Folate Supplementation: Is It Safe and Effective?

Sir: In the September 2008 issue of the *Journal*, Stahl[1] reviews L-methylfolate as a possibly helpful adjunctive antidepressant agent,[1] and Mischoulon and Fava[2] 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 B_{12}-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 study[12] showed that administration of B vitamins, including B_{12} 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 B_{12} deficient.

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

REFERENCES

1. Stahl SM. L-Methylfolate: a vitamin for your monoamines [BRAINSTORMS]. J Clin Psychiatry 2008;69(9):1352–1353
2. Mischoulon D, Fava M. Are nutritional supplements ready for prime time? [ASCP CORNER] J Clin Psychiatry 2008;69(9): 1497–1498
3. Kelly P, McPartlin J, Goggins M, et al. Unmetabolized folic acid in serum: acute studies in subjects consuming fortified food and supplements. Am J Clin Nutr 1997;65(6):1790–1795
4. Smith AD, Kim Y-I, Refsum H. Is folic acid good for everyone? Am J Clin Nutr 2008;87(3):517–533
5. Kim Y-I. Will mandatory folic acid fortification prevent or promote cancer? Am J Clin Nutr 2004;80(5):1123–1128
6. Mason JB, Dickstein A, Jacques PF, et al. A temporal association between folic acid fortification and an increase in colorectal cancer rates may be illuminating important biological principles: a hypothesis. Cancer Epidemiol Biomarkers Prev 2007;16(7):1325–1329
7. Albert CM, Cook NR, Gaziano JM, et al. Effect of folic acid and B vitamins on risk of cardiovascular events and total mortality among women at high risk for cardiovascular disease: a randomized trial. JAMA 2008;299(17):2027–2036
8. Ebbing M, Bleie O, Ueland PM, et al. Mortality and cardiovascular events in patients treated with homocysteine-lowering B vitamins after coronary angiography. JAMA 2008;300(7):795–804
9. Morris MC, Evans DA, Bienias JL, et al. Dietary folate and vitamin B_{12} intake and cognitive decline among community-dwelling older persons. Arch Neurol 2005;62(4):641–645
10. McMahon JA, Green TJ, Skeaff CM, et al. A controlled trial of homocysteine lowering and cognitive performance. N Engl J Med 2006;354(26):2764–2772
11. Aisen PS, Schneider LS, Sano M, et al. High-dose B vitamin supplementation and cognitive decline in Alzheimer disease: a randomized controlled trial. JAMA 2008;300(15):1774–1783
12. Ford AH, Flicker L, Thomas J, et al. Vitamins B_{12}, B_6, and folic acid for onset of depressive symptoms in older men: results from a 2-year placebo-controlled randomized trial. J Clin Psychiatry 2008;69(8):1203–1209

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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 B_{12}-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 B_{12} deficiency in the way folic acid might.[1–10] This form may therefore be preferable in cases in which there is a concern about B_{12} 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 studies[11–19] have demonstrated that folate supplementation can improve or reverse surrogate end point biomarkers of colorectal cancer, and some epidemiologic studies[20–27] 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 colleagues[43] 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 men[57] 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 B_{12} 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.

