Bioavailability of *S*-Adenosyl Methionine and Impact on Response in a Randomized, Double-Blind, Placebo-Controlled Trial in Major Depressive Disorder

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ABSTRACT

Objective: To characterize the impact of *S*-adenosyl methionine (SAMe) on homocysteine and potential risk of adverse cardiovascular effects by examining plasma levels of SAMe, *S*-adenosyl homocysteine (SAH), total homocysteine (tHCY), methionine (MET), and 5-methyltetrahydrofolate (5-MTHF) in 35 of 73 patients from a 6-week randomized double-blind, placebo-controlled trial of SAMe augmentation in serotonin reuptake inhibitor partial responders with *DSM-IV* major depressive disorder (MDD), published in 2010.

Method: Subjects were randomized from June 4, 2004, until August 8, 2008, to adjunctive placebo or SAMe 800–1600 mg/d for 6 weeks. Primary outcome measures included changes in one-carbon cycle intermediates within each treatment arm (by paired *t* test) and between treatment arms (by independent samples *t* test). Univariate analysis of variance and Fisher Protected Least Significant Difference were carried out to compare posttreatment levels of each one-carbon cycle intermediate. Secondary outcome measures included associations between clinical improvement and change in plasma intermediate levels, examined by linear regression (for change in Hamilton Depression Rating Scale scores) and logistic regression (for response or remission).

Results: We found significant differences in pretreatment plasma levels of tHCY ($P = .03$) between the SAMe and placebo arms. Following 6 weeks of treatment, plasma SAMe ($P = .002$) and SAH ($P < .0001$) levels increased significantly in the SAMe arm; no intermediates in the placebo group changed significantly. Posttreatment plasma SAMe ($P = .0035$), SAH ($P < .0001$), and tHCY ($P = .0016$) levels differed significantly between the SAMe and placebo groups. No significant associations were found between plasma intermediate levels and clinical improvement, response, or remission.

Conclusions: Despite concerns about the impact that SAMe therapy may have on homocysteine levels and risk of adverse cardiovascular effects, the lack of significant increase in tHCY levels after treatment suggests that no toxic effects from SAMe should be expected. Our findings, however, have some significant limitations and should be interpreted with caution.

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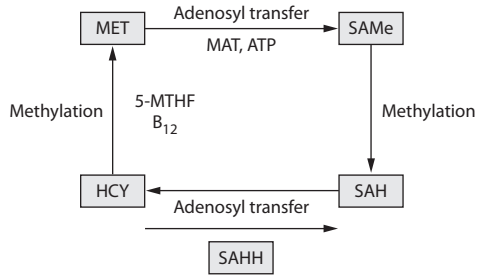
S-Adenosyl methionine (SAMe) is a natural antidepressant widely used throughout Europe for decades.[1] Since the introduction of SAMe as a dietary supplement to the US market in the late 1990s, its popularity has increased.[2] The literature overall has supported SAMe's efficacy and safety for acute treatment of major depressive disorder (MDD),[1] despite the fact that some early studies were limited by the rapid degradation of an unstable SAMe formulation that dampened treatment efficacy.[2] Most commercially available SAMe preparations nowadays are stable and have longer shelf-lives, although relatively few recent investigations have examined the stability and bioavailability of these newer compounds in the context of treatment studies.

Mechanisms of antidepressant action of SAMe may include methyl donation in neurotransmitter synthesis,[2] antioxidative effects (radical scavenging, glutathione precursor), anti-inflammatory effects, and neuroprotective effects.[3,4] Given that depression is increasingly considered an inflammatory disorder with activation of immune, oxidative, and nitrosative stress (IO&NS) pathways, which may cause decreased neurogenesis and enhanced neurodegeneration, and that attenuation of the IO&NS pathways is considered part of the working mechanisms of various antidepressants, such as selective serotonin reuptake inhibitors (SSRIs),[5,6] tricyclic antidepressants,[7] mirtazapine,[8] and riluzole (a drug that has antidepressant-like activity),[9] SAMe's putative antidepressant effect appears perfectly viable.

