A Double-Blind, Randomized, Placebo-Controlled Clinical Trial of *S*-Adenosyl-L-Methionine (SAMe) Versus Escitalopram in Major Depressive Disorder

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ABSTRACT

Objective: To examine the comparative antidepressant efficacy of *S*-adenosyl-L-methionine (SAMe) and escitalopram in a placebo-controlled, randomized, double-blind clinical trial.

Method: One hundred eighty-nine outpatients (49.7% female, mean [SD] age = 45 [15] years) with *DSM-IV*–diagnosed major depressive disorder (MDD) were recruited from April 13, 2005, to December 22, 2009, at the Massachusetts General Hospital and at Butler Hospital. Patients were randomized for 12 weeks to SAMe 1,600–3,200 mg/d, escitalopram 10–20 mg/d, or placebo. Doses were escalated at 6 weeks in the event of nonresponse. The main outcome measure was the 17-item Hamilton Depression Rating Scale (HDRS-17). Tolerability was assessed by the Systematic Assessment for Treatment of Emergent Events-Specific Inquiry (SAFTEE-SI).

Results: All 3 treatment arms demonstrated a significant improvement of about 5–6 points in HDRS-17 scores ($P < .001$ for all), and no significant differences were observed between the treatment arms ($P > .05$ for all). Response rates in the intent-to-treat sample were 36% for SAMe, 34% for escitalopram, and 30% for placebo. Remission rates were 28% for SAMe, 28% for escitalopram, and 17% for placebo. No comparisons between treatment groups attained significance ($P > .05$ for all). Tolerability was good, with gastrointestinal side effects (19% for stomach discomfort and 20% for diarrhea) as the most common in the SAMe arm. Significant differences were observed between treatment groups for dizziness, anorgasmia, diminished mental acuity, and hot flashes ($P < .05$ for all).

Conclusions: The results fail to support an advantage over placebo for either the investigational treatment SAMe or the standard treatment escitalopram for MDD.

Trial Registration: ClinicalTrials.gov identifier: NCT00101452

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S-adenosyl-L-methionine (SAMe) is a natural substance synthesized from the amino acid L-methionine and adenosine triphosphate through the 1-carbon cycle.[1] In the brain, SAMe functions as a methyl donor, shifting its methyl group to various key neurotransmitters via methyltransferase reactions.[2] Over the past 30 years, more than 45 randomized clinical trials have supported the efficacy of SAMe as monotherapy against placebo and tricyclic antidepressants.[3,4] In a recent double-blind, controlled study,[5] SAMe augmentation was shown to be effective in nonresponders to selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors.

Thus far, no published studies have compared SAMe monotherapy against newer antidepressants such as the SSRIs, the standard first-line treatment for depression. We therefore carried out a 3-armed, randomized, double-blind trial comparing SAMe against placebo and escitalopram in a sample of patients with major depressive disorder (MDD). Escitalopram is especially well suited for comparison with SAMe because both have comparable tolerability and attrition rates to placebo,[5,6] thus minimizing the risk of unblinding patients.

A 12-week treatment duration was selected to reduce transient improvement, increase treatment effect size, and provide statistical power equivalent to that of a larger sample.[7] Also, patients who obtain a true drug response within 6 weeks are likely to continue to respond after another 6 weeks of treatment, while those with a placebo-like response will most likely fail to sustain response.[7] The study included a crossover phase in which nonresponders to either escitalopram or SAMe received the combination of the 2 drugs, though this report will focus on the main outcome data for the first 12 weeks of double-blind treatment.

We assessed the acute effects of SAMe or escitalopram versus placebo on clinical improvement, quality of life, and psychosocial functioning. We also assessed the tolerability of the 3 treatments. We hypothesized that we would obtain similar efficacy findings for SAMe and escitalopram and that both would yield beneficial clinical effects significantly greater than placebo. Likewise, we expected differences in specific side effects between SAMe, escitalopram, and placebo, eg, a greater incidence of sexual dysfunction or gastrointestinal upset with escitalopram.

