

Preliminary results of a randomized controlled trial carried out with a fixed combination of S-adenosyl-L-methionine and betaine versus amitriptyline in patients with mild depression

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Background: S-adenosyl-L-methionine (SAME), a safe, endogenous, pleiotropic methyl donor well known for its antidepressant role, has been assumed to have a possible role in increasing plasma levels of compounds known to be able to raise cardiovascular risk. Although the issue is still being debated, betaine (trimethylglycine), a specific methyl donor involved in the homocysteine circuit, may be able to reduce such a risk and/or, by determining a sparing effect on endogenous SAME, may be able to improve the clinical efficiency of SAME itself. Indeed, preliminary results have shown clinical improvement determined by an add-on therapy with betaine administered along with SAME, versus SAME alone, to patients affected by mild/moderate depression.

Aim: To evaluate the safety and antidepressant role played by the association of SAME plus betaine versus amitriptyline administered in untreated individuals with a recent diagnosis of mild depression.

Methods: This small, open-label, randomized, observational study enrolled 64 individuals with a diagnosis of mild depression according to the Zung Self-Rating Depression Scale. After randomization, they were treated with either Laroxyl[®] (amitriptyline, 75 mg/day) or DDM Metile[®] (enteric-coated SAME, 500 mg/day, plus betaine, 250 mg/day) for 12 months. Assessment of clinical scores and tolerability was performed at T=0 and after 3, 6, and 12 months.

Results: After 3 months, both treatments showed a small and not statistically significant improvement. After 6 and 12 months, both treated groups demonstrated a more noticeable improved response, although the group treated with SAME plus betaine showed better results in terms of score, number of individuals in remission, and side effects. Compliance was overlapping in both treatments.

Conclusion: The association of SAME plus betaine seems to be a safe and effective tool to counteract mild depression and also when used as monotherapy in subjects with a recent diagnosis.

Keywords: amitriptyline, betaine, SAME, moderate depression, methyl donor

Introduction

Despite the increasingly large number of antidepressants available to treat depressive disorders, patients continue to experience relatively modest response and remission rates.^{1,2} In addition, patients treated with antidepressants may experience adverse side effects that not only hinder compliance and adherence to treatment but also, in some cases, may contribute to increasing disability, patient suffering, and morbidity.³ This evidence has recently prompted clinicians to become interested in

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nonpharmaceutical-grade supplements to counteract depression symptoms.⁴ From a strategic point of view, these supplements could be used mainly as a complementary therapy in order to enhance the efficacy of standard antidepressants without further worsening their tolerability or as initial monotherapy in those patients with moderate symptoms of disease. One of the supplements that has been more exhaustively and deeply studied is S-adenosyl-L-methionine (SAME), a naturally occurring methyl group donor present in the human body.⁵ Many controlled trials, some of them also double-blinded, have found SAME to be more effective than placebo and comparable with tricyclic antidepressants to treat depressive states.⁶ This seems to be particularly evident when SAME is administered either intravenously or intramuscularly. Although some trials also demonstrated its efficacy following oral administration, this seems to be true only when SAME is administered in high doses.⁷

One could argue that some doubts still remain about its safety, at least in terms of the possible production of toxic methylated compounds like homocysteine, S-adenosyl-homocysteine, methanol, formaldehyde, and formic acid.⁸ In consideration of this, a number of SAME-based supplements have recently been formulated with the addition of such active ingredients as folate and/or vitamin B6 and/or vitamin B12 – all of which are known to be able to enter the homocysteine circuit – to possibly avoid the risk of creating dangerous toxic methylated compounds and to be strictly linked to support SAME synthesis.⁹ Betaine, like folate, vitamin B6, and vitamin B12, is an active ingredient involved as a cofactor in the homocysteine circuit, and is known to be able to reduce plasma homocysteine levels when administered orally.¹⁰ Betaine is also known to generate a sparing effect for SAME and increase its plasma levels; for example, when used in Alzheimer's disease.¹¹ On this basis, we have recently tested, as add-on therapy, the association of SAME and betaine in improving the antidepressant effect of enteric-coated SAME in patients with mild/moderate depression. Results of this clinical trial, currently under new investigation on a larger number of patients, have shown that both treatments act similarly in improving symptoms such as anxiety, psychomotor agitation, feelings of helplessness and worthlessness, physical efficiency, and somatization. Since the association of SAME plus betaine determined better statistically significant results following 90-day therapy,¹² we decided to evaluate its efficacy and tolerability as monotherapy by comparing it with amitriptyline, chosen as a control substance due to its wide use in depression, in a 12-month pilot, open-label, randomized,

observational trial in individuals with a recent diagnosis of mild depression.

