A double-blind, randomized parallel-group, efficacy and safety study of intramuscular *S*-adenosyl-L-methionine 1,4-butanedisulphonate (SAMe) versus imipramine in patients with major depressive disorder

Paolo Pancheri[1,2], Pierluigi Scapicchio[3] and Roberto Delle Chiaie[1,2]

[1] *III Clinica Psichiatrica, Università ' La Sapienza ', Viale dell'Università 30 (00185), Rome, Italy*

[2] *Fondazione Italiana per lo studio della Schizofrenia, Via Tacito 90 (00193), Rome, Italy*

[3] *Società Italiana di Psichiatria, Via del Vignola 75 (00196), Rome, Italy*

Abstract

S-adenosyl-L-methionine (SAMe) is a natural substance which constitutes the most important methyl donor in transmethylation reactions in the central nervous system. Several clinical trials have shown that SAMe possesses an antidepressant activity. This multicentre study was carried out to confirm both efficacy and safety of SAMe in the treatment of major depression. SAMe was given intramuscularly (i.m.) at a dose of 400 mg/d, double-blind, vs. 150 mg/d oral Imipramine (IMI) in patients with a diagnosis of major depressive episode, with a baseline score on the 21-item Hamilton Depression Rating Scale (HAMD) of ⩾ 18. A total of 146 patients received SAMe whereas 147 received IMI for a period of 4 wk. The two main efficacy measures were endpoint HAMD score and percentage of responders to Clinical Global Impression (CGI) at week 4. Secondary efficacy measures were the final Montgomery–Asberg Depression Rating Scale (MADRS) scores and the response rate intended as a fall in HAMD scores of at least 50 % with respect to baseline. The analysis of safety and tolerability was conducted in all treated patients. SAMe and IMI did not differ significantly on any efficacy measure, either main or secondary. Adverse events were significantly less in patients treated with SAMe compared to those treated with IMI. These data show 400 mg/d i.m. SAMe to be comparable to 150 mg/d oral IMI in terms of antidepressive efficacy, but significantly better tolerated. These findings suggest interesting perspectives for the use of SAMe in depression.

Introduction

Although better recognized and better treated than in the past, depression remains a major cause of impaired quality of life and a social and economic burden for the individual as well as the community. Depression is one of the most common psychiatric diseases, with a worldwide distribution and lifetime prevalence rates estimated to be as high as 20 % (Campbell et al., 1997). In the management of depressive disorders, selecting the

Address for correspondence : Dr R. Delle Chiaie, III Clinica Psichiatrica, Università ' La Sapienza ', Via Cicerone, 44-00193 Roma – Italy.
Tel. : +39(06)3210327 *Fax* : +39(06)3202679
E-mail : delle.chiaie@flashnet.it

right treatment for the right patient is crucial. Not only are the clinical features of depression varied and requiring diverse therapeutic approaches, but this disease is also often associated with comorbid conditions, more or less linked with depression itself. Thus, many factors need to be considered when choosing an antidepressant therapy (i.e. specific diagnosis, stage of life, comorbid psychiatric and somatic illnesses, concomitant medications) and this has, in recent years, driven the development of a wide range of compounds with differing pharmacological profiles and improved tolerability. On the other hand, there has also been a renewed interest in the potential clinical use of naturally occurring psychotropic substances. One of these compounds, *S*-adenosyl-L-methionine also known as SAMe or ademetionine, is a molecule found in all living

organisms. SAMe, which is synthesized from methionine and ATP in a reaction catalysed by methionine adenosyltransferase (Cantoni, 1953), is involved in many metabolic pathways, and acts as a major methyl donor in enzymic transmethylation reactions in the central nervous system by donating its methyl group to a wide variety of acceptors, such as catecholamine and other biogenic amines, phospholipids, proteins, and nucleic acids (Baldessarini, 1975).

