

## Doença de Alzheimer e Média Diminuição da Cognição e Vitamina E

# Vitamin E for Alzheimer's disease and mild cognitive impairment

Isaac Mokhtar Gad El Kareem Nasr, Quinn Rebecca, Tabet Naji

This review should be cited as: Isaac Mokhtar Gad El Kareem Nasr, Quinn Rebecca, Tabet Naji. Vitamin E for Alzheimer's disease and mild cognitive impairment (Cochrane Review). In: The Cochrane Library, Issue 4, 2008. Oxford: Update Software.

### Synopsis

Vitamin E is a dietary compound with antioxidant properties involved in scavenging free radicals. Laboratory and animal studies have pointed towards a possible role for Vitamin E in the prevention and management of cognitive impairment. To date only one randomized controlled trial has assessed the efficacy of Vitamin E in the treatment of AD patients and only one assessed the role of Vitamin E in patients with mild cognitive impairment (MCI). In the Vitamin E study for moderately severe AD patients a lower number of those taking Vitamin E declined to incapacity over a two year period compared with the placebo group. However, AD patients taking Vitamin E experienced a greater number of falls. In the MCI study, Vitamin E 2000 IU daily produced no significant difference in the rate of progression to AD compared to the placebo group.

### Abstract

#### Background

Vitamin E is a dietary compound that functions as an antioxidant scavenging toxic free radicals. Evidence that free radicals may contribute to the pathological processes of cognitive impairment including Alzheimer's disease (AD) has led to interest in the use of Vitamin E in the treatment of Alzheimer's disease and Mild Cognitive Impairment (MCI).

#### Objective

To assess the efficacy of Vitamin E in the treatment of Alzheimer's disease and prevention of progression of Mild Cognitive Impairment to Alzheimer's disease.

#### Search strategy

The Cochrane Dementia and Cognitive Improvement's Specialized Register was searched on 8 January 2007 using the following terms: "Vitamin E", vitamin-E, alpha-tocopherol. The CDCIG Registers contains records from major health care databases and ongoing trial databases and is updated regularly.

#### Selection criteria

All unconfounded, double blind, randomized trials in which treatment with Vitamin E at any dose was compared with placebo for patients with Alzheimer's disease or Mild Cognitive Impairment.

#### Data collection and analysis

Two reviewers independently applied the selection criteria and assessed study quality and extracted and analysed the data. For each outcome measure data were sought on every patient randomized. Where such data were not available an analysis of patients who completed treatment was conducted.

#### Main results

Only 2 studies met the inclusion criteria. The primary outcome used in the AD study was survival time to the first of 4 endpoints: death, institutionalisation, loss of 2 out of 3 basic activities of daily living and severe dementia (defined as a global Clinical Dementia Rating of 3). The investigators reported the total numbers in each group who reached the primary endpoint within two years for participants completing the study ("completers"). There appeared to be some benefit from Vitamin E with fewer participants reaching endpoint - 58% (45/77) of completers compared with 74% (58/78) - a Peto odds ratio of 0.49, 95% confidence interval 0.25 to 0.96.

However, more participants taking Vitamin E suffered a fall (12/77 compared with 4/78; odds ratio 3.07, 95% CI 1.09 to 8.62). It was not possible to interpret the reported results for specific endpoints or for secondary outcomes of cognition, dependence, behavioural disturbance and activities of daily living.

The primary outcome used in the MCI study which had 769 participants (257 in the Vitamin E group and 259 in the placebo group; a third Donepezil group of 253 was not included in this review) was the time to progression from MCI to possible or probable AD. A total of 214 of the 769 participants had progression to dementia, with 212 being classified as having possible or probable AD. There was no significant difference in the probability of progression from MCI to AD between the Vitamin E group and the placebo group. There was no significant difference between the placebo group and the Vitamin E group in adverse events. Five subjects died in each group and 72 discontinued treatment in the Vitamin E group and 66 in the placebo group.

#### Reviewers' conclusions

There is no evidence of efficacy of Vitamin E in the prevention or treatment of people with AD or MCI. More research is needed to identify the role of Vitamin E, if any, in the management of cognitive impairment.

