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Is S-adenosylmethionine (SAMe) an Effective Drug to Help Treat Patients with Depression?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSTRACT

Objective: The objective of the selective EBM review is to determine whether or not "Is S-adenosylmethionine (SAMe) an Effective Drug to Help Treat Patients with Depression?"

Study Design: A systematic review of three randomized controlled trials (RCTs) published between 2016-2020.

Data Sources: All three RCTs were discovered using PubMed. The articles were published in English in peer-reviewed journals and selected based on applicability to the clinical question.

Outcome Measured: A reduction in depressive symptoms was the outcome measured in all three studies using the Montgomery-Asbery Depression Rating Scale (MADRS). The mean change in baseline was calculated once intervention was received.

Results: In the RCT led by Sarris J, Murphy J, Stough C, et al., monotherapy with SAMe in combination with co-factor vitamin B12 and folininc acid led to a reduction in depressive symptoms compared with the control group (P = 0.13), indicated by a mean change from baseline of -11.4. In the RCT led by Sarris J, Bryne GJ, Bousman C, et al., adjunctive therapy with SAMe, in combination with co-factor B12 and folinic acid, led to a reduction in depressive symptoms, indicated by a mean change from baseline of -11.4 (P = 0.51). Lastly, Sarris J, Byrne GJ, Stough C, et al. illustrated a reduction in depressive symptoms using a nutraceutical combination with SAMe, indicated by a mean change from baseline of -9.95 with a statistical significance of P = 0.33 in the SAMe treatment group.

Conclusion: All three studies in this review demonstrated that SAMe did not lead to a significant reduction in depressive symptoms as measured by the MADRS. In fact, two of the three studies showed a greater reduction in depressive symptoms with the placebo than with intervention with SAMe. This suggests that SAMe is not an effective or beneficial treatment for patients with depression. Due to high placebo response rates, future studies should include a placebo run-in period.

Key Words: S-adenosylmethionine, depression

INTRODUCTION

Major depressive disorder (MDD) is a medical illness characterized by the presence of five or more cardinal symptoms with at least one symptom being depressed mood or anhedonia.[1] These symptoms must occur at least two weeks in duration and cannot be attributed to another medical cause or effects of substance use.[1] Depression is extremely common and affects more than 300 million people worldwide.[1] The prevalence of depression in US adults is 6.7%, with an estimated lifetime risk as high as 30% for having at least one major depressive episode.[1] In the primary care setting, 30% of all patients have depressive symptoms.[2] Depression is quite disabling and can also lead to serious outcomes, such as suicide. Depression-related suicide is the second leading cause of death in adults 18-25 years old.[1] Depression costs the US an estimated $210.5 billion per year and accounts for about 10.6% of physician office visits.[3,4]

The exact etiology of depression is unknown; however, studies suggest it is a result of a complex interplay between several different factors. Evidence suggests that there is either a decrease in the number of monoamines or malfunction of them that causes depression.[5] These monoamines include serotonin, norepinephrine, and dopamine.[5] Most antidepressants enhance the availability of serotonin, norepinephrine, or dopamine, illustrating that these three monoamines play a central role in depression.[5] Other evidence demonstrates neurotrophic and endocrine factors play a role.[5] Studies show that depression is associated with loss of neurotrophic support.[5] This theory is also supported with the evidence that some antidepressants work by increasing neurogenesis and synaptic activity.[5]

There are several treatment options that can be used for depression, including both pharmacologic and non-pharmacologic options, as well as a combination of the two. Pharmacologic options include SSRIs, such as sertraline and fluoxetine, SNRIs, such as

venlafaxine and duloxetine, Tricyclic antidepressants (TCAs), such as amitriptyline, monoamine oxidase inhibitors (MAOIs), such as phenelzine, and atypical agents, such as bupropion and mirtazapine. Cognitive therapy can be used as a non-pharmacologic option, as well as an addition to medications. In the most severe and refractory cases, electroconvulsive therapy can be used.