Materials and methods

Study design

This 12-month, open-label, randomized, observational, controlled trial was conducted in the setting of routine practice, in accordance with the principles stated in the Declaration of Helsinki and consistent with Good Clinical Practice, as defined by the International Conference on Harmonization and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).¹³ The protocol, individuals' consent, and privacy forms were approved by the local review board. All the patients provided their written informed consent to participate in this study after a full explanation of the study had been given. The study was conducted in a single outpatients clinic in Italy (Bari) between February 2012 and September 2013 on 64 patients enrolled on the basis of a diagnosis of moderate depression as evaluated according to the Zung Self-Rating Depression Scale.¹⁴ Sixty patients completed the study and were evaluated from a statistical point of view.

Inclusion criteria

Inclusion criteria were age between 18 and 75 years; participants' signing of the informed consent; Zung Self-Rating Depression Scale score between 30 and 60; and use, if needed, of antihypertensive drugs, cardiovascular aspirin, ticlopidine, warfarin, anti-inflammatory drugs, analgesics, antipyretics, antibiotics, and antifungal drugs.

Exclusion criteria

Exclusion criteria were age below 18 or over 75 years; failure to sign the informed consent; being treated with any antidepressant drugs in the last 12 months; Zung Self-rating Depression Scale score over 60; suicidal ideation; neurological disease; epilepsy; pregnancy; breastfeeding; and diagnosis of liver cirrhosis, severe heart failure, hepatic, and/or renal impairment.

Study protocol

The study scheme is presented in Figure 1. After enrolling and randomizing, all the individuals started taking either amitriptyline or SAME plus betaine for the whole length of the study (12 months). Zung Self-Rating Depression Scale measurements were taken at T=0 (enrollment) and after 3, 6, and 12 months. For a further evaluation of treatment

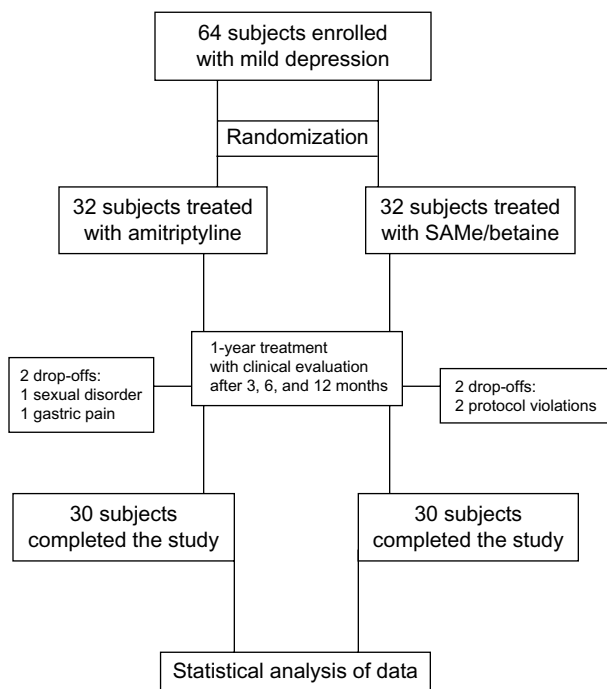


Figure 1 Scheme of the study.

Abbreviation: SAME, S-adenosyl-L-methionine.

tolerability, patients were also submitted to a physical examination every month. Patients also had the possibility of contact with clinicians at any time by phone.

Other assessment

Before starting the study, all patients underwent an initial screening assessment that included medical history, physical examination, vital sign measurement (blood pressure and heart rate), a 12-lead electrocardiogram (ECG), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) blood analysis, and evaluation of body weight. At the end of the study, or at drop-off, all the enrolled subjects again underwent blood pressure and heart rate examinations, ECG, AST and ALT blood analysis, and measurement of body weight.

Tested products

The patients were treated with 75 mg/day (25 mg three times a day at 8 am, 2 pm, and 10 pm) of amitriptyline formulated as tablets (Laroxyl; Teofarma, Valle Salimbene, Italy) or with an enteric-coated supplement (DDM Metile®; Omeopiacenza, Piacenza, Italy) containing 250 mg SAME per tablet (Gnosis, Desio, Italy) plus 125 mg of betaine (Procemsa, Nichelino, Italy). DDM Metile® was administered twice a day at 8 am and 8 pm on an empty stomach. Laroxyl is a nonreimbursable drug (C-type) with the following marketing authorization

number: 019906015. DDM Metile®; in agreement with Italian law, was registered as a food supplement with the Ministry of Health in 2010 (registration number: 52171). Both active ingredients (SAME and betaine) of DDM Metile® are accepted ingredients, as far as quality and quantity are concerned, for nutraceutical formulas; all excipients used to formulate DDM Metile® are also food-grade ingredients.