While SAMe appears to be safe and well-tolerated, its proposed activity and metabolism, which involve methylation, transsulfuration, and aminopropylation,[1,10] have raised some concerns about safety, particularly with regard to its role in the one-carbon cycle. SAMe is a ubiquitous molecule found in every cell of the body, the synthesis of which is dependent on the dietary intake of folate and vitamin B_{12}.[10] The folate form 5-methyltetrahydrofolate (5-MTHF) transfers a methyl group to homocysteine (HCY) to form methionine (MET), in a reaction that requires vitamin B_{12}. Methionine is in turn converted to SAMe by the enzyme methionine adenosyl transferase (MAT). The primary role of SAMe is as a universal methyl group donor that participates in a wide range of methylation reactions.[10] The byproduct of all methylation reactions is *S*-adenosyl homocysteine (SAH), which is in turn converted to homocysteine (HCY). HCY may then enter the transsulfuration pathway and synthesis of cystathionine or undergo remethylation to MET (Figure 1).

Methionine levels are closely related to HCY metabolism.[10] High intake of MET can increase plasma total HCY (tHCY) levels substantially as a result of increased metabolism through the methylation cycle. Methionine loading can be used to stress

Figure 1. Interconversions Between SAMe and Other One-Carbon Cycle Intermediates



Abbreviations: ATP = adenosine triphosphate, B_{12} = vitamin B_{12}, 5-MTHF = 5-methyltetrahydrofolate, HCY = homocysteine, MAT = methionine adenosine transferase, MET = methionine, SAH = *S*-adenosyl homocysteine, SAHH = *S*-adenosyl homocysteine hydrolase. SAMe = *S*-adenosyl methionine,

the methylation and transsulfuration pathways and thereby detect mild disturbances in enzyme activity related to these pathways. Under these conditions, a high oral dose of MET is administered, and increase and decline in plasma tHCY is monitored hourly over a 4-hour period.[11] By analogy, some investigators have expressed concern that the administration of supraphysiologic doses of SAMe could result in increased levels of plasma tHCY.[12] Increased plasma tHCY has been shown to be a risk factor for cardiovascular and cerebrovascular disease, a condition to which depressed populations may be especially vulnerable.[13]

Relatively few clinical trials have examined the impact of SAMe on plasma tHCY in depressed populations,[14] although our group found a modest decrease in tHCY in subjects taking SSRIs or serotonin-norepinephrine reuptake inhibitors (SNRIs) in combination with SAMe.[15] Nonetheless, it is generally advised that physicians monitor tHCY levels in certain patients receiving SAMe, particularly if they have a personal or family history of heart disease or have normally elevated levels of tHCY.[13] Continued investigation into the effect of SAMe on HCY and other one-carbon cycle intermediates could better clarify safety concerns associated with use of SAMe in depressed populations.

We recently completed a randomized, double-blind, placebo-controlled clinical trial of SAMe augmentation in antidepressant partial responders (ClinicalTrials.gov identifier: NCT00093847). Our results suggested efficacy and safety.[16] In this report, we present our analysis of plasma levels of SAMe before and after treatment in order to assess the absorption of this particular SAMe preparation. We also examined whether there were any significant changes in the levels of other one-carbon cycle components, specifically SAH, tHCY, MET, and 5-MTHF. It was hoped that the findings would provide insight into the overall biochemical impact of SAMe administration and clarify potential safety concerns for SAMe users. Likewise, we were interested in learning whether there were any associations between plasma levels of SAMe and other one-carbon cycle intermediates and clinical improvement. On the basis of the findings from Gören et al,[14] we predicted that patients who received SAMe would experience significant changes in blood levels of SAMe and speculated that greater changes in SAMe blood levels would be associated with a more robust clinical improvement.

Clinical Points

- Clinicians are concerned about the risk of homocysteine elevation and potential cardiac risk from administration of *S*-adenosyl methionine (SAMe).
- In depressed patients who received 1,600 mg/d of SAMe augmentation, we found no significant elevation of plasma levels of total homocysteine.
- SAMe at 1,600 mg/d appears to be safe to administer to patients with depression.