Cognitive therapy alone has shown some success when treating patients with depression but is more commonly effective when used in addition to pharmacologic agents. The medications mentioned above have proven to be effective in depression; however, patients do not always respond to them or are not always able to tolerate them due to unwanted side effects. Common side effects include weight gain, sexual dysfunction, and anxiety. Although more rare, other side effects include risk of QT prolongation and increased risk of suicidal idealation in adults younger than 25 years old. These limitations of undesirable side effects and some patients' resistance to standard therapy emphasizes the need for other treatment options. SAMe is a nutraceutical that has been used to treat depression in European countries but is not currently approved as a drug in the US. SAMe is associated with much milder side effects compared to those of the antidepressants.[6] Although the exact mechanism of SAMe is unknown, studies suggest it enhances the activity of monomanias, similar to the mechanism of action as antidepressants, and increases concentrations of norepinephrine and serotonin in the brain.[6]

This paper uses three randomized controlled trials (RCTs) to assess the efficacy of SAMe as an alternative treatment option for depression.

OBJECTIVE

The objective of the selective EBM review is to determine whether or not "Is S-adenosylmethionine (SAMe) an Effective Drug to Help Treat Patients with Depression?"

METHODS

The three articles discussed in this systematic review were found in published peer-reviewed journals. The articles were found on PubMed using keywords “S-adenosylmethionine” and “depression.” All articles were published in English and found using an exclusion criteria of articles published before 2016 and secondary research. All three of the studies included are double-blind, randomized, controlled trials published after 2016. The statistics used in these articles to measure a decreased in depressive symptoms include a mean change from baseline, using the Montgomery-Asbery Depression Rating Scale, and p-values.

All articles in this systematic review were chosen based on the applicability of the clinical question being asked. These articles were selected because they all include a patient-oriented outcome that helps answer whether or not SAMe is an effective drug to help treat patients with depression. These articles were also chosen based on their populations, intervention with SAMe, and outcome measured. The population of the studies in this selective EBM review included patients ages 18-75 years old diagnosed with mild-severe major depressive disorder. Table 1 illustrates the demographics of each of these studies, individually. Intervention with SAMe, whether as monotherapy or as adjunctive therapy was another criterion. Lastly, the outcomes measured were decrease in depressive symptoms all using the Montgomery-Asbery Depression Rating Scale (MADRS).

OUTCOME MEASURED

All three studies used the Montgomery-Asbery Depression Rating Scale (MADRS), a questionnaire that measures the severity of depression. MADRS assesses ten factors including apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts. Each item is

graded on a 0-6 scale and summed to get a total score, ranging from 0-60. Higher scores are associated with greater depressive severity. The outcome measured in this review is a decrease in depressive symptoms using the MADRS.

Table 1. Demographics & Characteristics of Included Studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Sarris[7] (2020)	RCT	49	18-75 years of age	Patients 18-75 who met the DSM-5 criteria for MDD, presenting with mild-moderate depression, and who were currently not taking antidepressants.	Patients currently taking an antidepressant or any other mood modulating drug or nutraceutical. Patients with severe depression, suicide idealation, or those who failed three or more trials of therapy. Patients with other medical or mental disorders.	8	SAMe vs. Placebo
Sarris[8] (2018)	RCT	107	18-75 years of age	Patients 18-75 who met the DSM-5 criteria for MDD, presenting with moderate-severe depression, and currently taking an SSRI, SNRI, NaRI, 5-cHT2c antagonist, or tetracyclic antidepressant.	Patients currently taking MAOIs, TCAS, or specified nutraceuticals. Patients with suicide idealation or those who have failed three or more trials of therapy. Patients with other medical or mental disorders.	30	Combination of SAMe, co-factor B12, and folinic acid vs. Placebo as adjunctive therapies
Sarris[9] (2019)	RCT	158	18-70 years of age	Patients 18-70 years old who met the DSM-5 criteria for MDD, presenting with moderate-severe depression, and were currently on an antidepressant or some other stable treatment as usual medical care.	Patients currently taking MAOIs, TCAs, or specified nutraceuticals. Patients presenting with suicide idealation or those who have failed three or more trials of therapy. Patients with other medical or mental disorders.	45	Combination of SAMe, folinic acid, omega-3 fatty acid, 5-HTP, and zinc picolinate vs. Placebo as adjunctive therapies

RESULTS

All the studies in this review looked at patients who met the DSM-5 criteria for Major Depressive Disorder (MDD). Sarris J, Murphy J, Stough C, et al. conducted a double-blind, randomized controlled trial to assess the efficacy of SAMe as monotherapy for depression. There were 49 patients, ages 18-75, enrolled in this study. The patients in this specific study had mild-moderate depression and were not taking any antidepressants. Patients were randomized in a 1:1 ratio and assigned to either the experimental group or control group. The experimental group received 800 mg/day of SAMe, in combination with co-factor vitamin B12 and folinic; whereas the control group received a placebo.[7] Each group received monotherapy whether with the SAMe combination or the placebo. Patients received treatment for a total of 8 weeks in duration. Five participants in total, one in the SAMe group and four in the placebo group, experienced worsening of depression and were dismissed from the study.[7] Additionally, two more participants left the study in the SAMe group, but the reason as to why was not provided.[7] Lastly, another patient left the placebo group for adverse effects.[7] These individuals were not included in the final analysis.