After donating the methyl group, SAMe is converted into taurine, glutathione and sulphates via the *trans*-sulphuration pathway. An alteration in endogenous SAMe metabolism has been observed in depressed patients, who show a significant decrease in SAMe concentration in the cerebrospinal fluid (Bottiglieri et al., 1990), as well as a decrease in the activity of methionine adenosyltransferase, the enzyme that promotes the endogenous biosynthesis of SAMe. This compound is very unstable chemically. Its stabilization by salt formation (first SAMe sulphate-*p*-toluensulphonate and, recently, the more stable SAMe 1,4-butanedisulphonate) made it possible to characterize its pharmacological activity and clinical efficacy.

Several preclinical studies have demonstrated the psychotropic activity of SAMe, particularly its antidepressant action (Benelli et al., 1999; Genedani et al., 2001; Spillmann and Fava, 1996). In various animal models SAMe increases monoamine synthesis and turnover (Curcio et al., 1978; Otero-Losada and Rubio, 1989a, b), acts on a number of central nervous system receptors (including β- and α_1-adrenergic, muscarinic and GABA receptors) (Cimino et al., 1984; Muccioli et al., 1992) and modifies intraneuronal signal transduction systems (Consogno et al., 2001; Zanotti et al., 1998).

Since its antidepressant activity was first identified in 1973 (Fazio et al., 1973) SAMe has been studied in a large number of clinical trials, including open investigations, studies vs. placebo and vs. tricyclic antidepressants (TCAs). Most of these studies found that SAMe was more effective than placebo and generally as effective as TCAs, while its safety and tolerability was similar to that of placebo and superior to that of TCAs. Two meta-analyses of double-blind controlled studies have indicated that the efficacy of SAMe in treating depressive disorders is superior to that of placebo and comparable to that of TCAs (Bressa, 1994; Pancheri et al., 1997).

The aim of the present study was to compare the efficacy and tolerability of intramuscular (i.m.) SAMe 1,4-butanedisulphonate salt with that of oral imipramine (IMI) in the treatment of patients with major depression.

Methods

Study population

Thirty-one Italian hospitals and university centres were involved in this trial. The experimental protocol envisaged the enrolment of outpatients, of both sexes, with an age range between 18 and 70 yr. The current diagnosis was major depressive episode according to DSM-IV criteria (APA, 1994), with a unipolar (depressive) course, without psychotic symptoms. Inclusion criteria comprised a Hamilton Depression Rating Scale (HAMD) score of at least 18 at baseline, with the score on the first item of the scale (depressed mood) $\geqslant 2$, and a severity score of at least 4 on the Clinical Global Impression (CGI) rating scale.

The investigation was carried out in accordance with the latest version of the Declaration of Helsinki and the study protocol was reviewed and approved by the appropriate Ethical Committees and Institutional Review Boards at each site. Written informed consent to participate in the study was obtained from all the patients. The trial was performed according to Good Clinical Practice Guidelines with monitoring and auditing procedures included.

Experimental design

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 inclusion/exclusion criteria were started on the double-blind treatment phase. During the active treatment period patients underwent to two further assessments: visit 2 (day 14), and visit 3 (day 28, corresponding to the endpoint).

Due to the different aspect of SAMe vials and IMI tablets, to ensure double-blindness the 'double-blind double-dummy' technique was used (i.e. patients assigned to treatment with i.m. SAMe received IMI oral placebo, while those assigned to oral IMI received i.m. SAMe placebo). The aspect of i.m. SAMe placebo vials and IMI placebo oral tablets was identical to that of the corresponding active compound.

Patients assigned to treatment with SAMe received:

08:00 hours   1 i.m. SAMe injection (400 mg) + 2 tablets of IMI placebo;
13:00 hours   2 tablets of IMI placebo;
21:00 hours   2 tablets of IMI placebo.

whereas the patient assigned to treatment with IMI received:

08:00 hours   2 IMI tablets (25 mg) + 1 SAMe placebo i.m. injection;
13:00 hours   2 IMI tablets (25 mg);
21:00 hours   2 IMI tablets (25 mg).

Each SAMe vial contained 760 mg SAMe 1,4-butanedisulphonate salt (equivalent to 400 mg SAMe ion).