METHOD

We recruited male and female subjects aged 18–80 years, from April 13, 2005, to December 22, 2009, at the Massachusetts General Hospital in Boston and at Butler Hospital in Providence, Rhode Island. The trial (ClinicalTrials.gov identifier: NCT00101452) was conducted according to the US Food and Drug Administration (FDA) guidelines and the Declaration of Helsinki.[8] Subjects were outpatients with MDD diagnosed according to the Structured Clinical Interview for *DSM-IV* Axis I Disorders-Patient Edition (SCID-I/P).[9] After complete description

Clinical Points

- In this clinical trial involving treatment of major depressive disorder, the natural product *S*-adenosyl-L-methionine (SAMe) and the selective serotonin reuptake inhibitor (SSRI) escitalopram did not demonstrate a significant advantage over placebo.
- While all 3 treatment groups experienced a significant clinical improvement, the abnormally high placebo response rate prevents any definitive statement about the efficacy of either of the antidepressants tested.
- This study is the first comparison of SAMe against an SSRI, and, therefore, further comparisons between SAMe and established antidepressants are necessary.

of the study to the subjects, written informed consent was obtained. Patients were recruited through clinician referral and general advertisement in local newspapers, radio, and television. The study was approved by both sites' institutional review boards.

Inclusion Criteria

In addition to the diagnostic criteria for MDD, scores of ≥ 25 on the Inventory of Depressive Symptomatology-Clinician-Rated (IDS-C)[10] at the screen and baseline visits were required. The 17-item Hamilton Depression Rating Scale (HDRS-17)[11–13] was used as the main outcome instrument for antidepressant efficacy.

Exclusion Criteria

Subjects were excluded if they met any of the following criteria: pregnancy or women of child-bearing potential who were not using a medically accepted means of contraception; serious suicidality or homicidality; unstable medical illness, including cardiovascular, hepatic, renal, respiratory, endocrine, neurologic, or hematologic; organic mental disorders; substance use disorders, including alcohol, active within the preceding 6 months; schizophrenia and other psychotic disorders or psychotic features; bipolar disorder; acute bereavement; severe borderline or antisocial personality disorder; current primary diagnoses of panic disorder or obsessive-compulsive disorder; seizure disorder; concurrent use of other psychotropic drugs; hypothyroidism; a ≥ 6-week course of either escitalopram ≥ 10 mg/d or SAMe ≥ 1,200 mg/d during the current depressive episode; intolerance to SAMe or escitalopram; having taken an investigational psychotropic drug within the last year; failure to respond to 2 or more antidepressant trials at adequate doses (eg, fluoxetine ≥ 40 mg/d) and duration (≥ 6 weeks) during the current depressive episode; any depression-focused ongoing psychotherapy; history of bleeding diatheses, low platelet counts, gastrointestinal bleeding, or use of medications that alter bleeding risk; and a Clinical Global Impressions-Improvement scale (CGI-I)[14] score of "much" or "very much improved" between the screen and baseline visits and/or an IDS-C score < 25 at either the screen or the baseline visit.

Randomization and Study Procedures

Eligible subjects were randomized in a 1:1:1 manner for 12 weeks of double-blind treatment with SAMe, escitalopram, or placebo. Randomization numbers were assigned by a biostatistician, in consecutive order, stratified by site and maintained by the research pharmacists at both sites. We used a double-dummy design to maintain the blind, since SAMe tablets differed in appearance from escitalopram tablets. Each patient took tablets from 2 bottles, with 1 bottle containing either SAMe or SAMe-placebo and the other containing either escitalopram or escitalopram-placebo, depending on the randomization. SAMe tosylate and matching placebo were supplied by Pharmavite LLC (Mission Hills, California). Escitalopram and matching placebo were purchased from Forest Pharmaceuticals (New York, New York). Preparation of blinded compounds took place at each site's research pharmacy. All patients, clinicians, and research coordinators remained blinded to the intervention. Subjects were compensated $25 for each completed visit.

During the screen visit, patients were administered the SCID-I/P, the 28-item Hamilton Depression Rating Scale (HDRS-28) (from which the HDRS-17 score was derived), the CGI-Severity of Illness scale (CGI-S),[14] the IDS-C,[10] the IDS-self-report (IDS-SR),[9] the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q),[15] the Medical Outcome Survey Short Form-36 (SF-36),[16,17] and the Anger Attacks Questionnaire (AAQ).[18]

During subsequent visits, patients were administered the mood module of the SCID, the HDRS-28, the CGI-S and CGI-I, the IDS-SR, and the Systematic Assessment for Treatment of Emergent Events-Specific Inquiry (SAFTEE-SI) scale.[19] At baseline and visit 7 (week 12), patients also were administered the IDS-C, Q-LES-Q, SF-36, AAQ, and consumptive history (use of alcohol, tobacco, and caffeine). Side effects and adverse events were documented with the SAFTEE-SI.

