# Efficacy and tolerability of oral and intramuscular *S*-adenosyl-L-methionine 1,4-butanedisulfonate (SAMe) in the treatment of major depression: comparison with imipramine in 2 multicenter studies[1–4]

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## ABSTRACT

**Background:** *S*-Adenosyl-L-methionine (SAMe), a natural compound, is the most important methyl donor in the central nervous system. In several clinical trials, SAMe showed antidepressant activity.

**Objective:** Two multicenter studies were conducted in patients with a diagnosis of major depressive episode [baseline score on the 21-item Hamilton Depression Rating Scale (HAM-D) ≥ 18] to confirm the efficacy and safety of SAMe in the treatment of major depression. In the first study (MC3), 1600 mg SAMe/d was given orally; whereas, in the second study (MC4), 400 mg SAMe/d was given intramuscularly. In both studies, the effects of SAMe were compared with those of 150 mg imipramine/d given orally in a double-blind design.

**Design:** In MC3, 143 patients received oral SAMe and 138 patients received imipramine for 6 wk. In MC4, 147 patients received SAMe intramuscularly and 148 patients received imipramine for 4 wk. In both studies the 2 main efficacy measures were the final HAM-D score and the percentage of responders to Clinical Global Impression at the endpoint. Secondary efficacy measures were the endpoint Montgomery-Asberg Depression Rating Scale scores and the percentage of responders, responders being those patients showing a decrease in HAM-D score of ≥ 50% from baseline.

**Results:** In both studies, the results of SAMe and imipramine treatment did not differ significantly for any efficacy measure. However, significantly fewer adverse events were observed in the patients treated with SAMe.

**Conclusions:** The antidepressive efficacy of 1600 mg SAMe/d orally and 400 mg SAMe/d intramuscularly is comparable with that of 150 mg imipramine/d orally, but SAMe is significantly better tolerated. *Am J Clin Nutr* 2002;76(suppl):1172S–6S.


**KEY WORDS** *S*-Adenosyl-L-methionine, SAMe, imipramine, major depression, efficacy, tolerability

## INTRODUCTION

*S*-Adenosyl-L-methionine (SAMe), a natural compound, is the main methyl group donor to a wide variety of acceptors (catecholamines, biogenic amines, phospholipids, proteins, and nucleic acids) in the central nervous system (1). In patients with clinical depression, cerebrospinal fluid concentrations of SAMe (2) and the activity of erythrocyte methionine adenosyltransferase (EC 2.5.1.6), the enzyme that regulates the biosynthesis of SAMe (3), are significantly lower than in healthy persons. In preclinical studies, SAMe showed pharmacologic effects consistent with antidepressant activity (4, 5). Moreover, in cyclic AMP–dependent phosphorylation systems in microtubules (cerebral cortex) and calcium- and calmodulin-dependent phosphorylation systems (frontal and prefrontal cortex and hippocampus), SAMe showed effects similar to those induced by antidepressants (eg, selective and nonselective 5-HT or sodium reuptake inhibitors). One effect observed was an increase in synapsin I [a vesicular substrate of calcium- and calmodulin-dependent protein kinase II (EC 2.7.1.123) regulating the number of vesicles available for exocytosis] in presynaptic terminals (6, 7).

From 1973 to 1995, 39 clinical studies with a total of 1359 patients were carried out to assess the antidepressant efficacy of SAMe. Of these, 14 were open label, 11 were controlled and had a placebo group, and 14 were controlled and compared the effects with those of tricyclic antidepressants. Two meta-analyses of the results of these studies were conducted and both agreed that the antidepressant efficacy of SAMe is superior to that of placebo and comparable with that of tricyclic antidepressants (8, 9).

To confirm these results, we carried out 2 studies to compare the efficacy and tolerability of SAMe with those of imipramine. In the first study (code name MC3), a comparison was performed between oral SAMe (1600 mg/d) and oral imipramine (150 mg/d). In the second study (code name MC4), intramuscular SAMe (400 mg/d) was compared with oral imipramine (150 mg/d). In both studies, the stable salt of SAMe was used.

## SUBJECTS AND METHODS

### Study population

Thirty-three hospitals and 39 university centers in Italy participated in the MC3 and MC4 studies. In both studies the experimental protocol envisaged the enrollment of outpatients aged

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18–70 y of both sexes. The current diagnosis per the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) criteria (10) was major depressive episode with a unipolar (depressive) course and no psychotic symptoms. Inclusion criteria were a score at baseline ≥ 18 on the Hamilton Depression Rating Scale (HAM-D) (11), with the score on the first item of the scale (depressed mood) being ≥ 2, and a severity score ≥ 4 on the Clinical Global Impression (CGI) rating scale (12).

