Serum Folate, Vitamin B_{12}, and Homocysteine in Major Depressive Disorder, Part 2: Predictors of Relapse During the Continuation Phase of Pharmacotherapy

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Objective: In the present study, we assessed the relationship between serum folate, vitamin B_{12}, and homocysteine levels on the rate of relapse in outpatients with remitted major depressive disorder (MDD) during a 28-week continuation phase of treatment with fluoxetine.

Method: Seventy-one outpatients (mean ± SD age = 40.2 ± 11.1 years; 56.3% women) with MDD (as assessed with the Structured Clinical Interview for DSM-III-R) who had remitted and who were enrolled in the continuation phase of treatment with fluoxetine had serum folate, vitamin B_{12}, and homocysteine measurements completed at baseline (prior to acute-phase treatment). Patients were followed for 28 weeks of continued treatment with fluoxetine 40 mg/day to monitor for depressive relapse. Folate levels were classified as either low (≤ 2.5 ng/mL) or normal. Vitamin B_{12} levels were classified as either low (≤ 200 pg/mL) or normal. Homocysteine levels were classified as either elevated (≥ 13.2 μmol/L) or normal. With the use of separate logistic regressions, we then assessed the relationship between folate, vitamin B_{12}, and homocysteine level status and relapse. The study was conducted from November 1992 to January 1999.

Results: The presence of low serum folate levels ($p = .004$), but not low B_{12} ($p > .05$) or elevated homocysteine levels ($p > .05$), was associated with relapse during continuation treatment with fluoxetine. The relapse rates for patients with (N = 7) and without (N = 64) low folate levels were 42.9% versus 3.2%, respectively.

Conclusion: Low serum folate levels were found to place patients with remitted MDD at risk for depressive relapse during the continuation phase of treatment with fluoxetine.

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In a previous study[1] conducted by our group, we found that patients with major depressive disorder (MDD) who had pretreatment serum folate levels less than or equal to 2.5 ng/mL were less likely to respond to an 8-week, fixed-dose, open trial of 20 mg/day of fluoxetine. In part 1 of this report,[2] low serum folate levels were found to be associated with further treatment resistance among patients with fluoxetine-resistant MDD. Patients who achieved remission at the end of the 8-week trial had their fluoxetine dose increased to 40 mg/day and were enrolled in a 28-week continuation phase of treatment. The purpose of the present study was to assess whether the presence of low serum folate, low vitamin B_{12}, or elevated homocysteine levels predicted relapse in outpatients with remitted MDD during the continuation phase of treatment with fluoxetine.

METHOD

This study focuses on a 28-week continuation phase of treatment with 40 mg/day of fluoxetine in 71 outpatients (mean ± SD age = 40.2 ± 11.1 years; 56.3% women) with MDD (as assessed with the Structured Clinical Interview for DSM-III-R, Patient Edition [SCID-III-R]) who had

remitted following an initial response to a 20-mg/day, 8-week, fixed-dose, open trial of fluoxetine (see part 1 for details[2]). Remission was defined as a Hamilton Rating Scale for Depression (HAM-D-17) score ≤ 7 for at least 3 weeks.[3] Additionally, the continuation-phase study recruited only remitted subjects who had a history of chronic or recurrent MDD, defined as (1) a history of 3 or more major depressive episodes, with the prior episode no more than 2.5 years before the onset of the current episode; (2) diagnosis of the current episode as chronic (onset of continuous depressive symptoms ≥ 36 months prior to the study onset); (3) a history of poor interepisode recovery; or (4) comorbid MDD and dysthymia. The study was conducted from November 1992 to January 1999. All enrolled patients signed an Institutional Review Board–approved written informed consent form.