Each treatment package contained the amount of drug needed for the entire treatment period. However, since current clinical guidelines recommend achieving the full dose gradually only for IMI, and not for SAMe, the first weekly packets administered to patients in the control group were prepared to allow gradual titration of IMI doses. In this way full doses of IMI were reached after 8 d, according to the following treatment schedule:

Days 1–3   IMI (or IMI placebo) 50 mg/d (1 tablet at 21:00 hours).
Days 4–7   IMI (or IMI placebo) 100 mg/d (2 tablets at 08:00 and 21:00 hours).
Days 8–28   IMI (or IMI placebo) 150 mg/d (3 tablets at 08:00, 13:00 and 21:00 hours).

All empty drug packets were returned at the end of the study. With patients who complained of side-effects, the drug dose could be reduced from week 3 onwards, down to a minimal dosage of 100 mg/d IMI and 1200 mg/d SAMe. If the patient poorly tolerated this dosage also, he/she was excluded from the study.

During the course of the study, only lorazepam (1, 2 or 5 mg/d p.o.) was allowed to facilitate sleep induction if required.

Efficacy assessment

The first objective of the study was to evaluate the equivalence of the antidepressant potency of SAMe and IMI. All assessments carried out at both baseline and during each time-point were performed using the following instruments: HAMD 21-item version; Clinical Global Impression (CGI), Montgomery–Asberg Depression Rating Scale (MADRS).

The antidepressant efficacy of the two drugs was quantified referring to the following main and secondary efficacy measures:

Main efficacy measures

(1) HAMD total score at the endpoint.
(2) Percentage of treatment *responders*, defining them as those patients who, at the end of the study, had a CGI score ⩽ 2.

Secondary efficacy measures

(1) MADRS total score at the endpoint.
(2) Percentage of treatment *responders*, defining them as those patients who, at the end of the study, had a drop of at least 50% from baseline in HAMD score.

Safety assessment

The second main objective was to evaluate the tolerability and safety of SAMe vs. IMI, assessing the incidence of adverse events (AEs) emerging during the treatment period. An AE was indicated when any event occurring in the course of the study changed the patient's well-being, including changes in laboratory measures. AE severity was defined as mild (if it did not interfere with daily activities), moderate (if it did interfere with normal daily activity) or severe (if it impaired the performance of normal daily activities). Based on objective criteria, their relation to drug treatment was classified as 'probable', 'possible' or 'not related'. Laboratory analyses ECG, and vital signs were performed at baseline and at final visit.

Statistical analyses

The alternative hypothesis to be tested was that the mean total HAMD score in the SAMe group would be comparable to, or better than, the mean score in the IMI group. In order to calculate the sample size required for the study, the assumption was made that there would be a clinically significant difference in efficacy between the two drugs of ⩾ 3 points on the 21-item HAMD score, as estimated from the results of previous clinical trials of antidepressants such as paroxetine, citalopram or moclobemide (Danish University Antidepressant Group, 1986, 1990, 1993). Thus, it was estimated that at least 138 patients per group (276 total) would be necessary to achieve a statistical power of 90% at a significance level of 5%.

The primary objective of the *confirmatory analysis* was to show the equivalence of SAMe and IMI as to the effect on HAMD scores obtained with each treatment.

To assess efficacy we analysed data according to intent-to-treat analysis (ITT) (analysis of data of all patients receiving at least one drug dose and for which at least one post-baseline assessment of efficacy measures was available).

For the assessment of safety we considered data of all randomized patients having received at least one drug dose.

The analyses of socio-demographic variables and baseline characteristics were carried out by means of descriptive statistics. Baseline homogeneity between

Table 1. Demographics (ITT population)

Treatment	Sex		Age (yr)		Height (m)		Body weight (kg)	
	M	F	Mean	S.D.	Mean	S.D.	Mean	S.D.
SAMe ($n=146$)	44	102	48.2	12.2	1.65	0.08	66.8	14.2
IMI ($n=147$)	64	83	48.8	14.0	1.66	0.08	66.8	12.8
Total ($n=293$)	108	185	48.5	13.1	1.65	0.08	66.8	13.5

the two treatment groups has been analysed using Pearson's χ^2 test for categorical variables (sex, ethnicity, diagnosis) and Student's t test for the continuous variables (age, weight, height, years of illness, baseline HAMD score).