Both investigations were carried out in accordance with the latest version of the Declaration of Helsinki, and the study protocols were reviewed and approved by appropriate ethical committees and institutional review boards at each site. Written, informed consent to participate in the study was obtained from all the patients. Trials were performed according to the *Good Clinical Practice Guidelines* of the US Food and Drug Administration with monitoring and auditing procedures included.

## Experimental design and treatment

After having signed the informed consent, patients admitted to the study underwent a first screening (visit 0: day −7). After 1 wk, during which no treatment was administered, the baseline assessment (visit 1: day 0) was performed. At this point, patients who still satisfied the inclusion and exclusion criteria began the double-blind treatment phase. During the study, only lorazepam (1–2.5 mg/d orally) was allowed to facilitate sleep induction if required.

### *MC3: oral SAMe compared with imipramine*

The experimental treatment in the MC3 trial was administered for 6 wk. During the active treatment period, patients underwent 3 assessments: visit 2 (day 14), visit 3 (day 28), and visit 4 (day 42: corresponding to the endpoint). Because of differences between the SAMe and imipramine tablets, we used the double-blind, double-dummy technique (ie, patients assigned to treatment with SAMe received imipramine placebo, whereas those assigned to treatment with imipramine received SAMe placebo) to ensure double-blindness. The appearance of SAMe and imipramine placebo tablets was identical to that of the corresponding active compound, ie, SAMe and imipramine. At the full dose (SAMe up to 1600 mg/d and imipramine up to 150 mg/d), the protocol for the 2 groups was as described below.

The patients assigned to treatment with SAMe received 2 SAMe tablets (400 mg) and 2 tablets of imipramine placebo at 0800, 2 SAMe tablets (400 mg) and 2 tablets of imipramine placebo at 1300, and 2 tablets of imipramine placebo at 2100.The patients assigned to treatment with imipramine received 2 imipramine tablets (25 mg) and 2 SAMe placebo tablets at 0800, 2 imipramine tablets (25 mg) and 2 SAMe placebo tablets at 1300, and 2 imipramine tablets (25 mg) at 2100.

The oral SAMe medication consisted of white, oval-shaped, enteric-coated tablets, each of which contained 759.6 mg SAMe 1,4-butanedisulfonate (equivalent to 400 mg SAMe cation). The placebo tablets were indistinguishable in appearance from the active compound and they contained cellulose and lactose. In both studies, each treatment package contained the amount of drug needed for the entire treatment period. However, because current clinical guidelines recommend reaching the full dose gradually for imipramine only and not for SAMe, the first 3 weekly packs administered to patients in the control group were prepared to allow gradual titration of imipramine. In this way, full doses of imipramine were reached after 15 d.

Current treatment guidelines for depression recommend starting imipramine, as all other tricyclics, at low doses and then titrating upward to reach the full dose in ≈15 d. This careful approach aims to minimize the anticholinergic side effects of imipramine. A patient who starts with the full dose from the first day of treatment would surely drop out of the study in < 24 h. Therefore, the therapeutic scheme adopted in this study agrees with clinical practice (13).

All empty drug packs were returned at the end of the study. In patients who complained of side effects, the drug dose could be reduced from the third week on, down to a minimal dose of 100 mg imipramine/d and 1200 mg SAMe/d. Patients who tolerated this dose poorly were excluded from the study.

### *MC4: intramuscular SAMe compared with imipramine*

The experimental treatment in the MC4 trial was administered for 4 wk. During the active treatment period, patients underwent 2 assessments: visit 2 (day 14) and visit 3 (day 28: corresponding to the endpoint). Because of differences between the SAMe vials and imipramine tablets, we used the double-blind, double-dummy technique (ie, patients assigned to treatment with SAMe intramuscularly received imipramine placebo orally, whereas those assigned to receive imipramine orally received SAMe placebo intramuscularly) to ensure double-blindness. The appearance of SAMe and imipramine placebo vials and tablets was identical to that of the corresponding active compound (vials of SAMe and imipramine tablets). In the SAMe group, daily treatment consisted of one intramuscular SAMe injection. At the full dose (400 mg SAMe /d and imipramine up to 150 mg/d), the protocol for the 2 groups was as described below.