REFERENCES

1. Scott JM, Weir DG. The methyl folate trap: a physiological response in man to prevent methyl group deficiency in kwashiorkor (methionine deficiency) and an explanation for folic-acid induced exacerbation of subacute combined degeneration in pernicious anaemia. Lancet 1981;2(8242):337–340
2. Stroes ES, van Faassen EE, Yo M, et al. Folic acid reverts dysfunction of endothelial nitric oxide synthase. Circ Res 2000;86(11):1129–1134
3. Hoffbrand AV, Jackson BF. Correction of the DNA synthesis defect in vitamin B_{12} deficiency by tetrahydrofolate: evidence in favour of the methyl-folate trap hypothesis as the cause of megaloblastic anaemia in vitamin B_{12} deficiency. Br J Haematol 1993;83(4):643–647
4. Baumgartner ER, Stokstad EL, Wick SH, et al. Comparison of folic acid coenzyme distribution patterns in patients with methylenetetrahydrofolate reductase and methionine synthetase deficiencies. Pediatr Res 1985;19(12):1288–1292
5. Fujii K, Nagasaki T, Huennekens FM. Accumulation of 5-methyltetrahydrofolate in cobalamin-deficient L1210 mouse leukemia cells. J Biol Chem 1982;257(5):2144–2146
6. Shane B, Stokstad EL. Vitamin B_{12}–folate interrelationships. Annu Rev Nutr 1985;5:115–141
7. Fowler B, Whitehouse C, Wenzel F, et al. Methionine and serine formation in control and mutant human cultured fibroblasts: evidence for methyl trapping and characterization of remethylation defects. Pediatr Res 1997;41(1):145–151
8. Horne DW, Briggs WT. Effect of dietary and nitrous oxide-induced vitamin B-12 deficiency on uptake of 5-methyltetrahydrofolate by isolated rat hepatocytes. J Nutr 1980;110(2):223–230
9. Sauer H, Wilmanns W. Cobalamin dependent methionine synthesis and methyl-folate-trap in human vitamin B_{12} deficiency. Br J Haematol 1977;36(2):189–198
10. Shin YS, Beuhring KU, Stokstad EL. The relationships between vitamin B_{12} and folic acid and the effect of methionine on folate metabolism. Mol Cell Biochem 1975;9(2):97–108
11. Cravo M, Fidalgo P, Pereira AD, et al. DNA methylation as an intermediate biomarker in colorectal cancer: modulation by folic acid supplementation. Eur J Cancer Prev 1994;3(6):473–479
12. Cravo ML, Pinto AG, Chaves P, et al. Effect of folate supplementation on DNA methylation of rectal mucosa in patients with colonic adenomas: correlation with nutrient intake. Clin Nutr 1998;17(2):45–49
13. Paspatis GA, Karamanolis DG. Folate supplementation and adenomatous colonic polyps. Dis Colon Rectum 1994;37(12):1340–1341
14. Kim YI, Baik HW, Fawaz K, et al. Effects of folate supplementation on two provisional molecular markers of colon cancer: a prospective randomized trial. Am J Gastroenterol 2001;96(1):184–195
15. Khosraviani K, Weir HP, Hamilton P, et al. Effect of folate supplementation on mucosal cell proliferation in high risk patients for colon cancer. Gut 2002;51(2):195–199
16. Biasco G, Zannoni U, Paganelli GM, et al. Folic acid supplementation and cell kinetics of rectal mucosa in patients with ulcerative colitis. Cancer Epidemiol Biomarkers Prev 1997;6(6):469–471
17. Lashner BA, Shapiro BD, Husain A, et al. Evaluation of the usefulness of testing for p53 mutations in colorectal cancer surveillance for ulcerative colitis. Am J Gastroenterol 1999;94(2):456–462
18. Patra SK, Patra A, Zhao H. DNA methyltransferase and demethylase in human prostate cancer. Mol Carcinog 2002;33(3):163–171
19. Pogribny I, Yi P, James SJ. A sensitive new method for rapid detection of abnormal methylation patterns in global DNA and within CpG islands. Biochem Biophys Res Commun 1999;262(3):624–628
20. Wolpin BM, Wei EK, Ng K, et al. Prediagnostic plasma folate and the risk of death in patients with colorectal cancer. J Clin Oncol 2008;26(19):3222–3228
21. Sanjoaquin MA, Allen N, Couto E, et al. Folate intake and colorectal cancer risk: a meta analytical approach. Int J Cancer 2005;113(5):825–828
22. Figueiredo JC, Levine AJ, Grau MV, et al. Colorectal adenomas in a randomized folate trial: the role of baseline dietary and circulating folate levels. Cancer Epidemiol Biomarkers Prev 2008;17(10):2625–2631
23. Jaszewski R, Misra S, Tobi M, et al. Folic acid supplementation inhibits recurrence of colorectal adenomas: a randomized chemoprevention trial. World J Gastroenterol 2008;14(28):4492–4498
24. Schernhammer ES, Ogino S, Fuchs CS. Folate and vitamin B_6 intake and risk of colon cancer in relation to p53 expression. Gastroenterology 2008;135(3):770–780
25. Giovannucci E, Rimm EB, Ascherio A, et al. Alcohol, low-methionine–low-folate diets, and risk of colon cancer in men. J Natl Cancer Inst 1995;87(4):265–273
26. Giovannucci E, Stampfer MJ, Colditz GA, et al. Multivitamin use, folate, and colon cancer in women in the Nurses' Health Study. Ann Intern Med 1998;129(7):517–524
27. Jacobs EJ, Connell CJ, Patel AV, et al. Multivitamin use and colon cancer mortality in the Cancer Prevention Study II cohort

