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Original article

SAMe and sexual functioning

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ABSTRACT

Background: Sexual dysfunction is a known side effect of antidepressant treatment (ADT), affecting up to 58–73% of those who receive ADT, potentially affecting antidepressant adherence. Consequently, it is vital to develop novel treatments that target antidepressant-induced sexual dysfunction.
Methods: We examined whether adjunctive S-adenosyl-L-methionine (SAMe) is associated with greater improvement in sexual functioning than adjunctive placebo by measuring changes in sexual functioning using the Massachusetts General Hospital–Sexual Functioning Questionnaire (MGH-SFQ) during a 6-week, single-center, randomized, double-blind trial of SAMe augmentation for SSRI/SNRI- nonresponders.
Results: Controlling for the degree of arousal dysfunction at baseline as well as the degree of change in HDRS-17 scale scores during the course of the study, men treated with adjunctive SAMe demonstrated significantly lower arousal dysfunction at endpoint than those treated with adjunctive placebo. In addition, controlling for the degree of erectile dysfunction at baseline as well as the degree of change in HDRS-17 scale scores, men treated with adjunctive SAMe demonstrated significantly lower erectile dysfunction at endpoint than those treated with adjunctive placebo.
Conclusions: In the present study, we have observed that adjunctive SAMe can have positive benefit on male arousal and erectile dysfunction, independent of improvement in depressive symptoms. These findings are preliminary, and warrant replication.
Clinical trials.gov identifier: NCT00093847; titled 'Optimizing the Effectiveness of Selective Serotonin Reuptake Inhibitors (SSRIs) in Treatment-Resistant Depression', accessible at: http://clinicaltrials.gov/ct2/show/NCT00093847.

1. Introduction

Sexual dysfunction can be associated with Major Depressive Disorder (MDD) but is also a known side-effect of antidepressant treatment (ADT), affecting up to 58–73% of those who receive ADT [10]. Antidepressant-induced sexual dysfunction may be so distressing to some patients that they may lower the dose of their antidepressant, or discontinue it altogether, thereby increasing their risk for nonresponse or relapse of depression [5,13]. In a recent survey of more than three thousand members of a patient advocacy group, antidepressant-induced sexual dysfunction was cited as one of the most common side effects resulting in treatment discontinuation [18]. Antidepressant-induced sexual dysfunction therefore remains a major obstacle to adherence to effective long-term treatment of depression.

Its potential adverse impact on antidepressant adherence and, consequently, long-term treatment outcome, calls for the development of novel treatments that target antidepressant-induced sexual dysfunction.

S-adenosyl-L-methionine (SAMe), a naturally occurring molecule available commercially in Europe since the late 1970s as a treatment for depression and other conditions, was released in the U.S. in a stable, enteric-coated oral formulation as an over-the-counter dietary supplement under the Dietary Health and Supplement Act (DHSEA) in 1999 [12]. SAMe also appears to be uniformly distributed in the brain where it serves as the major donor of methyl groups required in the synthesis of neuronal messengers and membranes [3]. The antidepressant efficacy of SAMe has been studied in over 45 randomized, controlled trials with depressed adults in Europe and the United States [8]. Meta-analyses of these trials consistently support a potential therapeutic role of parenteral and oral SAMe in the treatment of depression [14]. In an open-label study conducted by our group [1], we noted a small but statistically significant improvement in overall sexual satisfaction according to the Massachusetts General Hospital Sexual Functioning Questionnaire (SFQ) among antidepressant non-responders following the administration of adjunctive SAMe. In the present study, we therefore examined whether adjunctive SAMe is associated with greater improvement in sexual functioning than adjunctive placebo among antidepressant-resistant patients with MDD.

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In order to test this hypothesis, we utilized data from a recent randomized, double blind, placebo-controlled trial of adjunctive SAMe for SSRI/SNRI- nonresponders with MDD [15].

2. Methods

2.1. Study overview and eligibility criteria

The present analysis is a secondary analysis of a clinical trial involving the use of adjunctive SAMe for MDD. The results of the primary analysis, which indicate greater response and remission rates for adjunctive SAMe in MDD, are reported elsewhere [15].