Dosing

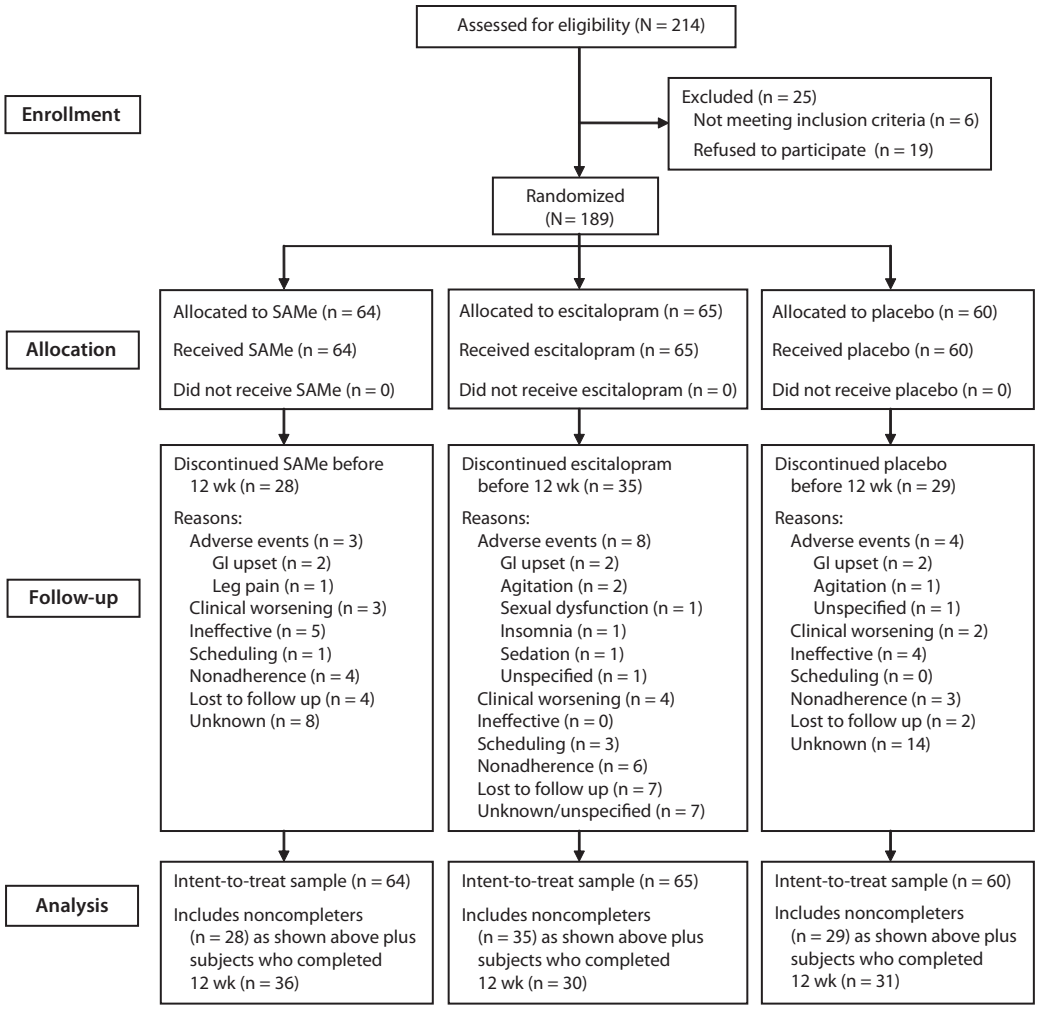
During the first 6 weeks, patients were randomly assigned to SAMe 1,600 mg/d, escitalopram 10 mg/d, or placebo. To maximize the probability of response, a dose increase was allowed for nonresponders (patients with a < 50% HDRS-17 score reduction) at week 6; escitalopram could be increased to 20 mg/d and SAMe to 3,200 mg/d for weeks 7–12. Patients who experienced intolerable side effects at the higher dose were allowed to decrease the dose to the previous level.