For the analysis of the main efficacy measure, the endpoint HAMD score, we used a covariance analysis (ANCOVA). Such a model considered the treatment group and the evaluation site as factors and the baseline HAMD total score as a covariate.

To test the hypothesis, we calculated the 90% confidence interval for the difference $[(\mu_{SAMe} - (\mu_{IMI} + 3)]$, where μ is mean total HAMD score at last visit, proceeding as needed according to the 'last observation carried forward' (LOCF) procedure.

For the second primary endpoint, the percentage of responders (R), defined as patients with a score $\leqslant 2$ on the CGI, we used a Mantel–Haenszel's χ^2 test considering treatment as a factor and evaluation site as a control variable.

To test the hypothesis of equivalence, we calculated the 90% confidence interval for the difference $[(R_{SAMe} - (R_{IMI} - 15\%)]$.

In order 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.

AEs emerging during the study were assessed through the analysis of the frequency of occurrence and percentage of patients with AEs. Laboratory analyses assessed at baseline (visit 1) and at final visit (visit 4) were analysed by comparison with the normal values. ECG parameters and vital signs were analysed at baseline and final visit through descriptive statistics. All statistical tests carried out for these variables were only considered for descriptive purposes (two-tailed; $\alpha = 0.05$).

Results

A total of 295 patients met the inclusion criteria required by the protocol. Of these, 147 were randomized to receive treatment with SAMe and 148 treatment with IMI. Thirty-one patients (13 SAMe, 18 IMI) out of the 294 patients who received at least one dose, discontinued treatment before the protocol term. One patient of the IMI-treated group did not take any treatment and one patient of the SAMe group had no post-baseline; they were excluded from the ITT efficacy analysis. Therefore, ITT population was composed of 293 patients (146 SAMe and 147 IMI, Table 1).

The two treatment groups (SAMe and IMI) were homogeneous and comparable for both demographic variables and baseline measures (such as duration of current depressive episode, number of patients who had received prior antidepressant treatment, patients at first depressive episode and those with recurrences).

Main efficacy measures

As reported in Table 2, the mean total HAMD scores at endpoint showed significant reductions from baseline, both in the SAMe- and IMI-treated sub-groups. Between groups the differences regarding the magnitude of such decreases were not found to be statistically significant.

At endpoint, the 90% confidence interval of the estimated difference between treatments [SAMe − (IMI + 3)] was −4.39 and −1.84. Since such intervals did not include zero, the null hypothesis of confirmatory analysis may be rejected, thus concluding for the equivalence between treatments.

Data regarding the percentage of responders at the end of the study using as a criterion a CGI score $\leqslant 2$ (moderately improved) are reported in Figure 1.

The 90% confidence interval of the estimated difference between the two treatments [SAMe − IMI − 15%)] varied between 7.8 and 25.9% for MC4. The interval did not include zero, allowing us to conclude for equivalence between treatments.

Secondary efficacy measures

As reported in Table 2, the mean total MADRS scores at endpoint showed significant reductions from baseline, both in the SAMe- and IMI-treated sub-groups.

Table 2. Symptom reduction (total HAMD and total MADRS score) at endpoint (population ITT)

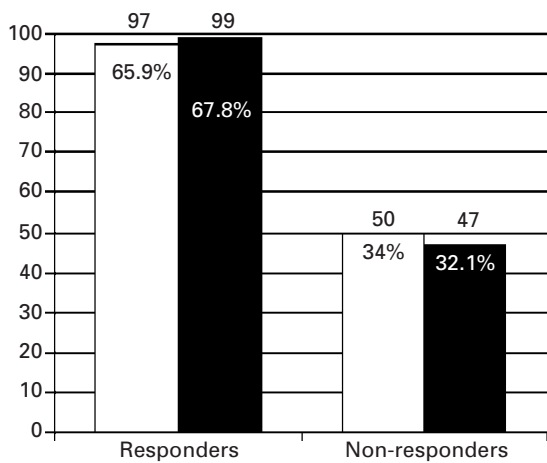| | SAMe | | | IMI | | | Difference | | | |
| | | | | | | | SAMe | | IMI | |
	n	Mean	S.D.	*n*	Mean	S.D.	Mean	S.D.	Mean	S.D.
HAMD										
Basal	146	24.3	4.0	147	26.0	4.5				
Endpoint	146	11.7	8.0	147	12.9	7.1	−12.6	7.3	−13.1	7.4
MADRS										
Basal	146	27.8	5.5	147	28.9	5.5				
Endpoint	146	13.3	9.0	147	14.6	7.8	−14.6	9.5	−14.3	8.7

