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Review

Cholinesterase inhibitors and add-on nutritional supplements in Alzheimer's disease
A systematic review of randomized controlled trials

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ABSTRACT

To date, single drug and nutrient-based interventions have failed to show a clinically relevant effect on Alzheimer's disease (AD). Multidomain interventions may alleviate symptoms and alter the disease course in a synergistic manner. This systematic review examines the effect of adding nutritional supplementation to cholinesterase inhibitors. A systematic PubMed and Cochrane search resulted in nine high quality studies. The studies had low to moderate risk of bias and focused on oxidative stress, homocysteine levels, membrane fluidity, inflammation and acetylcholine levels. Only the use of vitamin E supplements could reduce the rate of functional decline when combined with cholinesterase inhibitors in one study, whereas cognition was not affected in both this and other studies. None of the other nutritional supplements showed convincing evidence of a beneficial effect when combined with cholinesterase inhibitors. This shows that cognitive and functional improvement is difficult to achieve in patients with AD, despite epidemiological data and evidence of biological effects of nutritional supplements. Addressing one disease pathway in addition to cholinesterase inhibitor therapy is probably insufficient to alter the course of the disease. Personalized, multifactorial interventions may be more successful in improving cognition and daily functioning.

Contents

Abbreviations: AD, Alzheimer's disease; ADAS-cog, Alzheimer's Disease Assessment Scale, cognitive subdomain; ADAS-noncog, Alzheimer's Disease Assessment Scale, non-cognitive subdomain; ADCS-ADL, Alzheimer's Diseae Cooperative Study Activities of Daily Living; BADL, Basic Activities of Daily Living; CAS, Caregiver Activity Survey; CASI, Cognitive Abilities Screening Instrument; CDR, Clinical Dementia Rating scale; CGIC, Clinical Global Impression of Change; ChE-I, cholinesterase inhibitor; CSF, cerebral spinal fluid; DHA, docosahexaenoic acid; DSST, Digit Symbol Substitution Test; EPA, eicosapentaenoic acid; IADL, Instrumental Activities of Daily Living; MCI, mild cognitive impairment; MMSE, Mini Mental State Exam; ND, not done; NOSGER, Nurses Observation Scale for Geriatric patients; NS, non-significant; RCT, randomized controlled trial; SB, Social Behavior; TMT, Trail Making Test; UK, unknown.

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1. Introduction

There is wide interest in the role nutrition plays in the development and disease process of neurodegenerative diseases. Epidemiological evidence suggests that certain diet patterns or dietary elements can prevent or slow the development of Alzheimer's disease (AD) (Morris, 2009). In particular, low intake of omega-3 fatty acids, antioxidants and B-vitamins, have been associated with an increased risk of AD (Morris et al., 2003). Moreover, brain structure and cognitive performance have been shown to be positively influenced by dietary nutrients, such as B-vitamins (Bourre, 2006; Douaud et al., 2013). These findings raise the question whether supplementation with nutritional components may be of benefit to patients with Alzheimer's disease.

There are several disease pathways and risk factors in AD that could theoretically be affected by nutritional factors, such as oxidative stress, high homocysteine levels, reduced membrane fluidity, inflammation and low acetylcholine levels (Akiyama et al., 2000; Bartus et al., 1982; Clarke et al., 1998; Eckert et al., 2000; Markesbery, 1997).

A proposed mechanism of oxidative stress is that activation of protein kinases, enhancing beta- and gamma-secretase activity, and lipid DNA and protein oxidation are induced by reactive oxygen species (ROS), leading to neuronal cell death (Chauhan and Chauhan, 2006; Pratico, 2008). The increased neurofibrillary tangle and amyloid-beta load in turn increase the amount of ROS. High homocysteine levels may lead to neurodegeneration by amyloid-beta peptide generation, hyperphosphorylation of tau or direct neurotoxic effects, or through its role in cerebrovascular pathology (reviewed in Obeid and Herrmann, 2006). Reduced membrane fluidity may lead to impaired neuronal communication, since that is dependent on proper functioning of membrane related mechanisms such as postsynaptic receptor functioning, and presynaptic fusion and endocytosis of vesicles (Barnett-Norris et al., 2005). Neuroinflammation, albeit most likely a secondary event, can cause or exacerbate neuronal death and is most prominent in those brain areas with high levels of AD pathology (Akiyama et al., 2000). Finally, loss of cholinergic neurons in de nucleus basalis lead to actylcholine deficiencies and contribute to impaired memory in patients with AD (Bartus et al., 1982).

