

Folate Supplementation: Is It Safe and Effective?

Sir: In the September 2008 issue of the *Journal*, Stahl¹ reviews L-methylfolate as a possibly helpful adjunctive antidepressant agent,¹ and Mischoulon and Fava² briefly review the evidence that folates, including folic acid, a stable synthetic substance, could be useful augmenting antidepressant agents. However, there is some evidence of possibly harmful or, at the least, disappointing effects of folate supplementation.

1. There has long been a concern that folate supplementation might mask, or even worsen, the manifestations of B₁₂-deficiency anemia. L-Methylfolate may be less likely to do this than folic acid.³
2. Folates are growth-promoting substances and therefore may in fact be dangerous at the early stage of tumor growth in colon cancer.⁴⁻⁶
3. Since folate deficiency has been linked with elevated homocysteine levels, which in turn are linked to vascular pathology, there was hope that folate supplementation might be beneficial in promoting vascular health and slowing the rate of cognitive decline. Folate supplementation has been disappointing in prevention of cardiovascular morbidity in recent studies.^{7,8} In one community study,⁹ higher intake of folate was associated with a decline in cognition, and B vitamin administration has not been associated with a decrease in dementia.^{10,11}
4. A recent study¹² showed that administration of B vitamins, including B₁₂ and folic acid, led to a decrease in homocysteine levels without decreasing depression severity or incidence.
5. The use of synthetic folic acid may result in unmetabolized folic acid in the serum. The consequences of this are unknown.^{3,4}

It is not yet clear that folates will be safe and effective adjunctive agents in treating depression, particularly if the patient is B₁₂ deficient.

Dr. Frankenburg reports no financial or other relationship relevant to the subject of this letter.

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Drs. Mischoulon, Fava, and Stahl Reply

Sir: We appreciate Dr. Frankenburg's thoughtful letter outlining her reservations about the proposed use of folate supplementation in the psychiatric field. Dr. Frankenburg points out a number of concerns regarding potentially harmful effects of folate. We have considered these issues and conducted some additional literature review to address her questions.

The possibility that folate supplementation might mask B₁₂-deficiency anemia is a valid and well-documented problem, and care needs to be taken in patients who may be vulnerable to such a deficiency. Certain folate forms such as L-methylfolate are not likely to mask a B₁₂ deficiency in the way folic acid might.¹⁻¹⁰ This form may therefore be preferable in cases in which there is a concern about B₁₂ deficiency, the latter of which should, of course, be corrected if identified.

Regarding the role of folates as tumor-promoting substances, there is evidence both for increasing and for reducing the risk of cancer. At this time, there are no published studies associating L-methylfolate with colorectal cancer, and certain folate forms such as leucovorin are routinely used for folate rescue from cancer chemotherapies. There is currently no definitive human study evidence supporting protective anticancer effects of folate supplementation, but several small intervention studies¹¹⁻¹⁹ have demonstrated that folate supplementation can improve or reverse surrogate end point biomarkers of colorectal cancer, and some epidemiologic studies²⁰⁻²⁷ have shown a beneficial effect of folate-containing multivitamin supplements on colorectal cancer risk and mortality. Physicians should certainly exercise caution with at-risk patients, such as those with colon polyps or a strong family history of colorectal cancer, prior to initiating therapy with any folate form.

Regarding folate supplementation in the prevention of cardiovascular morbidity, it is true that reducing homocysteine with folate supplements did not improve cardiovascular morbidity in some studies. However, there were no folate-related adverse effects per se, and studies have found significant benefits from folate in comorbid disorders such as stroke.²⁸ L-Methylfolate has not been studied in reducing morbidity associated with cardiovascular disease, but it has demonstrated a

significant improvement in endothelial function and vasodilation.^{29–32} Regarding the potential association between folate and decline in cognition, folic acid dosed at 800 µg or greater leads to unmetabolized folic acid in the serum,^{33,34} which can reduce the amount of L-methylfolate that reaches the brain, thus leading to toxic complications,^{35,36} reduction in monoamines,³⁷ and a potential increase in depression.³⁸ L-Methylfolate is able to cross the blood-brain barrier^{39–41} and may therefore be safer in elderly populations in whom cognition decline may be a concern; it may also be less likely to result in other toxic complications such as the reduction of natural killer cell cytotoxicity in postmenopausal women.⁴²

