Efficacy of Multivitamin Supplementation Containing Vitamins B₆ and B₁₂ and Folic Acid as Adjunctive Treatment with a Cholinesterase Inhibitor in Alzheimer's Disease: A 26-Week, Randomized, Double-Blind, Placebo-Controlled Study in Taiwanese Patients

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ABSTRACT

Background: Elevated serum homocysteine levels have been associated with the development of Alzheimer's dementia (AD). The combined use of a mecobalamin capsule preparation, which contains vitamin B₁₂ 0.5 mg with an active methyl base, and an over-the-counter nutritional supplement that contains folic acid 1 mg and pyridoxine hydrochloride 5 mg may be effective as a homocysteine-lowering vitamin regimen.

Objective: The aim of this study was to determine whether oral multivitamin supplementation containing vitamins B₆ and B₁₂ and folic acid would improve cognitive function and reduce serum homocysteine levels in patients with mild to moderate AD.

Methods: This randomized, double-blind, placebo-controlled trial was conducted at En Chu Kong Hospital, Taipei, Taiwan. Male and female patients aged >50 years with mild to moderate AD and normal folic acid and vitamin B₁₂ concentrations were enrolled. All patients received treatment with an acetylcholinesterase inhibitor and were randomized to receive add-on mecobalamin (B₁₂) 500 mg + multivitamin supplement, or placebo, PO QD for 26 weeks. The multivitamin contained pyridoxine (B₆) 5 mg, folic acid 1 mg, and other vitamins and iron. Serum homocysteine level was measured and cognitive tests were conducted at baseline and after 26 weeks. The primary efficacy outcome was change in cognition, measured as the change in score from baseline to week 26 on the Alzheimer's Disease Assessment Scale 11-item Cognition subscale. Secondary efficacy outcomes included changes in function in performance of activi-

ties of daily living (ADLs) and concentrations of homocysteine, B₁₂, and folic acid. Tolerability was assessed by comparing the 2 study groups with respect to physical examination findings, including changes in vital signs, laboratory test abnormalities, concomitant medication use, and compliance of study medication was assessed using an interview with the patient's caregiver, as well as the monitoring of adverse events (AEs) throughout the study.

Results: Eighty-nine patients (45 men, 44 women; all Taiwanese; mean [SD] age, 75 [7.3] years) were enrolled and randomized. Overall, there were no significant differences in cognition or ADL function scores between the 2 groups. At week 26, the mean (SD) between-group difference in serum homocysteine concentration versus placebo was -2.25 (2.85) μ mol/L ($P = 0.008$), and the mean serum concentrations of vitamin B₁₂ and folic acid were significantly higher (but within normal range) in the multivitamin group compared with placebo (Δ , +536.9 [694.4] pg/mL [$P < 0.001$] and +13.84 ng/mL [11.17] [$P = 0.012$] at 26 weeks, respectively). The 2 most common AEs were muscle pain (11.1% and 6.8%) and insomnia (8.9% and 9.1%) in the multivitamin and placebo groups, respectively.

Conclusions: In this population of patients with mild to moderate AD in Taiwan, a multivitamin sup-

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plement containing vitamins B₆ and B₁₂ and folic acid for 26 weeks decreased homocysteine concentrations. No statistically significant beneficial effects on cognition or ADL function were found between multivitamin and placebo at 26 weeks. (*Clin Ther.* 2007;29:2204–2214) Copyright © 2007 Excerpta Medica, Inc.

Key words: homocysteine, vitamin supplements, Alzheimer's dementia, clinical trial.

INTRODUCTION

The prevalence rate of Alzheimer's dementia (AD) in individuals aged ≥65 years was 2.0% in Taiwan in 1995.¹ With the lack of a cure for AD, goals of drug therapy include temporary improvement, stabilization, or less-than-expected decline in cognitive, functional, and behavioral symptoms.² Acetylcholinesterase inhibitors (AChEIs) are US Food and Drug Administration (FDA)-approved drugs designed to inhibit the breakdown of acetylcholine in the brain and appear to improve cognition temporally.^{2,3}

Deficiency of certain vitamins, particularly vitamin B₁₂, can cause cognitive impairment, which can be reversed by correcting the deficiency.^{4–7} Methionine synthesis from homocysteine requires folic acid as a methyl donor and methyl cobalamin (vitamin B₁₂) as the intermediate methyl acceptor and donor. Vitamin B₆ has a role in the alternate homocysteine catabolic pathway leading to the production of cysteine. A B₆ deficiency can induce hyperhomocysteinemia.^{8,9} There is evidence that serum homocysteine concentration may be a modifiable risk factor for cognitive decline¹⁰; the homocysteine concentration has been reported to be higher in persons with AD.^{11–13} Several studies have found that homocysteine was inversely associated with cognitive function.^{14–16}

The inverse relationship between serum homocysteine concentration and serum vitamin B₁₂ and folic acid concentrations makes it difficult to distinguish the independent effects of each on cognitive function.

