Evidence for S-Adenosyl-l-Methionine (SAM-e) for the Treatment of Major Depressive Disorder

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Despite the increasingly large array of antidepressants available to treat major depressive disorder, patients continue to experience relatively modest response and remission rates. In addition, patients may experience adverse side effects from pharmacotherapy that not only hinder treatment compliance and adherence but, in some cases, may also contribute to increased disability, patient suffering, morbidity, and mortality. In order to enhance treatment efficacy and tolerability, patients and clinicians have become increasingly interested in nonpharmaceutical supplements for treating depression. One of the best-studied of these supplements is S-adenosyl-l-methionine (SAM-e), a naturally occurring molecule present in all living cells and a major methyl group donor in the human body. Controlled trials have found SAM-e to be more efficacious than placebo and equal in efficacy to the tricyclic antidepressants for treating major depressive disorder (MDD) when administered parenterally (either intravenously or intramuscularly). Less evidence supports the use of oral SAM-e, although some trials have demonstrated its efficacy as well. In addition, there is a paucity of evidence examining whether oral forms of SAM-e can be safe, well tolerated, and efficacious when used as adjunctive treatment for antidepressant nonresponders with MDD. Although preliminary data suggest SAM-e may be useful as an adjunctive therapy to antidepressants, controlled studies are needed to confirm or refute these preliminary findings.

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**Potential Role of SAM-e in the Pathophysiology of Depression**

Studies have provided preliminary evidence for a potential role of SAM-e in the pathophysiology and treatment of depression. In 1988, Bottiglieri and colleagues reported low serum SAM-e levels in patients with MDD, and, in a later study, reported low SAM-e levels in the cerebrospinal fluid (CSF) of patients with MDD. Interestingly, the latter of these 2 studies also noted that CSF SAM-e levels increased in patients following administration of oral or intravenous SAM-e, suggesting that both oral and intravenous formulations are bioavailable.

Low serum folate concentrations have also been associated with an increased risk of depression in several studies, lending indirect evidence in support of a potential role for low SAM-e levels in MDD, since folate is a natural precursor to SAM-e in human biosynthesis (see Figure 1). For instance, studies have found that folate deficiency in depressed patients correlates with low CSF metabolites of dopamine, norepinephrine, and serotonin. In addition, elevated levels of homocysteine—indicating impaired methylation of homocysteine to methionine—have also been correlated with folic acid deficiencies. In fact, several trials suggest that administration of elements of one-carbon cycle metabolism, including folic acid, methylfolate, and 5-MTHF, may improve treatment outcomes for patients with MDD.

Several hypotheses have been proposed for the antidepressant mechanisms of SAM-e in the human body. SAM-e serves as the methyl group donor for a number of substrates, most notably for phospholipids, DNA, RNA, neurotransmitters, and proteins. One hypothesis for the role of SAM-e in MDD is that, by methylating plasma phospholipids, SAM-e may alter the fluidity of the neuronal membrane, thereby affecting the function of proteins that transverse the membrane, including various monoamine receptors, monoamine transporters, and other elements of the second messenger system. Alternatively, SAM-e may exert antidepressant effects via DNA methylation by influencing the transcription of DNA. An additional hypothesis focuses on methylation reactions dependent on SAM-e that are required in the synthesis of neurotransmitter monoamines, as shown in Figure 1. An increase in SAM-e may result in increased synthesis of the neurotransmitters thought to be deficient in patients with MDD.

**Efficacy and Tolerability of SAM-e in MDD**

The antidepressant effects of SAM-e were first noted serendipitously in the early 1970s, an observation that was soon followed by several open-label studies of parenteral SAM-e for patients with MDD that showed promising, yet preliminary, results. Multiple randomized, double-blind studies comparing the use of SAM-e versus placebo or tricyclic antidepressants in patients with MDD followed soon thereafter.