Statistical Analysis

The primary efficacy measure was the change in HDRS-17 score over 12 weeks. Response was defined as a > 50% decrease in the HDRS-17 score and remission as a final HDRS-17 score of < 7. Secondary measures of efficacy included changes in scores on the IDS-C, IDS-SR, and CGI-S and CGI-I ratings over time.

Calculations for the originally proposed sample with n = 100 patients per treatment group projected at least

Figure 1. CONSORT Statement Flow Diagram



Abbreviations: GI = gastrointestinal, SAMe = *S*-adenosyl-L-methionine.

80% power (β = .20) to detect a treatment difference with .05 probability of occurring by chance (2-tailed α = .05), assuming a modest effect size[20] for continuous measures ($d = 0.39$) and for categorical measures (Cohen $w = 0.25$).

Analyses of treatment effectiveness were conducted for an intent-to-treat (ITT) sample, including all patients randomized to any of the 3 treatment arms (ie, completed a baseline visit and accepted supply of medications). Mixed model regression analysis was employed for the change in HDRS-17 score to adjust for the length of time actually spent in treatment. We used χ^2 analyses to compare response and remission rates.

Side effects documented on the SAFTEE-SI scale were categorized by severity as 0 (none), 1 (mild), 2 (moderate), and 3 (severe). Because some SAFTEE-SI items could be present at baseline, we defined *treatment emergent* as any SAFTEE-SI side effect for which severity increased by 2 or more levels from baseline. For example, a side effect with severity rating that changed from "none" to "moderate" or from "mild" to "severe" would be considered as treatment emergent. Analysis was based on the number of patients in each arm reporting these side effects at any time during the 12-week treatment. Differences between treatment groups were compared by χ^2 analyses.

Statistical analyses were carried out with SPSS version 17.0 (SPSS Inc; Chicago, Illinois) and SAS 9.2 software (SAS Institute Inc; Cary, North Carolina; 2001), which were used by L.B., E.L., and D.M., with assistance from A.J.C., R.W., and K.D. An α level of .05 was used to determine statistical significance.

RESULTS

We screened 214 subjects and randomized 189 (49.7% female, mean [SD] age = 45 [15] years; Figure 1). Race distribution included white (n = 137, 72%), African American (n = 33, 17%), Asian (n = 2, 1%), and Native American (n = 2, 1%). Eight subjects (4%) self-described as Hispanic. The remaining subjects did not self-identify a specific category (Table 1).

Ninety-seven subjects (SAMe, n = 36; escitalopram, n = 30; placebo, n = 31) completed the study. For the ITT analysis using last observation carried forward (LOCF), we selected

Table 1. Demographics for Intent-to-Treat Sample (N = 189)

Variable	Value
Study site, n (%)	
Massachusetts General Hospital	123 (65)
Butler Hospital	66 (35)
Age, mean (SD) [range], y	45 (15) [17–79]
Female gender, n (%)	94 (50)
Race/ethnicity, n (%)	
White	137 (72)
African American	33 (17)
Native American/Alaskan	2 (1)
Asian	2 (1)
Hispanic/Latino	8 (4)
No response	7 (4)
Education, n (%)	
Did not graduate high school	21 (11)
Graduated high school	33 (18)
Some college	45 (24)
Graduated 2-year college	16 (9)
Graduated 4-year college	27 (14)
Some graduate school	10 (5)
Graduated graduate school	28 (15)
No response	9 (5)
Marital status, n (%)	
Never married	86 (46)
Married/cohabitating	42 (22)
Separated/divorced	43 (23)
Widowed	8 (4)
No response	10 (5)
Employment status, n (%)	
Employed full-time	46 (24)
Employed part-time	32 (17)
Student	4 (2)
Retired	21 (11)
Unemployed	48 (25)
Volunteer	2 (1)
Disabled	20 (11)
Homemaker	1 (1)
Other/no response	15 (8)
Baseline IDS-SR score, mean (SD) [range]	36.6 (11.3) [10–73]
Baseline HDRS-17 score, mean (SD) [range]	19.2 (4.7) [4–32]

Abbreviations: HDRS-17 = 17-item Hamilton Depression Rating Scale, IDS-SR = Inventory of Depressive Symptomatology-Self-Rated.

