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S-Adenosylmethionine Compared to Placebo in Improving Depression Symptoms in Adults with Major Depressive Disorder

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Abstract:

Twenty to twenty-five percent of adults may suffer an episode of major depression at some point during their lifetime. Antidepressant and/or psychotherapy are the current recommended treatments for depression. The supplement S-Adenosylmethionine (SAMe), a naturally occurring compound that is found in the human body, as a possible method of treatment for depression for those who are resistant to traditional antidepressants or for those who cannot tolerate the side effects of antidepressants. Databases that were utilized for this paper were CINAHL and MEDLINE with the search parameters including SAMe, depression and adults.

Purpose – To assess the effectiveness of treatment with S-adenosylmethionine for major depression disorder, measured by the Hamilton Rating Scale for Depression.

Methods – Five random double-blind studies using HAM-D scores from inpatient and outpatients receiving SAMe and patients receiving a placebo were compared.

Results – Two of the five studies reviewed indicated no significant difference in symptom improvement for patients with depression utilizing the HAM-D tool when comparing the administration of SAMe and the administration of a placebo. There were two studies that did not show a significant difference between groups. Three of the studies did show a significant reduction in HAM-D score between SAMe and placebo groups. The p value for the three studies which showed a reduction in HAM-D scores was less than 0.05.

Conclusions – The study designs were strengths in all five studies. Weaknesses included the short term lengths of all studies and small sample sizes. Further studies will be required before recommendations can be included in guidelines pertaining to the use of SAMe for the treatment of depression. There does appear to be a role for SAMe in the treatment of major depression in adults after more studies are conducted.
The importance of this scholarly paper for clinical practice includes patients with depression may have severe side effects from traditional antidepressant therapy or they are resistant to antidepressant therapy. Several natural supplements, such as St. John’s Wort and SAMe, have been investigated and have shown success in improving symptoms of major depressive disorder.

Depression is described as a constant sense of hopelessness and despair. Those who have depression have difficulty working, studying, sleeping, eating and enjoying friends and activities. Depression seems to be passed on from one generation to the next, but may affect people with no family history of illness (Web MD, 2012). Almost seven percent of the U.S. population over age 18 suffers from depression. Twenty to twenty five percent of adults may suffer from major depression at some point during their lifetime. Depression may affect older adults, teens and children, but frequently goes undiagnosed and untreated in these populations. Twice as many women than men have been diagnosed with depression. Hormonal changes during puberty, menstruation, pregnancy, miscarriage and menopause may increase the risk for depression. Increased stress at home or at work, balancing life with career, and caring for an aging parent may increase one’s risk for depression. Men are less likely to seek help or talk about their depression. Signs in men may include irritability, anger, or drug and alcohol abuse. Repressive feelings can result in violent behavior directed both inwardly and outwardly. Depression in men can result in an increase in illness, suicide, and homicide (Web MD, 2012). Most elderly feel satisfied with their lives and depression is not a normal part of aging. Many elderly with depression are reluctant to seek help and the depression may go undiagnosed because symptoms may be less obvious and may seem to be caused by other illnesses. (Mayo Clinic, 2012).

DSM-IV symptoms for depression include: depressed mood most of the day, particularly in the morning; loss of interest in normal activities and relationships; fatigue or loss of energy
almost every day; feelings of worthlessness or guilt almost every day; impaired concentration and indecisiveness; insomnia or hypersomnia almost every day; markedly diminished interest or pleasure in almost all activities nearly every day; restlessness or feeling slowed down; recurring thoughts of death or suicide and significant weight loss or gain (Web MD, 2012). Common triggers for depression include: grief from losing a loved one through death, divorce, or separation; social isolation or feelings of being deprived; major life changes such as moving, graduation, a job change, or retirement; personal conflicts in relationships, either with significant other or superior; and physical, sexual or emotional abuse (Web MD, 2012). In some cases, depression can present with psychotic symptoms such as hallucinations and delusions (National Library of Medicine, 2011). The purpose of this paper is to compare S-Adenosylmethionine (SAMe) versus placebo in improving symptoms of depression in adults with major depressive disorder.

