

IS METHYLFOLATE EFFECTIVE IN RELIEVING MAJOR DEPRESSION IN CHRONIC ALCOHOLICS? A HYPOTHESIS OF TREATMENT

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ABSTRACT

Folate deficiency is often associated with depression. Chronic alcoholics, who usually present with reduced blood folate levels, are frequently affected by depression. After a 1-week run-in placebo period, 36 chronic alcoholics with major depression were treated with methylfolate (90 mg/d orally for 4 weeks) as an antidepressant. The surprisingly beneficial effects induced by methylfolate on depressive signs and symptoms of ethanol abusers should encourage more extensive experimental and clinical investigations to confirm these preliminary results. No adverse side effects were reported.

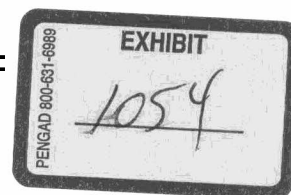
INTRODUCTION

Evidence in the literature suggests a relationship between depression and folate deficiency.¹⁻¹⁴ Folic acid derivatives are known to play a crucial role in the biosynthesis of serotonin and dopamine,¹⁵⁻¹⁷ both of which are implicated in the pathogenesis of depressive disorders.

Depression is a frequent complication in chronic alcoholics¹⁸⁻²²; its incidence rate is reported to be 28% to 70%.¹⁹⁻²² Alcoholics usually present with blood folate deficiency,²³⁻²⁸ which is often associated with depression and lassitude.²⁶⁻²⁸ In a double-blind controlled trial by Coppen et al,²⁹ 102 patients receiving lithium were randomized to receive treatment with either small supplements of 200 µg of folic acid daily or placebo. All of the patients receiving folic acid supplements showed a significant association between affective morbidity index (AMI) scores and end-of-trial plasma folate levels. Moreover, unipolar patients with plasma folate levels greater than 13 µg/L had significantly lower scores on Beck's Inventory for mood and AMI.

Godfrey et al³⁰ compared oral methylfolate (15 mg/d) with placebo in addition to standard psychotropic treatments in 41 acutely depressed and schizophrenic inpatients with borderline or definite (<200 µg/L) red blood cell (RBC) folate deficiency. Unlike placebo, methylfolate significantly im-

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proved clinical and social recovery in both depressed and schizophrenic patients after 6 months of treatment.

Crellin et al³¹ carried out a pilot double-blind trial comparing methylfolate (50 mg/d) versus amitriptyline (150 mg/d), each as monotherapy for 6 weeks, in 31 outpatients with moderate depression. Most of the patients had normal RBC folate levels. Patients with a 25% decrease in Montgomery-Åsberg Depression Scale (MADS) during a 2-week placebo run-in period were excluded. At the end of 6 weeks of treatment, the MADS response rate was very similar with methylfolate and amitriptyline. Surprisingly, 2 of 3 amitriptyline-treated nonresponders improved when crossed over to methylfolate. It is noteworthy that methylfolate-treated responders showed striking increases in RBC folate levels compared with nonresponders. Passeri et al³² found that methylfolate (50 mg/d orally) was as effective as trazodone (100 mg/d orally) in improving depressive symptoms in geriatric patients, as rated on the Hamilton rating scale for depression (HRSD), irrespective of folate status.

Guaraldi et al³³ demonstrated the antidepressant activity of methylfolate 50 mg/d for 5 weeks in geriatric normofolatememic nondemented patients with depression.

Pichot et al³⁴ performed a controlled study in 18 inpatients with major depression and a history of suicidal behavior versus 18 inpatients with major depression and no suicidal history. RBC folate levels were significantly lower in the suicidal depressed patients than in controls (190.1 ± 42.3 ng/mL vs 289.7 ± 87.8 ng/mL, $P < 0.01$). Results in the Pichot et al study suggest a role for folic acid as a biological correlate of suicidal behavior.

In the framework of the data reported in the literature,³⁵ we decided to study the effects and tolerability of methylfolate on depressive signs and symptoms in chronic ethanol abusers. Methylfolate, N⁵-methyltetrahydrofolic acid, donates its methyl group to homocysteine to form methionine, which in turn is activated to S-adenosyl-L-methionine (SAME).³⁵ SAME is the sole methyl donor in the central nervous system in a number of methylation reactions involving proteins, nucleoproteins, membrane phospholipids, neurotransmitters, and monoamines.^{15,36} In addition, SAME has antidepressant activity,³⁷⁻³⁹ and, in a recent investigation, we demonstrated its beneficial effects in depressed chronic alcoholics.⁴⁰

PATIENTS AND METHODS

Thirty-six inpatients (22 men and 14 women), aged 22 to 79 years (mean age, 42.04 ± 2.59 SE years) were enrolled from two psychiatric centers specializing in the treatment of drug and alcohol abuse. Twenty-two pa-

tients, 14 men and 8 women, were in their 40s and 60s. All of the patients gave informed consent. Diagnoses were made according to *DSM-III-R* criteria for major depression and alcohol dependence.

