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Is S-Adenosyl Methionine (SAME) for Depression Only Effective in Males? A Re-Analysis of Data from a Randomized Clinical Trial

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Abstract

Objective: The aim of this study was to examine whether gender differences may have affected treatment response to S-adenosyl methionine (SAME) in a recent failed randomized clinical trial (RCT) for adults with major depressive disorder.

Methods: Data from a 2-site, 12-week, double-blind RCT ($n=189$) assessing the efficacy of SAME vs. placebo and a comparator selective serotonin reuptake inhibitor (escitalopram) were subjected to post-hoc analyses to evaluate effects of patient gender on treatment response.

Results: When assessing the efficacy outcomes within each gender separately, SAME was superior to placebo among males ($n=51$), but not

among females ($n=62$). Males showed a significant reduction of depression severity from baseline to study endpoint on the 17-item Hamilton Depression Rating Scale (4.3 point difference; $p=0.034$; $d=0.95$), while females did not show significant change. This finding emerged despite equivalence on baseline measures of depression severity between the gender groups.

Conclusion: Results of this secondary data analysis suggest that gender might impact the antidepressant efficacy of SAME, with greater therapeutic effect found in males. The underlying mechanism is still relatively unknown. Further work is needed to replicate this observation in independent samples.

Clinicaltrials.gov identifier: NCT00101452

Introduction

S-Adenosyl methionine (SAME) is a sulphur-containing compound that is a critical neurochemical component of the one-carbon cycle, involved in the methylation of neurotransmitters responsible for mood regulation [1]. SAME may alleviate depressed mood via enhanced methylation of catecholamines, increased serotonin turnover, reuptake inhibition of norepinephrine, enhanced dopaminergic activity, and increased phosphatidylcholine conversion [2,3]. SAME has been proposed as a potential treatment for various medical conditions, particularly major depressive disorder (MDD). Double-blind randomized clinical trials (RCTs) have generally supported the efficacy of oral and parenteral SAME as comparable to tricyclic antidepressants, with fewer side effects [4]. Recent work supports SAME augmentation in partial and non-responders to selective serotonin reuptake inhibitors (SSRIs) and serotonin/norepinephrine reuptake inhibitors (SNRIs) [5].

We recently reported the first double-blind RCT comparing the efficacy of SAME vs. placebo and a standard SSRI (escitalopram) in treating MDD [6]. The 12-week 2-site study was essentially negative, with no significant differences in clinical response occurring between the 3 treatment groups. Given the considerable body of evidence supporting the antidepressant efficacy of SAME, we carried out various post-hoc analyses examining possible effects of site, gender, and other patient characteristics. The first of these investigations, a sub-analysis of data from site 1 only, which recruited the majority of participants, revealed a significant effect in favor of SAME, with a moderate-to-large effect size vs. placebo ($d=0.74$) and remission rates significantly higher for SAME (34%) than for escitalopram (23%) or placebo (6%) [7]. Because the only significant difference in patient characteristics between the 2 sites was gender (59% males in site 1 and 31% males in site 2; $\chi^2 p < 0.0001$), we explored whether this might explain the difference in outcome between the 2 sites. This report describes those findings.

Methods

The full methodology of the parent trial is detailed in Mischoulon et al. [6]. In brief, consenting outpatients with MDD were recruited from 4/13/05 to 12/22/09. Inclusion criteria consisted of a diagnosis of MDD by the Structured Clinical Interview for DSM-IV; age 18–80 years; and a score of 25 or greater on the Inventory of Depressive Symptomatology – Clinician-Rated. The HAM-D-17 was administered concurrently and used as the main outcome measure. Exclusion criteria consisted of: comorbid psychiatric and medical disorders, or use of various medications; current use of other psychotropic drugs; previous moderate use of SAME or escitalopram; ongoing psychotherapy; multiple treatment failures; and pregnancy or being of child-bearing potential and not using a medically accepted means of contraception.