S-Adenosylmethionine, or commonly called SAMe, is a naturally occurring compound that is found in almost every tissue and fluid in the body. It is not found in food and is produced by the body from ATP and the amino acid methionine. SAMe is involved in many body processes including a role in the immune system, to help maintain cell membranes and assist in production and break down of brain chemicals such as serotonin, melatonin and dopamine. SAMe interacts with Vitamin B12 and Folate to enhance these body processes. SAMe works more quickly than standard antidepressants and it is speculated that it increases the amount of serotonin in the brain (University of Maryland Medical Center, 2012).

The importance of implications for quality of life for the patient, their family and society are numerous. SAMe could be identified as an alternative to antidepressant monotherapy where it could be a solution for those who are resistant to traditional antidepressant therapy. If SAMe is
found to be effective in a depressed patient, this could improve their quality of life for themselves and their family by becoming more productive in society through work and other activities outside of the home. The patient population studied includes adults, ages eighteen to seventy five, with major depressive disorder. The intervention under study is either S-Adenosylmethionine compared with placebo. The intended outcome is improvement in depression symptoms utilizing the HAM-D scoring tool. This study analysis and recommendations are related to the nurse practitioner primary care practice because providers need to be aware of all possible treatments for their patients with major depressive disorder as they choose and individualize the course of treatment for each patient.

Analysis

Janicak, Lipinski, Davis, Comaty, Waternaux, Cohen, Altman, & Sharma (1988) compared SAMe and placebo in a randomized double-blind study in patients with depression who were hospitalized for two weeks. Seven patients received 400 mg of SAMe a day via intravenous access and three patients received a placebo. The authors found a reduction in HAM-D scores which decreased from 33.6 to 21.2 for the SAMe group and from 32.9 to 30.5 for the placebo group. The p value was less than 0.02 which is a significant finding. This study is considered to be a level one due to the randomized, double-blind study design, the quality ranked at a two, and the strength of this double-blind study is a D as the researchers indicated SAMe should not be administered for depression without specific considerations. The results were significant and the authors suggested that further studies were required before recommending SAMe solely for the treatment of depression.

In a six week study by Fava, Rosenbaum, Falk, Pollack, Cohen, Cohen, & Zubenko (1990), thirty nine outpatients with depression were randomized to receive either SAMe 1600 mg a day
orally or a placebo. The authors found there was no significant difference between the SAMe and placebo group with a p value of 0.15. This was a randomized, double-blind study designated to be a level one, the quality is ranked at a two, and the strength is a C since there was poor evidence to support or reject the use of SAMe in the treatment of depression.

Sixty outpatients with depression and rheumatoid arthritis were researched by Caruso, Fumagalli, Bosccassini, Puttini, Santandrea, & Ciniselli (1987) in a level one, randomized, double-blind experiment where the patients received either 200 mg of SAMe via intramuscular injection or a placebo. A key feature in this quality two study is that each subject had the diagnosis of rheumatoid arthritis and major depressive disorder. A p value of less than 0.01 was determined by the researchers with HAM-D scores reduced from 45.1 to 33.1 in the SAMe group and from 42.4 to 39.7 for the placebo group. The authors concluded that more studies were required for SAMe to be implemented into routine practice for the treatment of depression in patients who also have the co-morbidity diagnosis of rheumatoid arthritis. This designates the strength of this study at a D since SAMe should not be recommended for treatment of depression at this time.

In a randomized, double-blind study by Agnoli, Andreaoli, Casacchia, & Cerbo (1976), thirty patients with depression were hospitalized for twenty two days. The patient ages ranged from twenty six to seventy five years of age and there were eighteen women and twelve men who received either 45 mg of SAMe via intramuscular injection a day, or a placebo in this level one study. The researchers found there was an improvement in four to seven days in eighty percent of all the patients. There was considerable improvement in depressed mood in one hundred percent of SAMe patients and only thirty percent of placebo patients. They found a mean baseline in the SAMe group to be 21.6, and 19.1 for the placebo group with a p value of less than
0.05. The authors determined that it is too early to implement SAMe as a standard treatment for depression until more studies are conducted, which gives this research study a D for strength, and a quality of two.