Briefly, the original study was a single-center, 6-week, randomized, double blind trial of SAMe augmentation of SSRIs for SSRI-non-responders with MDD (clinicaltrials.gov identifier NCT00093847). Institutional review board (IRB)-approved written informed consent was obtained from all study patients before any study procedures were conducted. Eligibility was assessed, primarily, during the screen visit, and, secondarily, during the baseline visit, which occurred 7 days after the screen visit, patient inclusion and exclusion criteria were as follows.

2.1.1. Inclusion criteria

- Ages 18–80.
- Patients meeting criteria during the screen and baseline visit for MDD, current, according to the 4th edition of the diagnostic and statistical manual for mental disorders [2], as assessed by the Structured Clinical Interview for DSM-IV [4].
- 17-item, Hamilton depression rating scale (HDRS) [7], score of at least 16 at both screen and baseline visits.
- Treatment with an SSRI at adequate doses. This was defined as 20 mg/day or more of fluoxetine, citalopram, or paroxetine, 10 mg/day or more of escitalopram, 50 mg/day or more of sertraline, 60 mg/day or more of duloxetine, and 150 mg/day or more of venlafaxine.
- Treatment with SSRIs/SNRIs for an adequate duration, defined as treatment at an adequate dose for at least 6 weeks.
- At the baseline visit, patients must have been on a stable dose of SSRI/SNRI for the past 4 weeks.

2.1.2. Exclusion criteria

- Breastfeeding women, pregnant women or women of childbearing potential who are not using a medically accepted means of contraception.
- Patients who demonstrate a greater than 15% decrease in depressive symptoms as reflected by the HDRS-17 total score between screen and baseline.
- Serious suicide or homicide risk, or unstable medical illness as assessed by evaluating clinician.
- Alcohol or drug use disorders, active, within the last six months.
- History of mania, hypomania (including antidepressant-induced), psychotic symptoms, or seizure disorder.
- Clinical evidence of untreated hypothyroidism.
- Patients who have failed to experience sufficient symptom improvement following more than four antidepressant trials during the current major depressive episode.
- Prior course of SAMe, or intolerance to SAMe at any dose.

2.2. Study procedures

Patients found eligible during the baseline visit were enrolled in the study, and randomized to one of two treatment groups in a 1:1 fashion. One group of patients received two dummy pills daily, each identical to a 400 mg SAMe pill in appearance (administered as one pill BID). The second group received two 400 mg SAMe pills daily (administered as one pill BID).

Postbaseline study visits occurred weekly, for a total of six postbaseline visits. All patients had their number of pills doubled upon completion of 2 weeks of treatment (2 pills BID). SSRI/SNRI doses remained constant during the 6-week study. Subjects unable to tolerate the study medications as per protocol were withdrawn from the study. All patients were instructed to return any excess medication at each visit. A pill count was done to corroborate the study drug record. Protocol violation was defined as less than 80% compliance by pill count.

The HDRS and clinical global impression severity and improvement scale [6] were administered during all postscreen visits. In addition, in order to measure sexual functioning, the Massachusetts General Hospital Sexual Functioning Questionnaire (SFQ) was administered during the baseline (randomization) visit as well as the final visit (week 6 or earlier for patients who prematurely discontinue therapy). The SFQ consists of five questions pertaining to a subject's sexual functioning. Each question is graded on a 6-point scale, ranging from greater than normal (a score of 1 indicating superior functioning), to normal (a score of 2), to totally absent (a score of 6 indicating impairment in that domain). The five domains tested include: (1) interest in sex, (2) ability to become aroused, (3) ability to achieve orgasm, (4) ability to achieve and maintain an erection (men only), (5) overall sexual satisfaction. The SFQ has been validated in women [16].

