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S-Adenosyl-L-Methionine (SAMe) for Smoking Abstinence: A Randomized Clinical Trial

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Abstract

Objectives: *S*-Adenosyl-L-methionine (SAMe) is a dietary supplement commonly used to treat depression. SAMe facilitates dopamine and norepinephrine synthesis in the central nervous system. This study investigated the efficacy of SAMe for increasing tobacco abstinence among cigarette smokers.
Design: A randomized, blinded, placebo-controlled, three-arm, dose-ranging clinical trial was conducted. Subjects were randomly allocated to receive SAMe 1600 mg or 800 mg by mouth every day or a matching placebo for 8 weeks. All subjects received a behavioral smoking cessation intervention. Self-reported smoking abstinence was biochemically confirmed with exhaled-air carbon monoxide.
Subjects: Subjects in the study comprised 120 adults.
Results: One hundred and twenty (120) subjects with a mean age of 40.0 ± 14.0 (SD) years were enrolled. Participants smoked an average of 19.6 ± 8.6 cigarettes per day for 21 ± 13.2 years. The study dropout rate was high (42.5%). By intention-to-treat analysis, no significant differences were observed in abstinence rates at 8 and 24 weeks between SAMe dose groups and placebo. SAMe did not attenuate withdrawal symptoms among abstinent subjects. Rates of gastrointestinal side-effects were higher with SAMe 1600 mg/d compared to placebo.
Conclusions: SAMe did not increase smoking abstinence rates. Abstinence and tobacco withdrawal data from this clinical trial suggest that SAMe holds little promise for the treatment of tobacco dependence.

Introduction

The prevalence of current smoking among U.S. adults declined from 42% in 1965 to 20.6% in 2009.[1] However, the rate of decline may not allow us to meet the Healthy People 2020 national health objectives goal (adult smoking prevalence <12%).[2] This may be partially related to the limited efficacy of the available pharmacotherapies associated with an estimated 12-month biochemically confirmed continuous smoking abstinence rate of 12.3%.[3] New pharmacotherapeutic options need to be evaluated.

S-Adenosyl-L-methionine (SAMe) is an over-the-counter dietary supplement commonly used to treat depression. SAMe donates a methyl group for the presynaptic synthesis of dopamine, norepinephrine, epinephrine, and serotonin.[4–6] SAMe causes elevations in dopamine and norepinephrine levels and increases serotonin turnover.[4,7–9] SAMe use may enhance the efficiency of receptor–effector coupling and signal transduction.[4] SAMe crosses the blood–brain barrier and affects neurotransmission at the level of nucleus accumbens.[10] On neuroimaging studies, the effect of SAMe on the brain seems similar to that of other antidepressants.[11,12] A meta-analysis of 47 studies evaluating the efficacy of SAMe for the treatment of depression reported the overall effect size of −0.65 (95% confidence interval −1.05 to −0.25) with SAMe (parenteral or oral) compared to placebo. This corresponded to a difference in Hamilton Rating Scale for Depression (HAMD) of 5–6 points and a clinically significant improvement in depressive symptoms compared to placebo.[13]

By facilitating the synthesis of dopamine and norepinephrine in the central nervous system, it was hypothesized that SAMe may ameliorate the symptoms of nicotine withdrawal and improve tobacco abstinence rates among smokers trying to stop smoking. In order to test this hypothesis, the authors conducted a randomized, blinded, placebo-controlled, three-arm, parallel-group, dose-ranging clinical trial.

Materials and Methods

The Mayo Clinic Institutional Review Board (IRB) reviewed and approved the study protocol prior to subject recruitment.

Mayo Clinic, Rochester, MN.

Subjects

Individuals interested in stopping smoking were recruited from the community surrounding Mayo Clinic in Rochester, MN. Subjects were eligible to participate if they were (1) at least 18 years of age; (2) smoked ≥10 cigarettes per day for ≥6 months; and (3) willing to make a quit attempt.