Table 2. Changes in Main Outcome Instruments, Response, and Remission Rates for Intent-to-Treat Sample

	SAMe (n = 64)		Escitalopram (n = 65)		Placebo (n = 60)	
Instrument	Mean	SD	Mean	SD	Mean	SD
HDRS-17 score						
Baseline	18.98	5.09	19.25	4.88	19.43	4.07
End visit	12.79*	7.38	12.94*	6.98	14.32*	6.92
IDS-SR score						
Baseline	34.87	9.74	37.54	12.35	37.44	11.56
End visit	23.29*	12.53	26.84*	15.28	28.57*	14.21
CGI-S score						
Baseline	4.38	0.76	4.44	0.69	4.29	0.65
End visit	3.08*	1.46	3.14*	1.44	3.28*	1.37
CGI-I score, end visit	2.73	1.24	2.76	1.24	2.90	1.24
	n	%	n	%	n	%
Response[a]	23	35.9	22	33.8	18	30.0
Remission[a]	18	28.1	18	27.7	10	16.7

[a]There were no significant differences between the 3 treatment groups for response and remission rates based on ≥ 50% improvement in HDRS-17 score from baseline to end visit ($P > .05$ for all 2-way and 3-way comparisons) for the intent-to-treat sample.
*$P < .001$ for change from baseline to endpoint.
Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, HDRS-17 = 17-item Hamilton Depression Rating Scale, IDS-SR = Inventory of Depressive Symptomatology-Self-Rated, SAMe = *S*-adenosyl-L-methionine.

all 189 randomized patients (SAMe, n = 64; escitalopram, n = 65; placebo, n = 60). For all treatment groups, mean HDRS-17 scores, IDS-C scores, and CGI-S ratings decreased significantly over 12 weeks of treatment ($P < .001$ for all), but no comparisons between groups for these scales and CGI-I reached significance (Table 2).

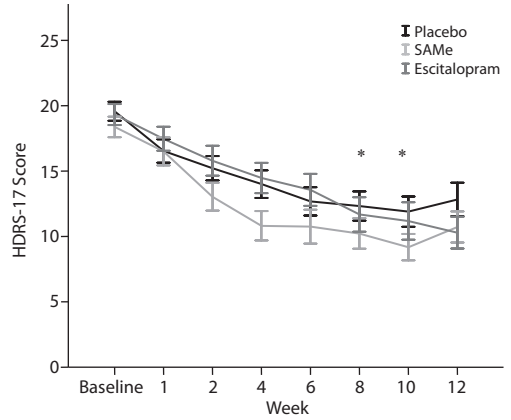
Mixed model random regression analysis (unstructured covariance matrix model with linear and quadratic terms for week) for change in HDRS-17 score showed in the test of fixed effects a significant effect for time by study week ($F = 51.50$, $P < .001$) but not for treatment ($F = 0.35$, $P = .705$), agreeing with the LOCF analysis that all treatment groups improved over time. There was a significant interaction between treatment and baseline HDRS-17 score ($F = 24.09$, $P < .001$). Because these scores did not appear significantly different by inspection (Table 2), we ran a 1-way analysis of variance with baseline HDRS-17 as dependent variable and treatment group as independent variable, showing no significant treatment group effect ($F = 0.14$, $P = .87$). The mixed effect model repeated measure interaction effect between baseline HDRS-17 and treatment group was significant only in the model containing visit number, visit number squared (quadratic), baseline HDRS-17, and all interactions with treatment group, suggesting that the significant difference occurred in the context of the covariates chosen. We also ran analyses using autoregressive covariance matrix and compound symmetry covariance matrix, but results were not substantially different.

Response rates were 35% for SAMe, 34% for escitalopram, and 30% for placebo. Remission rates were 28% for SAMe, 28% for escitalopram, and 17% for placebo. Differences between groups were not significant (Table 2).