The major inclusion criterion for depression was a baseline score of 17 on 21-item HRSD. For chronic alcoholism the criterion was a history of ethanol ingestion at ≥ 150 g daily for at least 6 months, accompanied by mean corpuscular volume (MCV) values $>97 \mu\text{m}^3$, gamma glutamyl-transpeptidase (γGT) values >50 U/L, aspartate aminotransferase (AST) >27 U/L and alanine aminotransferase (ALT) >21 U/L, and alkaline phosphatase (AP) values >40 U/L. Patients with liver cirrhosis, psychoses, overt suicidal ideation, severe renal, cardiovascular, endocrine, or neurologic impairment, pregnant or nursing women, opiate abusers, and patients who tested positive for hepatitis B or human immunodeficiency virus were excluded.

Before starting the trial, patients underwent a 7-day placebo run-in period. Patients who exhibited an improvement of 20% or more in the HRSD score were regarded as placebo responders and were excluded. Patients were strongly advised to abstain from ethanol consumption but patient compliance cannot be assumed.

Participants received oral methylfolate 90 mg daily (30 mg TID at 8 AM and 2 and 8 PM). The duration of treatment was 4 weeks.

Patients were evaluated at baseline and on days 7, 14, 21, and 28 of treatment with the following psychometric scales: the 21-item HRSD and 20-item Zung's self-rating scale for depression (ZSRS); the 14-item Hamilton rating scale for anxiety (HRSA); the Lorish and Maisiak face scale, in which the patient is invited to choose from pictures of faces ranked from 1 to 20, the one that best represents his/her mood⁴¹; and visual analogue scales (VAS) for pain, fatigue, sleep, and general well-being.

Administration of methylfolate and patient evaluations were performed by independent medical staff in order to assure blind conditions.

The following laboratory tests were performed at baseline and at the end of the study: complete blood count, MCV, blood urea nitrogen, blood glucose, creatinine, transaminases (with AST/ALT ratio), AP, γGT , bilirubin, and urinalysis. No concomitant drugs were permitted. In some cases, a short-life benzodiazepine was allowed as a sleep inducer no more than three times a week. The Friedman's and Newman and Keul's tests were used as appropriate for statistical evaluation.

RESULTS

All 36 patients completed the study. Efficacy of treatment was assessed by comparing the mean scores reported on the rating scales at baseline with those reported on days 7, 14, 21, and 28. The average baseline HRSD score

of 35.27 ± 1.38 SE dropped to 18.83 ± 2.12 SE (-46.61% , $P < 0.01$) (Figure 1). The mean baseline ZSRS score of 66.02 ± 1.32 SE dropped to 27.75 ± 4.16 SE (-57.97% , $P < 0.01$) (Figure 1).

The mean baseline value of 14.83 ± 0.38 SE on the face scale changed to 10.72 ± 0.61 SE (-27.71% , $P < 0.01$) (Figure 2). The mean baseline VAS values were 7.19 ± 0.37 SE for pain, 6.74 ± 0.34 SE for fatigue, 4.64 ± 0.58 SE for sleep, and 1.93 ± 0.37 SE for general well-being; at the end of treatment these were 3.62 ± 0.42 SE (-49.65% , $P < 0.01$), 2.82 ± 0.33

