Thiamine for Alzheimer's disease (Review)

Rodríguez JL, Qizilbash N, López-Arrieta J

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2001, Issue 2

http://www.thecochranelibrary.com

WILEY

Copyright © 2010 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

TABLE OF CONTENTS

HEADER 1
ABSTRACT 1
PLAIN LANGUAGE SUMMARY 2
BACKGROUND 2
OBJECTIVES 2
METHODS 2
RESULTS 4
DISCUSSION 5
AUTHORS' CONCLUSIONS 5
ACKNOWLEDGEMENTS 5
REFERENCES 5
CHARACTERISTICS OF STUDIES 6
DATA AND ANALYSES 9
Analysis 1.1. Comparison 1 THIAMINE (3mg/day) vs PLACEBO, Outcome 1 cognitive function (MMSE, high score = good) completers. 10
Analysis 1.2. Comparison 1 THIAMINE (3mg/day) vs PLACEBO, Outcome 2 Cognitive function (MMSE - change from baseline) completers. 11
Analysis 1.3. Comparison 1 THIAMINE (3mg/day) vs PLACEBO, Outcome 3 ADAS-Cog (worse compared with baseline) at 1 month ITT. 12
WHAT'S NEW 12
HISTORY 12
CONTRIBUTIONS OF AUTHORS 13
DECLARATIONS OF INTEREST 13
NOTES 13
INDEX TERMS 13

Copyright © 2010 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

[Intervention Review]

Thiamine for Alzheimer's disease

José-Luis Rodríguez[1], Nawab Qizilbash[2], Jess López-Arrieta[3]

[1]Department of Clinical Geratology, University of Oxford, Oxford, UK. [2]SmithKline Beecham, Harlow, UK. [3]Geriatric Department, Hospital Universitario La Paz-Cantoblanco, Madrid, Spain

Contact address: José-Luis Rodríguez, Department of Clinical Geratology, University of Oxford, Radcliffe Infimary, Woodstock Road, Oxford, OX2 6HE, UK. jose.rodriguez@clinical-medicine.oxford.ac.uk.

Editorial group: Cochrane Dementia and Cognitive Improvement Group.
Publication status and date: Stable (no update expected for reasons given in 'What's new'), published in Issue 1, 2010.
Review content assessed as up-to-date: 5 May 2008.

Citation: Rodríguez JL, Qizilbash N, López-Arrieta J. Thiamine for Alzheimer's disease. *Cochrane Database of Systematic Reviews* 2001, Issue 2. Art. No.: CD001498. DOI: 10.1002/14651858.CD001498.

Copyright © 2010 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

Vitamin B1 (thiamine) deficiency plays an important role in Wernicke-Korsakoff syndrome. This is a form of brain damage occurring in long-term alcoholics who rely mainly on alcohol for nutrition. The acute syndrome (Wernicke's encephalopathy) is normally reversible. Progression to the profound amnestic syndrome (Korsakoff's psychosis) can be averted by a timely injection of a large dose of thiamine. There have been suggestions that thiamine may have a beneficial effect in Alzheimer's disease.

Objectives

The objective of this systematic review is to evaluate the efficacy of thiamine for people with Alzheimer's disease.

Search methods

The trials were identified from a last updated search of the Specialized Register of the Cochrane Dementia and Cognitive Improvement Group on 12 February 2003 using the terms thiamin*, vitamin-B1, B1, "Vitmain B1". This Register is regularly updated with records from all major health care databases (MEDLINE, EMBASE, CINAHL, PsycINFO) and many trials databases.

In addition the reviewers searched bibliographies of published reviews and conference proceedings and contacted pharmaceutical companies and trial investigators to obtain additional data.

Selection criteria

All unconfounded, double-blind, randomized trials in which treatment with thiamine was administered for more than a day and compared with placebo in patients with dementia of the Alzheimer's type.

Data collection and analysis

Two reviewers extracted the data independently by and estimated the odds ratios (95% CI) or the average differences (95% CI).

Main results

Three studies were included. The two cross-over studies did not report results from the first phase. It was not possible to pool any results for a meta-analysis. Nolan 1991 reports results that show no evidence of an effect on MMSE at 3, 6, 9 and 12 months for thiamine compared with placebo for those who completed the trial. Meador 1993a noted that 3/8 on thiamine compared with 6/9 on placebo were worse as measured on the ADAS-Cog at 3 months compared with baseline, but the difference is not statistically significant.