2.3. Statistical analysis

In the analysis, we used the intent-to-treat approach (ITT), including all patients randomized to treatment. The primary outcome measure for the present study was defined as the difference in endpoint severity for each of the five (four for women, excluding the erectile function question) SFQ scores at study endpoint between the two treatment groups (adjunctive SAMe versus adjunctive placebo pill). This was accomplished with the use of five separate analyses of covariance (ANCOVA), with endpoint scores as the dependent variable and baseline SFQ scores, change in HDRS-17 scores as well as treatment assignment (SAMe vs placebo pill) as independent variables. These ANOVA's were then repeated in men only and in women only. All tests were conducted as two-tailed, and alpha was set at 0.05 for all tests.

3. Findings

Seventy-three patients (44 or 60.2% women) were randomized to treatment (34 to adjunctive placebo and 39 to adjunctive SAMe). Of 73 patients randomized, 55 (75.3%) completed the 6-week trial; among these patients, 24 (70.5%) received adjunctive placebo and 31 (79.4%) received adjunctive SAMe ($p = 0.42$). Baseline SFQ scores were available for 64 (37 women) of 72 (88.8%) patients randomized. Endpoint SFQ scores were available for 48 (87.2%) of 55 patients who completed the study. Seven patients who completed the study did not fill out the SFQ at endpoint. Endpoint SFQ scores were also available for 13 of 18 (72.2%) patients who did not complete the study. The SFQ could not be obtained in the remaining five non-completers due to loss to follow-up. Finally, three patients who completed the SFQ at endpoint did not complete the SFQ at baseline. Therefore, baseline and endpoint SFQ scores were obtained from 58 patients (59% women) enrolled in the trial.

Baseline clinical and demographic data, including mean SFQ scores, for these 58 patients are depicted in Table 1. Endpoint SFQ item mean scores for each treatment group along with ANCOVA results are depicted in Table 2. Controlling for the degree of arousal

Table 1
Baseline demographic and clinical characteristics.

	Adjunct Placebo	Adjunct SAMe	*P*-value	
N	27	31		
(Women)	17	17	0.59	[a]
Age	48.0 ± 9.7	51.0 ± 14.2	0.35	[b]
# Lifetime MDD episodes	2.3 ± 2.4	2.5 ± 1.8	0.80	[b]
# Failed trials	0.8 ± 0.9	1.0 ± 1.2	0.55	[b]
HDRS-17 baseline	20.0 ± 3.1	19.2 ± 3.2	0.40	[b]
CGI-S baseline	4.2 ± 0.5	4.2 ± 0.5	0.96	[b]
SFQ item scores				
Interest in sex	4.7 ± 1.4	4.5 ± 1.5	0.75	[b]
Ability to become aroused	4.6 ± 1.4	4.5 ± 1.5	0.70	[b]
Ability to achieve orgasm	4.5 ± 1.6	4.2 ± 1.5	0.58	[b]
Ability to achieve/maintain erection	4.1 ± 1.5	3.7 ± 1.4	0.56	[b]
Overall sexual satisfaction	4.9 ± 1.1	4.8 ± 1.4	0.77	[b]

[a] Fisher's Exact Test.
[b] *t*-test.

dysfunction at baseline as well as the degree of change in HDRS-17 scale scores during the course of the study, men treated with adjunctive SAMe demonstrated significantly lower arousal dysfunction at endpoint than those treated with adjunctive placebo. In addition, controlling for the degree of erectile dysfunction at baseline as well as the degree of change in HDRS-17 scale scores during the course of the study, men treated with adjunctive SAMe demonstrated significantly lower erectile dysfunction at endpoint than those treated with adjunctive placebo. None of the other items reached statistical significance.

4. Discussion

Our findings suggest that adjunctive SAMe in SSRI/SNRI nonresponders improves both arousal dysfunction and erectile dysfunction in men compared to those receiving adjunctive placebo, independent of change in the degree of depressive symptoms. Because many SSRI/SNRI nonresponders may experience sexual dysfunction as a result of their untreated depressive illness or as a side effect of therapy, the availability of an augmentation strategy that improves sexual dysfunction has the potential to greatly enhance compliance and improve quality of life for these patients. We emphasize, however, that these promising results suggesting the potential utility of adjunctive SAMe in relieving arousal and erectile dysfunction, are merely suggestive and warrant replication.