Individuals were excluded from study enrollment if they (1) had clinically significant levels of current depression as assessed by the Center for Epidemiologic Studies Depression Scale[14] or had a lifetime diagnosis of bipolar disorder, schizophrenia, or dementia; (2) had an unstable medical condition; (3) were currently (past 30 days) using antipsychotics or antidepressants; (4) were currently (past 30 days) using any treatment for tobacco dependence; (5) had recent use (past 30 days) of an investigational drug; (6) had a recent history (past 3 months) of alcohol abuse or dependence; (7) had a recent history (past 3 months) of drug abuse; (8) were pregnant, lactating, or of child-bearing potential, or likely to become pregnant during the medication phase and not willing to use a reliable form of contraception; (9) had a recent cardiovascular event (past 3 months); (10) had a clinically significant acute or chronic progressive or unstable medical condition; (11) were currently on medications interacting with SAMe; (12) had another household member or relative participating in the study; or (13) had an allergy to SAMe.

Procedures

Potential subjects interested in study participation were prescreened for eligibility over the telephone. If subjects passed the phone screening, an appointment was made for a clinic visit. During the clinic visit, subjects signed the informed consent and completed baseline questionnaires.

Eligible subjects were randomized to (1) SAMe 1600 mg/d; (2) SAMe 800 mg/d; or (3) matching placebo by mouth for 8 weeks. SAMe was available in 400-mg tablet strength. Medication was increased over a 2-week period in order to minimize the risk of adverse effects. The target dose was 800 mg twice a day for the first group, 400 mg twice a day for the second group, and two tablets twice a day for the placebo group. All participants were taking an equal number of tablets. All subjects received behavioral counseling using the "Smoke Free and Living It" manual used in our previous smoking-cessation clinical trials.

SAMe

SAMe was supplied by Pharmavite LLC., USA under its Nature Made™ brand (Table 1).

Assessments

Demographic and tobacco use history information was collected, screening questionnaires were completed, and nicotine dependence was assessed with the Fagerström Test for Nicotine Dependence.[15] Readiness to quit smoking was assessed using the Contemplation Ladder.[16] During each study visit, vital signs were measured, and side-effects and concomitant medications were recorded.

Tobacco craving and nicotine withdrawal were assessed with a daily diary that contained a tobacco use self-report and the Minnesota Nicotine Withdrawal Scale–Revised.[17–19] This measure consisted of the following items: desire or craving to smoke; anger, irritability, or frustration; anxiety or nervousness; difficulty concentrating; impatience; restlessness; increased appetite or hunger; insomnia, sleep problems, or awakening at night; and depressed mood or sadness. Based upon the previous 24 hours, items were rated on a 5-point scale ranging from 0 (not present) to 4 (severe). Daily nicotine withdrawal data were obtained from the information session visit to 2 weeks after the target quit date (TQD). Medication adherence was assessed by conducting pill counts at each weekly visit and by self-reports of missed doses.

Table 1. *S*-Adenosyl-l-Methionine (SAMe) Product Information

Manufacturer	Gnosis, Italy (Distributed by Pharmavite LLC)
Salt	Tosylate
Isomers	The minimum observed value for SAMe SS to RS ratio was 65:35
Tablet strength	Enteric-coated tablet with 400-mg SAMe/tablet
Storage	Room temperature
Batch stability	Over 2 years
Certificate of analysis	High-pressure liquid chromatography

SS, active isomer; RS, inactive isomer.

Smoking abstinence outcomes

The primary endpoint was the 7-day point-prevalence smoking abstinence rate at end-of-treatment and secondary endpoints were the point-prevalence and prolonged abstinence rates at 6 months.[20] The 7-day point-prevalence smoking abstinence was determined by (1) self-reported smoking abstinence for the previous 7 days, and (2) exhaled air carbon monoxide ≤8 ppm. Prolonged smoking abstinence was verified by (1) self-reported smoking abstinence from TQD (initial 2 weeks grace period following TQD was allowed); (2) exhaled air carbon monoxide ≤8 ppm at each visit; and (3) exhaled air carbon monoxide ≤8 ppm at end-of-treatment and 6 months. Subjects reporting use of tobacco products other than cigarettes were considered treatment failures.