A total of 134 patients at the end of the open phase met the above criteria for entry into the continuation phase. Patients had their acute fluoxetine dose of 20 mg increased to 40 mg/day at the first continuation visit and were randomly assigned to cognitive-behavioral therapy (CBT) or medication management and followed for 28 weeks. The CBT protocol has been described elsewhere.[4] Psychopharmacologists were instructed not to make psychotherapy or behavioral interventions, following a standard protocol for medication management.[5]

All subjects were administered the HAM-D-17 at each study monthly visit during the 28 weeks of continuation therapy. Depressive relapse was defined as meeting SCID-III-R criteria for a new episode of MDD at any continuation visit or a HAM-D-17 score ≥ 15 at 2 consecutive visits. Relapse was confirmed by a follow-up visit 1 week later with another clinician, who was blinded to treatment status. All subjects who took at least 1 week of study medication and had at least 1 postbaseline efficacy assessment in the continuation phase were included in the intent-to-treat analysis. For demographic and laboratory variables, all values are mean ± SD unless otherwise stated.

Statistical Tests

Chi-square and t tests were used to compare patients in the continuation phase of the trial who did and did not have serum folate, vitamin B_{12}, or homocysteine levels assessed at baseline. Chi-square and t tests were used to compare patients with low (≤ 2.5 ng/mL) and normal folate levels with respect to age, gender, body mass index (BMI, in kg/m^2), and the severity of depression during the final visit for the acute phase of treatment as reflected by the HAM-D-17 total score during that visit. This comparison was repeated for the samples with low (≤ 200 pg/mL) and normal serum B_{12} levels and for the samples with elevated (≥ 13.2 μmol/L) and normal serum homocysteine levels. A logistic regression was performed with folate level status (low vs. normal), homocysteine level status (elevated vs. normal), and vitamin B_{12} level status (low vs. normal) as the independent variables and relapse as the dependent variable. For all analyses, statistical significance was set at $p \leq .05$. For demographic and laboratory variables, all values are mean ± SD unless otherwise stated.

RESULTS

The results of the acute and continuation phases of the trial are reported elsewhere.[4,6] In summary, CBT did not significantly prevent depressive relapse. Of the 134 patients enrolled in the continuation phase, 71 had serum folate, vitamin B_{12}, and homocysteine levels measured at baseline. Between patients enrolled in the continuation phase who did (N = 71) and did not (N = 63) have folate, B_{12}, or homocysteine levels measured at baseline, there was no statistically significant difference in gender ratio (40/71 women vs. 30/63 women, $p > .05$), age (40.2 ± 11.1 vs. 40.5 ± 9.1 years, $p > .05$), BMI in kg/m^2 (25.9 ± 5.1 vs. 26.2 ± 4.8, $p > .05$), duration of the current major depressive episode (3.8 ± 5.7 vs. 3.0 ± 6.0 years, $p > .05$), number of lifetime major depressive episodes (4.2 ± 5.4 vs. 5.4 ± 9.4, $p > .05$), age at onset of the first major depressive episode (22.9 ± 10.7 vs. 24.6 ± 14.1 years, $p > .05$), or the severity of depression during the baseline visit of the open trial as reflected by the HAM-D-17 total score (18.9 ± 2.9 vs. 18.6 ± 2.9, $p > .05$).

Of the 71 patients enrolled in the continuation phase who had serum folate levels measured at baseline, 7 (9.9%) had low folate levels while 64 (90.1%) had levels within normal limits. The mean folate level for our sample was 6.9 ± 5.6 ng/mL. Patients with low folate levels did not differ from patients with normal folate levels with respect to age in years (37.7 ± 11.9 vs. 40.3 ± 11.1), BMI in kg/m^2 (22.7 ± 2.3 vs. 26.0 ± 4.8), gender ratio (71.4% vs. 53.1% women), or HAM-D-17 scores during the final visit for the acute phase of the trial (3.4 ± 2.5 vs. 4.5 ± 2.2) ($p > .05$ for all comparisons).

Of the 71 patients who had serum vitamin B_{12} levels measured at baseline, 8 (11.3%) had low B_{12} levels while 63 (88.7%) had normal levels. The mean vitamin B_{12} level for our sample was 365.6 ± 184.7 pg/mL. Patients with low vitamin B_{12} levels did not differ from patients with normal vitamin B_{12} levels with respect to age in years (34.7 ± 12.6 vs. 40.7 ± 10.8), BMI in kg/m^2 (27.0 ± 6.8 vs. 25.7 ± 4.8), gender ratio (62.5% vs. 55.3% women), or HAM-D-17 scores during the final visit for the acute phase of the trial (3.5 ± 2.6 vs. 4.5 ± 2.1) ($p > .05$ for all comparisons).