The primary outcome evaluated in this study was decrease in the number of depressive symptoms. Mean values were used to measure the outcomes after receiving treatment. The SAMe group showed a decrease in mean values of -9.90 ± 1.49, resulting in a mean change from baseline of -11.4.[7] The placebo group showed a decrease in mean values of -12.5 ± 1.54, resulting in a mean change from baseline of -7.70.[7] Although the mean change in baseline was greater in the SAMe group than the placebo group, there was not a statistically significant difference between groups or after the intervention ($P = 0.13$). These results are summarized in Table 2 below.

Table 2. MADRS Change in Depressive Symptoms from Baseline to Study Endpoint[7]

	Before Treatment (Mean ± SD)	**Week 8** (Mean ± SD)	**Mean Change from Baseline**	**P-value**
SAMe Group	22.4 ± 2.01	9.90 ± 1.49	-11.4	0.13
Placebo Group	22.2 ± 3.11	12.5 ± 1.54	-7.70	

Sarris J, Bryne GJ, Bousman C, et al. led another similar double-blind, randomized controlled trial that assessed the efficacy of a combination of SAMe as an adjunctive treatment for depression. In this study, 800 mg of SAMe was combined with folinic acid and co-factor vitamin B12.[8] This study looked at 107 patients, ages 18-75, with moderate to severe depression, who were already taking an SSRI, SNRI, NaRI, 5-cHT2c antagonist, or tricyclic antidepressant. This study also ran for a duration of 8 weeks and patients were assigned to either receive the combination with SAMe or a placebo as an adjunctive therapy. There were 55 participants assigned to the SAMe group and 52 assigned to the placebo group. Of the 107 participants, only 77 of them completed the entire 8 weeks, with 40 trial completers in the SAMe group and 37 completers in the placebo group.[8] Seven patients experienced adverse events, 5 in the SAMe group and 2 in the placebo group.[8] Two more patients in the SAMe group discontinued the study for worsening of symptoms.[8] Additionally, 21 other participants were dismissed from the study either due to their own decision, loss of follow up, non-compliance, or unrelated medical events.[8] These participants were not included in the final analysis.

A decrease in the number of depressive symptoms was also the main outcome measured in this study. Mean values were used to measure the outcomes after receiving the treatment for 8 weeks. The SAMe group illustrated a mean change from baseline of -11.4.[8] The placebo group showed a mean change from baseline of -12.1.[8] In this study, the placebo group had a slightly

greater mean change from baseline than that of the SAMe group; however, difference in the values between groups and following the intervention did not reach the level of statistical significance (P = 0.511). These results are summarized in Table 3 below.

Table 3. Change in Primary Endpoints in Sarris J, Bryne GJ, Bousman C, et al. Study[8]

	Mean Change from Baseline	P-value
SAMe Group	11.4 ± 7.54	0.511
Placebo Group	-12.1 ± 7.02	

Lastly, Sarris J, Byrne GJ, Stough C, et al. conducted another double-blind, randomized controlled trial that assessed a combination of SAMe with other nutraceuticals as an effective treatment for MDD. This studied had 158 patients, ages 18-70, who had moderate to severe depression. This study also lasted 8 weeks in duration and included patients who were currently on an antidepressant or other stable treatment regimen. Patients either received a combination of SAMe, folinic acid, omega-3 fatty acid, 5-HTP, and zinc picolinate as an adjunctive therapy or a placebo.[9] Of the 158 patients that were initially enrolled in the study, only 113 fully completed the entire trial with 56 completers in the SAMe group and 57 completers in the placebo group. Twelve of the participants discontinued the study due to adverse events, 9 from the SAMe group and 3 from the placebo group.[9] Thirty-three other participants discontinued intervention due to the investigators or their own decision, noncompliance, unrelated medical issue, or loss to follow up.[9] These participants were not included in the final analysis.