### References to studies included in this review

#### Petersen 2005 {published data only}

Petersen R, Grundman R, Thomas R, Thal L. Donepezil and Vitamin E as Treatments for Mild Cognitive Impairment. *NeuroBiology of Aging* 2004;25:20-.

Petersen RC, Thomas RG, Grundman M, Bennett D, Doody R, Ferris S. Vitamin E and Donepezil for the treatment of mild cognitive impairment. *The New England Journal of Medicine* 2005;352:2379-2388.

#### Sano 1996 {published data only}

Sano M, Ernesto C, Klauber MR, Schafer K, Woodbury P, Thomas R. Rationale and design of a multicenter study of selegiline and a-Tocopherol in the treatment of Alzheimer's disease using novel clinical outcomes. *Alzheimer Disease and Associated Disorders* 1996;10:132-40.

Sano M, Ernesto C, Thomas RG, Klauber MR, Schafer K, Grundman M. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. *New England Journal of Medicine* 1997;336:1216-22.

Sano M, Ernesto C, Thomas RG. Effects of Selegiline and alpha-Tocopherol on cognitive and functional outcome measures in moderately impaired patients with Alzheimer's disease. *Neurology* 1997;48:A377-8.

Sano M, Growdon J, Klauber M. Expanding the severity range of patients in clinical trials for Alzheimer's disease: a multicentre clinical trial of Selegiline and a-Tocopherol. *Neurology* 1996;45:289-.

**Sano 1997** {published data only}

Sano M, Ernsto C, Thomas RG, Klauber MR. A controlled trail of selegiline, alpha tocopherol, or both as treatment for Alzheimer's disease. *The New England Journal of Medicine* 1997;336:1216-17.

\* indicates the major publication for the study

#### References to studies excluded from this review

**Clarke 2003** {published data only}

Clarke R, Harrison G, Richards S. Effects of vitamins and aspirin on markers of platelet activation, oxidative stress and homocysteine in people at high risk of dementia. *Journal of Internal Medicine* 2003;245:67-75.

Jacoby RJ. A pilot study for the VITAL trial (Vitamins and Aspirin for the treatment of Dementia). 2002:-.

**Jacoby 2002** {published and unpublished data}

Jacoby RJ. A pilot study for the VITAL trial (Vitamins and Aspirin for Treatment of Dementia). 2002:-.

**Onofri 2002** {published data only}

Onofri M, Thomas A, Luciano AL, Lacono D. Donepezil versus vitamin E in Alzheimer's disease: part 2: mild versus moderate-sever Alzheimer's disease. *Clinical Neuropharmacology* 2002;25:207-15.

#### Ongoing studies

**Gopal 2005** {published data only}

Gopal V. A pilot study of effect of vitamin E on cognition and measures of activities of daily living in patients with moderately severe Alzheimer's disease. 2005:-.

**Markesbery 2002** {published and unpublished data}

Markesbery W, Schmitt F, Kryscio R. Prevention of Alzheimer's disease by vitamin E and selenium. 2002:-.

#### Additional references

**Ahlskog 1995**

Ahlskog JE, Uitti RJ, Low PA. No evidence for systemic oxidant stress in Parkinson's or Alzheimer's disease. *Movement Disorders* 1995;10:566-573.

**APA 1994**

In: *Diagnostic and Statistical Manual of Mental Disorders* Washington DC: American Psychiatric Press, 1994:-.

**Behl 1992**

Behl C, Davis J, Cole GM. Vitamin E protects nerve cells from amyloid-beta protein toxicity. *Biochemical and Biophysical Research Communication* 1992;186:944-950.

**Berg 1988**

Berg L. Clinical Dementia Rating (CDR). *Psychopharm Bull* 1988;24:637-9.

**Blessed 1968**

Blessed B, Tomlinson BE, Roth M. The association between quantitative measures of dementia and of senile change in the cerebral gray matter of elderly subjects. *British Journal of Psychiatry* 1968;114:797-811.