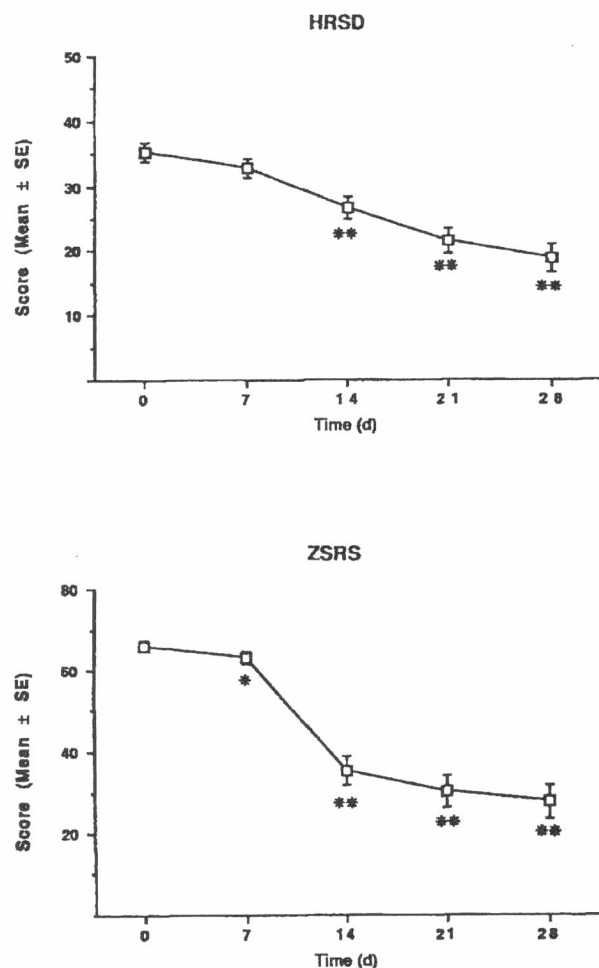


Figure 1. Effects of treatment with methylfolate as measured by the Hamilton rating scale for depression (HRSD) and Zung's self-rating scale for depression (ZSRS). * $P < 0.05$ vs baseline; ** $P < 0.01$ vs baseline.

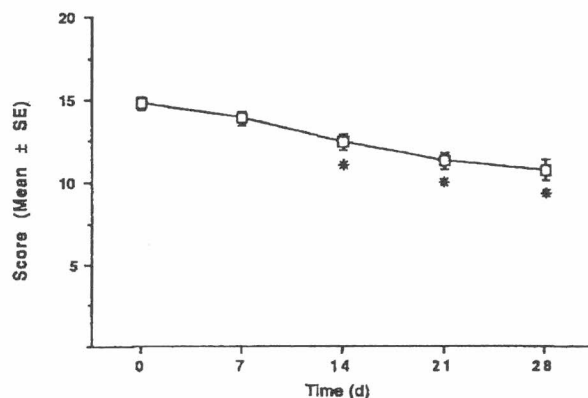


Figure 2. Effects of treatment with methylfolate as measured by the face scale. * $P < 0.01$ vs baseline.

SE (-58.16% , $P < 0.01$), 3.04 ± 0.43 SE ($+34.48\%$, $P = \text{NS}$), and 4.05 ± 0.36 SE ($+127.13\%$, $P < 0.01$), respectively (Figure 3).

Significant changes were also observed in HRSA scores on day 7 versus baseline (-6.30% , $P < 0.05$); and on day 14 both compared with baseline ($+42.49\%$, $P < 0.01$) and versus day 7 ($+52.07\%$, $P < 0.01$). These effects on HRSA may be interpreted as transient psychoactivation induced by methylfolate.

Improvements were noted on day 14 and continued progressively through the end of treatment; ZSRs showed a statistically significant difference as early as day 7 compared with baseline. Methylfolate treatment induced a statistically significant difference versus baseline in VAS for fatigue on day 7, and VAS for pain and well-being on day 14; no change was observed for sleep (Figure 3). The table shows the changes in laboratory parameters relating to γ GT, AST, ALT, and AP, which dropped significantly, and AST/ALT ratio, which remained below 2 (1.12 versus 1.36). MCV values dropped from $99 \pm 3 \mu\text{m}^3$ to $97 \pm 6 \mu\text{m}^3$.

No adverse side effects were reported. No change from depression to hypomania was observed, although hypomania has been reported by other authors.^{42,43}

DISCUSSION

Folate deficiency is frequently observed in psychiatric disorders, particularly in depression and dementia.³⁵ In chronic alcoholics with depression dietary folate deficiency may play a role in the pathogenesis of the affective disorder.²³⁻²⁵ However, it is probably not the sole cause of the mental impairment. There is growing evidence that, irrespective of whether the folate deficiency is primary or secondary to the psychiatric condition, folate