Participants who met criteria for MDD and had a baseline HAM-D-17 score of ≥ 14 were analyzed as intent-to-treat using last observation carried forward (LOCF), in which all patients randomized to any of the 3 treatment arms had their data included in the analysis. We analyzed each gender group to determine whether there were any treatment-based differences. The primary efficacy measure was the difference in change in HAM-D-17 score across the 3 treatment groups from baseline to week 12 endpoint. Analysis of covariance (ANCOVA), using baseline HAM-D-17 score as the covariate, was conducted to assess differences between Group \times Time from baseline to study endpoint. Response rates (HAM-D-17 reduction of $\geq 50\%$) were also calculated using a chi-square analysis.

All analyses were carried out using SPSS version 20.0 software, with statistical significance set at $\alpha=0.05$.

Results

Baseline HAMD-17 levels were not significantly different between gender groups. While the Group \times Time interaction between all 3 treatments (covarying for baseline HAMD depression level) was not significant for either gender (male: $F_{2,74} 1.41$; $p=0.16$; female $F_{2,88}=0.77$; $p=0.71$), significant results were revealed for males when directly comparing SAME to placebo. A significant reduction of depression was seen in males between treatments from baseline to study endpoint; males treated with SAME had a decline of 8.9 points on the HAM-D compared to 4.6 points for placebo (4.3 point difference, $F_{1,48} 4.77$; $p=0.034$;

Fig. 1). This represents a large effect size, $d=0.95$. Conversely, females taking placebo had a 6.0-point reduction compared to a 5.4-point reduction for SAME (n.s). Comparisons of changes in HAM-D-17 score for SAM vs. escitalopram and for escitalopram vs. placebo in each gender group did not yield any significant findings (data not shown). Gender differences likewise did not impact response rates to treatment (data not shown).

Discussion

The present findings suggest that SAME may be more effective for males than females in reducing depression. This could help explain the negative results from the parent study. While results between sites differed, we saw no obvious reason for this. Both sites employed identical methodologies and staff were highly trained. Further, sample demographics were comparable (Boston and Providence). Other variables such as age, also revealed no significant impact of differential response (data not shown). While these initial analyses suggested that between-site effects might have contributed to the failure to detect treatment differences, the present analysis suggests that gender-based response differences could have impacted outcome in the overall sample. There are precedents for gender differences in pharmacological antidepressant effects. For example, in a 12-week RCT [8] involving 235 male and 400 female outpatients randomized to sertraline or imipramine, females were significantly more likely to respond to sertraline than to imipramine, and men were significantly more likely to respond to imipramine than to sertraline. Previous studies have also suggested possible gender-based effects for SAME. Koch et al. [9] examined activity-related effects on plasma epinephrine, norepinephrine, dopamine and renin in 16 adults (males and females aged 22–34 years) and 9 athletic adolescent boys (aged 16–17 years). Epinephrine, norepinephrine, and renin activity increased exponentially with exercise, and the effect was greatest in the adolescent boys. Because the assay required conversion of epinephrine, norepinephrine, and dopamine into methyl derivatives in the presence of catechol O-methyltransferase and SAME, the findings suggest a possible link between SAME and gender-specific effects (although we cannot rule out age differences influencing this effect).

Inoue-Choi et al. [10] conducted a cross-sectional analysis of associations between plasma concentrations of one-carbon cycle metabolites and plasma SAME concentrations in healthy Chinese subjects. Plasma betaine and folate were positively

