

Abstract

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High-Dose B Vitamin Supplementation and Cognitive Decline in Alzheimer Disease: A Randomized Controlled Trial

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Alzheimer Disease Cooperative Study

CONTEXT: Blood levels of homocysteine may be increased in Alzheimer disease (AD) and hyperhomocysteinemia may contribute to disease pathophysiology by vascular and direct neurotoxic mechanisms. Even in the absence of vitamin deficiency, homocysteine levels can be reduced by administration of high-dose supplements of folic acid and vitamins B6 and B12. Prior studies of B vitamins to reduce homocysteine in AD have not had sufficient size or duration to assess their effect on cognitive decline.

OBJECTIVE: To determine the efficacy and safety of B vitamin supplementation in the treatment of AD.

DESIGN, SETTING AND PATIENTS: A multicenter, randomized, double-blind controlled clinical trial of high-dose folate, vitamin B6, and vitamin B12 supplementation in 409 (of 601 screened) individuals with mild to moderate AD (Mini-Mental State Examination scores between 14 and 26, inclusive) and normal folic acid, vitamin B12, and homocysteine levels. The study was conducted between February 20, 2003, and December 15, 2006, at clinical research sites of the Alzheimer Disease Cooperative Study located throughout the United States.

INTERVENTION: Participants were randomly assigned to 2 groups of unequal size to increase enrollment (60% treated with high-dose supplements [5 mg/d of folate, 25 mg/d of vitamin B6, 1 mg/d of vitamin B12] and 40% treated with identical placebo); duration of treatment was 18 months.

MAIN OUTCOME MEASURE: Change in the cognitive subscale of the Alzheimer Disease Assessment Scale (ADAS-cog).

RESULTS: A total of 340 participants (202 in active treatment group and 138 in placebo group) completed the trial while taking study medication. Although the vitamin supplement regimen was effective in reducing homocysteine levels (mean [SD], -2.42 [3.35] in active treatment group vs -0.86 [2.59] in placebo group; $P < .001$), it had no beneficial effect on the primary cognitive measure, rate of change in ADAS-cog score during 18 months (0.372 points per month for placebo group vs 0.401 points per month for active treatment group, $P = .52$; 95% confidence interval of rate difference, -0.06 to 0.12; based on the intention-to-treat generalized estimating equations model), or on any secondary measures. A higher quantity of adverse events involving depression was observed in the group treated with vitamin supplements.

CONCLUSION: This regimen of high-dose B vitamin supplements does not slow cognitive decline in individuals with mild to moderate AD.