Figure 1. Responders rate based on end-point CGI (population ITT). Responders defined as patients showing at least a 'moderate improvement' at endpoint (CGI ⩽2). □, IMI; ■, SAMe.
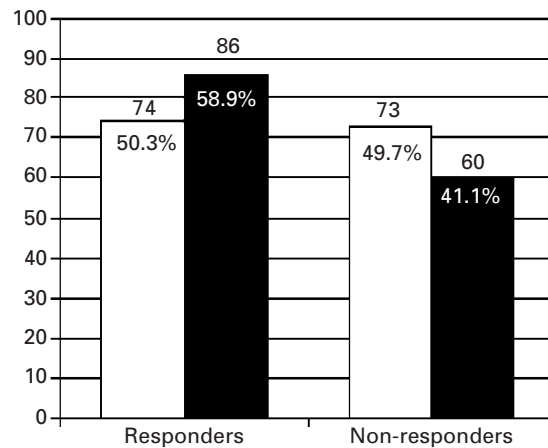

Figure 2. Responders rate based on HAMD reduction at endpoint (population ITT). Responders defined as patients showing an endpoint HAMD score reduction from baseline of at least 50%. □, IMI; ■, SAMe.

Between groups, the difference regarding the magnitude of such decreases was not found to be statistically significant.

Data regarding the percentage of responders at the end of the study using as a criterion a ⩾50% HAMD score drop from baseline to the end of the study are reported in Figure 2.

Further using this comparison between SAMe and IMI, the two treatments proved to possess identical antidepressive efficacy.

Safety results

All treated patients ($n = 294$) were included in safety evaluation. Mean treatment duration was 28 d and similar for SAMe (26.9 d) and IMI (26.2 d) groups.

Overall, 31 patients (SAMe 13, IMI 18) of those who received at least one dose, discontinued the treatment before the protocol term. Of these, 9 patients (SAMe 2, IMI 7) abandoned the study before term following the onset of AEs. In one of these (2 SAMe patients), drug suspension was due to the onset of a serious AE (suicide attempt).

No relevant difference was observed for laboratory measures within or between the two treatment groups. In the same way, no significant differences between treatment groups was found regarding vital signs (body weight, blood pressure and heart rate under both supine and upright positions) or ECG parameters (ventricular beat, PQ interval, QRS interval, QT interval, ST segment).

Table 3 summarizes the number and frequency of treatment-emergent AEs (patients with at least one AE

Table 3. Summary of adverse events (AEs) appearing during treatment

	SAMe		IMI		
	n	%	n	%	p value*
Total patient number	147	100	147	100	
Patients with at least one AE	47	32.0	80	54.4	0.001
Study drug-related AEs	14	9.5	49	33.3	0.001

* χ^2 Pearson.

and study drug-related AE). Overall, these data indicate that SAMe is endowed with a better tolerability profile than IMI.

The most frequently reported AEs were dry mouth, constipation and tachycardia; these effects were significantly more frequent in IMI-treated patients than in SAMe-treated patients.

Discussion

Despite the availability of a wide array of therapeutic agents of different chemical and pharmacological classes, the treatment of depression remains a challenge for the clinician. The unfavourable tolerability profile of many agents with proven antidepressant efficacy, the high percentage of patients who are treatment resistant and the relatively long delay between start of treatment and onset of activity which characterizes the mechanism of action of most antidepressants are some of the main reasons which, in recent years, have fostered the development of an increasing number of compounds with proven or potential antidepressant efficacy.