Carney, Edeh, Bottiglieri, Reynolds, & Toone (1986) studied thirty two subjects for fourteen days in a hospital setting. The patients received either 20 mg of SAMe intravenously a day or a placebo in this level one randomized, double-blind study. A reduction in HAM-D scores for both the SAMe and placebo group was discovered by the authors, although they determined that it was not a significant difference leading to a quality of two and a strength of C since there was poor evidence to support or reject the use of SAMe for depression treatment. The SAMe group scores went from 26.5 to 20.1 and the placebo group went from 25.5 to 22.5.

All five studies had a similar aim to assess the effectiveness of treatment with SAMe for major depression disorder utilizing the HAM-D scoring tool. Designation of moderate to high quality for all five studies was impressive as they were double blind, random studies. The strength of the overall evidence was moderate and significant in the studies conducted by Janicak et al. (1989), Caruso et al. (1987) and Agnoli et al. (1976), and was poor and not significant in the studies conducted by Fava & Rosenbaum et al. (1990) and Carney et al. (1986).

The study design was a strong trait in all five studies. Carney et al. (1986), Agnoli et al. (1976) and Janicak et al. (1989) all monitored the patients closely in the hospital which gave them a very controlled setting. Agnoli, et al. (1976), Caruso et al. (1987), and Janicak et al. (1989) all had significant findings with p values of less than 0.01. Caruso et al. (1987) had a fairly large number of patients which added strength. There were also several weaknesses to the five studies. The length of all five studies reviewed was short, anywhere from two weeks to six weeks. In addition, the sample sizes were not very large in the five studies which varied from
seven to sixty patients (Agnoli et al., 1976, Carney et al., 1986, Caruso et al., 1987, Fava & Rosenabum et al., 1990 and Janicak et al., 1989).

There is concern with all five studies when analyzing the social justice component. None of the studies put ample consideration or emphasis into specifically assessing specific age groups, genders, socioeconomic status or ethnicity of the subject groups. Fava & Rosenbaum, et al. (1990) was the only one of the five studies to point out geographical location of the study, which was in Italy. Agnoli et al. (1976) was the only one of the five studies to state the actual numbers of the genders and the age range of the subjects. Social justice was upheld in all five studies as far as educating the subjects on the aim and treatment modalities utilized in each study. The participants had the option to leave the study at any time in all five studies. Since these studies were all double-blind and random, no researcher bias was present which also added credence to the social justice aspect (Agnoli et al., 1976, Carney et al., 1986; Caruso et al., 1987, Fava & Rosenabum et al., 1990 and Janicak et al., 1989).

An additional note of interest is that Fava, Giannelli, Rapisarda, Patralia, & Guaraldi (1994) and Fava, Rosenbaum, Pollack, Cohen, Zubenko (1988) conducted two additional open labeled pilot studies with the same topic being the impact of SAMe on depression symptoms. Fava et al. (1994) conducted a study in Italy with 195 outpatients and many clinical sites, and Fava & Rosenbaum et al. (1988) conducted a study in Massachusetts with twenty outpatients. Although the study utilized for the purposes of this scholarly paper was chosen for its design and was found insignificant, Fava et al. (1994) and Fava & Rosenbaum et al. (1988) had significant findings in their studies. In addition, Caruso et al. (1989) conducted an open label second study a few years after their original study on the same topic, and again had significant findings that SAMe- treated participants did show an improvement in depression symptoms.
Synthesis

The main conclusion to draw after evaluating the five studies in this scholarly paper is that there is significant evidence present that the administration of S-Adenosylmethionine can reduce HAM-D depression scores in patients with major depression. In the conclusion for each study it was recommended that further studies were required to strengthen the evidence of the effects of SAMe on depression symptoms before it can be put into practice (Agnoli et al., 1976, Carney et al., 1986; Caruso et al., 1987, Fava & Rosenabum et al., 1990 and Janicak et al., 1989).

Janicak et al. (1989), Agnoli et al. (1976) and Caruso et al. (1987), all had significant findings in their perspective studies. Larger sample sizes and additional length to future studies are issues that need to be addressed to strengthen their findings. Social justice elements need to be addressed in addition to assuring as many representatives of society are included in their samples as possible. This means equal representation of both genders, significant numbers from various age groups, and representation from many ethnic and socioeconomic groups.