Statistical analyses

For smoking abstinence outcomes, each SAMe dose was compared to placebo using a one-sided Fisher's exact test. For this analysis, subjects with missing outcome information were assumed to be smoking. Baseline scores for nicotine withdrawal and craving were calculated using data from the 7 days prior to starting medication. For these endpoints, data from the first 2 weeks following TQD were analyzed as change from baseline using generalized estimating equations (GEE). The explanatory variables for these models were treatment group (placebo versus 800 mg/d versus 1600 mg/d) and time (in days, treated as a continuous variable). The percentage of subjects in each of the SAMe groups experiencing adverse events possibly, probably, or definitely related to study drug were compared to placebo using Fisher's exact test. The sample size for this investigation was determined for the primary aim of obtaining preliminary evidence of the efficacy of SAMe (1600 mg/d or 800 mg/d) for the endpoint of 7-day point-prevalence tobacco abstinence at week 8

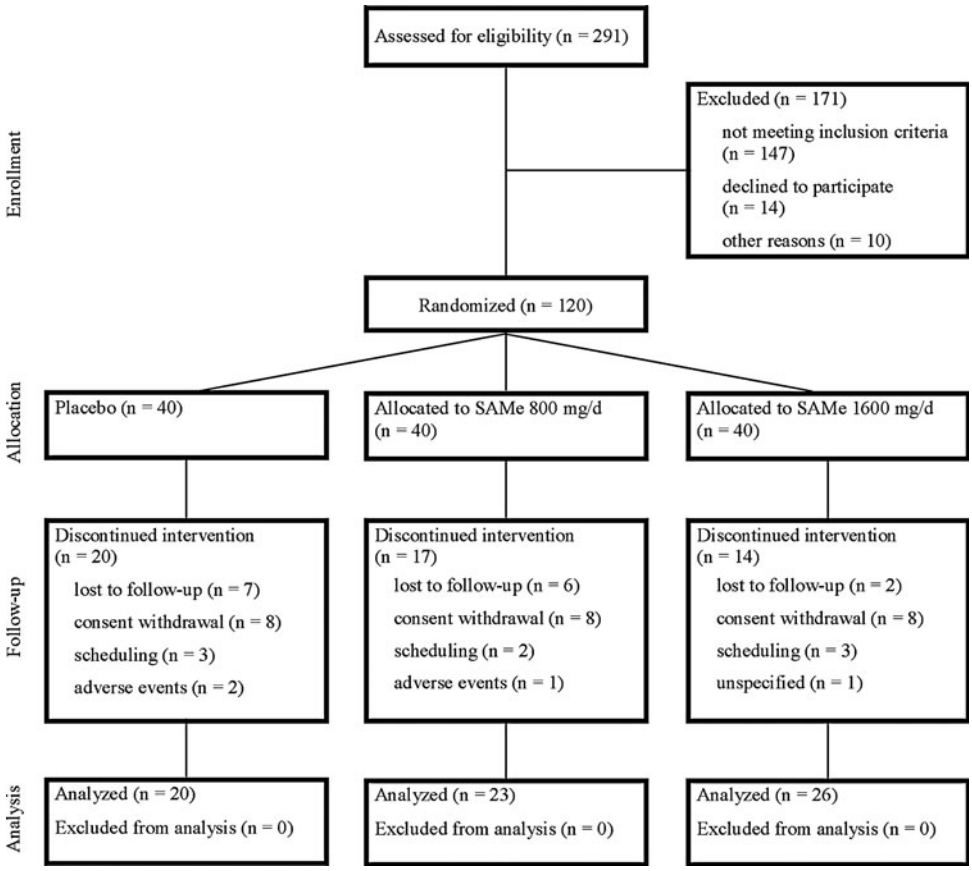

FIG. 1. Consolidated Standards of Reporting Trials diagram of a clinical trial to assess the efficacy of *S*-adenosyl-L-methionine (SAMe) versus placebo for smoking abstinence.