End points

The primary efficacy end points of the study were assessed through the scores resulting from the Zung Depression Self-Rating Scale. The secondary end points included the occurrence of side effects, tolerability, and compliance. Tolerability and compliance were scored as very poor, poor, fairly good, good, or excellent. Primary and secondary end points were evaluated at 3, 6, and 12 months after enrolling. The individuals could contact the physicians in charge of the study at any time if needed. To check individuals' adherence to therapy, each patient had to report the number of tablets used per day, giving back the empty boxes of the drugs as soon as tablets were finished.

Statistical analysis

The Wilcoxon signed-rank test was used to analyze any differences from baseline scores in the same treatment group. The Mann–Whitney *U* test and Fisher exact test were used to analyze any score differences between the two groups. Values were considered significant at $P < 0.05$.

Results

A total of 64 individuals with a diagnosis of mild depression according to the Zung Depression Self-Rating Scale were enrolled in the trial. Of these, 60 completed the study. A total of 32 were randomized to receive amitriptyline and 32 were randomized to receive SAME plus betaine. The characteristics of the randomized groups are shown in Table 1, where no significant differences between the two groups are observable. The results of the treatments are shown in Tables 2 and 3. On the basis of the scores calculated at

Table 1 Features of participants on enrollment

	Amitriptyline (N=30)	SAME/betaine (N=30)
Sex (males/females)	16/14	15/15
Female age (years)	46.2±14.4	47.7±14.7
Male age (years)	53.9±15.9	46.0±17.6
Months from diagnosis	2.2±0.3	1.9±0.2

Note: All values are expressed as median ± standard deviation.

Abbreviation: SAME, S-adenosyl-L-methionine.

Table 2 Score according to the Zung Depression Self-Rating Scale

Time	Amitriptyline (A)	P (vs T=0)	SAMe/betaine (B)	P (vs T=0)	P (B vs A)
T=0	50.6±3.8		50.7±3.8		ns
T=3	47.9±4.0 (-4.4%)	ns	47.3±3.7 (-6.7%)	ns	ns
T=6	39.4±4.9 (-22.2%)	<0.01	33.2±5.8 (-34.6%)	<0.01	<0.05
T=12	41.6±6.1 (-17.8%)	<0.01	31.7±7.8 (-37.5%)	<0.01	<0.01

Notes: All values are expressed as median ± standard deviation. Time expressed as months. In brackets: % reduction versus T=0.

Abbreviations: SAMe, S-adenosyl-L-methionine; ns, not significant.

T=0 and at T=3 months, the two groups do not show any statistically significant difference. At T=6 months and at T=12 months, both treatments demonstrate effectiveness. However, the statistical analysis performed to establish a direct comparison between the two treatments demonstrates better performance of the SAMe/betaine therapy in comparison with the results obtained with amitriptyline (Table 2). While the percentage of the score reduction was similar in both groups at T=3 months (4.4% and 6.7%), at T=6 months, and at T=12 months, the score reduction was about 22% and 17% for the amitriptyline group and about 34% and 37% for the SAMe/betaine group. In addition, treatment with SAMe plus betaine seems to determine more important results than amitriptyline in terms of the number of people considered depression free. Respectively, at T=6 months and T=12 months, only four and one out of 30 patients treated with amitriptyline exhibited a global score below 30, while the depression-free individuals of the SAMe/betaine group were, at the same time, 15 and 19 out of 30 (Table 3).

As for tolerability (Table 4), both treatments seem to be well tolerated, even if during the study two (males) individuals of the amitriptyline group did not complete the study because of side effects (gastric pain and sexual disorders). Also in the SAMe/betaine group, two individuals (a male and a female) did not complete the study, but in this case the reason for their early withdrawal was protocol violation. In terms of compliance, the two treatments resulted to be overlapping (Table 5). At the end of the study, or at time of drop-off, no significant difference versus T=0 was observed in terms of blood pressure heart rate examinations, ECG, AST, ALT, and body weight (data not shown).

Discussion

Amitriptyline is a tricyclic antidepressant introduced in the 1960s for the treatment of major depressive disorders. To date, this is the only US-approved indication, although amitriptyline has already been used for a number of other symptoms, including migraine prophylaxis, neuropathic pain disorders and fibromyalgia, nocturnal enuresis, and irritable bowel syndrome. Anti-inflammatory and antimicrobial properties of the drug have been reported as well.¹⁵ Amitriptyline cannot be considered excellent in terms of safety, and in a recent paper it was found to be the least safe among the treatments included in a study that assessed six antidepressants.¹⁶ Nevertheless, amitriptyline is largely used to counteract depressive disorders.