It is interesting to note that the above benefits were observed only in men with arousal and erectile dysfunction. This is similar to findings from the phosphodiesterase inhibitor studies, in which the benefits on sexual functioning were seen in men, specifically with regard to improved arousal and erection rather than libido [11]. The phosphodiesterase inhibitors increase nitric oxide, leading to a relaxation of smooth muscle of the vessel walls in the penis, which in turn causes vasodilation by increased blood flow to the penis, resulting in erection. While the mechanism of SAMe on male arousal and erection is not known, we can speculate as to its possible mechanism of action on the male sexual response cycle. S-adenosylmethionine has been associated with high flow mediated vasodilation and may have beneficial effects on vessel walls in an elderly population [17]. Moreover SAMe is a regulator of cystathionine beta-synthase, the enzyme that produces hydrogen sulfide in the brain and relaxes smooth muscle in synergy with nitric oxide [9]. These observations suggest that SAMe may result in vasodilation increasing the likelihood of penile erection in a fashion analogous to nitric oxide. Another possible mechanism for the association between SAMe and improvement in sexual functioning is that SAMe through its ability to be neuroprotective to dopaminergic neurons may enhance the role dopamine plays in promoting sexual functioning [19].

There are several limitations to the present work. First, this was a posthoc analysis examining the effects of adjunctive SAMe on sexual functioning in patients with MDD who were considered nonresponders to other antidepressants. A prospectively designed study, employing several different scales measuring sexual dysfunction would be better suited to definitively answer whether adjunctive SAMe is indeed effective when used in this capacity. Second, the present study was underpowered and consequently may have not been able to detect improvement in other aspects of the sexual response cycle in men, or in women.

Another limitation of our study was that we made no attempts to distinguish whether sexual dysfunction at baseline was secondary to antidepressant (SSRI/SNRI) therapy or due to depression itself. However, given that our findings were independent of changes in depression severity suggests that any improvement in sexual functioning in men was not related to an overall improvement in depressive symptomatology. Finally, it

Table 2
SFQ endpoints.

Overall sample	Adjunct placebo (n = 27) (mean ± sd)	Adjunct SAMe (n = 31) (mean ± sd)	*P*-value*
Interest in sex	4.1 ± 1.5	4.1 ± 1.6	0.93
Ability to become aroused	4.3 ± 1.5	3.8 ± 1.6	0.13
Ability to achieve orgasm	4.4 ± 1.5	4.1 ± 1.5	0.27
Ability to achieve/maintain erection	4.2 ± 1.2	3.1 ± 1.3	0.01
Overall sexual satisfaction	4.8 ± 1.2	4.4 ± 1.5	0.19
Men only	**Adjunct placebo (n = 10) (mean ± sd)**	**Adjunct SAMe (n = 14) (mean ± sd)**	***P*-value***
Interest in sex	4.0 ± 1.3	3.4 ± 1.4	0.22
Ability to become aroused	4.4 ± 1.4	3.0 ± 1.2	0.0012
Ability to achieve orgasm	4.3 ± 1.4	3.6 ± 1.4	0.17
Ability to achieve/maintain erection	4.3 ± 1.3	3.0 ± 1.3	0.01
Overall sexual satisfaction	4.9 ± 1.1	3.9 ± 1.4	0.07
Women only	**Adjunct placebo (n = 17) (mean ± sd)**	**Adjunct SAMe (n = 17) (mean ± sd)**	***P*-value***
Interest in sex	4.2 ± 1.6	4.7 ± 1.6	0.17
Ability to become aroused	4.3 ± 1.6	4.6 ± 1.5	0.36
Ability to achieve orgasm	4.5 ± 1.6	4.5 ± 1.5	0.73
Overall sexual satisfaction	4.7 ± 1.3	5.0 ± 1.4	0.61

ANOVA, controlling for baseline scores as well as change in HDRS-17 during treatment.
**P*-value.

is not possible to directly generalize the present findings to patient populations who were excluded from this trial (i.e. children, adolescents, patients with active alcohol or drug use disorders, patients with unstable medical disorders, at imminent risk of suicide, or patients who are on non-SSRI antidepressants).