The combined use of a methylcobalamin capsule preparation,* which contains vitamin B₁₂ 0.5 mg with an active methyl base, and an over-the-counter (OTC) nutritional supplement† (originally available in Taiwan

for use in pregnant women) that contains folic acid 1 mg and pyridoxine hydrochloride 5 mg, may meet the daily requirements of vitamin B₁₂, folic acid, and pyridoxine found by the Homocysteine Lowering Trialists' Collaboration¹⁷ to be effective in decreasing homocysteine concentrations. A literature search (MEDLINE; key terms: *Alzheimer's dementia*, *Alzheimer's disease*, and *homocysteine lowering therapy*; years: 1950–2007) did not identify any reports of homocysteine-lowering treatment for mild to moderate AD. In this study, we investigated the effects of 26 weeks of multivitamin supplementation on cognition; function in performing activities of daily living (ADLs); and homocysteine, B₁₂, and folic acid concentrations and patients with mild to moderate AD and normal serum B₁₂ and folic acid concentrations.

PATIENTS AND METHODS

Study Design and Participants

This 26-week, randomized, double-blind, placebo-controlled clinical trial was conducted in En Chu Kong Hospital, Taipei, Taiwan, from July 2003 to March 2006, during which time patients were consecutively enrolled. The study was conducted in accordance with the Declaration of Helsinki¹⁸ and its amendments and the Guideline for Good Clinical Practice,¹⁹ and the protocol was approved by the hospital's institutional review board.

Male and female patients aged >50 years were eligible for inclusion if they had visited the neurologic Outpatient Department for the treatment for AD and had a history of cognitive decline with a gradual onset that was progressive over a period of >6 months; clinical diagnosis of mild to moderate AD, as defined in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*²⁰; a score of 10 to 26 on the Mini-Mental State Examination (MMSE)^{21,22}; and a score of 1 to 2 on the Clinical Dementia Rating (CDR) Scale²³ at screening.

Patients were excluded if they had a history of epilepsy; clinically significant hepatic, renal, pulmonary, metabolic, or endocrine disturbances or significant cardiovascular disease that might impede the patient's ability to complete the trial; vascular dementia or evidence of cerebrovascular disease; low serum concentrations of vitamin B₁₂ (<180 pg/mL) and folic acid (<5 ng/mL); use of any vitamin supplement or any agent for the treatment of dementia (approved, experimental, or OTC) except for AChEIs; and/or

*Trademark: Methycobal® (Eisai Co., Tokyo, Japan).

†Trademark: Pramet® FA (Genovate Biotechnology Co., Ltd., Taipei, Taiwan).

cognitive impairment due to acute cerebral trauma, hypoxic cerebral damage, infection, primary or metastatic cerebral neoplasm, significant endocrine or metabolic disease, or mental retardation. All patients underwent computed tomography or magnetic resonance imaging to rule out structural brain lesion (ie, stroke, tumor, chronic subdural hematoma).

Written informed consent was provided by each patient (or a representative or caregiver) participating in this study.

Study Drug Administration

For ethical reasons, all enrolled patients were prescribed the AChEI donepezil,* the FDA-approved treatment for AD. Patients were randomly allocated, in a 1:1 ratio using a computer-generated list of random numbers, to receive 26 weeks of add-on mecobalamin (0.5 mg) + multivitamin supplement, or placebos, PO QD after breakfast. In addition to folic acid and pyridoxine HCl, the supplement contained iron ferrous 60 mg, nicotinamide 10 mg, calcium carbonate 250 mg, riboflavin 2 mg, thiamine mononitrate 3 mg, calcium pantothenate 1 mg, ascorbic acid 100 µg, iodine 100 µg, copper 150 µg, vitamin B₁₂ 3 µg, vitamin A 4000 IU, and vitamin D₃ 400 IU.