Copyright © 2010 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Blass 1988 and Nolan 1991 reported that no significant side-effects were noted during the study, and Meador 1993a did not mention side-effects. Blass 1998 noted that 5/16 and Nolan 1991 that 5/15 did not complete the study, but neither mentioned the groups to which these people belonged.

Authors' conclusions

It is not possible to draw any conclusions from this review. The number of people included in the studies is less than 50 and the reported results are inadequate.

PLAIN LANGUAGE SUMMARY

Insufficient evidence of the efficacy of thiamine for people with Alzheimer's disease

Preclinical and laboratory studies show an effect of thiamine on the release and breakdown of acetylcholine. Some intellectual functions, including attention and memory, are influenced by neurons which release acetylcholine. Cholinergic function is impaired in Alzheimer's disease. It has therefore been hypothesized that thiamine may be beneficial in Alzheimer's disease. Biochemical abnormalities in thiamine-dependent enzymes have been found in the brains of patients with Alzheimer's disease. The three included randomized controlled trials totaled less than 50 participants and insufficient detail in the results did not allow combination of the data. Thus the review found no evidence of the efficacy of thiamine for people with Alzheimer's disease.

BACKGROUND

Vitamin B1 (thiamine) plays an important role in Wernicke-Korsakoff syndrome (a form of amnesia caused by brain damage occurring in long-term alcoholics who rely mainly on alcohol for nutrition). The acute syndrome is potentially reversible but may proceed to profound dementia. Its progress can be stopped by a timely injection of a large dose of thiamine (Kril 1996). There have been suggestions that thiamine may have a beneficial effect in Alzheimer's disease (Butterworth 1993; Mastrogiacoma 1996; Mimori 1996).

There are two studies relating vitamins, particularly thiamine, to cognitive functioning. A study that compared the intake and functional levels of vitamins B6, C and thiamine, in 15 pairs of Alzheimer's disease and normal subjects, found a tendency for the Alzheimer's group to show lower vitamin B1 intakes than controls, despite both groups having a "normal" intake (Agbayewa 1992). Another study found that taking long-term vitamin supplements may improve cognitive functioning (Benton 1995). In vitro studies of animal tissue suggests there is evidence of a link between thiamine and the presynaptic release of acetylcholine. Thiamine binds to nicotinic receptors and may exhibit anticholinesterase activity. The relationship of thiamine to nicotinic receptors and its effects on acetylcholine might be beneficial in patients with Alzheimer's disease because it is generally accepted that memory and some intellectual functions are mediated by acetylcholine.

OBJECTIVES

The objective of this systematic review is to evaluate the efficacy of thiamine for people with Alzheimer's disease.

METHODS

Criteria for considering studies for this review

Types of studies

Only unconfounded, double-blind, randomized controlled trials of longer than one day were considered for inclusion. Trials in which the allocation to treatment or placebo was not random, or in which treatment allocation was not concealed were excluded. Prior knowledge of treatment allocation may lead to biased patient allocation (Schulz 1995).

In studies where a cross-over design was used, only data from the first treatment period were used. Studies may include a titration period prior to the randomization phase of the study. Data from any non-randomized titration period were not used to assess safety or efficacy.

Copyright © 2010 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Types of participants

Patients with Senile Dementia of the Alzheimer Type (SDAT) or probable or possible Alzheimer's disease as diagnosed by accepted criteria such as APA 1987 or ICD 10 or NINCDS-ADRDA (McKhann 1984) of any age or gender.

Types of interventions

1. Vitamin B1 (thiamine) or a derivative in any dose and any method of administration
2. Placebo

Types of outcome measures

The primary outcomes of interest are:

- Dependency (such as institutionalization)
- Global impression
- Functional performance
- Behavioural disturbance
- Quality of life
- Cognitive function (as measured by psychometric tests)
- Effect on carer
- Death
- Acceptability of treatment as measured by withdrawal from trial
- Safety as measured by the incidence of adverse effects (including side-effects) leading to withdrawal

Search methods for identification of studies

The trials were identified from a last updated search of the Specialized Register of the Cochrane Dementia and Cognitive Improvement Group on 12 February 2003 using the terms thiamin*, vitamin-B1, B1, "Vitamin B1".
The Specialized Register at that time contained records from the following databases:

- CCTR/Central: July 2002 (issue 3);
- MEDLINE: 1966 to 2002/09 (week 4);
- EMBASE: 1980 to 2002/08;
- PsycINFO: 1887 to 2002/7;
- CINAHL: 1982 to 2002/08;
- SIGLE (Grey Literature in Europe): 1980 to December 2001 (no further updates available at 29/09/02);
- ISTP (Index to Scientific and Technical Proceedings): to May 2000;
- INSIDE (BL database of Conference Proceedings and Journals): to June 2000;
- Aslib Index to Theses (UK and Ireland theses): 1970 to June 2001;
- Dissertation Abstract (USA): 1861 to June 2001;
- ADEAR (Alzheimer's Disease Clinical Trials Database): to September 2002;
- National Research Register: issue 3/2002;
- Current Controlled trials (last searched September 2002) which includes:
  - Alzheimer Society
  - GlaxoSmithKline
  - HongKong Health Services Research Fund
  - Medical Research Council (MRC)
  - NHS R&D Health Technology Assessment Programme
  - Schering Health Care Ltd
  - South Australian Network for Research on Ageing
  - US Dept of Veterans Affairs Cooperative Studies
  - National Institutes of Health (NIH)
  - ClinicalTrials.gov: last searched September 2002;
  - LILACS:Latin American and Caribbean Health Science Literature: 40th edition, May 2001 (last one available on 29/09/02).

The search strategies used to identify relevant records in MEDLINE, EMBASE, PsycINFO, CINAHL and LILACS can be found in the Group's module on *The Cochrane Library*.
The reviewers manually searched bibliographies of previously published reviews and conference proceedings and contacted pharmaceutical companies and trial investigators to obtain additional information.

Data collection and analysis

SELECTION OF STUDIES
A single reviewer (JLR) discarded irrelevant citations, based on the title of the publication and its abstract. If an article could possibly be relevant, it was retrieved for further assessment.
Two reviewers independently selected the trials for inclusion in the review from the culled citation list. There were no disagreements between the two reviewers.
QUALITY ASSESSMENT
Two reviewers assessed the methodological quality of each trial. The quality of the methodology of each selected trial was rated using the methods described in the Cochrane Collaboration Handbook.
Category A (adequate) is where the report describes allocation of treatment by: (i) some form of centralised randomized scheme, such as having to provide details of an enrolled participant to an office by phone to receive the treatment group allocation; (ii) some form of randomization scheme controlled by a pharmacy; (iii) numbered or coded containers, such as in pharmaceutical trial in which capsules from identical-looking numbered bottles are administrated sequentially to enrolled participants; (iv) an on-site or coded computer system, given that the allocations were in a locked, unreadable file that could be accessed only after inputting the characteristics of an enrolled participant; or (v) if assignment envelopes were used, the report should at least specify that they were sequentially numbered, sealed, opaque envelopes; (vi) other

Copyright © 2010 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

combinations of described elements of the process that provides assurance of adequate concealment.

Category B (Intermediate) is where the report describes allocation of the treatment by: (i) use of a list or table to allocate assignments; (ii) use of envelopes or sealed envelopes; (iii) stating the study as randomized without further detail.

Category C (inadequate) is where the report describes allocation of treatment by: (i) alternation; (ii) reference to case record numbers, dates of birth, day of week, or any other such approach; (iii) any allocation procedure that is entirely transparent before assignment, such as an open list of random number or assignments.

Empirical research has shown that lack of adequate allocation concealment is associated with bias. Trials with unclear concealment measures have been shown to yield more pronounced estimates of treatment effects than trials that have taken adequate measures to conceal allocation schedules, but less pronounced than inadequately concealed trials (Schulz 1995). Thus trials are included if they conform to categories A or B, while those falling into category C are excluded.

Other aspects of trial quality were not assessed by the scoring system although details were noted of blinding, whether intention-to-treat analyses were extractable from the published data, and of the number of patients lost to follow-up.

DATA EXTRACTION

Data were independently extracted by two reviewers and cross-checked. Any discrepancies were discussed and resolved by a third independent reviewer (JLA).

Data were sought on every patient with each outcome measure to allow an intention-to-treat analysis. Data were sought irrespective of compliance, whether or not the patient was subsequently deemed ineligible, or otherwise excluded from treatment or follow-up.

In studies where a cross-over design was used, only data from the first treatment period were eligible for inclusion.