We examined the time course of improvement for each treatment arm and outcome measure. The HDRS-17 improvement course is illustrated in Figure 2. Differences in scores at individual time points illustrated trends to significance between SAMe and escitalopram (see Supplementary eTable 1 at PSYCHIATRIST.COM) and a significant difference between SAMe and placebo (Figure 2).

Tolerability data were available for 166 subjects. The most common side effects reported were gastrointestinal, with rates of 19% for stomach discomfort and 20% for diarrhea in the SAMe group, although these did not separate from placebo or escitalopram ($P > .05$ for all comparisons). The SAMe group had a significant advantage over escitalopram regarding anorgasmia, escitalopram had a significant advantage over placebo in diminished mental acuity/sharpness, and SAMe had a significant advantage over placebo in dizziness or faintness (Table 3). The large number of SAFTEE-SI symptoms (total 55) would render all comparisons insignificant after Bonferroni correction. Since this is the first comparison of SAMe versus an SSRI, we erred on the side of false positives to give a sense of what differences in adverse effects one should expect. Fifteen subjects (SAMe,

Figure 2. Time Course of HDRS-17 Scores (intent-to-treat sample)



*Significant difference in HDRS-17 score between SAMe and placebo at week 8 ($P = .026$) and week 10 ($P = .034$). All other comparisons were nonsignificant.
Abbreviations: HDRS-17 = 17-item Hamilton Depression Rating Scale, SAMe = *S*-adenosyl-L-methionine.

Table 3. SAFTEE-SI Scale Adverse Effects in the Safety Sample (statistically significant differences only)

	Placebo (n = 52)		SAMe (n = 59)		Escitalopram (n = 55)	
Adverse Effect	n	%	n	%	n	%
Dizziness or faintness[a]	4	7.6	0	0.0	2	3.6
Delayed or absent orgasm[b]	4	7.6	2	3.4	10	18.2
Diminished mental acuity/ sharpness[c]	6	11.5	1	1.7	0	0.0
Hot flashes[d]	0	0.0	0	0.0	4	7.3

[a]$\chi^2 = 4.54$; $P = .049$ (placebo vs SAMe).
[b]$\chi^2 = 8.43$; $P = .015$ (3-way comparison); $\chi^2 = 7.31$; $P = .011$ (SAMe vs escitalopram).
[c]$\chi^2 = 9.95$; $P = .007$ (3-way comparison); $\chi^2 = 6.61$; $P = .012$ (placebo vs escitalopram).
[d]$\chi^2 = 8.20$; $P = .017$ (3-way comparison).
Abbreviations: SAFTEE-SI = Systematic Assessment for Treatment of Emergent Events-Specific Inquiry, SAMe = *S*-adenosyl-L-methionine.

n = 3; escitalopram, n = 8; placebo, n = 4) discontinued from the study specifically due to adverse effects (Figure 1).

DISCUSSION

This randomized placebo-controlled study comparing SAMe monotherapy against SSRI monotherapy must be considered a failed trial. Both active treatments, including an established, FDA-approved antidepressant, demonstrated comparable antidepressant efficacy, but neither separated from placebo at the end of 12 weeks. On the HDRS-17 scale only, significant separation between SAMe and placebo was obtained at treatment weeks 8 (visit 5) and 10 (visit 6), with separation lost by week 12 (visit 7) (Figure 2). This depressive worsening at the last visit likely also affected the findings in the mixed effect model repeated measure analysis. Given that a treatment change awaited nonresponders, week 12 may have caused uncertainty as to whether it was the final visit, and clouded issues of expectancy. However, the additional gain for the escitalopram group after week 10 does not suggest any general psychological effects contributing to this change.

Response and remission rates for both active treatments (30%–36% response and 28% remission) were lower than expected, based on what is known about the efficacy of established antidepressants.[21] However, most responders attained full remission, particularly with the active treatments (about 28% for SAMe and escitalopram vs 17% for placebo). This result suggests that the active treatments produced a more robust or "true" effect compared to placebo, arguing in favor of their purported efficacy. Placebo response rates were in the range of 30% in the ITT sample, a rate not unusual in antidepressant studies. This finding may also reflect the fact that the greater the chance of receiving an active treatment (in this case a 2 in 3 chance), the greater the placebo response rate.[22] A recent meta-analysis by Iovieno and Papakostas[23] found that placebo response rates of ≥ 30% correlated with a lower risk ratio of responding to antidepressant versus placebo and a greater number needed to treat for response, which appears consistent with our findings. A meta-analysis from our group[24] does not suggest a greater placebo-response rate for studies of complementary and alternative medicine interventions. Conversely, a reanalysis of data from the Hypericum Depression Trial Study Group,[25] which compared hypericum against sertraline, suggests that patient's beliefs that they are receiving a particular drug may be more important than the actual drug itself.[26]