**Controlled Studies of SAM-e as Monotherapy for MDD**

**Parenteral SAM-e studies.** Five early studies with 18 to 92 subjects compared the use of intravenous SAM-e, administered at doses ranging from 150 mg/d to 400 mg/d, to treatment with clomipramine, amitriptyline, or imipramine. These studies reported that SAM-e resulted in a reduction of depressive symptoms that was statistically and clinically comparable to that of the tricyclic antidepressants. More recently, Bell and colleagues found that 400 mg/d of intravenous SAM-e resulted in clinical effects that were superior to those of imipramine following 2 weeks of treatment among 22 outpatients with MDD. Finally, in the largest study published to date (N = 295) comparing parenteral SAM-e with tricyclics, Delle Chiaie and colleagues reported that 400 mg/d of intramuscular SAM-e was as effective as 150 mg/d of imipramine among outpatients with MDD.

Studies have also examined the use of parenteral SAM-e versus placebo in MDD. Five small studies conducted between 1976 and 1988 reported intravenous (200–400 mg/d) or intramuscular (45–50 mg/d) SAM-e to be more effective than placebo in the treatment of MDD. In a separate study, although Carney and colleagues reported 200 mg/d of intravenous SAM-e to be equivalent to placebo in antidepressant effect among patients with MDD overall, a significant treatment effect in favor of SAM-e versus placebo was reported among the subset of patients with endogenous depression (P ≤ .05, N = 32). Finally, in the largest...
study published to date (N = 60) of parenteral SAM-e versus placebo, Caruso and Pietrogrande33 demonstrated that 200 mg/d of intravenous SAM-e was superior to placebo as a treatment for outpatients with depression and comorbid rheumatoid arthritis.

**Oral SAM-e studies.** Taken together, the aforementioned studies suggest that SAM-e is more effective than placebo and equivalent in efficacy to the tricyclic antidepressants in the treatment of MDD, although the route of administration (ie, intravenous or intramuscular) considerably limits the clinical usefulness of these findings. The question then becomes, is oral SAM-e an effective monotherapy for MDD?

Three randomized, double-blind trials have examined the use of oral SAM-e versus a tricyclic antidepressant for depression. Two small studies34,35 (N ≤ 26) and a large study28 (N = 281) all demonstrated that 1600 mg/d of oral SAM-e was equivalent to a tricyclic antidepressant in treating depression.

Three placebo-controlled studies have examined the use of oral SAM-e as monotherapy for depression. Two of these studies36,37 demonstrated that the antidepressant effects of 1600 mg/d of oral SAM-e were superior to those of placebo among patients with MDD. However, the third study38 showed the same dosage of SAM-e to be no more effective than placebo. This study noted that the particular oral preparation of SAM-e (1,4-butanedisulfonate) used was responsible for the absence of a significant treatment effect in that study. In fact, shortly after the completion of that trial, the US Food and Drug Administration stopped clinical trials of 1,4-butanedisulfonate at US sites because of issues regarding the poor dissolution of the tablets.

**Meta-analysis.** A 2002 meta-analysis39 was conducted of randomized, double-blind studies of intramuscular, intravenous, and oral SAM-e as monotherapy treatment for MDD. Comparing the pooled results of treatment with SAM-e to treatment with placebo for MDD, the meta-analysis found a statistically significant overall effect size of −0.65 (95% CI, −1.05 to −0.25) in favor of SAM-e over placebo, which translated to an improvement in Hamilton Depression Rating Scale40 scores of almost 6 points. In comparing SAM-e to the tricyclic antidepressants, the meta-analysis found an effect size of 0.08 (95% CI, −0.17 to 0.32), indicating that treatment with SAM-e for MDD is approximately equivalent to treatment with tricyclic antidepressants.

**Controlled Studies on SAM-e as Adjunctive Therapy for MDD**

The majority of studies focusing on the use of SAM-e examine whether or not it is an efficacious, safe, and well-tolerated treatment when administered as monotherapy for MDD. However, given that the majority of clinicians prescribe antidepressants combined with some form of psychotherapy for MDD, of greater relevance to the field is whether SAM-e is an effective treatment when used adjunctively for patients with MDD. To date, only a single randomized, double-blind, placebo-controlled trial evaluating the use of SAM-e as an adjunctive therapy in MDD has been conducted. In this 2-week study, Berlanga and colleagues41 assigned 40 antidepressant-naive patients to receive either a placebo injection or 200 mg/d of intramuscular SAM-e, while simultaneously receiving imipramine, which was titrated to 150 mg/d by the end of the first week. By day 4, patients receiving both SAM-e and imipramine had experienced a significant advantage in antidepressant effect versus the monotherapy group (P < .05); the advantage continued to be significant through day 12 of treatment, although not at day 14 (Figure 2). Thus, these preliminary results suggest that the use of SAM-e, when combined with antidepressants from the onset of therapy, may accelerate symptom improvement in MDD.