(United States). Cancer Causes Control 2001;12(10):927–934
28. Bønaa KH, Njølstad I, Ueland PM, et al; NORVIT Trial Investigators. Homocysteine lowering and cardiovascular events after acute myocardial infarction. N Engl J Med 2006;354(15):1578–1588
29. Antoniades C, Shirodaria C, Warrick N, et al. 5-methyltetrahydrofolate rapidly improves endothelial function and decreases superoxide production in human vessels: effects on vascular tetrahydrobiopterin availability and endothelial nitric oxide synthase coupling. Circulation 2006;114(11):1193–1201
30. Verhaar MC, Wever RM, Kastelein JJ, et al. 5-methyltetrahydrofolate, the active form of folic acid, restores endothelial function in familial hypercholesterolemia. Circulation 1998;97(3):237–241
31. van Etten RW, de Koning EJ, Verhaar MC, et al. Impaired NO-dependent vasodilation in patients with Type II (non-insulin-dependent) diabetes mellitus is restored by acute administration of folate. Diabetologia 2002;45(7):1004–1010
32. De Vriese AS, Van de Voorde J, Blom HJ, et al. The impaired renal vasodilator response attributed to endothelium-derived hyperpolarizing factor in streptozotocin-induced diabetic rats is restored by 5-methyltetrahydrofolate. Diabetologia 2000;43(9):1116–1125
33. Kelly P, McPartlin J, Goggins M, et al. Unmetabolized folic acid in serum: acute studies in subjects consuming fortified food and supplements. Am J Clin Nutr 1997;65(6):1790–1795
34. Kalmbach RD, Choumenkovitch SF, Troen AM, et al. Circulating folic acid in plasma: relation to folic acid fortification. Am J Clin Nutr 2008;88(3):763–768
35. Smith I, Howells DW, Hyland K. Pteridines and mono-amines: relevance to neurological damage. Postgrad Med J 1986;62(724): 113–123
36. Smith I, Hyland K, Kendall B. Clinical role of pteridine therapy in tetrahydrobiopterin deficiency. J Inherit Metab Dis 1985;8 (suppl 1):39–45
37. Hunter R, Barnes J, Curzon G, et al. Effect of folic acid by mouth on cerebrospinal fluid homovanillic acid and 5-hydroxyindoleacetic acid concentration. J Neurol Neurosurg Psychiatry 1971;34(5):571–575
38. Aisen PS, Schneider LS, Sano M, et al. High-dose B vitamin supplementation and cognitive decline in Alzheimer disease: a randomized controlled trial. JAMA 2008;300(15):1774–1783
39. Spector R, Lorenzo AV. Folate transport in the central nervous system. Am J Physiol 1975;229(3):777–782
40. Wu D, Pardridge WM. Blood-brain barrier transport of reduced folic acid. Pharm Res 1999;16(3):415–419
41. Levitt M, Nixon PF, Pincus JH, et al. Transport characteristics of folates in cerebrospinal fluid; a study utilizing doubly labeled 5-methyltetrahydrofolate and 5-formyltetrahydrofolate. J Clin Invest 1971;50(6):1301–1308
42. Troen AM, Mitchell B, Sorensen B, et al. Unmetabolized folic acid in plasma is associated with reduced natural killer cell cytotoxicity among postmenopausal women. J Nutr 2006;136(1):189–194
43. Ford AH, Flicker L, Thomas J, et al. Vitamins B_{12}, B_6, and folic acid for onset of depressive symptoms in older men: results from a 2-year placebo-controlled randomized trial. J Clin Psychiatry 2008;69(8): 1203–1209
44. Godfrey PS, Toone BK, Carney MW, et al. Enhancement of recovery from psychiatric illness by methylfolate. Lancet 1990;336(8712): 392–395
45. Passeri M, Cucinotta P, Abate G, et al. "Oral" 5-MTHF acid in senile organic mental disorders with depression: results of a double-blind multicenter study. Aging (Milano) 1993;5(1):63–71
46. Alpert JE, Mischoulon D, Rubenstein DEF, et al. Folinic acid (Leucovorin) as an adjunctive treatment for SSRI-refractory depression. Ann Clin Psychiatry 2002;14(1):33–38
47. Guaraldi GP, Fava M, Mazzi F, et al. An open trial of methyltetrahydrofolate in elderly depressed patients. Ann Clin Psychiatry 1993;5(2):101–105
48. Reynolds EH, Crellin R, Bottiglieri T, et al. Methylfolate as monotherapy in depression: a pilot randomized controlled trial. Presented at the annual meeting of the Royal College of Psychiatrists; July 24–27, 1992; Edinburgh, UK
49. Di Palma C, Urani R, Agricola R, et al. Is methylfolate effective in relieving major depression in chronic alcoholics? a hypothesis of treatment. Curr Ther Res 1994;55(5):559–568
50. Coppen A, Bailey J. Enhancement of the antidepressant action of fluoxetine by folic acid: a randomized, placebo controlled trial. J Affect Disord 2000;60(2):121–130
51. Coppen A, Chaudhry C, Swade C. Folic acid enhances lithium prophylaxis. J Affect Disord 1986;10(1):9–13
52. Resler G, Lavie R, Campos J, et al. Effect of folic acid combined with fluoxetine in patients with major depression on plasma homocysteine and vitamin B_{12}, and serotonin levels in lymphocytes. Neuroimmunomodulation 2008;15(3):145–152
53. Morris MS, Fava M, Jacques PF, et al. Depression and folate status in the US population. Psychother Psychosom 2003;72(2):80–87
54. Papakostas GI, Petersen T, Lebowitz BD, et al. The relationship between serum folate, vitamin B_{12}, and homocysteine levels in major depressive disorder and the timing of improvement with fluoxetine. Int J Neuropsychopharmacol 2005;8(4):523–528. Epub 2005 May 9
55. Papakostas GI, Petersen T, Mischoulon D, et al. Serum folate, vitamin B_{12}, and homocysteine in major depressive disorder, pt 2: predictors of relapse during the continuation phase of pharmacotherapy. J Clin Psychiatry 2004;65(8):1096–1098
56. Fava M, Borus JS, Alpert JE, et al. Folate, vitamin B_{12}, and homocysteine in major depressive disorder. Am J Psychiatry 1997;154(3): 426–428
57. Almeida OP, McCaul K, Hankey GJ, et al. Homocysteine and depression in later life. Arch Gen Psychiatry 2008;65(11):1286–1294
58. Stahl SM. Stahl's Essential Psychopharmacology. 3rd ed. New York, NY: Cambridge University Press; 2008