Given the generally encouraging body of evidence for the efficacy of SAMe, as well as for escitalopram, our findings of equivalence with placebo were surprising. To examine whether baseline depressive severity may have impacted on the findings, we ran separate post hoc outcome analyses for changes in HDRS-17, IDS-SR, CGI-S, and response/remission rates for patients with baseline HDRS-17 scores ≥ 20 (n = 80) and for those with HDRS-17 scores < 20 (n = 109). The results were essentially the same for both groups as for the complete sample, suggesting that the findings were not influenced by depressive severity (data not shown).

Both active treatments were available to individuals without participating in a study if they were inclined to see a physician and had medical insurance or could afford to pay for the drugs. In addition, there may be unique characteristics about subjects who opt to participate in a study of a nutritional supplement, and this might explain a number of factors that could have contributed to the lack of separation from placebo: (1) nearly 60% of the sample had pretreatment HDRS scores of 19 or less, a level of severity for which it is difficult to show significant drug-placebo differences; (2) we had an unusually high rate of randomization of screened subjects (88%); (3) we enrolled only 63% of the projected sample; and (4) only 51% completed the study.

In addition to sample characteristics, some unique characteristics of this study may have contributed to the lack of separation from placebo. There are few 12-week placebo-controlled trials in MDD. In 2 trials pooled by Golden et al,[27] placebo response and remission rates were 41.5% and 20.5% after 6 weeks of treatment and increased to 61.2% and 44.0% after 12 weeks. Placebo response and remission rates in those

ranges can reduce the ability to detect active treatment effects because of a "ceiling" effect. As shown previously,[28] there is a cumulative risk of spontaneous improvement, and such risk may be maximized in 12-week trials. The decision to delay up-titration of escitalopram until after week 6 may have also compromised efficacy. Finally, the separation between SAMe and placebo at the penultimate visits suggests that this trial may have been subject to type II error, ie, the "false-negative" study that can occur based on chance. Other factors may include limitations of our conception of MDD and current trial methods.

Tolerability of all treatments was good, with gastrointestinal complaints as the most commonly reported adverse effects for both active treatment arms and, surprisingly, for the placebo arm as well. Gastrointestinal complaints are common with SSRIs and with SAMe, and our previous study[5] of SAMe augmentation also resulted in high rates of gastrointestinal side effects. It is possible that suggestiveness on the part of patients who were informed of the most common side effects with these treatments may have resulted in higher rates of gastrointestinal side effects.

Like all clinical trials, our study has limitations. The trial was originally powered for 300 subjects, and the actual sample size obtained, even after a 1-year no-cost extension, was slightly under two-thirds of that expected, representing the study's major limitation. While this limitation would inevitably diminish power to detect a difference between active treatments and placebo, our sample is large enough to provide a conclusive statement about the efficacy of SAMe as a monotherapy for MDD. We did not discern a clinically meaningful difference with placebo, and it seems unlikely that a larger sample would have yielded a significant difference between treatments. Although every effort was made to ensure that ratings, recruitment practices, and inclusion/exclusion criteria were consistent between sites, there may have been site-related factors that impacted on outcomes.

To conclude, in this first head-to-head comparison of SAMe against an SSRI, neither SAMe nor escitalopram separated from placebo after 12 weeks, constituting a failed study. Despite the smaller than expected sample, this study was more rigorously designed than most previous trials. It is possible that SAMe may be better suited as an augmentation therapy[5,29] than as a monotherapy; another interpretation of the findings is that SAMe possesses comparable antidepressant efficacy to escitalopram, but an unusually high placebo response rate confounded our findings. The findings may not be generalizable to all antidepressants or even all SSRIs, and future comparisons with other agents will be needed to better clarify SAMe's potential antidepressant effect and its place in the psychopharmacologic armamentarium.