DATA ANALYSIS

For continuous or ordinal variables (such as psychometric test scores, clinical global impression scales, functional and quality of life scales) the main outcomes of interest are the final assessment score (corrected for baseline) and the change in score from baseline (i.e. pre-randomization or at randomization) to the final assessment. If ordinal scale data appeared to be approximately normally distributed or if the analysis that the investigators perform suggested parametric tests are appropriate, then the outcome measures were treated as continuous data.

For binary outcomes such as institutionalisation, global impression and death, the endpoint itself is of interest and the Peto method of the typical odds ratio was used.

The hypothesis to be tested was that thiamine has no effect compared with placebo.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Three trials met the criteria for inclusion in this review. Meador 1993a describes two different experiments; the first experiment met the inclusion criteria, the second was excluded. All three studies were conducted in the USA, and all had fewer than 20 patients randomized. Blass 1988 is described as a pilot study. Two trials have a cross-over design, one of two months and the other of six months' total duration, and one with a parallel group design of one year's duration. All compare 3mg per day of thiamine, divided into three doses, with placebo.

Patients with probable or possible Alzheimer´ s disease of mild to moderate severity were diagnosed using recognised criteria (NINCDS-ADRDA). The mean MMSE at baseline for the three trials was 14, 18 and 16, and the mean age was between 71 and 76 years.

The primary outcome in the three studies was cognitive function. Behaviour was assessed in one study. The studies included the following rating scales:

1. Mini Mental State Examination (MMSE) (Folstein 1975), evaluates cognition in five areas: orientation, immediate recall, attention and calculation, delayed recall, and language. The test takes only 15 minutes to administer and the score ranges from 0 (severe impairment) to 30 (normal).

2. The Alzheimer's Disease Assessment Scale (ADAS-Cog) (Rosen 1984) comprises 11 individual tests, spoken language ability (0-5), comprehension of spoken language (0-5), recall of test instructions (0-5), word finding difficulty (0-5), following commands (0-5), naming object (0-5), construction drawing (0-5), ideational proaxis (0-5), orientation (0-8), word recall (0-10) and word recognition (0-12). The total score ranges from 0-70, the high score indicating greater impairment.

3. The behavioural scale of Haycox (Haycox 1984) uses information supplied by the carer.

4. The CERAD (Consortium to Establish a Registry for Alzheimer's Disease) neuropsychological battery (Morris 1989) includes a measure of verbal fluency, a short version of the Boston Naming Test, the MMSE, a constructional praxis test, a 10 item word list learning test, and a test of delayed recall .

5. The Blessed Dementia Scale (BDS) (Blessed 1968) consists of 6 sections . The first three sections measure changes in performance of everyday activities, habits and personality, interests and drive and are answered by the carer. The second three sections form a cognitive test.

Risk of bias in included studies

Copyright © 2010 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

A cross-over design is not an appropriate design for a clinical trial where the disease being treated is progressive as is Alzheimer's disease. Results from cross-over trials cannot be used unless those from the first phase are reported separately. There is no mention of a wash-out phase for Blass 1988, a cross-over study , and Meador 1993a does not have a wash-out phase between treatments. The proportion of drop-outs was not large especially considering the length of these studies, the age of the patients and the severity of their dementia.

Effects of interventions

Three studies could be included (Blass 1988; Meador 1993a; Nolan 1991). Two were excluded (Meador 1993b; Mimori 1996). Of the included studies, the cross-over studies (Meador 1993a; Blass 1988) did not report results from the first phase. It was not possible to pool any results for a meta-analysis. Nolan 1991reports results that show no evidence of an effect for MMSE at 3, 6, 9 and 12 months for thiamine compared with placebo for those who complete the trial. Meador 1993a noted that 3/8 on thiamine compared with 6/9 on placebo were worse as measured on the ADAS-Cog at 3 months compared with baseline, but the difference was not statistically significant.

Blass 1988 and Nolan 1991reported that no significant side-effects were noted during the study, and Meador 1993a did not mention side-effects. Blass 1988 noted that 5/16 and Nolan 1991 that 5/15 did not complete the study, but neither mentioned the groups to which these people belonged.

DISCUSSION

It is not possible to draw any conclusions from this review. The total number of people included in the studies was less than 50. The results were reported in insufficient detail to allow combination of the data.

AUTHORS' CONCLUSIONS

Implications for practice

There is no reliable evidence on which to base a decision to use thiamine to treat patients with Alzheimer's disease.