METHOD

Methods for the parent clinical trial are reported in Papakostas et al.[16] Briefly, 73 serotonin reuptake inhibitor (SRI; including SSRIs and SNRIs) nonresponders with MDD (*Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, criteria) who signed a consent form approved by our institutional review board (IRB) were enrolled from June 4, 2004, until August 8, 2008, in a 6-week, randomized, double-blind, placebo-controlled trial of adjunctive oral SAMe, at a starting dose of 800 mg daily and final target dose of 1600 mg daily (divided on a twice-daily regimen). The 400-mg tablet form of SAMe was provided by Pharmavite LLC (Northridge, California). Patients continued on their antidepressant regimens at a stable dose throughout the 6-week trial. Other concomitant psychotropic drugs, such as benzodiazepines, non-SRI antidepressants, mood stabilizers, and antipsychotics were not allowed. Patients with unstable medical illness, including cardiovascular disease, were excluded. The primary outcome measure for the study was response rates according to the 17-item Hamilton Depression Rating Scale (HDRS-17).[17]

Participants in the study were asked to provide a blood sample to be analyzed for SAMe, SAH, tHCY, MET, and 5-MTHF, prior to randomization and at the completion of the study. Blood samples were processed and analyzed as follows:

Plasma was separated from blood within 30 minutes and stored at −80°C until time of analysis. Plasma levels of SAMe and SAH were measured by a modification of the stable-isotope dilution liquid chromatography-electrospray injection tandem mass spectrometry (LC-ESI-MS/MS) previously described.[18] Plasma tHCY and MET levels were determined by LC-ESI-MS/MS as previously described.[19] 5-MTHF in plasma was determined by LC-ESI-MS/MS by diluting the sample 5:1 (v/v) with a solution of dithiothriotol, ascorbic acid, and $^{13}C_5$5-MTHF (Shircks, Jona, Switzerland). The sample was deproteinized with acetonitrile, and supernatant was extracted and analyzed by LC-ESI-MS/MS on a 4000 QTRAP as previously described with some modification.[20]

Table 1. Pretreatment and Posttreatment Plasma Levels of SAMe and Other One-Carbon Cycle Intermediates

	Pretreatment						Posttreatment					Changes in Treatment Arms			
	SAMe (n = 20)		Placebo (n = 15)		Significance[a] (SAMe vs placebo)		SAMe (n = 20)		Placebo (n = 15)		Significance[b] (SAMe vs placebo), *P*	Significance[c] (SAMe arm)		Significance[d] (placebo arm)	
Intermediate	Mean	SD	Mean	SD	*t*	*P*	Mean	SD	Mean	SD		*t*	*P*	*t*	*P*
SAMe (nmol/L)	82.90	22.44	71.24	12.44	1.81	.08	503.77	535.76	81.27	31.52	.0035	−3.5	.002	−1.14	.29
SAH (nmol/L)	35.70	6.74	30.87	10.56	1.65	.11	56.10	18.25	30.14	8.25	< .0001	−4.9	< .0001	0.24	.81
tHCY (μmol/L)	9.78	2.27	8.04	2.31	2.22	.03	10.57	3.64	7.97	1.90	.0016	−1.4	.19	0.18	.86
MET (μmol/L)	13.28	10.07	11.13	7.65	0.69	.49	12.34	6.35	11.07	5.73	.51	0.43	.68	0.04	.97
5-MTHF (nmol/L)	34.59	18.19	26.53	10.06	1.54	.13	50.68	83.04	30.28	13.79	.19	−1.0	.32	−0.92	.37

[a]Based on 2-sample *t* test for SAMe vs placebo.
[b]Based on Fisher Protected Least Significant Difference after adjusting for pretreatment levels for SAMe vs placebo.
[c]Paired *t* test for pretreatment and posttreatment levels of intermediates for SAMe arm.
[d]Paired *t* test for pretreatment and posttreatment levels of intermediates for placebo arm.
Abbreviations: 5-MTHF = 5-methyltetrahydrofolate, MET = methionine, SAH = *S*-adenosyl homocysteine, SAMe = *S*-adenosyl methionine, tHCY = total homocysteine.

Comparisons of mean levels of one-carbon cycle intermediates between the treatment and placebo group for pretreatment and posttreatment samples were carried out using the 2-sample *t* test. To further characterize the impact of SAMe on one-carbon cycle components, we carried out a univariate analysis of variance for each posttreatment one-carbon intermediate as the dependent variable(s), treatment and baseline levels of each intermediate as fixed factors, and we examined treatment × baseline intermediate levels as well. Fisher Protected Least Significant Difference (PLSD) was used to compare posttreatment levels of each one-carbon cycle intermediate, after adjusting for respective pretreatment levels.