The patients assigned to treatment with SAMe received 1 intramuscular injection of SAMe (400 mg) and 2 tablets of imipramine placebo at 0800, 2 tablets of imipramine placebo at 1300, and 2 tablets of imipramine placebo at 2100. The patients assigned to treatment with imipramine received 2 imipramine tablets (25 mg) and 1 intramuscular injection of SAMe placebo at 0800, 2 imipramine tablets (25 mg) at 1300, and 2 imipramine tablets (25 mg) at 2100. Each SAMe vial contained 759.6 mg SAMe 1,4-butanedisulfonate (equivalent to 400 mg SAMe cation). The placebo vials contained mannitol.

## Efficacy assessment

The first objective of both studies was to compare the antidepressant potencies of SAMe and imipramine. All assessments at baseline and during each time point were performed with the use of the following instruments. The 21-item version of HAM-D (11) was used to assess depressive symptoms. Scores > 18 indicate a clinically relevant depressive state, whereas scores > 26 indicate severe forms of depression. The CGI (12) was used to evaluate the severity of the illness and the degree of improvement after treatment on a scale from 1 to 7. The Montgomery-Asberg Depression Rating Scale (MADRS) (14) was used to detect the rapid mood variations occurring during antidepressant therapy. The antidepressant efficacy of the 2 drugs was quantified relative to the main and secondary efficacy measures.

The main efficacy measures were *1*) the HAM-D total score at the endpoint (MC3: visit 4; MC4: visit 3) and *2*) the percentage of treatment responders (ie, those patients who had a CGI score ≤ 2 at the end of the study). The secondary efficacy measures were *1*) the MADRS total score at the endpoint (MC3: visit 4; MC4: visit 3) and *2*) the percentage of treatment responders (ie, those patients

**TABLE 1**
Demographics of the 2 groups of patients in the MC3 and MC4 studies[1]

| | SAMe | Imipramine | Total |
|---|---|---|---|
| MC3 | | | |
| Number of patients | | | |
| Men | 40 | 42 | 82 |
| Women | 103 | 93 | 196 |
| Age (y) | 45.3 ± 11.9[2] | 44.6 ± 13.2 | 45.0 ± 12.6 |
| Height (m) | 1.65 ± 0.10 | 1.65 ± 0.08 | 1.65 ± 0.09 |
| Body weight (kg) | 66.7 ± 13.6 | 68.1 ± 12.4 | 67.4 ± 13.1 |
| MC4 | | | |
| Number of patients[3] | | | |
| Men | 44 | 64 | 108 |
| Women | 102 | 83 | 185 |
| Age (y) | 48.2 ± 12.2 | 48.8 ± 14.0 | 48.5 ± 13.1 |
| Height (m) | 1.65 ± 0.08 | 1.66 ± 0.08 | 1.65 ± 0.08 |
| Body weight (kg) | 66.8 ± 14.2 | 66.8 ± 12.8 | 66.8 ± 13.5 |

[1] SAMe, *S*-adenosyl-L-methionine.
[2] $\bar{x}$ ± SD.
[3] Differences between groups were significant, $P = 0.01$ (Pearson's chi-square test).

who had a decrease in the HAM-D score from baseline of ≥50% at the end of the study).

### Safety assessment

In both studies, the second main objective was to evaluate the tolerability and safety of SAMe relative to that of imipramine. The incidence of adverse events was assessed during the treatment period. An adverse event was indicated when any event occurring during the study changed the patient's well-being, including changes in laboratory measures. The severity of adverse events was defined as mild (no interference with daily activities), moderate (interference with normal daily activities), or severe (impairment of normal daily activities). On the basis of objective criteria, the relation between any adverse events and drug treatment was classified as probable, possible, or not related. Laboratory analyses, an electrocardiogram, and vital signs were performed at baseline (visit 1) and at the final visit (visit 4).

### Statistics

The primary objective of the confirmatory analysis was to show that the effects of SAMe and imipramine on the HAM-D scores obtained with each treatment are equivalent. To assess efficacy we analyzed data according to an intent-to-treat analysis (ie, analysis of data from all patients receiving at least one drug dose and for which at least one postbaseline assessment of efficacy measures was available). For patients who were withdrawn from the study before the end, the last observation was carried forward (LOCF) for data analysis. To assess safety we considered data from all randomized patients who received at least one dose of the drug.