Since the mood-elevating potential of exogenous SAMe was first identified in 1973 (Fazio et al., 1973), this agent has undergone several clinical investigations. The results of these first SAMe studies were reviewed in two recent meta-analyses. Bressa (1994) examined 6 placebo-controlled studies (including a total of 200 patients) and 7 studies vs. TCAs ($n=201$) from which the effect size of the therapeutic interventions (based on HAMD response) could be calculated. The efficacy of SAMe proved to be superior to that of placebo and similar to that of TCAs, while the incidence of AEs was lower for SAMe than for TCAs. In the meta-analysis by Pancheri et al. (1997) only studies which used HAMD-based enrolment criteria were included [6 placebo-controlled ($n=216$) and 8 TCA-controlled (258)] and the effect size was calculated for each study from the percentage change in HAMD score. Among the placebo-controlled studies, two thirds of the trials with

parenteral and two thirds of those with oral SAMe revealed a significant superiority of the active drug vs. placebo (Barberi and Pusateri, 1978; Caruso et al., 1987; Kagan et al., 1990; Muscettola et al., 1982) with global effect sizes of 0.39 ($p<0.001$) and 0.46 ($p<0.001$), respectively, while, among the 6 TCA-controlled studies which utilized parenteral administration, 2 showed a superiority of SAMe (Bell et al., 1988; Scaggion et al., 1982), 1 revealed a superiority of TCAs (Salmaggi et al., 1993) and 3 showed a comparable efficacy between treatments (Del Vecchio et al., 1978; Kufferle and Grunberger, 1982; Miccoli et al., 1978), the global effect size being 0.11.

The two TCA-controlled oral studies failed to reveal a significant superiority of either treatment (Bell et al., 1994; De Vanna and Rigamonti, 1992), with a global effect size of -0.04. Overall, the results of the first investigations of SAMe suggest an antidepressant efficacy superior to placebo and similar to that of TCAs, but caution is warranted when interpreting these conclusions because of the limitations of many studies (i.e. small patient numbers, diagnostic and efficacy criteria not always standardized, treatment duration often insufficient).

In the present study, the largest clinical trial of SAMe carried out so far, 295 patients meeting DSM-IV criteria for major depression (mean baseline HAMD 24.3; moderately severe symptom level) were randomized to receive, in double-blind fashion, intramuscular treatment with 400 mg/d SAMe or 150 mg/d oral imipramine for 4 wk. The intramuscular route of administration of SAMe was chosen in order to produce a prompt onset of pharmacological action, and also to ensure a 100% drug bioavailability and patient compliance.

No potential confounding factors were identified that may have skewed the results in favour of either study drug. The two treatment groups were similar for demographical and clinical characteristics.

A possible limitation of our study was the lack of a placebo arm. The choice of excluding the placebo was mainly based on the consideration that placebo-controlled trials should be used only when there is no current treatment for a disease, while in all other cases an active comparator must be used.

This point of view is supported by the recently expressed opinion of pharmaceutical regulatory experts (Garattini and Bertele, 2001).

As expected, IMI was found to be a highly effective antidepressant, reducing HAMD scores by 50.4% after 4 wk oral treatment. SAMe also proved to be similarly effective in this patient population, with reductions of 51.8%.

Given that the confidence interval of the difference between the two drugs, at the end of the treatment, lies within the range of equivalence, the two drugs can be considered equivalent based on the study hypothesis (see the Methods section). In support of the comparability between the two drugs' effects, no statistically significant differences between study groups were apparent on the other primary and secondary efficacy parameters.

It came as no surprise that IMI should prove to be effective in this group of patients with a history of severe depression, since TCAs are generally considered the most powerful weapon available for the treatment of severe depression (Anderson, 1998; Danish University Antidepressant Group, 1986, 1990, 1993), SAMe also proved to be remarkably effective in this clinical setting.