SAMe is an endogenous molecule endowed with methyl donor properties and is involved in the pathway for synthesis of hormones, neurotransmitters, nucleic acids, proteins, and phospholipids. The antidepressant role played by SAMe is mainly due to its role as intermediate in the synthesis of norepinephrine, dopamine, and serotonin. This role suggests SAMe to be endowed with mood modulator properties too. Moreover, low SAMe levels have been found in the cerebrospinal fluid of depressed individuals, and higher plasma SAMe levels have been associated with improvement in depressive symptoms. On the other hand, because of the much debated topic of the possibility that it increases the plasma levels of methylated compounds such as homocysteine, SAMe is also believed to be able to increase cardiovascular risk. Co-administration of betaine – a cofactor involved in reducing plasma homocysteine level – should reduce such a risk and should be able to determine a sparing effect on

Table 3 Number of subjects with score >30 according to the Zung Depression Self-Rating Scale

Time	Amitriptyline (A)	P (vs T=0)	SAMe/betaine (B)	P (vs T=0)	P (B vs A)
T=0	30		30		ns
T=3	30	ns	30	ns	ns
T=6	26	ns	15	<0.01	<0.01
T=12	29	ns	11	<0.01	<0.01

Notes: All values are expressed as median ± standard deviation. Time expressed as months.

Abbreviations: SAMe, S-adenosyl-L-methionine; ns, not significant.

Table 4 Tolerability assessment (N=32/group)

Tolerability	N (Amitriptyline)	N (SAME/betaine)
Very poor	2	0
Poor	8	0
Fair	12	1
Good	10	4
Excellent	0	27

Abbreviations: N, number of individuals per group; SAME, S-adenosyl-L-methionine.

endogenous SAME. Due to these assumptions, administration of SAME plus betaine could be considered a possible and valid optional treatment in place of SAME alone.

As described in “Introduction”, in a recent trial, our group has indeed observed a better clinical performance of the association of SAME plus betaine versus SAME alone, both as add-on therapy, in patients with mild/moderate depression.¹² In the light of this finding, we decided to evaluate the antidepressant role played by the administration of SAME plus betaine as monotherapy in individuals with a recent diagnosis of mild depression, comparing its effectiveness and tolerability with amitriptyline. The results seem to demonstrate that SAME/betaine treatment is a valid therapeutic option that is more effective and safer than the control treatment with amitriptyline. The effectiveness seems to become statistically appreciable at T=6 months, lasting until the end of the trial (T=12 months).

In our experience, and according to literature, the treatment of depression with SAME in responsive individuals normally occurs quickly, even in a few weeks of treatment.¹⁷ Unfortunately, we have no tools to understand the delay observed in our trial. It may be due to the type of enrolled individuals (with a recent diagnosis of depression and never treated with antidepressant), to the SAME dose used (for patients with Zung Self-Rating Depression Scale score between 45 and 60, the administered dose could be too low), or to the presence of betaine. Enrolled patients were also taking other drugs (see “Materials and methods”). Therefore, in the absence of multivariate analysis to determine whether taking other drugs might affect the results, the delay of activity seems to be difficult to interpret. In our trial, co-administration of SAME plus betaine did not determine

Table 5 Compliance assessment (N=30/group)

Compliance	N (Amitriptyline)	N (SAME/betaine)
Very poor	0	2
Poor	24	10
Fair	4	11
Good	2	7
Excellent	0	2

Abbreviations: N, number of individuals per group; SAME, S-adenosyl-L-methionine.

important side effects, and in our opinion the association can be considered safe.

Limits of the trial are 1), it not being double-blind and 2), the low number of people involved. To overcome these two important possible biases, our group is trying to organize a larger double-blind, placebo-controlled study to confirm the antidepressant role of the association of SAME plus betaine versus antidepressant different from SAME. The study, by plasma analysis, will also provide us with an idea of the possible toxic methylated compounds that could be generated by the long-term administration of an SAME-based formula and whether the presence of betaine can effectively reduce them.

Conclusion

On the basis of our study results, it may be assumed that the administration of SAME plus betaine is a valid and safe monotherapeutic option to treat individuals with a recent diagnosis of mild depression.

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Disclosure

FDP is the main formulator of DDM Metile®. RS reports no conflicts of interest in this work.

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