**Boothby 2005**

Boothby LA, Doering PL. Vitamin C and Vitamin E for Alzheimer's disease. *The Annals of Pharmacotherapy* 2005;39:2073-2079.

**Butterfield 2002**

Butterfield DA, Castegna A, Lauderback CM, Drake J. Evidence that amyloid beta-peptide- induced lipid peroxidation and its sequelae in Alzheimer's disease brain contribute to neuronal death. *Neurobiology of Aging* 2002;23 (5):655-664.

**Chalmers 1983**

Chalmers TC, Celano P, Sacks HS, Smith H. Bias in treatment assignment in controlled clinical trials. *New England Journal of Medicine* 1983;309:1358-61.

**Folstein 1975**

Folstein MF, Folstein SE, McHugh PR. 'Mini-Mental State': A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189-98.

**Grundman 2000**

Grundman M. Vitmain E and Alzheimer disease: the basis for additional clinical trials. *American Journal of Clinical Nutrition* 2000;71:630S-6S.

**Grundman 2004**

Grundman M, Petersen RC, Ferris SH, Thomas RG, Aisen PS, Bennett DA. Mild cognitive impairment can be distinguished from Alzheimer's disease and normal aging for clinical trials. *Archives of Neurology* 2004;61:59-66.

**Hara 1990**

Hara H, Kato H, Kogure K. Protective effect of alpha-tocopherol on ischemic neuronal damage in the gerbil hippocampus. *Brain Research* 1990;510:335-8.

**Hensley 1995**

Hensley K, Hall N, Subramaniam R, Cole P, Harris M, Aksenov M. Brain regional correspondence between Alzheimer's disease histopathology and biomarkers of protein oxidation. *Journal of Neurochemistry* 1995;65:2146-56.

**Hochberg 1988**

Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. *Biometrika* 1988;75:800-2.

**Hsiao 1995**

Hsiao KK, Borchelt DR, Olson K, Johannsdottir R, Kitt C, Yunis W. Age-related CNS disorder and early death in transgenic FVB/N mice overexpressing Alzheimer amyloid precursor proteins. *Neuron* 1995;15:1203-18.

**ICD 10**

The ICD-10 Classification of Mental and Behavioural Disorders: Diagnostic Criteria for Research. In: *World Health Organization Geneva: WHO, 1993:-.*

**Ichitani 1992**

Ichitani Y, Okaichi H, Yoshikawa . Learning behaviour in chronic vitamin E-deficient and supplemented rats: radial arm maze learning and passive avoidance response. *Behavioural Brain Research* 1992;51:157-164.

**Irizarry 2004**

Irizarry MC. Biomarkers of Alzheimer disease in plasma. *NeuroRx* 2004;1 (2):226-234.

**Jeandel 1989**

Jeandel C, Nicolas MB, Dubois F. Lipid peroxidation and free radical scavengers in Alzheimer's disease. *Gerontology* 1989;35:275-282.

**Jimenez-Jimenez 1997**

Jimenez-Jimenez FJ, Bustos F, Molina JA. Cerebrospinal fluid levels of alpha-tocopherol (vitamin E) in Alzheimer's Disease. *Journal of Neural Transmission* 1997;104:703-710.

**Koppal 1998**

Koppal T, Subramaniam R, Drake J. Vitamin E protects against Alzheimer's amyloid peptide (25-35)-induced changes in neocortical synaptosomal membrane lipid structure and composition. *Brain Research* 1998;786:270-273.

**Marcus 1998**

Marcus DL, Thomas C, Rodriguez C. Increased peroxidation and reduced antioxidant enzyme activity in Alzheimer's disease. *Experimental Neurology* 1998;150:40-44.

**McKhann 1984**

McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's Disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services task Force on Alzheimer's Disease. *Neurology* 1984;34:939-944.

**Mecocci 1994**

Mecocci P, MacGarvey U, Beal MF. Oxidative damage to mitochondrial DNA is increased in Alzheimer's disease. *Ann Neurol* 1994;36:747-51.

**Mecocci 2004**

Mecocci P. Oxidative stress in mild cognitive impairment and Alzheimer's disease: a continuum. *Journal of Alzheimer's disease* 2004;6:159-63.

