Author's response to reviews

Title: The Use of S-Adenosylmethionine (SAM-e) for the Treatment of Depression in People Living with HIV/AIDS

Authors:

R. Andrew Shippy (ashippy@acria.org)  
Douglas Mendez (dmendez@acria.org)  
Kristina Jones (kjonesmail@yahoo.com)  
Irene Cergnul (Ilgcergnul@aol.com)  
Stephen E Karpiak (skarpiak@acria.org)

Version: 4 Date: 13 October 2004

Author's response to reviews: see over
Authors’ Response
This document provides a point-by-point response to reviewers’ comments on:
MS: 1886808991381125 - The Use of S-Adenosylmethionine (SAM-e) for the Treatment of Depression in People Living with HIV/AIDS

Reviewer 1: George Papakostas

Revision 1: An outline of inclusion/exclusion criteria in the methods

Response: The following description was added to the Methods section . . .
. . . Criteria for exclusion were (a) unstable medical illness, (b) pregnancy, lactation or refusal by participants to employ an acceptable contraceptive, (c) history of substance abuse in the prior month, (d) treatment with another psychotropic medication within two weeks prior to initiation of SAM-e treatment, (e) concurrent MAOI treatment, (f) active suicidal ideation and/or psychotic symptoms, (g) reversible medical pathology that is thought to be causing the depression, and (h) history of mania or diagnosed bipolar disorder.

Revision 2: A description of how a depressive disorder was established for inclusion in the study (ie SCID? MINI?)

Response: SCID-IV criteria were used to diagnose Major Depression . . .
. . . HIV-positive patients were then invited to be interviewed by a study psychiatrist at ACRIA for a clinical psychiatric examination. Patients who met DSM-IV criteria for Major Depression (assessed with the SCID-IV) and who did not meet any of the exclusion criteria were eligible for participation after giving informed consent . . .

Revision 3: Authors must also report an intent-to-treat analysis for endpoint (week 8)

Response: Intent-to-treat analysis was added to the results section . . .
The intent-to-treat analysis yielded similar results. The last reported BDI and HAM-D scores for each of the 20 patients who initiated treatment (i.e., received at least one dose of SAM-e) were used in this analysis. The mean BDI score at Baseline was 33.5 ($SD = 11.1$) and at Week 8, the mean was 6.6 ($SD = 6.1$). Mean HAM-D scores dropped from 26.5 ($SD = 6.8$) at Baseline to 7.7 ($SD = 10.1$). This reduction in self-reported (i.e., BDI) depressive symptomatology was significant, $t(1, 19) = 8.85, p < .001$. The results were equivalent for the psychiatrist-rated HAM-D, $t(1, 18) = 7.23, p < .001$.

Revision 4: Authors must report all numbers with accompanying standard deviation.

Response: The Results section was revised to include standard deviations for all mean values reported.

Revision 5: Reasons for discontinuation must be stated in the results.

Response: The first paragraph of the Results contains reasons for discontinuation . . .
. . . Five patients did not complete the study, but Week 1 data were recorded and were included in the analysis of early onset of therapeutic SAM-e effects. These five subjects were excluded from subsequent
analyses. Two subjects did not return for study participation after Week 1: both had a history of IDU; one was co-infected with Hepatitis C and had a comorbid obsessive compulsive disorder (OCD). Three patients did not return after Week 4, one with a history of IDU and one with a history of suicide attempts. Of those who dropped out of the study, two met criteria for AIDS.

**Revision 6: There is no limitations section (i.e. lack of placebo comparator, etc).**
The paper would need a limitations section.

**Response:** A paragraph was added to the Discussion section to address study limitations . . .

The results of the current study must be interpreted in the context of the study’s limitations. Limitations of this study include the lack of a placebo group, the lack of a double-blind design and small sample size. Without a placebo control group, we cannot assess the effect of meeting with a study psychiatrist, which may have contributed to improved depressive symptom ratings. Nonetheless, the study results provide useful and clinically relevant information for treating depression in HIV-positive individuals. Future studies employing a double-blind, placebo-control design are warranted.