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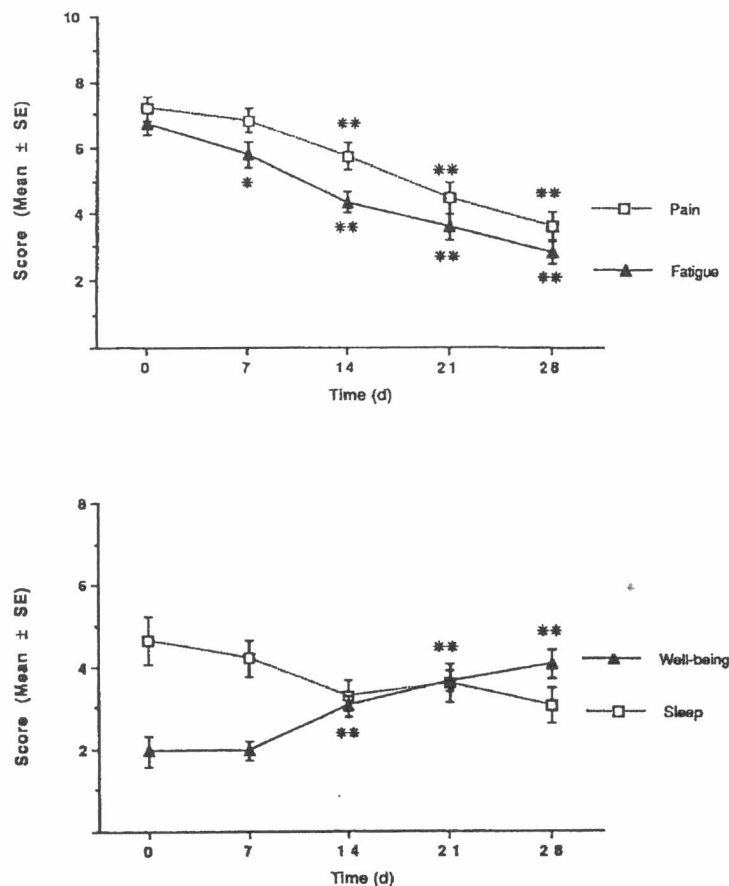


Figure 3. Effects of treatment with methylfolate as measured on the visual analogue scale for pain, fatigue, well-being, and sleep. * $P < 0.05$ vs baseline; ** $P < 0.01$ vs baseline.

replacement may improve mental function, when used alone or added to standard psychodrugs.^{26,28-33,44,45} This assumption appears to be supported by the beneficial antidepressant results obtained with methylfolate in our patients.

In agreement with Crellin et al,³⁵ RBC folate assay should be performed for all psychiatric patients, with particular emphasis on depressive and organic mental states, including ethanol-induced conditions. It appears that RBC folate levels are a much more reliable guide to folate status than plasma folate level. Even a borderline deficiency (150 to 200 $\mu\text{g/L}$) can be harmful to the mental state.³⁰ Methylfolate and folates are group-B vitamin compounds, which are remarkably free of adverse side effects. Only epileptics may have their seizures precipitated or exacerbated by high-dose long-term folates.⁴⁵ Some authors reported occasional occur-

Table. Mean \pm SE values (and percent changes) in gamma glutamyl transpeptidase (γ GT), transaminases, and alkaline phosphatase after 4 weeks of treatment with methylfolate.

	γ GT (μm^3)	Aspartate Aminotransferase (U/L)	Alanine Aminotransferase (U/L)	Alkaline Phosphatase (U/L)
Before	92 \pm 13	81 \pm 10	72 \pm 11	63 \pm 7
After	61 \pm 7	53 \pm 4	39 \pm 4	38 \pm 5
% change	-34	-35	-46	-40

rence of sleeplessness, overactivity, increased anxiety, vivid dreaming, and poor concentration.⁴⁶ These side effects cannot be regarded as toxic, instead, they reflect a tendency to overarousal, which is an event also occurring with SAME, a methyl donor metabolically similar to folate, and with other antidepressants.³⁵ As far as the present study is concerned, the methylfolate-induced psychoactivation observed in our patients, as rated by HRSA on days 7 and 14 of treatment, compared with day 0, resolved with the end of treatment.

Interestingly, a clear improvement in liver function parameters was observed (see the table) and MCV values did not change, indicating that MCV is folate-resistant, as reported by other authors.^{47,48}

This investigation should be regarded as a preliminary approach to a novel treatment of depression in ethanol-dependent patients. The aim of our study was to verify whether methylfolate monotherapy could control depressive signs and symptoms in alcoholics. We did not take into consideration a control group, nor did we assess the severity of ethanol dependence in our patients. However, the clinical results reported in our study appear to support our hypothesis that methylfolate (30 mg TID) has a positive effect on depressive signs and symptoms in alcoholics. Our preliminary results should be verified in controlled trials.

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