The analyses of sociodemographic variables and baseline characteristics were carried out by means of descriptive statistics. Baseline homogeneity between the 2 treatment groups was analyzed by using Pearson's chi-square test for categorical variables (sex, ethnicity, and diagnosis) and Student's *t* test for the continuous variables age, weight, height, years of illness, and baseline HAM-D score.

For the analysis of the main efficacy measure, the endpoint HAM-D score, we used an analysis of covariance. Such a model considered the treatment group and the evaluation site as factors and the baseline HAM-D total score as a covariate. To test the hypothesis of noninferiority (one-sided test), we calculated the 90% CI for the difference $[(\mu_{SAMe} - (\mu_{imipramine} + 3)]$, where m is the mean total HAM-D score at the last visit, proceeding as needed according to the LOCF procedure.

For the second primary endpoint, the percentage of responders, defined as patients with a score of ≤2 on the CGI, we used a Mantel-Haenszel's chi-square test considering treatment as a factor and evaluation site as a control variable. To test the hypothesis of equivalence, we calculated the 90% CI for the difference $[(\text{responder}_{SAMe} - (\text{responder}_{imipramine} - 15\%)]$. For both endpoints, if the calculated CI did not include 0, we concluded the noninferiority of SAMe with respect to imipramine. To keep a global significance level of 5%, the null hypothesis for the second primary endpoint could be refused only if the first one had been refused.

Adverse events emerging during the study were assessed through the analysis of the frequency of occurrence and percentage of patients with adverse events. Laboratory analyses assessed at visits 1 and 4 were analyzed through a comparison with the normal values. Electrocardiographic parameters and vital signs were analyzed at visits 1 and 4 through the use of descriptive statistics. All statistical tests carried out for these variables were only considered for descriptive purposes (two-tailed, $\alpha = 0.05$). SPSS software (version 8.0; SPSS Inc, Chicago) was used.

## RESULTS

### Patients

In the MC3 study, 281 patients met the inclusion criteria (**Table 1**); 143 of the patients were randomly assigned to receive treatment with SAMe and 138 to receive treatment with imipramine.

As is usual in a multicenter clinical study, each center was provided with a portion of an overrepresented randomization list, on the basis of the number of patients the center planned to enroll. The slight difference in the number of patients in each group resulted because of a discrepancy between the planned number of patients and the number actually enrolled in some centers. Three patients in the imipramine-treated group were excluded from the intention-to-treat efficacy analysis because 1 patient received no treatment and 2 patients received no postbaseline assessment. Therefore, 278 patients (143 in the SAMe group and 135 in the imipramine group) underwent the intention-to-treat analysis.

In the MC4 study, 295 patients met the inclusion criteria (Table 1); 147 were randomly assigned to receive treatment with SAMe and 148 to receive treatment with imipramine. One patient in the imipramine-treated group received no treatment and one patient in the SAMe group received no postbaseline assessment; these 2 patents were excluded from the intention-to-treat efficacy analysis. Thus, 293 patients (146 in the SAMe group and 147 in the imipramine group) underwent the intention-to-treat analysis.

In both studies, the 2 treatment groups (SAMe and imipramine) were tested for the homogeneity of demographic variables and of other baseline measures (eg, the duration of the current depressive episode, the number of patients who had received prior antidepressant treatment, the number of patients with a first depressive episode, and the number of patients with recurrences). The resulting subgroups were homogeneous, ie, intergroup differences in a subset of demographic variables were not significantly different.

**TABLE 2**
Total reductions in Hamilton Depression Rating Scale scores at the endpoint: intention-to-treat analysis[1]

| | SAMe | Imipramine |
|---|---|---|
| MC3 | | |
| Baseline | 25.1 ± 4.9 [143] | 25.5 ± 5.2 [135] |
| Endpoint | 12.5 ± 8.1 [143] | 12.4 ± 8.6 [135] |
| Difference[2] | −12.6 ± 9.0 | −13.1 ± 9.5 |
| MC4 | | |
| Baseline | 24.3 ± 4.0 [146] | 26.0 ± 4.5 [147] |
| Endpoint | 11.7 ± 8.0 [146] | 12.9 ± 7.1 [147] |
| Difference[3] | −12.6 ± 7.3 | −13.1 ± 7.4 |

[1] $\bar{x}$ ± SD; *n* in brackets. SAMe, *S*-adenosyl-L-methionine. There were no significant between-group differences (analysis of covariance).
[2] 90% CI of the difference [$\mu_{SAMe} - (\mu_{imipramine} + 3)$]: −4.04, −1.01.
[3] 90% CI of the difference [$\mu_{SAMe} - (\mu_{imipramine} + 3)$]: −4.39, −1.84.