Drug names: escitalopram (Lexapro and others), fluoxetine (Prozac and others), sertraline (Zoloft and others).

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Supplementary Material

Article Title: A Double-Blind, Randomized, Placebo-Controlled Clinical Trial of *S*-Adenosyl-L-Methionine (SAMe) Versus Escitalopram in Major Depressive Disorder

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List of Supplementary Material for the article

1. **eTable 1** Time course of Main Outcome Instruments for Intent-to-Treat Sample (N=189)

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary eTable 1: Time course of Main Outcome Instruments for Intent-to-Treat Sample (N = 189)

Group	Baseline		Week 1		Week 2		Week 4		Week 6		Week 8		Week 10		Week 12	
HAM-D-17	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
PBO	19.43	4.07	16.71	5.06	15.37	5.19	14.42	5.67	13.32	5.66	13.08	5.95	12.17	6.93	12.00	6.96
SAMe	18.98	5.09	16.27	6.29	13.83	6.14	11.91	7.25	11.09	7.22	9.68	6.87	8.85	5.85	11.12	6.74
ESC	19.25	4.88	17.51	5.47	15.81	5.70	14.43	6.16	13.23	7.00	11.86	7.08	12.18	8.14	10.77	6.58
IDS-SR																
PBO	37.44	11.56	32.78	11.34	31.45	11.59	28.23	11.66	27.88	12.60	28.89	12.60	26.41	14.22	24.17	13.58
SAMe	34.87	9.74	29.26	10.15	25.14	11.13	22.77	12.59	22.14	13.23	19.99	12.31	18.30	10.58	18.83	10.90
ESC	37.54	12.35	32.47	12.89	31.32	14.21	29.94	14.01	25.80	13.59	25.78	16.21	25.18	16.75	24.72	16.00
CGI-S																
PBO	4.29	0.65	3.96	0.89	3.63	0.85	3.38	1.19	3.17	1.20	3.14	1.29	3.00	1.37	2.93	1.51
SAMe	4.38	0.76	3.84	1.23	3.42	1.23	3.09	1.41	2.78	1.46	2.73	1.39	2.31	1.21	2.65	1.39
ESC	4.44	0.69	3.90	0.91	3.66	0.89	3.46	1.21	3.19	1.26	2.83	1.27	2.84	1.35	2.61	1.42
CGI-I																
PBO	3.91	0.48	3.48	0.75	3.30	0.73	2.83	0.96	2.76	0.99	2.94	1.15	2.74	1.21	2.53	1.36
SAMe	3.90	0.63	3.36	0.80	3.14	1.00	2.84	1.29	2.62	1.25	2.30	1.15	2.11	1.08	2.41	1.18
ESC	3.97	0.26	3.42	0.85	3.11	0.78	2.95	1.02	2.73	1.05	2.43	1.07	2.53	1.16	2.39	1.29

HAMD-17: 17-item Hamilton Depression Rating Scale

IDS-SR: Inventory of Depressive Symptomatology – Self-Rated

CGI-S: Clinical Global Improvement Scale - Severity

CGI-I: Clinical Global Improvement Scale – Improvement

SAMe: S-Adenosyl methionine

ESC: Escitalopram

PBO: Placebo

SAMe vs ESC: No significant difference in HAM-D-17 score was found at any time point, but trends were seen at Week 4 (p=0.083) and Week 10 (p=0.055). Significant difference in IDS-SR was seen at Week 2 (p= 0.019), Week 4 (p=0.013), and Week 10 (p=0.047). No significant difference in CGI-S was seen at any time point, but a trend was seen at Week 10 (p=0.094).

ESC vs PBO: No significant differences were seen in HAM-D-17, IDS-SR, or CGI-S at any time point. A trend was seen for CGI-I at Week 8 (p= 0.054).

SAMe vs PBO: Significant differences in HAM-D-17 scores were seen at Week 8 (p=0.026) and Week 10 (p=0.034). Significant differences in IDS-SR were seen at Week 4 (p=0.033), Week 6 (p=0.044), Week 8 (p=0.003), and Week 10 (p=0.010). Significant differences were seen for CGI-S at Week 10 (p=0.031), and for CGI-I at Week 8 (p=0.019) and Week 10 (p=0.028).