The primary outcome evaluated in this study was a decrease in the number of depressive symptoms. Mean values were used to measure the outcomes after receiving treatment. The SAMe group had a mean change of baseline of -9.5 ± 8.57. The placebo group showed a mean change from baseline of -11.7 ± 7.82.[9] Although the mean change in baseline was greater in the

SAMe group than the placebo group, analysis of group-by-time ANOVA did not show a statistically significant difference (P = 0.33). These results are summarized in Table 4 below.

Table 4. Change in Primary Endpoints in Sarris J, Byrne GJ, Stough C, et al. Study [9]

	Mean Change from Baseline	P-value
SAMe Group	-9.5 ± 8.57	0.33
Placebo Group	-11.7 ± 7.82	

DISCUSSION

Major depressive disorder is a very common and disabling health condition. Although there are both non-pharmacologic and pharmacologic options that have shown some success in treating depression, they are not always effective. Some patients do not always respond to treatment and others are unable to tolerate medication due to undesirable side effects. SAMe, a nutraceutical used to treat depression in Europe, has been associated with few side effects. However, other barriers with the use of SAMe exist including its long-term safety and possible interactions with other drugs and dietary supplements that increase levels of serotonin.[10] In the United States, SAMe is only sold as a dietary supplement. It does not have the FDA's approval for any medical use; however, its use as been evaluated in several studies for osteoarthritis and liver diseases, in addition to depression.[10] Although there are not contraindications with use of SAMe, evidence suggests it is not safe in those with bipolar disorder or those who are immunocompromised.[10] Additionally, there is not enough evidence to understand its safety in pregnancy.[10]

This review evaluated the effectiveness of SAMe as treatment for depression. None of the three studies found any statistically significant decrease in depressive symptoms with use of SAMe as monotherapy or as adjunctive therapy. In fact, of all three studies, only the study by Sarris J, Murphy J, Stough C, et al. showed a greater reduction in depressive symptoms with

SAMe compared to that of the placebo. Although an absolute difference was observed between the two groups, the p-values of both the intervention and placebo groups illustrate no statistical significance. In both studies by Sarris J, Bryne GJ, Bousman C, et al. and Sarris J, Byrne GJ, Stough C, et al. the placebos achieved a greater reduction in depressive symptoms than the actual interventions with SAMe. Furthermore, the groups in these studies had p-values that revealed no statistical significance in these findings. In summary, these studies showed no support for SAMe as an effective treatment for depression.

The studies in this selective EBM review all had their fair share of bias and limitations. None of the studies carried out a worst-case analysis which compromised the validity of the results. The three studies also all used small sample sizes and only had a short duration of treatment, which further compromised the validity and reliability of the results. Furthermore, the studies all were found to have high placebo response rates which could have obscured the results. Other limitations are directly related to the approach of each study and how they were all designed slightly different. In the study by Sarris J, Murphy J, Stough C, et al., SAMe was used alone as monotherapy, whereas, in the studies by Sarris J, Bryne GJ, Bousman C, et al. and Sarris J, Byrne GJ, Stough C, et al., SAMe was used as adjunctive therapy. Furthermore, in the studies by Sarris J, Murphy J, Stough C, et al. and Sarris J, Bryne GJ, Bousman C, et al., SAMe was combined with folinic acid and co-factor vitamin B12, while in the study by Sarris J, Byrne GJ, Stough C, et al., SAMe was combined with folinic acid, omega-3 fatty acid, 5-HTP, and zinc picolinate. In the study by Sarris J, Murphy J, Stough C, et al., only patients with mild-moderate depression were enrolled, while in the studies by Sarris J, Bryne GJ, Bousman C, et al. and Sarris J, Byrne GJ, Stough C, et al., patients with moderate-severe depression were enrolled. These distinct qualities made direct comparison very difficult amongst the three studies.

CONCLUSION

In conclusion, SAMe did not prove to be effective in treating patients with depression. There was no statistically significant reduction in depressive symptoms between the placebo or intervention groups in any of the studies. In fact, in two of the three studies SAMe failed to outperform the placebo, altogether. Future studies should incorporate larger sample sizes to help minimize expectancy bias, as well as allow a longer duration for intervention and consider using a higher dosage of SAMe. Additionally, future studies should try to achieve a more stable placebo-response pattern due to the high placebo response rates. Future studies could also try different nutraceutical combinations then the ones used in these studies. Currently, there are no studies being conducted on SAMe and its role in depression in the United States; however, hopefully future studies can be carried out to help find other treatment options for patients struggling with depression.

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