**Parkinson's SG 1993**

Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease. *New England Journal of Medicine* 1993;328:176-183.

**Perrig 1997**

Perrig WJ, Perrig P, Stahelin HB. The relation between antioxidants and memory performance in the old and very old. *Journal of American Geriatric Society* 1997;45:718-724.

**Peyser 1995**

Peyser CE, Folstein M, Chase GA. Trial of d-alpha-tocopherol in Huntington's disease. *American Journal of Psychiatry* 1995;152:1771-1775.

**Pham 2005**

Pham DQ, Plakogiannis R. Vitamin E supplementation in Alzheimer's disease, Parkinson's disease, tardive dyskinesia and cataract: part 2. *The Annals of Pharmacotherapy* 2005;39:2065-72.

**Polidori 2002**

Polidori MC, Mecocci P. Plasma susceptibility to free radical -induced antioxidant consumption and lipid peroxidation is increased in very old subjects with Alzheimer disease. *Journal of Alzheimers Disease* 2002;4:517-22.

**Rosen 1984**

Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. *American Journal of Psychiatry* 1984;141:1356-64.

**Schoenfeld 1982**

Schoenfeld D. Partial residuals for the proportional hazards regression model. *Biometrika* 1982;69:239-41.

**Schulz 1995**

Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias: dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;273:408-12.

**Socci 1995**

Socci DJ, Crandall BM, Arendash GW. Chronic antioxidant treatment improves the cognitive performance of aged rats. *Brain Research* 1995;693:88-94.

**Stern 1994**

Stern Y, Albert SM, Sano M, Richards M, Miller L, Folstein M, Albert M, Bylsma FW, Lafleche G. Assessing patient dependence in Alzheimer's disease. *J Gerontology* 1994;49:M216-M222.

**Tariot 1995**

Tariot PN, Mack JL. The behavior rating scale for dementia Consortium to establish a registry for Alzheimer's disease. *Am J Psychiatry* 1995;152:1349-57.

**Tohgi 1994**

Tohgi H, Abe T, Nakanishi M. Concentrations of alpha-tocopherol and its quinone derivative in cerebrospinal fluid from patients with vascular dementia of the Binswanger type and Alzheimer type dementia. *Neuroscience Letters* 1994;174:73-76.

**Uneri 2006**

Uneri C, Sari M, Akboga J, Yuksel M. Vitamin e-coated tympanostomy tube insertion decrease the quantity of free radicals in tympanic membrane. *Laryngoscope* 2006;116:140-3.

**Vatassery 1988**

Vatassery GT, Brin MF, Fahn S, Kayden HJ, Traber MG. Effect of high doses of dietary vitamin E on the concentrations of vitamin E in several brain regions, plasma, liver, and adipose tissue of rats. *Journal of Neurochemistry* 1988;51:621-3.

**Wang 2005**

Wang J, Xiong S, Xie C, Markesbery WR, Lovell MA. Increased oxidative damage in nuclear and mitochondrial DNA in Alzheimer's disease. *Journal of Neurochemistry* 2005;93:953-62.

**Wang 2006**

Wang J, Markesbery WR, Lovell MA. Increased oxidative damage in nuclear and mitochondrial DNA in mild cognitive impairment.. *Journal of Neurochemistry* 2006;96:825-32.

**Wortwein 1994**

Wortwein G, Stackman RW, Walsh TJ. Vitamin E prevents the place learning deficit and the cholinergic hypofunction induced by AF64A. *Experimental Neurology* 1994;125:15-21.

**Zaman 1992**

Zaman Z, Roche S, Fielden P. Plasma concentrations of vitamin A and E and Carotenoids in Alzheimer's disease. *Age and Ageing* 1992;21:91-4.

**Zhou 1996**

Zhou Y, Gopalakrishanan V, Richardson JS. Actions of neurotoxic beta-amyloid on calcium homeostasis and viability of PC12 cells are blocked by antioxidants but not by calcium channel antagonists. *Journal of Neurochemistry* 1996;67:1419-25.