Implications for research

There are currently insufficient randomized controlled trial data to allow any conclusions to be drawn about whether further research into the effect of thiamine is warranted. No trends were apparent in the data.

ACKNOWLEDGEMENTS

We are grateful to Felicia Huppert for helpful comments as the reviewing editor on the original review, and to Jacqueline Birks for her help with the methodological part of the review. We also gratefully acknowledge the contributions of the consumer editor Bill Perberdy.

REFERENCES

References to studies included in this review

Blass 1988 *{published data only}*
Blass JP, Gleason P, Brush D, DiPonte P, Thaler H. Thiamine and Alzheimer's disease. A pilot study. *Arch Neurol* 1988;**45**(8):833–5.

Meador 1993a *{published data only}*
Meador K, Loring D, Nichols M, Zamrini E, Rivner M, Posas H, Thompson E, Moore E. Preliminary Findings of High-Dose Thiamine in Dementia of Alzheimer's Type. *J Geriatric Psychiatry and Neurology* 1993;**6**(4):222–9.

Nolan 1991 *{published data only}*
Nolan KA, Black RS, Sheu KFR, Langberg J, Blass JP. A trial of thiamine in Alzheimer's disease. *Arch Neurol* 1991; **48**(1):81–3.

References to studies excluded from this review

Meador 1993b *{published data only}*
Meador K, Loring D, Nichols M, Zamrini E, Rivner M, Posas H, Thompson E, Moore E. Preliminary Findings of High-Dose Thiamine in Dementia of Alzheimer's Type. *J Geriatric Psychiatry and Neurology* 1993;**6**:222–229.

Mimori 1996 *{published data only}*
Mimori Y, Katsuoka H, Nakamura S. Thiamine Therapy in Alzheimer's Disease. *Metabolic Brain Disease* 1996;**11**: 89–94.

Additional references

Agbayewa 1992
Agbayeba OM, Bruce V, Siemens V. Pyrioxine, ascorbic acid and thiamine in Alzheimer and comparison subjects. *Can J Psychiatry* 1992;**37**:661–2.

APA 1987
American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 3rd Edition. Washington: APA, 1987.

Benton 1995
Benton D, Fordy J, Haller J. The impact of long-term vitamin supplementation on cognitive functioning. *Psychopharmacology-Berl* 1995;**117**(3):298–305.

Copyright © 2010 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

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

Butterworth 1993
Butterworth RF, Kril JJ, Harper CG. Thiamine-dependent enzyme changes in the brains of alcoholics: relationship to the wernicke-korsakoff syndrome. *Alcohol Clin Exp Res* 1993;**17**(5):1084–8.

Folstein 1975
Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State" A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research* 1975;**12**:189–98.

Haycox 1984
Haycox JA. A simple, reliable clinical behavior scale for assessing demented patients. *J Clin Psychiatry* 1984;**45**: 23–4.

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

Kril 1996
Kril JJ. Neuropathology of thiamine deficiency disorders. *Metabolic Brain Disease* 1996;**11**(1):9–17.

Mastrogiacoma 1996
Mastrogiacoma F, Bettendorff L, Grisar T, Kish SJ. Brain thiamine, its phosphate esters, and its metabolizing enzymes in Alzheimer's disease. *Annals of Neurology* 1996;**39**(5): 585–91.

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;**4**:939–44.

Morris 1989
Morris JM, Heyman J, Mohs RC. The consortium to establish a registry for Alzheimer's disease (CERAD), I: clinical and neuropsychological assessment of Alzheimer's disease. *Neurology* 1989;**39**:1159–65.

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

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.

References to other published versions of this review

Rodríguez-Martín 2001
Rodríguez-Martín JL, Qizilbash N, López-Arrieta JM. Thiamine for Alzheimer's disease. *Cochrane Database of Systematic Reviews* 2001, Issue 2. [DOI: 10.1002/ 14651858.CD001498]

* *Indicates the major publication for the study*

Copyright © 2010 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Blass 1988

Methods	Double-blind, placebo-controlled randomized cross-over study of 3 x 2 months
Participants	Country: USA Number: 16 randomized, 11 completed (4 male 7 female) Mean age: 71.6 (7.5) range 59-83 well nourished with no vitamin deficiency Diagnostic criteria: NINCDS-ADRDA AD confirmed at autopsy in 90% of cases MMSE mean 14.2 (4.6) Hachinski <= 4
Interventions	1. Thiamine hydrochloride (3 mg/day divided into 3 doses) 2. niacinamide (750mg/day divided into 3 doses)
Outcomes	MMSE BDS Haycox
Notes	There appears to have been no washout period between phases.