SAMe not only induced a substantial benefit in severely depressed patients, but also showed a better tolerability profile than IMI, with a significantly lower incidence of anticholinergic side-effects, such as dry mouth, constipation and tremor. In conclusion, SAMe has been used in clinical practice for many years, especially in patients with comorbid medical illnesses or other conditions that entail increased vulnerability to the potential side-effects of standard antidepressants. The findings of this large-sized study indicate that intramuscular SAMe induced a clinical benefit which was equivalent to that of IMI, while showing an excellent tolerability profile. The results support the clinical use of SAMe in subjects who are poor candidates for treatment with TCAs or with other antidepressant regimens that raise concerns in terms of AEs or pharmacokinetic/pharmacodynamic interactions potential. The short-term treatment with parenteral SAMe may be followed by the administration of oral SAMe which has also proved to be effective and equally well tolerated.

Acknowledgements

References

Anderson IM (1998). SSRIs versus tricyclic antidepressants in depressed inpatients: a meta-analysis of efficacy and tolerability. *Depression and Anxiety 7* (Suppl. 1), 11–17.

APA (1994). *Diagnostic and Statistical Manual of Mental Disorders* (4th edn). Washington, DC: American Psychiatric Association.

Baldessarini RJ (1975). Biological transmethylation involving S-adenosylmethionine: development of assay methods and implications for neuropsychiatry. *International Review of Neurobiology 18*, 41–67.

Barberi A, Pusateri P (1978). The clinical effects of S-adenosyl-L-methionine (SAMe) in depressive disorders [in Italian]. *Minerva Medica 19*, 235–243.

Bell KM, Plon L, Bunney WE, Potkin SG (1988). SAMe treatment of depression: a controlled clinical trial. *American Journal of Psychiatry 145*, 1110–1114.

Bell KM, Potkin SG, Carreon D, Plon L (1994). S-adenosyl-methionine blood levels in major depression: changes with drug treatment. *Acta Neurologica Scandinavica 154*, 15–18.

Benelli A, Filaferro M, Bertolini A, Genedani S (1999). Influence of S-adenosyl-L-methionine on chronic mild stress-induced anhedonia in castred rats. *British Journal of Pharmacology 127*, 645–654.

Bottiglieri T, Godfrey P, Flynn T, Carney MWP, Toone BK, Reynolds EH (1990). Cerebrospinal fluid S-adenosylmethionine in depression and dementia: effect of treatment with parenteral and oral S-adenosylmethionine. *Journal of Neurology, Neurosurgery, and Psychiatry 53*, 1096–1098.

Bressa GM (1994). S-adenosyl-L-methionine (SAMe) as antidepressant: meta-analysis of clinical studies. *Acta Neurologica Scandinavica 89* (Suppl. 154), 7–14.

Campbell LK, Robison LM, Skaer TL (1997). Depression: interventions and their effectiveness. *Disease Management and Health Outcomes 2*, 223–237.

Cantoni GL (1953). S-adenosylmethionine; a new intermediate formed enzymatically from L-methionine and adenosine triphosphate. *Journal Biological Chemistry 204*, 403–416.

Caruso I, Fumagalli M, Boccassini L (1987). Treatment of depression in rheumatoid arthritic patients. A comparison of S-adenosylmethionine (Samyr) and placebo in a double-blind study. *Clinical Trials 24*, 305–310.

Cimino M, Vantini G, Algeri S (1984). Age modification of dopaminergic and beta-adrenergic receptor systems: restoration to normal activity by modifying membrane fluidity with S-adenosylmethionine. *Life Science 34*, 2029–2039.

Consogno E, Tiraboschi E, Juliano E, Gennarelli M, Racagni G, Popoli M (2001). Long-term treatment with S-adenosylmethionine induced changes in presynaptic CaM kinase II and synapsin I. *Biological Psychiatry 50*, 337–344.

Curcio M, Catto E, Stramentinoli G, Algeri S (1978). Effect of S-adenosylmethionine on serotonin metabolism in rat brain. *Progress in Neuro-Psychopharmacology 2*, 65–71.

Danish University Antidepressant Group (DUAG) (1986). Citalopram: clinical effect profile in comparison with clomipramine. A controlled multicenter study. *Psychopharmacology 90*, 131–138.