Alpert and colleagues42 conducted an open-label trial to examine the efficacy of oral SAM-e as an adjunctive treatment for 30 outpatients with MDD who had not experienced significant symptom improvement following open-label treatment with either a selective serotonin reuptake inhibitor (SSRI) or venlafaxine. Patients received 400 mg bid of
the tosylate formulation of SAM-e for the first 2 weeks of the trial, followed by 800 mg bid for an additional 4 weeks. In the intent-to-treat analysis, 50% of the patients responded during the course of therapy, and 43% remitted, indicating that oral SAM-e as adjunctive therapy is a potentially useful clinical treatment strategy for antidepressant nonresponders with MDD. The decrease from baseline in depressive symptom severity reached significance by week 1 and remained significant through week 6 (P < .0001, Figure 3). Of note, patients experienced a significant decrease in homocysteine levels during the course of treatment, from 8.2 µmol/L to 7.8 µmol/L (P = .0029).

Table 1. Comparison of Adverse Events in 2 Studies of SAM-e Versus Imipramine for Major Depressive Disorder

<table>
<thead>
<tr>
<th>Study 1 (1600 mg oral SAM-e)</th>
<th>Study 2 (400 mg IM SAM-e)</th>
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</thead>
<tbody>
<tr>
<td>Total number of patients</td>
<td>143 137</td>
</tr>
<tr>
<td>Patients with ≥ 1 adverse event</td>
<td>42 (29.4) 59 (43.1)*</td>
</tr>
<tr>
<td>Study drug-related adverse events</td>
<td>7 (4.9) 28 (20.4)**</td>
</tr>
<tr>
<td>Total number of patients</td>
<td>147 147</td>
</tr>
<tr>
<td>Patients with ≥ 1 adverse event</td>
<td>47 (32.0) 80 (54.4)**</td>
</tr>
<tr>
<td>Study drug-related adverse events</td>
<td>14 (9.5) 49 (33.3)**</td>
</tr>
</tbody>
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Safety and Tolerability of SAM-e

Studies published to date suggest that SAM-e is generally well tolerated, with adverse effects such as gastrointestinal symptoms, dry mouth, headache, vertigo, insomnia, tachycardia, and restlessness.39 In the largest trials of SAM-e monotherapy,28,43 considerably fewer patients receiving either oral or intramuscular SAM-e reported side effects than patients receiving a tricyclic antidepressant (Table 1). However, psychiatric effects such as increased anxiety have been reported, as well as mania or hypomania in patients with bipolar depression.44

The most common side effects reported in the trial by Alpert and colleagues,42 which examined SAM-e as an adjunctive treatment to an SSRI or venlafaxine, were gastrointestinal symptoms, including constipation, gastrointestinal upset, and diarrhea, and musculoskeletal side effects such as headaches, anxiety, irritability, fatigue, and sedation. No significant changes in weight or increases in the severity of sexual dysfunction occurred during the course of the trial.

CONCLUSION

SAM-e, along with Hypericum perforatum (St John’s wort) and omega-3 fatty acids, is one of the most-studied natural remedies for MDD. Ample evidence supports parenteral SAM-e as being superior to placebo and equivalent to the tricyclic antidepressants in efficacy as monotherapy for patients with depression. However, this finding is clinically limited by the route of administration, ie, intravenous or intramuscular. A smaller evidence base supports the use of oral SAM-e as monotherapy for MDD. The most widespread clinical use for SAM-e may be as an oral augmenting agent for treating antidepressant nonresponders with MDD. Unfortunately, only a single open-label study examining this usage has been published to date. Due to its relative safety, tolerability, and novel mechanism of action, SAM-e may have several advantages as a treatment for MDD, although additional controlled trials are needed to support its clinical relevance.
Drug names: clomipramine (Anafranil and others), imipramine (Tofranil and others), venlafaxine (Effexor and others).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, S-adenosyl-l-methionine is not approved by the US Food and Drug Administration for the treatment of major depressive disorder.

REFERENCES