## Efficacy

In both studies, the mean total HAM-D scores at the endpoint (first efficacy measure) decreased significantly from baseline in the SAMe and the imipramine groups ($P < 0.001$, Student's *t* test); the magnitude of the differences between the 2 groups was not significant (**Table 2**).

At the endpoint, the 90% CIs of the estimated difference between treatments [SAMe − (imipramine + 3)] were −4.04 and −1.01 in the MC3 study and −4.39 and −1.84 in the MC4 study. Because such intervals did not include zero, we rejected the null hypothesis of confirmatory analysis and concluded that the effects of both treatments were equivalent.

Data regarding the second main efficacy measure, ie, the percentage of responders at the end of the study on the basis of a CGI score ≤2 (moderately improved), are reported in **Table 3**. The 90% CIs of the estimated difference between the 2 treatments [(SAMe − (imipramine − 15%)] varied between –1.00% and 17.70% in the MC3 study and between 7.8% and 25.9% in the MC4 study. In the MC3 study, the lower limit of this interval lied beyond zero for one point, indicating that imipramine was mildly superior to SAMe. In the MC4 study, the interval did not include zero, indicating an equivalence between treatments.

As reported in **Table 4**, the mean total MADRS scores (secondary efficacy measure) at the endpoint showed significant reductions from baseline in both the SAMe- and the imipramine-treated groups. The differences in the magnitude of the decreases were not significantly different between groups.

**TABLE 3**
Percentage of patients in the 2 groups whose depression improved at least moderately: intention-to-treat analysis[1]

| | SAMe | Imipramine |
|---|---|---|
| | % | |
| MC3[2] | | |
| Nonresponders | 37.8 [54] | 31.1 [42] |
| Responders | 62.2 [89] | 68.9 [93] |
| MC4[3] | | |
| Nonresponders | 32.2 [47] | 34.0 [50] |
| Responders | 67.8 [99] | 66.0 [97] |

[1] *n* in brackets. SAMe, *S*-adenosyl-L-methionine. There were no significant between-group differences (Cochran-Mantel-Haenszel chi-square test).
[2] 90% CI of the difference [%responders SAMe − (%responders imipramine − 15%)]: −1.00, 17.70.
[3] 90% CI of the difference [%responders SAMe − (%responders imipramine − 15%)]: 7.8, 25.9.

**TABLE 4**
Total reductions in Montgomery-Asberg Depression Rating Scale scores in the 2 groups at the endpoint: intention-to-treat analysis[1]

| | SAMe | Imipramine |
|---|---|---|
| MC3 | | |
| Baseline | 29.3 ± 5.9 [143] | 29.4 ± 6.1 [135] |
| Endpoint | 14.5 ± 9.4 [143] | 14.4 ± 10.4 [135] |
| Difference | −14.9 ± 9.6 | −15.0 ± 11.0 [135] |
| MC4 | | |
| Baseline | 27.8 ± 5.5 [146] | 28.9 ± 5.5 [147] |
| Endpoint | 13.3 ± 9.0 [146] | 14.6 ± 7.8 [147] |
| Difference | −14.5 ± 9.5 | −14.3 ± 8.7 |

[1] $\bar{x}$ ± SD; *n* in brackets. SAMe, *S*-adenosyl-L-methionine. There were no significant between-group differences (analysis of covariance).

The percentages of responders in both groups at the end of the study, on the basis of the secondary efficacy measure (a decrease in the HAM-D score of ≥50% from baseline), are reported in **Table 5**. The antidepressive efficacy of SAMe administered either orally or parenterally was not significantly different from that of imipramine.

## Safety

All treated patients were included in the safety evaluation. No relevant differences in laboratory measures were observed within or between the 2 treatment groups. No significant differences in vital signs (body weight, blood pressure, and heart rate in both lying and upright positions) or in electrocardiographic parameters (ventricular beat, PQ interval, QRS interval, QT interval, and ST segment) were found between treatment groups. The number and frequency of patients with treatment-emergent adverse events (patients with at least one adverse event and study drug–related adverse events) are summarized in **Table 6**. Overall, these data indicate that SAMe, administered both orally and intramuscularly, was better tolerated than was imipramine. The most frequently reported adverse effects were dry mouth, constipation, and tachycardia. In both studies these effects were significantly more frequent in the imipramine-treated patients than in the SAMe-treated patients.