Table 2. Baseline Characteristics

Characteristic	*Placebo* (N = *40*)	*800 mg/d* (N = *40*)	*1600 mg/d* (N = *40*)
Age, years (mean ± SD)	37.0 ± 13.6	42.1 ± 16.0	40.8 ± 12.3
Gender, *N* (%)			
Male	20 (50)	23 (58)	20 (50)
Female	20 (50)	17 (42)	20 (50)
Race, *N* (%)			
White, non-Hispanic	40 (100)	37 (92)	37 (92)
Other[a]	0 (0)	3 (8)	3 (8)
Marital status, *N* (%)			
Never married	17 (42)	11 (28)	12 (30)
Separated/divorced	9 (22)	10 (25)	14 (35)
Married/living as married	14 (35)	17 (42)	14 (35)
Widowed	0 (0)	2 (5)	0 (0)
Level of education, *N* (%)			
High school graduate or less	10 (25)	12 (30)	19 (48)
Some college or technical school	26 (65)	22 (55)	17 (42)
4-year college degree or more	4 (10)	6 (15)	4 (10)
Cigarettes per day (mean ± SD)	19.5 ± 8.0	19.5 ± 9.3	19.9 ± 8.4
Number of years smoked (mean ± SD)	17.6 ± 11.6	23.8 ± 15.3	22.5 ± 12.7
Fagerström Test for Nicotine Dependence (mean ± SD)	4.7 ± 2.1	5.4 ± 2.1	5.5 ± 2.2
Previous stop attempts, *N* (%)			
None	5 (12)	7 (18)	5 (12)
1–2	17 (42)	13 (32)	18 (45)
3–5	16 (40)	15 (38)	8 (20)
6 or more	2 (5)	5 (12)	9 (22)
Other tobacco users in the household, *N* (%)			
No	22 (55)	23 (58)	31 (78)
Yes	18 (45)	17 (42)	9 (22)

[a]These include: black/African American (*N* = 3), white Hispanic (*N* = 2), and more than 1 race (N = 1).
SD, standard deviation.

(end of treatment). For a randomized phase II trial, a one-sided test with a false-positive (type I error) rate of 0.20 is considered appropriate for the primary comparison to assess whether additional studies of the given regimen are warranted.[21,22] The 7-day point-prevalence smoking abstinence rate at end-of-treatment of was hypothesized to be 15% for placebo.[23] Based on this assumption, it was determined that a total sample size of 120 subjects (40 in placebo, 40 in 800 mg/d SAMe, and 40 in 1600 mg/d SAMe) would provide statistical power of approximately 80% to detect an end-of-treatment abstinence rate of 30% or greater for an active SAMe group compared to placebo (using a one-sided, $\alpha = 0.20$ level test).

Results

A total of 120 smokers were enrolled (Fig. 1 and Table 2).[24] Of the 120 participants, 51 (42.5%) discontinued study participation prior to the end of the medication phase (20, 17, and 14 for placebo, 800 mg/d and 1600 mg/d, respectively). Reasons for discontinuing the study early included consent withdrawal (8, 8, and 8), loss to follow-up (7, 6, and 2), scheduling difficulties (3, 2, and 3), adverse events (2, 1, and 0), and unspecified reasons (0, 0, and 1).

Smoking abstinence

No differences in smoking abstinence rates were observed between the groups at end-of-treatment (week 8) and week 24 (Table 3). With the exception of 1 subject in the 800 mg/d group, all of the subjects who were biochemically confirmed abstinent for the last 7 days at end-of-medication and 6 months also met the criteria for prolonged abstinence.

Nicotine withdrawal and tobacco craving

In all cases, neither SAMe group differed significantly from placebo using GEE analyses for the composite withdrawal score nor the individual diary item assessing craving for the first 14 days following the TQD (Table 4).

Adverse events

Overall, 25 subjects (6, 7, and 12 in placebo, 800 mg/d and 1600 mg/d, respectively) reported one or more adverse events considered possibly, probably, or definitely related to the study drug. No significant differences were observed in the rates of adverse events, although the rates of gastrointestinal side-effects were higher in the SAMe 1600 mg/d group for abdominal pain (12.5% versus 2.5% for placebo) and diarrhea (7.5% versus 0% in placebo) (Table 5).