While B vitamin administration has decreased homocysteine levels without decreasing a risk for developing depression in an elderly population, these data were not based on prospectively treating depressive episodes. The article by Ford and colleagues⁴³ referenced in Dr. Frankenburg's letter is a prospective trial, but the main outcome was prevention, and the investigators excluded individuals who were clinically depressed. B vitamins did not protect this population from developing depression even though there was a significant drop in homocysteine. However, all prospective trials with folate in patients experiencing a depressive episode have, to our knowledge, been positive.^{44–52} Homocysteine has not always been observed to be a risk factor for depression, but most studies have found that low folate levels predict depression or a poor response to antidepressant therapy.^{53–56} A recent cross-sectional study of 3752 older men⁵⁷ suggested that there is an association between higher concentrations of homocysteine and an increased risk of depression and that lowering homocysteine could significantly reduce the odds of depression. Likewise, homocysteine may be a marker for reduced methyl groups, but is not known to be directly associated with the pathology of depression or the synthesis of monoamines.⁵⁸

It is not yet clear whether folates will ultimately be shown to be safe and effective adjunctive agents in treating depression. However, folate supplementation has demonstrated symptomatic improvement in several small studies with depressed patients both with and without a folate deficiency,^{44–52} although it has not been studied in the context of B₁₂ deficiency. There are, of course, risks associated with any medication, and clinicians must carefully weigh these risks against the benefits. Given the availability of L-methylfolate, this compound may ultimately prove to be a better choice than standard folic acid to minimize some of the aforementioned risks. In the absence of larger, controlled clinical trials, we recommend that physicians proceed with usual caution when prescribing any type of folate supplementation.

Drs. Mischoulon, Fava, and Stahl have financial associations with many companies that produce psychoactive pharmaceutical agents; these include consultancies, receipt of research grants and honoraria, participation in advisory boards, equity holdings, and patents.

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Lupus Anticoagulant and Anticardiolipin Antibodies in Serum of Patients Treated With Risperidone

Sir: In recent years, several studies¹ reported an increased rate of cerebrovascular events in patients treated with risperidone. In April 2005, the U.S. Food and Drug Administration issued a health advisory warning concerning an increased risk of death among patients with dementia who were treated with atypical antipsychotic agents.²

Risperidone is a second-generation antipsychotic agent that reportedly increases the blood level of glucose and alters changes in lipid profiles. These factors may account for the increased rate of cerebrovascular events.

An association between antipsychotic treatment and increased antiphospholipid antibodies (aPLs) was reported, but was not linked with vascular events.^{3,4} Our investigation sought to determine whether aPL levels increased in patients receiving risperidone.

Method. Thirty patients with schizophrenia according to DSM-IV were included in the study, which was conducted from December 1, 2004, to December 31, 2007. The mean age was 31.9 years (range, 19–50 years). Patients with antecedents of cardiovascular disease, coagulation disturbances, and autoimmune diseases, as well as those receiving antipsychotics other than risperidone, were excluded. All patients had received risperidone for at least 3 months prior to the study.

Blood tests included cell blood count, prothrombin time, partial thromboplastin time, anticardiolipin antibody (aCL) lev-

Table 1. Characteristics of Risperidone-Treated Schizophrenia Patients and Results of Blood Examinations