Previous reviews have focused on nutrient status in patients with AD (Lopes da Silva et al., 2012) or on the effect of single nutrients, such as vitamin E (Isaac et al., 2008), or nutrient groups, such as B-vitamins (Balk et al., 2007) on cognition. To date, single nutrients have failed to show an indisputable, clinically significant effect on the severity or course of the disease, despite consistent epidemiological evidence of protective effects. This may be due to the heterogeneity of AD, which may be based on the multi-causal nature of the disease, thus suggesting that a multidimensional intervention is necessary to reach an improvement in cognition or daily function (Olde Rikkert et al., 2006; Richard et al., 2012). Treatments in which multiple elements are combined may have the potential to create a synergistic effect on the disease process, and interest in combination treatment has grown over the years. Therefore, this systematic review examines the effect of nutritional supplements combined with cholinesterase inhibitors on cognition and functional performances in patients with Alzheimer's disease.

2. Methods

This review has been reported according to guidelines of the Dutch Cochrane Centre (Higgins and Green, 2011) and meta-analyses (PRISMA) guidelines for reporting systematic reviews (Moher et al., 2009).

A comprehensive search strategy was developed to identify intervention trials which assessed the impact of cholinesterase inhibitors with nutritional supplements on Alzheimer's disease using both medical subject headings (MeSH) and key word terms. A complete listing of search terms is provided in the appendices (A, PubMed; and B, Cochrane Library). A preliminary search was performed in PubMed on January 16, 2012 and in the Cochrane Library on January 24, 2012; no language or date restrictions were applied in the search. However, studies in a language other than English were later excluded. E-mail notifications identifying new studies matching the search terms in PubMed were evaluated (AR) for eligible studies until May 17, 2013. Reference lists of all eligible studies were further cross-checked to identify additional trials.

Eligible studies included randomized controlled trials (RCTs) in which:

1. patients with Alzheimer's disease were included (based on internationally accepted criteria);
2. the intervention consisted of one or more nutritional supplements;
3. the subjects where either given cholinesterase inhibitors as part of the intervention or were stable on cholinesterase inhibitors at the start of the study;
4. the population was aged 50 years or older.

Studies conducted in patients with major physical or cognitive disabilities (other than AD) and other types of dementia (e.g. Parkinson's disease dementia, Lewy Body dementia, vascular dementia) were excluded, as they were beyond the scope of this review. Studies in a language other than English were also excluded.

Risk of bias for the selected studies was independently assessed by two reviewers (OM and AR) using form II for RCT from the Evidence Based Guideline Development (EBRO; workgroup on guideline development, including the Dutch Cochrane Centre). After consensus was reached a judgment of low risk (+), unclear risk (?) or high risk (−) of bias was made on six types of bias: (1) 'Allocation' refers to the random allocation to treatment groups; (2) 'blinding' refers to the degree of blinding that was applied (e.g. of participants or investigators); (3) 'incomplete outcome data' refers to loss to follow up; (4) 'selective reporting' refers to not reporting on all outcome measures; (5) 'comparable treatment groups' refers to whether there were any relevant differences between the treatment groups (e.g. age or age at onset of AD); (6) 'other bias' refers to other sources that could increase the risk of bias, such as carry-over effects in cross-over designs or conflicts of interest. Data on study and participant characteristics, supplement dose, method of cognitive assessment, and relevant outcomes were independently