Meador 1993a

Methods	Double-blind placebo controlled randomized cross-over study (1month x 2, without washout period)
Participants	Country: USA Number: 18 randomized (5 male 13 female) Mean age: 71 range 61-86 Diagnostic criteria: NINCDS-ADRDA MMSE mean 18 (7) Hachinski <= 4
Interventions	1. Thiamine hydrochloride (3 mg/day divided into 3 doses) 2. placebo
Outcomes	ADAS MMSE
Notes	

Copyright © 2010 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Nolan 1991

Methods	Unconfounded, double-blind, randomized, placebo-controlled, parallel group study of 1 year
Participants	Country: USA Number: 15 (5 male, 10 female) Mean age: 76.3 (7.7) range 59-87 well nourished with no vitamin deficiency Diagnostic criteria: NINCDS-ADRDA MMSE mean 16.3 (5.7) range 8-23 Diagnosis: AD probable, AD possible Criteria of diagnosis: NINCDS-ADRDA
Interventions	1. Thiamine hydrochloride (3 mg/day divided into 3 doses) 2. placebo
Outcomes	MMSE CERAD neuropsychological battery
Notes	5/15 patients unavailable for analysis at 12 months, reported as evenly distributed between groups (2 versus 2) and one due to clerical error

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Meador 1993b	No randomization
Mimori 1996	No control group/no randomization

Copyright © 2010 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

DATA AND ANALYSES

Comparison 1. THIAMINE (3mg/day) vs PLACEBO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 cognitive function (MMSE, high score = good) completers	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 at 3 months	1	10	Mean Difference (IV, Fixed, 95% CI)	-2.40 [-10.82, 6.02]
1.2 at 6 months	1	10	Mean Difference (IV, Fixed, 95% CI)	-1.00 [-12.24, 6.24]
1.3 at 9 months	1	10	Mean Difference (IV, Fixed, 95% CI)	-1.20 [-10.24, 7.84]
1.4 at 12 months	1	10	Mean Difference (IV, Fixed, 95% CI)	-4.20 [-14.33, 5.93]
2 Cognitive function (MMSE - change from baseline) completers	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 at 3 months	1	10	Mean Difference (IV, Fixed, 95% CI)	-3.0 [-14.00, 8.00]
2.2 at 6 months	1	10	Mean Difference (IV, Fixed, 95% CI)	-3.6 [-15.24, 8.04]
2.3 at 9 months	1	10	Mean Difference (IV, Fixed, 95% CI)	-1.80 [-13.28, 9.68]
2.4 at 12 months	1	10	Mean Difference (IV, Fixed, 95% CI)	-4.80 [-17.15, 7.55]
3 ADAS-Cog (worse compared with baseline) at 1 month ITT	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only

Copyright © 2010 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 1.1. Comparison 1 THIAMINE (3mg/day) vs PLACEBO, Outcome 1 cognitive function (MMSE, high score = good) completers.

Review: Thiamine for Alzheimer's disease

Comparison: 1 THIAMINE (3mg/day) vs PLACEBO

Outcome: 1 cognitive function (MMSE, high score = good) completers

Study or subgroup	thiamine N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 at 3 months							
Nolan 1991	5	14.6 (7.02)	5	17 (6.56)		100.0 %	-2.40 [-10.82, 6.02]
Subtotal (95% CI)	**5**		**5**			**100.0 %**	**-2.40 [-10.82, 6.02]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.56 (P = 0.58)							
2 at 6 months							
Nolan 1991	5	13.4 (7.2)	5	16.4 (7.7)		100.0 %	-3.00 [-12.24, 6.24]
Subtotal (95% CI)	**5**		**5**			**100.0 %**	**-3.00 [-12.24, 6.24]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.64 (P = 0.52)							
3 at 9 months							
Nolan 1991	5	12.2 (8.07)	5	13.4 (6.43)		100.0 %	-1.20 [-10.24, 7.84]
Subtotal (95% CI)	**5**		**5**			**100.0 %**	**-1.20 [-10.24, 7.84]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.26 (P = 0.79)							
4 at 12 months							
Nolan 1991	5	10.4 (9.13)	5	14.6 (7.09)		100.0 %	-4.20 [-14.33, 5.93]
Subtotal (95% CI)	**5**		**5**			**100.0 %**	**-4.20 [-14.33, 5.93]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.81 (P = 0.42)							
Test for subgroup differences: Chi^2 = 0.20, df = 3 (P = 0.98), I^2 =0.0%							

Copyright © 2010 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 1.2. Comparison 1 THIAMINE (3mg/day) vs PLACEBO, Outcome 2 Cognitive function (MMSE - change from baseline) completers.