All of the study personnel and participants were blinded to study group. To maintain blinding, the size and color of the placebos were identical to those of the active treatment.

Efficacy Assessments

Efficacy measurements were obtained at weeks 0 (baseline) and 26. Patients were assessed at baseline using detailed history taking (provided either by the patient or caregiver), laboratory analysis, neuroimaging studies, and neuropsychological testing. For laboratory analysis, a 10-mL fasting venous blood sample was obtained for blood chemistry (hepatic and renal function and fasting blood glucose); complete blood count; thyroid function testing (T3, thyroid stimulating hormone); syphilis test; and serum concentrations of homocysteine, B₁₂, and folic acid. Venous blood samples for homocysteine measurement were collected into tubes containing EDTA. Samples were centrifuged within 30 minutes after collection at 2000 rpm for 10 minutes at 20°C and stored at -20°C if not imme-

diately analyzed. Total homocysteine concentrations were measured using fluorescence polarization immunoassay (IMx System, Abbott Laboratories, Abbott Park, Illinois).^{24,25} All samples were analyzed in the laboratory at En Chu Kong Hospital, which is qualified and certified by the International Commission on Office Laboratory Accreditation.

Enrolled patients underwent baseline cognitive testing administered by a neurologist blinded to study group and evaluated by an independent rater, who was blinded to the patients' assigned study medication and other study information, such as adverse events (AEs). The primary efficacy outcome was cognitive function, as measured by change from baseline to week 26 in score on the Alzheimer's Disease Assessment Scale 11-item Cognition subscale (ADAS-Cog/11, Chinese version)²⁶⁻²⁸ (spoken language, comprehension, recall of test instruction, word-finding difficulty, following commands, naming, constructions, ideational praxis, orientation, word recall, and word recognition).

Secondary efficacy outcomes included ADL function, measured as changes from baseline to week 26 in scores on the MMSE, Cognitive Abilities Screening Instrument (CASI, Chinese version, C-2.0),²⁹⁻³¹ Simplified Barthel ADL Index,³² and the Instrumental ADL (IADL) Scale.³³ The CASI complete form provided quantitative assessment (scale, 0-100) of attention, concentration, orientation, short-term memory, long-term memory, language abilities, visual construction (copying 2 intersecting pentagons), list-generating fluency, abstraction, and judgment. These assessments were based on information collected independently from the patient and caregiver. The ADL indices were measured using a 10-item score for assessing function in performing ADLs (toilet use, grooming, feeding, physical ambulation, dressing, bathing, bowel and bladder voiding, transfers [bed to chair], and stairs), while the IADL scale (based on a report by Lawton and Brody³³) used an 8-item assessment of the ability to use the telephone, shop, prepare food, perform housekeeping and laundry tasks, use modes of transportation, accept responsibility for medications, and handle finances. An increase in score on the MMSE, CASI, or ADL indicates improvement in cognition and daily function. However, a higher score on the ADAS-Cog/11 or IADL suggests a deterioration in cognitive ability. Secondary outcomes also included the change from baseline in concentrations of homocysteine, B₁₂, and folic acid.

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Patients underwent physical and neurologic examination by the same neurologist at weeks 2, 6, 10, 14, 18, 22, and 26. Any subjective or objective findings (eg, memory status, psychiatric symptoms), as well as any favorable effects or AEs that occurred during the study period, were recorded. At week 26, serum concentrations of homocysteine, B₁₂, and folic acid were remeasured, and cognitive and ADL function were assessed using the MMSE, CASI, ADAS-Cog/11, ADL Index, and IADL.

Tolerability Assessment

Tolerability was assessed by comparing the 2 study groups with respect to physical examination findings, including changes in vital signs; laboratory test abnormalities; concomitant medication use; and compliance of study medicine was assessed by interview with family, as well as the monitoring of AEs throughout the study. An AE was any undesirable effect experienced by a patient during the trial, whether or not related to treatment. A *serious AE* (SAE) was any AE that was life-threatening or resulted in death, hospitalization, prolongation of hospitalization, or significant disability.

Statistical Analysis

To compare the effects of multivitamin treatment and placebo on cognitive function, as assessed using the ADAS-Cog/11 scale from baseline to week 26, according to an intent-to-treat strategy with all patients who received ≥ 1 dose of study medication and had data from ≥ 1 postbaseline assessment analyzed, the initial assumption was that there were 2 points of differences in the ADAS-Cog/11 scale between the 2 groups, with a common SD of 4. We estimated that the sample size required for a 2-tailed significance level of 0.05 and a power of 0.90 would be 43 patients per group. Assuming a dropout rate of 20%, the ideal number of total enrolled participants was 108.