Table 3. Biochemically Confirmed 7-day Point-Prevalence Abstinence[a]

Time/group	*Abstinent* N *(%)*	p-*Value*[b]
End of medication (week 8)		
Placebo ($N = 40$)	7 (17.5)	
800 mg/d ($N = 40$)	7 (17.5)	0.615
1600 mg/d ($N = 40$)	5 (12.5)	0.826
Six months		
Placebo ($N = 40$)	5 (12.5)	
800 mg/d ($N = 40$)	3 (7.5)	0.868
1600 mg/d ($N = 40$)	4 (10.0)	0.759

[a]Self-reported 7-day point-prevalence abstinence confirmed by expired CO < 8 ppm.
[b]One-tailed Fisher's exact test comparing the biochemically confirmed abstinence rate for the given group versus placebo.

Table 4. Symptoms of Nicotine Withdrawal and Tobacco Craving in a Clinical Trial to Assess the Efficacy of *S*-Adenosyl-l-Methionine Versus Placebo for Smoking Abstinence

	Parameter estimate	*SE*[a]	p-*Value*
Nicotine withdrawal			
Placebo	Referent		
800 mg/d	−0.11	0.12	0.35
1600 mg/d	−0.04	0.12	0.72
Tobacco craving			
Placebo	Referent		
800 mg/d	−0.08	0.26	0.76
1600 mg/d	−0.25	0.29	0.39

[a]SE, standard error.

Discussion

In this randomized, blinded study, SAMe did not significantly increase tobacco abstinence rates nor decrease nicotine withdrawal compared to placebo. Study dropout was high and no differences in abstinence rates were observed.

Several reasons may account for the lack of efficacy of SAMe for smoking abstinence in this study. First, SAMe may lack efficacy for tobacco abstinence. Second, the dose of medication used may not have been high enough to observe an effect. In a meta-analysis of 47 clinical trials, however, all of the studies evaluating oral preparations of SAME used 1600 mg/d.[13] Among the three placebo-controlled studies using this dose, SAMe was superior to placebo in two and similar in one.[25]

Table 5. Adverse Events[a] in a Clinical Trial to Assess the Efficacy of *S*-Adenosyl-l-Methionine Versus Placebo for Smoking Abstinence

Event	*Placebo* (N = *40*)	*800 mg/d* (N = *40*)	*1600 mg/d* (N = *40*)
Abdominal pain	1 (2.5)	2 (5.0)	5 (12.5)
Nausea	2 (5.0)	2 (5.0)	2 (5.0)
Headache	2 (5.0)	2 (5.0)	0 (0.0)
Diarrhea	0 (0.0)	0 (0.0)	3 (7.5)
Insomnia	1 (2.5)	0 (0.0)	1 (2.5)
Anorexia	0 (0.0)	0 (0.0)	1 (2.5)
Confusion	0 (0.0)	0 (0.0)	1 (2.5)
Constipation	0 (0.0)	1 (2.5)	0 (0.0)
Dizziness	1 (2.5)	0 (0.0)	0 (0.0)
Drowsiness	0 (0.0)	1 (2.5)	0 (0.0)
Fatigue	0 (0.0)	1 (2.5)	0 (0.0)
Flatulence	0 (0.0)	0 (0.0)	1 (2.5)
Vivid dreams	1 (2.5)	0 (0.0)	0 (0.0)
Vomiting	0 (0.0)	0 (0.0)	1 (2.5)

[a]Adverse events considered to be possibly, probably, or definitely related to study drug are summarized according to the treatment group.

The major limitation of this study was a high dropout rate (42.5%). This observed dropout rate is consistent with the dropout rate observed in previous tobacco cessation studies in placebo groups.[26,27] A high dropout rate in the present study could be related to significant patient burden with taking numerous pills. In this study, SAMe was used in 400-mg formulation and participants had to take up to four tablets a day, which likely adversely affected treatment adherence. The high dropout rate may also relate to the lack of efficacy of SAMe for smoking abstinence perceived by the subjects. However, the low adherence rate to SAMe suggests that, even if efficacious, low adherence to SAMe in the clinical setting would translate into an ineffective intervention.

Conclusions

In summary, it was observed that SAMe did not increase smoking abstinence rates and did not decrease tobacco withdrawal symptoms. Given the lack of apparent efficacy at an appropriately justified dose and low adherence to this medication, further testing of SAMe for tobacco cessation is not warranted.

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Disclosure Statement

No competing financial interests exist.

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