**Revision 7: The authors need to clarify the phrase, "at week 8, all patients scored below the minimum score for depression on both the BDI and HAMD (discussion section). This is not supported in the results section, as no range for endpoint HAMD or BDI is offered.**

**Response:** We revised the statement in the Discussion . . .

**Discussion:** . . . Results of this study demonstrate that SAM-e significantly reduces depression in people living with HIV. At Week 8, mean depression scores indicated the absence of depression, as measured by the BDI and the HAM-D (below 10 and 7, respectively). This finding supports previous research demonstrating the efficacy of SAM-e for use in treating depression.

**Measures:**

**BDI.** The BDI is a self-report measure for depressive symptoms [16]. Total scores range from 0 – 63 and are calculated by summing the scores to each of the 21 items. Higher scores on this measure indicate greater severity of depression. Scores above 30 indicate severe depression. Scores of 30 - 10 describe moderate depression, while **scores less than 10 indicate the absence of depression.**

**HAM-D.** The HAM-D is a 17-item, clinician-rated instrument. It was designed to assess the changes in severity of depressive symptomatology over time in patients who had been diagnosed with Major Depressive Disorder [17]. Scores above 24 reflect severe depression, while scores ranging from 17 – 7 indicate mild symptomatology. **Scores below 7 indicate an absence of depression.**

**Reviewer 2:** Arlene Kochman

**Revision 1: The author makes generalized statements regarding "depression in this population is largely untreated"-should give citations to back this up and should refer to work done example: Heckman et al on depression/suicidal ideation for HIV men and women 50 +. "Stigma remains large"-should give citations. "Primary care physicians are often unprepared and so on"-entire paragraph needs citations. More reading in this area and citations would make this paper more academically credible.**
Response: The background has been updated and includes several references that have been added per reviewer’s comments.

Under-treated depression in the HIV population may be the result of multiple factors. People of color, women, substance abusers, and those living in poverty are less likely to have access to or to accept mental health outpatient services [5-7]. Many patients with HIV who are managing their disease are on complex regimens of medications (HAART) and diet to treat their illness. Adding another pill with significant side effects is often viewed by both patient and primary treating physician as an unacceptable burden, either in terms of number of pills per day, or in terms of anticipated side-effect profiles, or risk/benefit analysis. Primary care physicians are often unprepared to recognize depression, which can present as fatigue, weakness, insomnia or loss of appetite, and may seek medical explanations for depressive symptoms. HIV-related dementia, which presents with apathy and amotivation, can also be mistaken for depression. Physicians may be unfamiliar with mental health interventions and place depression as a lower priority after management of the primary HIV infection [8]. The stigma of HIV remains large and the addition of the potential stigma of a mental illness (i.e. depression) further contributes to the patient’s reluctance to pursue or engage treatments for depression [9]. Many patients fear that substance abuse, homosexuality, or HIV itself may be grounds for discrimination from a mental health provider [10-11].

Revision 2: There should be a section headed “Study limitations. There is no control group. There may be the halo effect of just seeing a clinician and getting attention and the “n” is very small…

Response: A paragraph was added to the Discussion section to address study limitations . . .

The results of the current study must be interpreted in the context of the study’s limitations. Limitations of this study include the lack of a placebo group, the lack of a double-blind design and small sample size. Without a placebo control group, we cannot assess the effect of meeting with a study psychiatrist, which may have contributed to improved depressive symptom ratings. Nonetheless, the study results provide useful and clinically relevant information for treating depression in HIV-positive individuals. Future studies employing a double-blind, placebo-control design are warranted.

Revision 3: The author states that of the participants the majority were people of color-what % or # were people of color to be consistent.

Response: The following sentence was added to the Participants section . . .

Of the 15 patients that completed the study, eleven (11) were male, four (4) were female and the majority were people of color (53% Black, 27% Hispanic, 20% Caucasian).