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Featured Articles

Efficacy of a medical food in mild Alzheimer's disease: A randomized, controlled trial

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Abstract

Objective: To investigate the effect of a medical food on cognitive function in people with mild Alzheimer's disease (AD).

Methods: A total of 225 drug-naïve AD patients participated in this randomized, double-blind controlled trial. Patients were randomized to active product, Souvenaid, or a control drink, taken once-daily for 12 weeks. Primary outcome measures were the delayed verbal recall task of the Wechsler Memory Scale–revised, and the 13-item modified Alzheimer's Disease Assessment Scale–cognitive subscale at week 12.

Results: At 12 weeks, significant improvement in the delayed verbal recall task was noted in the active group compared with control ($P = .021$). Modified Alzheimer's Disease Assessment Scale–cognitive subscale and other outcome scores (e.g., Clinician Interview Based Impression of Change plus Caregiver Input, 12-item Neuropsychiatric Inventory, Alzheimer's disease Co-operative Study–Activities of Daily Living, Quality of Life in Alzheimer's Disease) were unchanged. The control group neither deteriorated nor improved. Compliance was excellent (95%) and the product was well tolerated.

Conclusions: Supplementation with a medical food including phosphatide precursors and cofactors for 12 weeks improved memory (delayed verbal recall) in mild AD patients. This proof-of-concept study justifies further clinical trials.

Keywords: Alzheimer's disease; Nutritional intervention; Synapse formation; Membrane phosphatide synthesis; B vitamins; Omega-3 fatty acids; Nucleotides; Uridine; Phospholipids; Choline; Antioxidants; ADAS-cog, delayed verbal recall; Medical food; Dietary management; Randomized clinical trial; Dementia

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1. Introduction

Alzheimer's disease (AD) is the leading cause of dementia. The underlying neurodegenerative mechanism involves several interacting processes—membrane degeneration, central oxidative stress, abnormal protein processing (beta-amyloid, tau), and mitochondrial dysfunction. These result in the characteristic accumulation of beta-amyloid plaques, neurofibrillary tangles, and synaptic loss, ultimately leading to cerebral atrophy and enlargement of ventricles. Ongoing neurodegeneration, particularly synaptic loss [1,2], leads to the classic clinical features of AD—memory impairment, language deterioration, and executive and visuospatial dysfunction. Current therapies, presumed to act by modulating central cholinergic or glutaminergic neurotransmission, provide only symptomatic relief.

New approaches to prevent and treat AD are urgently needed. Because the cognitive disturbances of AD best correlate with loss of hippocampal and cortical synapses [2], a possible therapeutic strategy might involve steps to restore such synapses. Preclinical studies indicate that such an effect can be induced by co-administration of rate-limiting precursors for membrane phosphatide synthesis, such as the nucleotide uridine, omega-3 polyunsaturated fatty acids, and choline [3–5]. These nutrients synergistically increase brain levels of the phosphatide molecules that comprise the bulk of synaptic membranes, and brain levels of specific synaptic proteins, suggesting that they also increase synapse formation [3–5]. Moreover, administration of combinations of these nutrients produces major increases in hippocampal dendritic spines [6], the anatomical precursor of and surrogate marker of new synapses [7–9], and enhances cognitive function [10,11]. These combined observations raise the question as to whether these nutrients have a role in the management of AD, especially of its main symptom—memory dysfunction.

The hypothesis that combinations of certain nutrients could provide clinically relevant benefits to patients with AD formed the basis of the development of the medical food* Souvenaid, which is a multinutrient drink designed to improve synapse formation. Souvenaid contains the necessary precursor and supporting nutrients to act synergistically to enhance membrane formation and function in patients with AD. All components contained in this medical food have a history of safe use in other foods. This report presents the results of the first clinical trial evaluating the efficacy, tolerability, and safety of a medical food designed to restore synapses in brains of patients with mild AD. We designed a proof-of-concept clinical trial to investigate whether supplementation with Souvenaid could affect cognitive functions in AD. We chose a 12-week study period based on the fast-acting response seen in animal studies [3,6], and elected to study patients with (very) mild disease—a stage where intervention of this nature is likely to exert the highest effect. The coprimary outcome measures were the delayed verbal recall test of the Wechsler Memory Scale—revised (WMS-r) [13], which is seen as a sensitive measure of episodic memory [14,15], impaired in the early stage of AD [14,15]; and the 13-item modified Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog) [16], often seen as the ''golden standard'' assessment tool in studies of AD intervention.

2. Methods

2.1. Participants

Patients had a diagnosis of probable AD according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke-AD and Related Disorders Association [17]; a Mini-Mental State Examination (MMSE) [18] score of 20–26, representing mild AD, and a recent magnetic resonance imaging or computed tomography scan compatible with AD. Other inclusion criteria included age ≥ 50 years; >2 years postmenopausal or surgically sterile (women); current outpatient status; Hachinski Ischemia Scale [19] score ≤ 4; and Geriatric Depression Scale (GDS) [20] score ≤ 4 on the 15-item scale. Patients needed to have a caregiver who visited them ≥ 5 days a week, and could assist the patient in taking the study products, completing diary entries, and participating in study visits.

Exclusion criteria included neurological disease other than AD that could explain dementia; previous use of cholinesterase inhibitors, *N*-methyl-D-aspartate-receptor antagonists or medications with marked cholinergic/anticholinergic effects, or expected need for these within 24 weeks; use of antidepressants, tranquillizers, sleeping pills, or lipid-lowering medications unless on a stable dose for ≥ 3 months before baseline; use of antipsychotics, antiepileptics, ginkgo biloba, intake of $>200\%$ of the recommended daily intake of vitamins B, C, or E within 1 month before baseline; fatty acid supplements taken regularly within 6 months before baseline; participation in other studies involving investigational/marketed products; excessive alcohol intake or drug abuse; or investigator's uncertainty about patient's ability to comply with protocol requirements.

Participants were recruited from AD treatment centers in The Netherlands (11), Germany (11), Belgium (5), United Kingdom (1), and United States (1) between June 2006 and June 2007. Written informed consent was obtained from patients and caregivers. The institutional review board

*A medical food is in USA defined in 21 U.S.C. § 360ee(b)(3) as ''a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognisable scientific principles, are established by medical evaluation'' [12]. A comparable definition exist in the harmonized legislation of the European Union (cf. Article 1,2(b) of Commission Directive 1999/21/EC of 25 March 1999 on dietary foods for special medical purposes.