In conclusion, in the present study we have observed that adjunctive SAMe can have positive benefit on male arousal and erectile dysfunction, independent of improvement in depressive symptoms. These findings are preliminary, and warrant replication.

Conflict of interest statement

C.M.D. has received research support from Abbott Laboratories, Alkermes, Aspect Medical Systems, Astra-Zeneca, Bristol-Myers Squibb Company, Cephalon, Eli Lilly & Company, Forest Pharmaceuticals Inc., GlaxoSmithkline, J & J Pharmaceuticals, Lichtwer Pharma GmbH, Lorex Pharmaceuticals, Novartis, Organon Inc., PamLab, LLC, Pfizer Inc, Pharmavite, Roche, Sanofi-Aventis, Solvay Pharmaceuticals, Inc., Synthelabo, Wyeth-Ayerst Laboratories; has served as an advisor/consultant for Takeda; and has been a speaker for Wyeth-Ayerst Laboratories.

D.M. has received research support (usually as donated medications for clinical trials) from Laxdale (Amarin), Nordic Naturals and Ganeden; has served as an advisor/consultant for Bristol-Meyers Squibb Company; has received speaking and writing honoraria from Pamlab; has received royalties from Back Bay Scientific for PMS Escape (patent application pending), royalties from Lippincott Williams & Wilkins, for textbook "Natural Medications for Psychiatric Disorders: Considering the Alternatives" (David Mischoulon and Jerrold F Rosenbaum, Eds.); has received honoraria from Reed Medical Education (a company working as a logistics collaborator for the MGH Psychiatry Academy). The education programs conducted by the MGH Psychiatry Academy were supported through Independent Medical Education (IME) grants from pharmaceutical companies cosupporting programs along with participant tuition. Commercial entities currently supporting the MGH Psychiatry Academy are listed on the Academy's website www.mghcme.org. No payment from any individual entity or company has exceeded $10,000/year.

I.S. reports no competing interests.

J.E.A. has received research support from Abbott Laboratories, Alkermes, Lichtwer Pharma GmbH, Lorex Pharmaceuticals; Aspect Medical Systems, Astra-Zeneca, Bristol-Myers Squibb Company, Cephalon, Cyberonics, Eli Lilly & Company, Forest Pharmaceuticals Inc., GlaxoSmithkline, J & J Pharmaceuticals, Novartis, Organon Inc., PamLab, LLC, Pfizer Inc, Pharmavite, Roche, Sanofi/Synthelabo, Solvay Pharmaceuticals, Inc., and Wyeth-Ayerst Laboratories; has participated on advisory boards for or consulted to Eli Lilly & Company, Pamlab LLC, and Pharmavite LLC; and has received speakers' honoraria from Eli Lilly & Company, Janssen, Organon, Reed Medical Education. He has no relevant equity holdings, patents, or royalties.

G.I.P. has served as a consultant for AstraZeneca PLC, Bristol-Myers Squibb Company, Eli Lilly Co., GlaxoSmithKline, Evotec AG, Inflabloc Pharmaceuticals, Jazz Pharmaceuticals, Otsuka Pharmaceuticals, PAMLAB LLC, Pfizer Inc., Pierre Fabre Laboratories, Shire Pharmaceuticals, and Wyeth, Inc.; has received honoraria from Astra Zeneca PLC, Bristol-Myers Squibb Company, Eli Lilly Co., Evotec AG, GlaxoSmithKline, Inflabloc Pharmaceuticals, Jazz Pharmaceuticals, Lundbeck, Otsuka Pharmaceuticals, PAMLAB LLC, Pfizer, Pierre Fabre Laboratories, Shire Pharmaceuticals, Titan Pharmaceuticals, and Wyeth Inc.; has received research support from Bristol-Myers Squibb Company, Forest Pharmaceuticals, the National Institute of Mental Health, PAMLAB LLC, Pfizer Inc., and Ridge Diagnostics (formerly known as Precision Human Biolaboratories); and has served (not currently) on the speaker's bureau for BristolMyersSquibb Co and Pfizer, Inc.

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