Review: Thiamine for Alzheimer's disease

Comparison: 1 THIAMINE (3mg/day) vs PLACEBO

Outcome: 2 Cognitive function (MMSE - change from baseline) completers

Study or subgroup	thiamine N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 at 3 months							
Nolan 1991	5	-2 (9.06)	5	1 (8.69)		100.0 %	-3.00 [-14.00, 8.00]
Subtotal (95% CI)	**5**		**5**			**100.0 %**	**-3.00 [-14.00, 8.00]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.53 (P = 0.59)							
2 at 6 months							
Nolan 1991	5	-3.2 (9.2)	5	0.4 (9.58)		100.0 %	-3.60 [-15.24, 8.04]
Subtotal (95% CI)	**5**		**5**			**100.0 %**	**-3.60 [-15.24, 8.04]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.61 (P = 0.54)							
3 at 9 months							
Nolan 1991	5	-4.4 (9.89)	5	-2.6 (8.58)		100.0 %	-1.80 [-13.28, 9.68]
Subtotal (95% CI)	**5**		**5**			**100.0 %**	**-1.80 [-13.28, 9.68]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.31 (P = 0.76)							
4 at 12 months							
Nolan 1991	5	-6.2 (10.77)	5	-1.4 (9.09)		100.0 %	-4.80 [-17.15, 7.55]
Subtotal (95% CI)	**5**		**5**			**100.0 %**	**-4.80 [-17.15, 7.55]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.76 (P = 0.45)							
Test for subgroup differences: Chi^2 = 0.13, df = 3 (P = 0.99), I^2 =0.0%							

Copyright © 2010 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 1.3. Comparison 1 THIAMINE (3mg/day) vs PLACEBO, Outcome 3 ADAS-Cog (worse compared with baseline) at 1 month ITT.

Review: Thiamine for Alzheimer's disease

Comparison: 1 THIAMINE (3mg/day) vs PLACEBO

Outcome: 3 ADAS-Cog (worse compared with baseline) at 1 month ITT

Study or subgroup	thiamine n/N	placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Meador 1993a	3/8	6/9			0.33 [0.05, 2.12]
Subtotal (95% CI)	**0**	**0**			**0.0 [0.0, 0.0]**
Total events: 3 (thiamine), 6 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P < 0.00001)					
Test for subgroup differences: Not applicable					

WHAT'S NEW

Last assessed as up-to-date: 5 May 2008.

Date	Event	Description
6 May 2008	Review declared as stable	No more updates are necessary for this review as it has been proven that it is of no use for AD

HISTORY

Protocol first published: Issue 3, 1997

Review first published: Issue 2, 1999

Date	Event	Description
9 February 2004	Amended	February 2004: the review has been updated to reflect the comments of the peer reviewers

Copyright © 2010 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

(*Continued*)

12 February 2003	New search has been performed	An update search in February 2003 retrieved no new studies for inclusion/exclusion
26 February 2001	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

-JLR drafts of the review, updating, correspondence

-JAL clinical aspects of the review and updates

-NQ work on the original protocol and review

-CDCIG contact editor: Jacqueline Birks

-Consumer editor: Bill Perberdy

The review has been peer reviewed

DECLARATIONS OF INTEREST

None known

NOTES

October 2000: The review was updated following a new search for studies. None was found, and no substantive changes have been made to the review although most sections of the text have been revised and a number of corrections and edits made.

February 2003: The review was updated following a new search for studies. None was found, and no substantive changes have been made to the Review.

November 2003: The review has been updated to reflect the consumer editor's comments.

INDEX TERMS

Medical Subject Headings (MeSH)

Alzheimer Disease [*drug therapy; psychology]; Cognition Disorders [drug therapy]; Thiamine [*therapeutic use]

MeSH check words

Humans

Copyright © 2010 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.