To examine whether clinical improvement was associated with change in plasma levels of the one-carbon intermediates in patients receiving SAMe, we carried out multiple linear regression using the final HDRS-17 score as the dependent variable, and the baseline HDRS-17 score and pretreatment and posttreatment levels of the one-carbon intermediates as independent variables. Logistic regression was performed to examine any association between response or remission (dependent variables) and pretreatment and posttreatment levels of the one-carbon intermediates (independent variables).

All calculations were performed with Statview software (SAS Institute, Cary, North Carolina). All significance levels were set at $P < .05$.

RESULTS

Data for both pretreatment and posttreatment levels of the one-carbon cycle intermediates were available for 35 of the original 73 patients from the parent study. Some patients had declined to have the additional blood draws or were lost to follow-up, thus having no posttreatment data available. Some blood samples were damaged during storage and could not be analyzed. The 35 patients consisted of 20 from the SAMe arm (mean ± SD age = 55 ± 13 years, 50% female) and 15 from the placebo arm (mean ± SD age = 47 ± 11 years, 87% female). The differences in age were not significant ($P = .06$). In the SAMe arm, 80% of patients were receiving SSRIs, and 20% were receiving SNRIs; in the placebo arm, 80% of patients were receiving SSRIs, and 20% were receiving SNRIs. Full distribution of antidepressants is reported in Papakostas et al.[16]

Given that the intermediates are interdependent, Bonferroni correction for multiple comparisons was not used in the analysis. Prior to randomization, there were no significant differences in plasma levels of SAMe, SAH, MET, and 5-MTHF between patients who were randomized to SAMe or to placebo, but SAMe patients had significantly greater tHCY levels compared to placebo patients ($P = .03$; Table 1).

Outcomes analysis focused on both the within-treatment (SAMe group before and after treatment and placebo group before and after treatment) change in the one-carbon cycle intermediates as well as the between-treatment change (for SAMe versus placebo groups). Following 6 weeks of treatment, plasma SAMe ($P = .002$) and SAH ($P < .0001$) levels increased significantly in subjects randomized to the SAMe arm, but there were no significant changes in levels of tHCY, MET, and 5-MTHF (Table 1). In the placebo arm, there were no significant changes in any of the one-carbon cycle intermediate levels (Table 1).

To compare outcomes in patients receiving SAMe with those receiving placebo, we used Fisher PLSD after adjusting for baseline plasma levels of each intermediate. We found significant differences in plasma levels of SAMe ($P = .0035$), SAH ($P < .0001$), and tHCY ($P = .0016$) between the 2 treatment arms. Total plasma MET, and 5-MTHF levels were not significantly different between SAMe and placebo groups following treatment (Table 1).

When adjusting for baseline plasma levels of each intermediate, univariate analysis of variance found a significant effect for baseline tHCY on posttreatment tHCY ($P < .0001$) and a significant effect of baseline MET on posttreatment MET ($P = .008$) (Table 2). Regarding posttreatment 5-MTHF, significant effects were found for assigned treatment ($P = .03$), pretreatment 5-MTHF ($P = .01$), and the interaction between assigned treatment and pretreatment 5-MTHF ($P = .02$) (Table 2).

Baseline mean ± SD HDRS-17 scores were 18.95 ± 2.61 for the SAMe group and 19.80 ± 2.43 for the placebo group

Table 2. Univariate Analysis of Variance Examining Impact of Baseline Levels of One-Carbon Cycle Intermediates on Posttreatment Levels

Intermediate	*df*	*F*	*P*	Power
SAMe Post				
Treatment	1	0.06	.81	0.06
SAMe Pre	1	0.47	.50	0.10
Treatment × SAMe Pre	1	0.58	.45	0.11
SAH Post				
Treatment	1	0.57	.46	0.11
SAH Pre	1	0.80	.38	0.13
Treatment × SAH Pre	1	0.13	.72	0.06
tHCY Post				
Treatment	1	1.58	.22	0.22
tHCY Pre	1	25.39	< .0001	1.00
Treatment × tHCY Pre	1	2.75	.11	0.35
MET Post				
Treatment	1	1.09	.30	0.17
MET Pre	1	8.11	.008	0.80
Treatment × MET Pre	1	1.07	.31	0.16
5-MTHF Post				
Treatment	1	5.03	.03	0.58
5-MTHF Pre	1	7.29	.01	0.75
Treatment × 5-MTHF Pre	1	5.70	.02	0.64

Abbreviations: 5-MTHF = 5-methyltetrahydrofolate, MET = methionine, Post = posttreatment, Pre = pretreatment, SAH = *S*-adenosyl homocysteine, SAMe = *S*-adenosyl methionine, tHCY = total homocysteine.