Characteristic variables between the treatment and placebo groups were compared, including baseline serum levels of homocysteine, vitamin B₁₂, and folic acid, as well as cognitive screening tests using the χ^2 test for categorical data and the *t* test for continuous data. The changes in serum concentrations of homocysteine, B₁₂, and folic acid were compared from baseline to 26 weeks using the nonparametric 2-sample Wilcoxon signed rank test because the values of the variables were not normally distributed.

A paired *t* test was used to assess the efficacy of the intervention on cognition (ADAS-Cog/11, MMSE, and CASI) and ADL function (ADL Index and IADL) by comparing the changes from baseline to 26 weeks between the treatment and placebo groups. All analyses were based on intent-to-treat analysis. A multiple linear model was used for the assessment of the association between the change of homocysteine level and changes in cognition. An analysis of covariance test was used to compare the efficacy of intervention, using baseline cognitive status, age, and sex as covariates. The homocysteine values were assessed from baseline to week 26 in each patient, and patients were classified into the homocysteine-increase or -decrease group, regardless of regimen received. The mean change and the 95% CI in each cognition scale were evaluated. Linear regression was used to assess the association between the score change in cognition, and the homocysteine change after adjustment for baseline homocysteine values, age, and sex. The prevalence of AEs in the treatment and placebo groups was compared using the χ^2 and Fisher exact tests if the expected number was <5 . Patients who withdrew from the study prematurely were to be included in the tolerability analysis. All statistical analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, North Carolina).

RESULTS

Participants

Of the 154 patients (all Taiwanese) who were screened, 65 withdrew consent ($n = 36$) or did not meet the inclusion criteria ($n = 29$) and were not randomized or further evaluated. The remaining 89 patients (45 men, 44 women; mean [SD] age, 75 [7.3] years) with mild to moderate AD were randomized, with 45 patients assigned to the multivitamin group and 44 to the placebo group. Seven participants in the multivitamin group and 10 in the placebo group were lost to follow-up. Five participants in the multivitamin group and 4 in the placebo group were withdrawn due to AEs or SAEs. Of the remaining 63 study participants, 54 completed the cognitive tests and were included in the final analysis (27 in each group) (Figure 1). The demographic characteristics of the 2 groups at baseline were not statistically different between the multivitamin and placebo groups with regard to age; sex; baseline concentrations of homocysteine (mean [SD], 11.6 [−3.7] vs 11.2 [−3.5] $\mu\text{mol/L}$), B₁₂ (488.0 [−378.0] vs 409.5 [−307.4] pg/mL), or folic acid (9.0

[−4.5] vs 8.4 [−6.6] ng/mL); or baseline scores on the MMSE (18.7 [−4.6] vs 18.6 [−5.3]) or CASI (54.8 [−14.4] vs 55.5 [−16.1]) (Table I).

All patients concurrently received donepezil in addition to the study drugs, except for 1 patient in the multivitamin group who had been treated with rivastigmine* before this study, and we did not change their AChEIs and their dose in both groups. Study withdrawals included 12/45 (26.7%) in the multivitamin group and 14/44 (31.8%) in the placebo group (Figure 1). Five patients in the multivitamin group and 4 in the placebo group were withdrawn due to AEs.

Efficacy

The concentrations of homocysteine, vitamin B₁₂, and folic acid were not normally distributed at 26 weeks and were significantly different between the 2 groups (mean [SD] Δ vs placebo, −2.25 [2.85] μmol/L [*P* = 0.008]; B₁₂, +536.9 [694.4] pg/mL [*P* < 0.001]; and folic acid, +13.84 [11.17] ng/mL [*P* = 0.012], respectively). B₁₂ and folic acid were increased at week 26 in the multivitamin group. The median changes were a

significant increase in B₁₂ and folic acid (+237 pg/mL and +9.9 ng/mL, respectively; both, *P* < 0.001) in the multivitamin group, whereas the median changes in B₁₂ and folic acid were not significantly changed in the placebo group (+0.2 ng/mL and −38.0 pg/mL, respectively) (Table II). There were significant differences between the 2 groups in changes from baseline in serum B₁₂ and folic acid concentrations (both, *P* < 0.001).