Of the 71 patients who had serum homocysteine levels measured at baseline, 11 (15.5%) had elevated homocysteine levels while 60 (84.5%) had normal levels. The mean homocysteine level for our sample was 9.4 ± 3.8 μmol/L. Patients with elevated homocysteine levels did not differ from patients with normal homocysteine levels with respect to age in years (41.3 ± 11.6 vs. 39.9 ± 11.1), BMI

in kg/m^2 (27.7 ± 7.6 vs. 25.5 ± 4.5), gender ratio (63.6% vs. 55.7% women), or HAM-D-17 scores during the final visit for the acute phase of the trial (3.9 ± 2.5 vs. 4.4 ± 2.2) ($p > .05$ for all comparisons).

The presence of low serum folate levels ($\chi^2 = 8.072$, $p = .004$) but not low vitamin B_{12} ($p > .05$) or homocysteine levels at baseline ($p > .05$) was related to an increased risk of relapse during the continuation phase. Of the 7 patients with low serum folate levels, 3 (42.9%) relapsed, while of 64 patients with normal folate levels, 2 (3.1%) relapsed.

DISCUSSION

The results of the present study reveal a significant relationship between serum folate level status at baseline and the risk of subsequent relapse in patients with remitted MDD during the continuation phase of treatment with fluoxetine. Specifically, the presence of hypofolatemia was found to confer an increased risk of depressive relapse in these patients. In fact, while 42.9% of patients with low folate levels relapsed, only 3.1% of patients with normal folate levels relapsed. What was striking is that almost half of hypofolatemic patients relapsed despite having doubled their dose of fluoxetine at the onset of the continuation phase and while in full remission. Similar to our previous reports,[1,2] the presence of hyperhomocysteinemia or low vitamin B_{12} levels was not found to confer poorer prognosis in the present study. That B_{12} or homocysteine levels did not predict relapse suggests that the relationship between hypofolatemia and relapse most likely does not represent a nonspecific reflection of poor nutritional status, which may confer an increased risk of relapse for any number of reasons.

To our knowledge, the present study is the first to demonstrate an adverse impact of hypofolatemia on the course of remitted MDD. Whether supplementing folate improves the long-term outcome of MDD treatment is, at present, unclear, as there is a paucity of studies looking at the relationship between folate supplementation and long-term outcome in the treatment of MDD. A single study by Coppen and colleagues[7] (1986) involving 70 depressed outpatients treated with lithium and double-blind folate or placebo for 6 months revealed a significantly greater reduction in depressive symptoms in patients with MDD ($N = 53$), but not in patients with bipolar depression ($N = 17$), treated with lithium and adjunct folate rather than adjunct placebo ($p < .02$). Further studies exploring the role of various folates and *s*-adenosylmethionine (SAMe) in preventing depressive relapse are warranted.

Limitations

In addition to limitations stated in part 1 of this report,[2] one limitation that particularly applies to the present study is its very low relapse rate. This low relapse rate is likely to have been related to the study design, which included an increase in the dose of fluoxetine from 20 to 40 mg/day following acute treatment and also CBT for half of the subjects enrolled in the continuation phase. It is interesting that, despite the relatively small number of relapsers, the impact of low serum folate levels was highly significant. Hypothetically, in a less vigorously treated sample, other factors would have obscured the effect of low serum folate levels on relapse rates. Finally, another limitation of the present study is the relatively small sample size.

CONCLUSION

The results of the present study reveal a relationship between serum folate levels and depressive relapse in patients with remitted MDD during the continuation phase of treatment with fluoxetine. Specifically, the presence of hypofolatemia conferred an increased risk of depressive relapse, with striking differences in relapse rates.

Part 1 of this 2-part series appears in this issue on pages 1090–1095.

Drug names: fluoxetine (Prozac and others), lithium (Eskalith, Lithobid, and others).

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