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

Sir: In recent years, several studies[1] 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 autonomic 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 reported[7–10]; 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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REFERENCES

1. Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. JAMA 2005;294(15):1934–1943

2. Center for Drug Evaluation and Research. Deaths with antipsychotics in elderly patients with behavioral disturbances. April 11, 2005. US Food and Drug Administration Web site. Drug Information page. Available at: http://www.fda.gov/CDER/drug/advisory/antipsychotics.htm. Accessibility verified Feb 9, 2009
3. Schwartz M, Rochas M, Weller B, et al. High association of anticardiolipin antibodies with psychosis. J Clin Psychiatry 1998;59(1):20–23
4. Schwartz M, Rochas M, Toubi E, et al. The presence of lupus anticoagulant and anticardiolipin antibodies in patients undergoing long-term neuroleptic treatment. J Psychiatry Neurosci 1999;24(4):351–352
5. Zuckerman E, Toubi E, Shiran A, et al. Anticardiolipin antibodies and acute myocardial infarction in nonsystemic lupus erythematosus patients: a controlled prospective study. Am J Med 1996;101(4):381–386
6. Brandt JT, Triplett DA, Alving B, et al, on behalf of the Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of the ISTH. Criteria for the diagnosis of lupus anticoagulant: an update. Thromb Haemost 1995;74(4):1185–1190
7. Janssen-Ortho, Inc. Risperdal (risperidone) and cerebrovascular adverse events in placebo-controlled dementia trials. Letter to Health Care Professionals. Oct 11, 2002. Accessed Oct 17, 2007. Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/risperdal_hpc-cps-eng.pdf
8. US Food & Drug Administration. 2003 Safety alert: Risperdal (risperidone).Washington, DC: US Dept Health Human Services. April 16, 2003. Available at: http://www.fda.gov/medwatch/SAFETY/2003/safety03.htm#risper. Accessibility verified Feb 9, 2009
9. Percudani M, Barbui C, Fortino I, et al. Second-generation antipsychotics and risk of cerebrovascular accidents in the elderly. J Clin Psychopharmacol 2005;25(5):468–470
10. Douglas IJ, Smeeth L. Exposure to antipsychotics and risk of stroke: self-controlled case series study. BMJ 2008;337:a1227

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