## DISCUSSION

Several early investigations compared the efficacy of SAMe with that of other antidepressants (tricyclic antidepressants in nearly all cases) and they were reviewed in previous meta-analyses

**TABLE 5**
Percentage of responders in the 2 groups on the basis of the secondary efficacy measure (a decrease in the Hamilton Depression Rating Scale of ≥50% from baseline): intention-to-treat analysis[1]

| | SAMe | Imipramine |
|---|---|---|
| | % | |
| MC3 | | |
| Nonresponders | 49.0 [70] | 43.0 [58] |
| Responders | 51.0 [73] | 57.0 [77] |
| MC4 | | |
| Nonresponders | 41.1 [60] | 49.7 [73] |
| Responders | 58.9 [86] | 50.3 [74] |

[1] *n* in brackets. SAMe, *S*-adenosyl-L-methionine. There were no significant between-group differences (Cochran-Mantel-Haenszel chi-square test).

**TABLE 6**
Summary of adverse events in the 2 groups during treatment[1]

| | SAMe | Imipramine |
|---|---|---|
| | *n* (%) | |
| MC3 | | |
| Total number of patients | 143 | 137 |
| Patients with ≥1 adverse event | 42 (29.4) | 59 (43.1)[2] |
| Study drug–related adverse events | 7 (4.9) | 28 (20.4)[3] |
| MC4 | | |
| Total number of patients | 147 | 147 |
| Patients with ≥1 adverse event | 47 (32.0) | 80 (54.4)[3] |
| Study drug–related adverse events | 14 (9.5) | 49 (33.3)[3] |

[1] Percentages in parentheses. SAMe, *S*-adenosyl-L-methionine.
[2,3] Significantly different from SAMe (Pearson's chi-square test): [2] $P = 0.017$, [3] $P = 0.001$.

(8, 9). The main studies were conducted in populations heterogeneous in terms of age, specific diagnosis, disease severity, and length of illness. Despite these limitations, the overall data analysis showed a beneficial effect of SAMe, which provided at least equivalent effects (as measured by an improvement in HAM-D scores) to other standard antidepressants and a quick onset of the antidepressant response.

The findings of these 2 new studies are of interest because they confirmed, in a large multicenter study, the results of the previous studies (8, 9). In particular, the findings indicate that treatment of outpatients with a diagnosis of major depression with oral or intramuscular SAMe has an antidepressant potency comparable with that of oral imipramine, but the tolerability and safety of SAMe are significantly superior to that of imipramine.

These results are important and deserve special consideration among all SAMe investigations for many reasons. The MC3 and MC4 studies were conducted in large patient populations and thus had sufficient power to detect clinically significant differences between the drugs under investigation. A randomized, double-blind design was used to reduced bias and variations, and standardized diagnostic and efficacy criteria were used: patients met the DSM-IV criteria for major, unipolar, nonpsychotic depression, and their symptoms were evaluated with the use of the HAM-D, CGI, and MADRS. Moreover, the comparator used in these studies was imipramine, which is generally considered the gold standard in the treatment of depression.

Unlike many other previous comparative trials, imipramine was used in the current study at the full therapeutic dose commonly used in European countries (13). The daily oral dose of SAMe used in the MC3 study was similar to the dose previously identified as being effective by others (15–17) in small clinical settings. Rosenbaum et al (15) treated their patients with an initial oral dose of 400 mg SAMe/d, which was increased over 20 d to 1600 mg/d. The most significant therapeutic response was obtained at 1200–1600 mg/d. Also, the 400-mg/d intramuscular dose used in the MC4 study is the dose identified as being effective and well tolerated by Bell et al (18). Compared with oral administration, the lower intramuscular dose of SAMe was more bioavailable; this probably reflects the better bioavailability of SAMe when given parenterally (19).

The oral imipramine dose (150 mg/d) used in both the MC3 and MC4 studies is compatible with the usual dose used for the treatment of the most severe forms of major depression. Therefore, considering the indisputable potency of the comparison drug and that it was administered at a full clinical dose, we conclude that both oral and intramuscular SAMe may exert clinically significant antidepressant effects.

The results indicate that the tolerability and safety of both oral and intramuscular SAMe are superior to those of imipramine. Considering that SAMe is a natural molecule, it is not surprising that it is probably one of the best-tolerated antidepressant compounds. SAMe's tolerability indicates that this compound may be useful in clinical settings, where it is crucial to ensure antidepressant activity without side effects, for example, in patients with somatic comorbidity or in psychogeriatry (20).

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