($P = .33$). In subjects receiving SAMe (n = 20), multiple regression showed no significant association between change in HDRS-17 score and plasma levels of any of the one-carbon cycle intermediates following treatment. Logistic regression analysis showed no significant association between response or remission and plasma levels of any of the one-carbon intermediates.

DISCUSSION

The enteric-coated SAMe formulation used in this study was absorbed, as indicated by an approximate 6-fold increase in plasma levels of SAMe compared to pretreatment values, representing a level much greater than our (per T.B.'s laboratory) observed normal reference range of 22–131 nmol/L in 62 subjects aged 56 to 82 years. This also suggests good compliance with study treatment, which renders the positive findings of the parent study[16] even more convincing.

The metabolic links between SAMe and HCY have raised the question about the possibility that SAMe could result in increased plasma tHCY levels, a risk factor for occlusive vascular disorders. Thus far, no evidence has been found to suggest that tHCY levels rise in patients receiving oral SAMe.

Our subjects who received SAMe had a statistically significant increase in plasma levels of SAH, and this was significantly greater than in placebo patients, suggesting that SAMe was metabolized through methylation-dependent pathways leading to increased levels of SAH, which were somewhat higher than our observed reference range of 8–43 nmol/L in 62 subjects aged 56 to 82 years. Patients in the SAMe arm had higher pretreatment levels of tHCY, SAMe, and SAH than patients randomized to placebo, but only tHCY was significantly greater, and this difference became more strongly significant at the end of the treatment period. The significant difference in tHCY levels at baseline may represent an idiosyncrasy of a small sample. In any case, the change in tHCY levels in SAMe patients after 6 weeks was modest and not significant. There were no significant pretreatment or posttreatment differences between SAMe and placebo patients in total MET or 5-MTHF levels, the latter of which remained in the normal range of 8 to 75 nmol/L.[21]

One might expect that an elevated level of SAH would result in a robust elevation in tHCY and/or MET, yet this was not the case in our sample. Homocysteine remained within our observed normal range of 2 to 14 μmol/L and below 15 μmol/L, which is generally considered the upper limit of safety. Methionine remained below the normal mean level of 35 μmol/L.[22] There are at least 2 possible explanations for this observation: (1) HCY may initially elevate as a result of conversion of SAH via SAH hydrolase but could in turn be rapidly converted to MET via MET synthase and in turn converted back to SAMe via MAT. (2) HCY could be rapidly converted to cystathionine via transsulfuration, thus leaving the rest of the cycle unaffected.

Our findings suggest that humans may have a capacity to self-regulate the one-carbon cycle so as to prevent excessive levels of potentially harmful intermediates from building up. If this is so, then SAMe administration would therefore be very safe from the standpoint of pathological homocysteine elevation. While SAH is generally considered toxic,[23] it is not clear what impact it may have on mood per se. One particular concern might be about subjects who have elevated plasma tHCY before treatment due to folate and or vitamin B_{12} deficiency. Such individuals may be unable to metabolize HCY, and this may be exacerbated after SAMe treatment. Since we did not examine vitamin B_{12} levels in our sample, it is unclear why the SAMe arm had a baseline level of tHCY significantly greater than the placebo arm. However, neither treatment arm experienced a significant change in tHCY levels by the conclusion of the study, suggesting that the SAMe group was not at a metabolic disadvantage compared to the placebo group. Likewise, our examination of pretreatment levels of the intermediates as predictors of response did not suggest that they impacted clinical improvement differently between the 2 treatment arms. These issues merit further investigation.

