	20	200	IV	Amitriptyline	100	IV	HAM-D	<i>P</i> value for comparison not provided ^a
Del Vecchio et al. ⁵⁵	1978	28	14	14	double-blind	21	150	IV	Chlorimipramine	100	IV	HAM-D	SAME = Other
Scarzella et al. ^{56,b}	1978	20	10	10	double-blind	15	250	IV	Chlorimipramine	100	IV	HAM-D	SAME = Other
Calandra et al. ⁵⁷	1979	24	12	12	no blind	15	150	IV	Chlorimipramine	100	IV	HAM-D	SAME = Other
Monaco et al. ⁵⁸	1979	20	11	9	double-blind	15	200	IV	Amitriptyline	100	IV	HAM-D	SAME = Other
Scaggion et al. ⁵⁹	1982	40	22	18	double-dummy	15	300	IV	Nomifensine	200	PO	HAM-D	SAME = Other
Kufferle et al. ⁶⁰	1982	20	10	10	double-blind	18	150	IV	Chlorimipramine	50	IV	HAM-D	SAME = Other
Ubago et al. ⁶¹	1984	30	15	15	double-blind	30	100	IV	Chlorimipramine	50	PO	HAM-D	SAME = Other
Bell et al. ^{62,b}	1988	22	11	11	double-dummy	14	400	IV	Imipramine	150	PO	HAM-D	SAME > Other ^c
Janicak et al. ⁴³	1988	20	12	3	double-dummy	14	400	IV	Imipramine	150	PO	HAM-D	SAME = Other
Cerutti et al. ⁶³	1989	20	20	20	cross-over	21	800	PO	Minaprine	200	PO	HAM-D	SAME > Other ^c
Bell et al. ⁶⁴	1990	28	14	14	double-blind	28	1600	PO	Desipramine	250	PO	HAM-D	SAME = Other
De Vanna et al. ^{65,b}	1992	30	15	15	double-blind	42	1600	PO	Imipramine	140	PO	MADRS	<i>P</i> value for comparison not provided ^a
Bell et al. ⁶⁶	1994	17	11	6	double-blind	28	1600	PO	Desipramine	250	PO	HAM-D	<i>P</i> value for comparison not provided ^a

Trial	Year	Patients enrolled		Experimental Design	Duration (days)	SAmE dose (mg/day)	Route	Other Antidepressant	Other dose (mg/day)	Route	Primary Outcome Measure	Relative Efficacy (SAmE vs. Other)
		Total	Other									
Delle Chiaie et al. ⁶⁰	1997	122	57	65	21	800	IV	Chlorimipramine	100	IV	HAM-D	Other > SAmE ^d
Delle Chiaie et al. ⁶⁷	2000	281	143	138	42	1600	PO	Imipramine	150	PO	HAM-D	SAmE = Other
Delle Chiaie et al. ⁶⁷	2000	295	147	148	28	400	IM	Imipramine	150	PO	HAM-D	SAmE = Other
Pancheri et al. ⁶⁸	2002	293	146	147	28	400	IM	Imipramine	150	PO	HAM-D	SAmE = Other
Mischoulon et al. ⁵²	2014	189	64	65	84	1600-3200	PO	Escitalopram	10-20	PO	HAM-D	SAmE = Other

^aBoth groups demonstrated significant ($p < 0.05$) improvements on primary outcome measure. *P* value for between-group comparison not provided.

^bSAmE-treated groups only. Significant ($p < 0.05$) improvement by Day 10.

^cSAmE group demonstrated significant ($p < 0.05$) improvement compared to other antidepressant group on primary outcome measure

^dOther antidepressant demonstrated significant ($p < 0.05$) improvement compared to SAmE on primary outcome measure

Abbreviations.

HAM-D, Hamilton Rating Scale for Depression

MADRS, Montgomery-Asberg's Rating Scale for Depression