Danish University Antidepressant Group (DUAG) (1990). Paroxetine: a selective serotonin reuptake inhibitor showing better tolerance, but weaker antidepressant effect than clomipramine in a controlled multicenter study. *Journal of Affective Disorders 18*, 289–299.

Danish University Antidepressant Group (DUAG) (1993). Moclobemide: a reversible MAO-A-inhibitor showing weaker antidepressant effect than clomipramine in a controlled multicenter study. *Journal of Affective Disorders 28*, 105–116.

Del Vecchio M, Iorio G, Cocorullo M, Vacca I, Amati A (1978). Has SAMe an antidepressant effect? A preliminary trial vs. clomipramine. *Rivista Sperimentale di Freniatria 102*, 344–358.

De Vanna M, Rigamonti R (1992). Oral *S*-adenosylmethionine in depression. *Current Therapeutic Research 52*, 478–485.

Fazio C, Andreoli V, Agnoli A, Casacchia M, Cerbo R (1973). Therapeutic effects and mechanism of action of *S*-adenosylmethionine (SAMe) in depressive disorders [in Italian]. *Minerva Medica 64*, 1515–1529.

Garattini S, Bertele V (2001). Adjusting Europe's drug regulation to public health needs. *Lancet 358*, 64–67.

Genedani S, Saltini S, Benelli A, Filaferro M, Bertolini A (2001). Influence of SAMe on the modifications of brain polyamine levels in an animal model of depression. *NeuroReport 12*, 1–4.

Kagan BL, Sultzer DL, Rosenlicht N, Gerner RH (1990). Oral *S*-adenosylmethionine in depression: a randomized, double-blind, placebo-controlled trial. *American Journal of Psychiatry 147*, 191–195.

Kufferle B, Grunberger J (1982). Early clinical double blind study with SAMe: a new potential antidepressant. In: Costa E, Racagni G (Eds.), *Typical and Atypical Antidepressants: Clinical Practice*. New York: Raven Press.

Miccoli L, Porro V, Bertolino A (1978). Comparison between the antidepressant activity of *S*-adenosylmethionine (SAMe) and that of some tricyclic drugs. *Acta Neurologica 33*, 243–255.

Muccioli G, Scordamaglia A, Bertacco S, Di Carlo R (1992). Effect of *S*-adenosylmethionine on brain muscarinic receptors of aged rats. *European Journal of Pharmacology 227*, 293–299.

Muscettola G, Galzenati M, Balbi A (1982). SAMe versus placebo: a double blind comparison in major depressive disorder. In: Costa E, Racagni G (Eds.), *Typical and Atypical Antidepressants: Clinical Practice* (pp. 151–156). New York: Raven Press.

Otero-Losada ME, Rubio MC (1989a). Acute changes in 5-HT metabolism after *S*-adenosylmethionine administration. *General Pharmacology 20*, 403–406.

Otero-Losada ME, Rubio MC (1989b). Acute effects of *S*-adenosylmethionine on catecholaminergic central function. *European Journal of Pharmacology 163*, 353–356.

Pancheri P, Racagni G, Delle Chiaie R, Popoli M (1997). New experimental and clinical acquisitions on the efficacy and tolerability of SAMe as an antidepressant [in Italian]. *Giornale Italiano di Psicopatologia 2*, 1–23.

Salmaggi P, Bressa GM, Nicchia G, Coniglio M, La Greca P, Le Grazie C (1993). Double-blind, placebo-controlled study of *S*-adenosyl-L-methionine in depressed postmenopausal women. *Psychotherapy and Psychosomatics 59*, 34–40.

Scaggion G, Baldan L, Domanin S (1982). Antidepressant activity of SAMe compared with nomifensine maleate. *Minerva Psichiatrica 23*, 93–97.

Spillmann M, Fava M (1996). *S*-adenosylmethionine (SAMe) in psychiatric disorders. Historical perspective and current status. *CNS Drugs 6*, 416–428.

Zanotti S, Mori S, Radaelli R, Perez J, Racagni G, Popoli M (1998). Modification in brain cAMP- and calcium/calmodulin-dependent protein kinases induced by treatment with *S*-adenosylmethionine. *Neuropharmacology 37*, 1081–1089.