Patient No.	Age, y	Gender	PT, %	PTT, s	aCL-IgM, U/mL	aCL-IgG, U/mL	LA Screen/ LA Confirm	DRVVT
1	25	M	96	25.9	7	23*	1.45*	45.4*
2	28	M	98	29.4	11	7	1.39*	41.4*
3	29	F	86	34.1	4	6	1.29	39.3
4	29	M	94	31.2	2	8	1.3	39.5
5	19	F	92	32.7	6	10	1.2	37.7
6	39	M	112	29.5	4	6	1.32	38.7
7	26	M	103	24.9	3	8	1.05	24.3
8	23	M	89	31.0	4	8	1.11	32.7
9	44	F	103	32.9	8	3	1.19	36.4
10	25	F	117	33.0	7	8	1.1	30.3
11	49	F	102	29.3	4	7	1.11	32.7
12	32	M	85	29.5	12	14	1.27	36.2
13	46	M	136	28.5	7	3	0.96	26.2
14	36	M	101	29.8	21*	13	...	36.0
15	24	F	114	29.7	2	9	1.25	36.3
16	22	M	97	33.9	8	9	1.38*	40.6*
17	45	F	120	45.2*	22*	5	1.96*	62.6*
18	36	M	82	30.8	4	7	...	35.3
19	26	M	88	30.4	3	7	1.32	37.4
20	25	M	80	35.2*	2	6	1.3	39.3
21	32	F	117	30.4	11	8	1.27	36.3
22	42	M	93	24.8	1	2	1.27	36.5
23	22	F	105	28.5	5	6	1.26	35.7
24	28	M	115	31.6	3	4	1.22	35.1
25	35	M	96	34.9*	5	5	1.25	39.2
26	31	M	90	34.0	6	11	1.17	34.8
27	45	F	96	26.2	3	5	1.17	32.4
28	27	M	73	33.4	2	5	1.05	32.1
29	25	M	74	32.9	1	14	1.1	33.1
30	42	M	127	32.7	4	3	1.39*	41.6*

*Positive values.

Abbreviations: aCL = anticardiolipin antibodies, DRVVT = dilute Russell's viper venom time,

Ig = immunoglobulin, LA = lupus anticoagulant, PT = prothrombin time, PTT = partial thromboplastin time.

Symbol: ... = not available.

els (immunoglobulin [Ig] G and IgM), and lupus anticoagulant (LA) levels (through dilute Russell's viper venom time and LA screen/LA confirm). Anticardiolipin antibody IgG levels were considered positive if > 18 U/mL, and IgM levels were considered positive if > 15 U/mL. Patients with positive LA and/or aCL results were followed for a period of 37 months. The statistical analysis was performed using binomial tests. Written informed consent was obtained from all participants, and the study was approved by the local ethical committee.

Results. Most of the patients received concomitant medication, such as paroxetine, biperiden, oxazepam, clonazepam, carbamazepine, nifedipine, and folic acid. One patient received only risperidone. In 6 patients (20%), we detected abnormal values in the LA or aCL levels. We found positive LA values in 5 patients (16.7%) and high aCL values in 3 patients (10%). Two patients (6.7%) had abnormal values in both LA and aCL levels (Table 1). Two additional patients had abnormal values of partial thromboplastin time but without positive LA or aCL values. In patients with high aCL values, 2 had mildly increased values in IgM and 1 had mildly increased values in IgG levels. During the 37-month follow-up, no patients had cerebrovascular events or antiphospholipid syndrome.

The statistical analysis revealed that patients treated with risperidone had significantly increased serum anticardiolipin antibodies compared with the general population. In a normal healthy population, aCL can be detected in approximately 3% to 5%⁵ and LA in approximately 1% to 2%⁶ of the samples. The

presence of LA in our patients was statistically significant ($p < .0001$) in comparison with a healthy population, while for patients with positive values for both LA and aCL, the p value was $< .008$.

This is the first report on the presence of aPL in patients receiving risperidone. Lupus anticoagulant and aCL levels were markedly higher than in the general population, although no cerebrovascular events were reported in these patients. However, an association between risperidone treatment and strokes was previously reported⁷⁻¹⁰; thus, the presence of aPL in these patients should be taken seriously.

A large-scale investigation of aPL in the serum of patients treated with risperidone is warranted, and for patients with positive aPL results, a more extensive follow-up should be required.

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