Table III lists the changes in neuropsychological test scores from baseline to 26 weeks. There were no significant differences between the multivitamin and placebo groups. The mean changes in test scores for the multivitamin group versus the placebo group were as follows: ADAS-Cog/11, +0.67 versus −0.9; MMSE, +0.15 versus +0.41; and CASI, −1.7 versus +0.12. Changes in ADL Index and IADL scores were not statistically different (ADL, −0.33 vs −0.19; IADL, +0.04 vs −0.04) between the 2 groups.

Age and sex were stratified to determine whether these factors influenced the effects of multivitamin supplementation on cognitive function. All outcomes of cognition were analyzed as dichotomous parameters. The scores of all the measurement parameters between baseline and 26 weeks were compared. *Improvement* was defined as an increase in score on the MMSE, CASI, or ADL Index, or a decrease in

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Table I. Baseline demographic and clinical characteristics of the study population (intent-to-treat).*

Characteristic	Multivitamin (n = 45)	Placebo (n = 44)
Age, y		
Mean (SD)	74.9 (7.1)	74.6 (7.5)
Median	75	77
Sex, no. (%)		
Female	24 (53.3)	20 (45.5)
Male	21 (46.7)	24 (54.5)
Serum concentrations, mean (SD)		
Homocysteine, $\mu\text{mol/L}$	11.6 (3.7)	11.2 (3.5)
Vitamin B ₁₂ , pg/mL	488.0 (378.0)	409.5 (307.4)
Folic acid, ng/mL	9.0 (4.5)	8.4 (6.6)
Scale scores, mean (SD)		
ADAS-Cog/11	24.0 (12.3)	21.2 (10.5)
MMSE	18.7 (4.6)	18.6 (5.3)
CASI	54.8 (14.4)	55.5 (16.1)

ADAS-Cog/11 = Alzheimer's Disease Assessment Scale²⁶⁻²⁸ 11-item Cognition subscale; MMSE = Mini-Mental State Examination^{21,22}; CASI = Cognitive Abilities Screening Instrument.²⁹⁻³¹

*No significant between-group differences were found.

Table II. Serum concentrations from baseline to 26 weeks with combined multivitamins or placebo in patients with mild to moderate Alzheimer's dementia.* Values are median interquartile range.

Component	Multivitamin (n = 45)	Placebo (n = 44)	P
Homocysteine, $\mu\text{mol/L}$			
Baseline	+10.6 (8.8 to 12.7)	+11.3 (7.2 to 12.6)	0.48
Δ From baseline	-1.4 (-3.1 to 0.0)	+1.3 (-0.7 to 2.7)	<0.001
Vitamin B ₁₂ , pg/mL			
Baseline	+359.0 (244.0 to 545.0)	+333.0 (223.5 to 530.5)	0.19
Δ From baseline	+10.6 (8.8 to 12.7)	+11.3 (7.2 to 12.6)	<0.001
Folic acid, ng/mL			
Baseline	+7.6 (5.5 to 10.7)	+7.3 (4.5 to 10.1)	0.14
Δ From baseline	+9.9 (5.0 to 23.2)	+0.2 (-2.5 to 1.5)	<0.001

*Intent-to-treat analysis set using nonparametric Wilcoxon 2-sample test (Mann-Whitney *U* test).

score on the ADAS-Cog/11 or IADL after intervention. The odds ratio (OR) of improvement in either group was calculated with age ≥ 75 or < 75 years. Neither group had significant treatment effects in every assessment scale. The results after stratification of sex showed no

effect of intervention. The age and sex-adjusted ORs (95% CI) for MMSE, CASI, ADAS-Cog/11, and IADL were 1.90 (0.69–5.24), 1.20 (1.47–3.07), 1.32 (0.50–3.46), and 0.77 (0.32–1.86), respectively (Figure 2). There were no significant changes in score

Table III. Changes from baseline to 26 weeks in cognition and daily living function with combined multivitamins or placebo in patients with mild to moderate Alzheimer's dementia (intent-to-treat population).