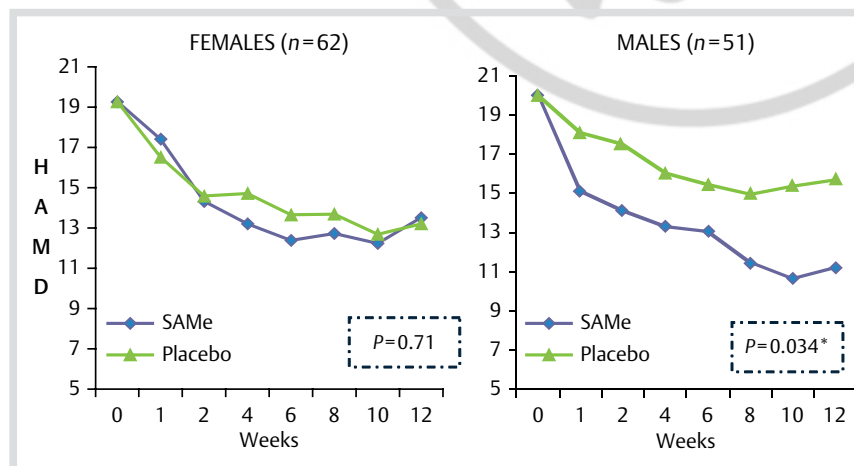


Fig. 1 Gender and response to SAME vs. placebo. Group \times Time ANCOVAs were conducted in males and in females. HAMD = Hamilton Depression Rating Scale 17. SAME = S-adenosyl methionine (Color figure available online only).

associated with plasma SAME in men only. Men carrying the variant methionine adenosyltransferase (MAT1A) genotype and having low plasma methionine had significantly lower plasma SAME concentrations than men carrying the wild type genotype. Again, these findings further suggest the potential for gender-related effects of SAME.

A healthy population study [11] ($n=581$) investigating the relationship between fasting concentrations of plasma one-carbon cycle biomarkers [e.g., homocysteine, SAME, and S-adenosylhomocysteine (SAH)] revealed that, compared to females, males had a significantly lower SAME:SAH ratio, suggesting that SAME supplementation could have a greater impact on men. A 6-week double-blind RCT of SAME augmentation for SSRI/SNRI non-responders revealed that males treated with adjunctive SAME demonstrated significantly lower sexual arousal dysfunction at study endpoint compared to the adjunctive placebo group [12], perhaps due to SAME being a regulator of cystathionine beta-synthase, resulting in nitric oxide-mediated vasodilation of penile tissues [12]. A neuroprotective effect via SAME on dopaminergic neurons might also enhance dopamine's role in enhancing sexual functioning in men. Despite the data supporting a more specific effect of SAME in males, an 8-week double-blind RCT with 18 participants with chronic schizophrenia given either SAME 800 mg or placebo found improvement of depressive symptoms only in females [13].

While these studies are suggestive, they do not provide a clear line of evidence for the potential mechanism underlying a gender difference of SAME in depression. A few studies have also reported gender-based differences in one-carbon cycle activity in rats and mice. Factors linked to gender effects include the N-acetyltransferase (NAT) enzyme, which plays a role in catabolism of folate, a vitamin on which SAME synthesis depends [14]. In another study, glycine N-methyltransferase (GNMT), an enzyme that regulates SAME and can impact methylation and folate metabolism, was significantly increased in the liver of male rats after retinoid administration and SAME-dependent creatinine synthase was significantly reduced; these effects were less pronounced in female rats [15]. The enzyme S-adenosylmethionine synthetase (AdoMet synthetase) is responsible for the synthesis of SAME, and is less active in male than female rats [16].

Collectively, these studies suggest that gender-related effects involving SAME may be due to variances in the one-carbon cycle pathways, perhaps in part secondary to hormonal regulation, but current data do not provide clear support for a single unified theory. The breadth of findings, however, suggests the need for further research in this area.

In summary, our results suggest a gender-based difference in response to SAME in subjects with MDD, and there are precedents in human and animal studies to suggest mechanisms that might account for this differential. Our investigation is limited by the post-hoc nature of the analysis, and requires prospective studies to replicate the findings. Re-analyses of other published SAME studies in MDD would also be informative. While we cannot yet say whether a true gender difference in clinical response to SAME exists, such an effect would represent a novel and important finding that could have implications for the application of this natural product in the treatment of mood disorders.

Author's Contributions



JS and DM drafted the initial version of this manuscript. All authors contributed intellectual content to the manuscript and read and approved the final manuscript.

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Conflict of Interest



JS has received a research consultancy honorarium from Bioceuticals, a company which sells SAME (though not the subject of this research).

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