Although we found no significant association between clinical improvement and changes in plasma levels of SAMe or the other intermediates, we did not control the timing of blood collection after SAMe dosing. The absorption of SAMe can vary between individuals and may peak from 2 to 5 hours after ingestion, and the decay curve can also vary.[24] The interval of time between the last SAMe dose and blood collection is therefore a factor that determines blood SAMe concentration. In addition, we do not know how plasma levels of SAMe and related intermediates correlate with those found at the level of the brain, where it presumably exerts its psychotropic effects. This makes it difficult to extrapolate

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between plasma levels and treatment response. It should be noted, however, that not all antidepressants have a linear dose-response curve,[25] and this may reflect a limited association between plasma levels and efficacy. This finding should therefore not cast doubt on the antidepressant efficacy of SAMe. Future investigations would benefit from collection of blood samples for analyses of SAMe and its intermediates at several interim time points between randomization and completion of the study in order to evaluate the course or any fluctuations in plasma levels.

Even without this limitation, the sample may have been too small to detect any changes, or there may be a ceiling effect, given that patients received high doses (1,600 mg/d) of SAMe, which could result in saturation of the relevant pathways and receptors. Given that there is no consensus on a maximum dose of SAMe and that our clinical practice experience has shown that many patients require doses in the range of 2,000 to 3,000 mg/d, further dose-finding studies may be called for in which plasma levels of SAMe and related intermediates could be examined for associations with dose and response.

Our study is limited by the relatively small patient sample and the short term (6 weeks) of the trial, which does not allow us to determine whether longer-term treatment would have resulted in different levels of the one-carbon intermediates. As discussed in the Results section, we obtained pretreatment and posttreatment blood samples for only 35 of the 55 subjects who completed the study. We compared demographic and clinical characteristics in the 35 sampled patients against the 38 nonsampled patients and found no significant differences in age, sex, age at depressive onset, number of lifetime depressive episodes, duration of current depressive episode, and baseline severity of depression ($P > .05$ for all comparisons; data not shown), suggesting that the sampled patients are a reasonable representation of the parent study sample.

We do not know whether patients were taking B-vitamin supplements such as vitamin B_{12} or folate, and we did not measure plasma B_{12} levels in any of our patients; supplementation could conceivably have had an impact on the efficacy findings of the main outcome article, since these vitamins may facilitate the metabolism of HCY in some cases of hyperhomocysteinemia,[12] and the addition of folate and vitamin B_{12} supplements for patients taking SAMe has been recommended.[12]

Another limitation in our study is that patients were allowed only SSRIs and SNRIs, so the findings may not be generalizable to patients who are taking other antidepressants. Finally, our study did not have a comparison arm of nondepressed patients, who could in theory have had different degrees of SAMe-related change in the one-carbon intermediates compared to their depressed counterparts. Given what we have learned from the myriad studies that have identified putative biomarkers of depression,[26,27] it is reasonable to suggest that one-carbon cycle–related differences may exist between depressed individuals and healthy controls.

Our results support the recommendation of Alpert et al[12] that, at least in the short term, it should not be necessary to monitor tHCY levels in patients taking SAMe, unless they have a significant personal history or family history of cardiovascular illness or are already known to have significantly elevated tHCY levels.[12] In the absence of more data about the impact of elevated levels of SAH, it is not clear whether monitoring SAH in individuals receiving SAMe would be desirable. Further investigation is necessary to better clarify the role of SAH in the treatment of depression and its relationship with SAMe.

Drug names: mirtazapine (Remeron and others), riluzole (Rilutek and others).

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and bupropion in major depressive disorder; and receives copyright royalties for the following Massachusetts General Hospital assessment tools: the Cognitive and Physical Functioning Questionnaire, the Sexual Functioning Inventory, the Antidepressant Treatment Response Questionnaire, the Discontinuation-Emergent Sign and Symptom scale, and SAFER. **Dr Papakostas** has served as a consultant for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Evotec AG, Inflabloc, Jazz, Otsuka, Pamlab, Pfizer, Pierre Fabre, Shire, and Wyeth; has received honoraria from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Evotec AG, GlaxoSmithKline, Inflabloc, Jazz, Lundbeck, Otsuka, Pamlab, Pfizer, Pierre Fabre, Shire, Titan, and Wyeth; has received research support from Bristol-Myers Squibb, Forest, the National Institute of Mental Health, Pamlab, Pfizer, and Ridge Diagnostics (formerly known as Precision Human Biolaboratories); and has served on the speakers bureau for Bristol-Myers Squibb and Pfizer. **Dr Arning** reports no relevant conflicts of interest.

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