Parker-Pope (2010) states in the New York Times, that SAMe has been a frequently used treatment for depression across Europe for more than twenty years. Fava & Rosenbaum et al. (1988) introduced their studies to American researchers in Massachusetts when they collaborated in an open-label study and found significant results on their depressed subjects when treated with SAMe. Since then, a peaked interest has risen in this depression treatment modality. Papakostas, Cassiello, & Iovieno (2012) from Harvard Medical School and Massachusetts General Hospital, conducted a recent open-label study which mimics some of the earlier study results researched in this scholarly paper (Parker-Pope, 2010). This is a solid indication that studies will continue as researchers and health care professionals strive to find alternatives for their patients with depression.
The design by Fava et al. (1990) and Carney et al. (1986) were solid choices. However, both sample sizes were small and the length of study for both was short. This may have been a contributing factor to their insignificant findings. Agnoli et al. (1976), Caruso et al. (1987) & Janicak et al. (1988) also had small sample sizes and shorter lengths of study, but Agnoli et al. (1976) and Janicak et al. (1988), took place in highly controlled settings within hospitals which may have given them an opportunity to monitor their subjects more closely with more significant results.

Similar design, subjects, treatment modalities and measurement tools were the primary aims for this scholarly paper. All five studies were randomized and double blind, treated the subjects with either SAMe or a placebo, and utilized the HAM-D scoring tool to measure their results (Agnoli et al., 1976, Carney et al., 1986; Caruso et al., 1987, Fava & Rosenabum et al., 1990 and Janicak et al., 1989). Future studies with these continued commonalities engrained into their development, along with larger, more diverse sample sizes and increased study timeframes, will be the next step in strengthening the reality of adding SAMe as a depression treatment modality into evidenced-based practice.

Recommendations

The overall recommendation from evaluating the five studies is that further studies are required before implementing SAMe into routine treatment for depression (Agnoli et al., 1976, Carney et al., 1986; Caruso et al., 1987, Fava & Rosenabum et al., 1990 and Janicak et al., 1989). It is recommended to follow established guidelines for depression. DSM-IV criteria and the use of a HAM-D or other depression screening tools is an effective way to evaluate a patient for depression. In addition, both resources can be used to monitor the patient at intervals after diagnosis. If the diagnosis of depression is made, then antidepressant therapy and/or
psychotherapy is recommended by guidelines (Institute for Clinical Systems Improvement [ICSI], 2011).

Per ICSI guidelines (2011), it is important to monitor the patient closely at regular intervals to determine if the ordered medication is working and to titrate the dose up or adjust the medication until the patient’s mental state is at an adequate level. Most patients are on an antidepressant for at least six to twelve months even after they display an adequate response to symptoms. Patients with recurrent depression should be treated for three years or more. If psychotherapy is ordered, it takes approximately eight to 10 weeks of regular therapy to show improvement. It is also important to have a documented system to assure ongoing contacts with the patient for the first six to twelve months of treatment based on a standardized tool used at each contact to document and track treatment response.

ICSI Guidelines (2011) also have recommendations for the patient and family to attend counseling and education when the diagnosis of depression is made. The patient and family should be actively engaged in self-management of depression. It is important to educate them on the nature of the disease. Risks and benefits of the treatment plan for the depression should be reviewed. Finally, it is important to consider patient preferences for treatment and education.

When SAMe is approved for treatment of depression in standardized guidelines such as ICSI guidelines, it will be an option for nurse practitioners and other providers to review and consider with their patients who are diagnosed with major depression. It will be a professional courtesy to share this new treatment mode with other providers and to monitor the success of the treatment utilizing the HAM-D or other standardized depression scoring tool in patients who are taking SAMe for their depression. There are many ways that the nurse practitioner could communicate the use of SAMe for depression once it is approved, including newsletters, continuing education
opportunities, provider to provider discussions, and through articles. In conclusion, the comparison of S-Adenosylmethionine (SAMe) versus placebo in improving symptoms of depression in adults with major depressive disorder requires further study before it can be implemented into practice. The evidence produced does suggest that SAMe has the potential to become a treatment choice for patients with depression in the future. This could be beneficial for those who have been resistant to standard antidepressant therapy or for those who have exhibited side effects from standard therapy.
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