Scale	Multivitamin (n = 45)	Placebo (n = 44)	P
ADAS-Cog/11			
Mean	+0.67	-0.9	0.34
95% CI	-2.33 to 3.69	-2.77 to 0.85	
MMSE			
Mean	+0.15	+0.41	0.79
95% CI	-1.06 to 1.35	-1.12 to 1.93	
CASI			
Mean	-1.7	+0.12	0.51
95% CI	-5.30 to 1.89	-4.32 to 4.55	
ADL			
Mean	-0.33	-0.19	0.70
95% CI	-1.03 to 0.36	-0.57 to 0.20	
IADL			
Mean	+0.04	-0.04	0.89
95% CI	-1.01 to 1.08	-0.41 to 0.33	

ADAS-Cog/11 = Alzheimer's Disease Assessment Scale²⁶⁻²⁸ 11-Item Cognition subscale; MMSE = Mini-Mental State Examination^{21,22}; CASI = Cognitive Abilities Screening Instrument²⁹⁻³¹; ADL = Simplified Barthel Activities of Daily Living Index³²; IADL = Instrumental Activities of Daily Living Scale.³³

on any cognitive scale or between the homocysteine-increase and -decrease groups (Figure 3).

Tolerability

The tolerability analysis was based on 89 patients (multivitamin group, 45; placebo group, 44). Five patients in the multivitamin group and 4 from the placebo group were withdrawn due to AEs. Three of these patients from each group withdrew due to SAEs (placebo group: dizziness, muscle pain, and insomnia [1 patient each]; multivitamin group: gastric upset, diarrhea, and dizziness [1 patient each]). The proportions of patients who experienced ≥ 1 AE during the study period were not significantly different between the 2 groups (21 [46.7%] and 14 [31.8%] in the multivitamin and placebo groups, respectively).

The 2 most common AEs experienced in the multivitamin and placebo groups were muscle pain (5

[11.1%] and 3 [6.8%], respectively) and insomnia (4 [8.9%] and 4 [9.1%]) (Table IV). More patients in the multivitamin group experienced delirium than in the placebo group (4 [8.9%] vs 1 [2.3%]). The majority of AEs were rated as mild to moderate. Three patients were hospitalized due to SAEs during the study period: 2 (4.4%) patients in the multivitamin group were admitted due to stroke and Parkinson's disease with rigidity worsening; 1 (2.3%) patient in the placebo group was hospitalized due to coronary artery disease. None of these SAEs were considered related to study treatment.

DISCUSSION

In this 26-week, randomized, double-blind, placebo-controlled trial in patients with mild to moderate AD, the daily use of an OTC supplement containing folic acid and vitamins B₆ and B₁₂ was associated with a significant mean decrease in homocysteine concentration (by 2.25 $\mu\text{mol/L}$). However, there were no significant differences in changes in cognition or ADL function between the 2 groups, even after stratification by age and sex. There was no significant cognitive improvement in either group and no significant association between the change in cognition and the change in homocysteine concentration in either study group at 26 weeks.

Regarding homocysteine-lowering treatment, different dosages and combinations have been studied and recommended in several reports.^{17,35-40} Vitamins B₆ and B₁₂ and folic acid supplementation has been used successfully in selected settings (folate 0.5–10 mg; B₆, 2–50 mg; B₁₂, 0.02–1 mg)^{17,35-40} to treat mild to moderate hyperhomocysteinemia (7.0–30.6 $\mu\text{mol/L}$) in patients with normal or abnormal B₁₂ concentration.^{17,35-40} Among the 3 vitamins, however, only folic acid appears to have a potential for reducing fasting serum homocysteine levels.³⁹ Daily supplementation with both folic acid 0.5 to 5 mg and vitamin B₁₂ ~0.5 mg appears to be sufficient.¹⁷ Additional combination with vitamin B₆ 5 to 10 mg has been reported to be effective in reducing homocysteine concentration.¹⁷ Based on the results from our study, the combined use of mecobalamin and a nutritional supplement containing folic acid and pyridoxine may meet the requirement of a homocysteine-lowering vitamin regimen.

Although observational studies have found an inverse relationship between homocysteine concentra-

Figure 2. Odds ratios (95% CI) for the effects on cognition and daily living scores of 26 weeks of combined multivitamins or placebo in patients with mild to moderate Alzheimer's dementia. Outcomes were defined as dichotomous variables with improvement or not on the cognition as comparing the scores between baseline and 26 weeks. IADL = Instrumental Activities of Daily Living Scale³³; ADAS-Cog/11 = Alzheimer's Disease Assessment Scale²⁶⁻²⁸ 11-item Cognition subscale; CASI = Cognitive Abilities Screening Instrument²⁹⁻³¹; MMSE = Mini-Mental State Examination.^{21,22}

Figure 3. Mean (95% CI) changes from baseline in cognition scale scores in the homocysteine-increase (○) and homocysteine-decrease (●) groups with 26 weeks of combined multivitamins or placebo in patients with mild to moderate Alzheimer's dementia. MMSE = Mini-Mental State Examination^{21,22}; CASI = Cognitive Abilities Screening Instrument²⁹⁻³¹; ADAS-Cog/11 = Alzheimer's Disease Assessment Scale²⁶⁻²⁸ 11-item Cognition subscale.

tion and cognitive performance,⁴¹⁻⁴⁴ a Cochrane review of randomized controlled trials of folic acid with or without vitamin B₁₂,⁴¹ as well as a review of a vitamin B₆ supplement,⁴² concluded that there was no benefit in cognitively impaired but otherwise healthy

people. The participants in those studies had cognitive impairment but not all were diagnosed with AD. Some studies did not mention the participants' serum concentrations of B₆, B₁₂, or folic acid, which could influence the results of vitamin treatment. Moreover,

Table IV. Adverse events (AEs) experienced with 26 weeks of combined multivitamins or placebo in patients with mild to moderate Alzheimer's dementia (intent-to-treat population). Values are no. (%) of patients.

System/AE ³⁴	Multivitamin (n = 45)	Placebo (n = 44)	System/AE ³⁴	Multivitamin (n = 45)	Placebo (n = 44)
Cardiovascular			Psychiatric		
Need for adjustment of antihypertensive medication			Insomnia	4 (8.9)	4 (9.1)
dosage	2 (4.4)	1 (2.3)	Delirium	4 (8.9)	1 (2.3)
Chest pain	1 (2.2)	0	Depression	1 (2.2)	0
Respiratory			Others		
Asthma	1 (2.2)	0	Dizziness	3 (6.7)	1 (2.3)
Cough	1 (2.2)	0	Need to adjust dosage of antiparkinsonian drug	2 (4.4)	1 (2.3)
URTI	0	1 (2.3)	Allergy	0	1 (2.3)
Gastrointestinal			SAE		
Constipation	2 (4.4)	1 (2.3)	Parkinson's disease with rigidity worsening	1 (2.2)	0
Diarrhea	2 (4.4)	0	Stroke	1 (2.2)	0
Gastric upset	1 (2.2)	0	Ischemic heart disease	0	1 (2.3)
Nausea	1 (2.2)	0	Totals		
Neuromuscular			Patients who experienced ≥ 1 AE	21 (46.7)	14 (31.8)
Muscle pain	5 (11.1)	3 (6.8)	Patients who experienced ≥ 1 SAE	2 (4.4)	1 (2.3)
Cramp	1 (2.2)	2 (4.5)			
Neuralgia	1 (2.2)	0			

URTI = upper respiratory tract infection; SAE = serious adverse event.

the intervention periods were no more than 12 weeks. A 2-year controlled trial of potential homocysteine-lowering treatment with folate (1 mg), B₆ (10 mg), and B₁₂ (0.5 mg) reported no significant improvement in healthy older people (age ≥ 65 years).⁴³ B₁₂ or folic acid deficiency can be reversible in cognitive performance, but most of the aforementioned studies did not clarify the vitamin status in the included participants.^{35–37} A randomized controlled trial of potential homocysteine-lowering treatment in patients with mild to moderate AD and with normal B₁₂ and folic acid status has not been reported in reviewed literature. The current study was specifically designed to address the diagnosis of AD as an inclusion criterion; cognitive performance and ADL function were assessed, as well as change in homocysteine concentration after 26 weeks of intervention.

Our study had several limitations. The duration was relatively short; thus, longer-lasting cognitive benefits from homocysteine-lowering treatment in patients with AD cannot be ruled out. Additionally,

some of the patients experienced symptoms of gastric upset, nausea, and vomiting, which have been associated with the use of AChEIs.⁴⁵ Hence, some patient withdrawals were possibly due to these AEs, causing a smaller-than-desired final sample size. Further large, randomized controlled trials with longer periods are needed.

CONCLUSIONS

In this small population of Taiwanese patients with mild to moderate AD and normal serum levels of vitamin B₁₂ and folic acid, combination treatment with mecobalamin + a multivitamin decreased homocysteine concentrations. However, the active treatment had no statistically significant beneficial effects on cognition or ADL function at 26 weeks in these patients.

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