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Thiamine for prevention and treatment of Wernicke-Korsakoff Syndrome in people who abuse alcohol (Review)

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[Intervention Review]

Thiamine for prevention and treatment of Wernicke-Korsakoff Syndrome in people who abuse alcohol

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ABSTRACT

Background

Autopsy studies suggest that Wernicke-Korsakoff syndrome (WKS) is not a rare disorder, particularly in individuals who abuse alcohol. Thiamine has been established as the treatment of choice for over 50 years, but uncertainty remains about appropriate dosage and duration. Current practice guidelines are based on case reports and clinical experience. This is an update of a review first published in 2004 and last updated in 2008.

Objectives

• To assess the efficacy of thiamine in preventing and treating the manifestations of WKS due to excess alcohol consumption.
• To determine the optimum form, dose and duration of thiamine treatment for this indication.

Search methods

ALOIS, the Specialized Register of the Cochrane Dementia and Cognitive Improvement Group (CDCIG), *The Cochrane Library,* MEDLINE, EMBASE, PsycINFO, CINAHL and LILACS were searched on 6 September 2012 using the term thiamine OR aneurine. ALOIS contains records from all major health care databases (*The Cochrane Library*, MEDLINE, EMBASE, PsycINFO, CINAHL, LILACS) as well as from many trial databases and grey literature sources.

Selection criteria

Any randomised trials comparing thiamine with alternative interventions or comparing different thiamine regimens (varying in formulation, dose or duration of administration).

Data collection and analysis

All abstracts were independently inspected by two reviewers (ED and PWB), and relevant articles were retrieved and assessed for methodological quality using criteria provided in the *Cochrane Handbook for Systematic Reviews of Interventions*.

Main results

Two studies were identified that met the inclusion criteria, but only one contained sufficient data for quantitative analysis. Ambrose (2001) randomly assigned participants (n = 107) to one of five doses of intramuscular thiamine and measured outcomes after 2 days of treatment. We compared the lowest dose (5 mg/day) with each of the other four doses. A significant difference favoured 200 mg/day compared with

the 5-mg/day dose in determining the number of trials needed to meet inclusion criteria on a delayed alternation test (mean difference (MD) -17.90, 95% confidence interval (CI) -35.4 to -0.40, P = 0.04). No significant differences emerged when the other doses were compared with 5 mg/day. The pattern of results did not reflect a simple dose-response relationship. The study had methodological shortcomings in design and in the presentation of results that limited further analysis.

Authors' conclusions

Evidence from randomised controlled clinical trials is insufficient to guide clinicians in determining the dose, frequency, route or duration of thiamine treatment for prophylaxis against or treatment of WKS due to alcohol abuse.

PLAIN LANGUAGE SUMMARY

Thiamine for prevention and treatment of Wernicke-Korsakoff syndrome in people who abuse alcohol

Wernicke-Korsakoff syndrome (WKS) is a disorder of the brain caused by a deficiency of vitamin B_1 (thiamine). It is characterised by an acute onset of some or all of an eye movement disorder, lack of voluntary coordination of muscle movement (ataxia) and confusion. Patients may die in the acute phase, and many survivors go on to develop permanent memory impairment. Alcohol abuse is an important cause of WKS, although it is not the only consideration. Heavy drinking may lead to particular problems with uptake of thiamine from the diet.

When recognised, WKS is treated with thiamine, but it is not clear how effective this is, particularly in managing the mental features. Recommendations about dosage and duration of thiamine treatment are acknowledged to be arbitrary. We searched for randomised controlled trials comparing thiamine with placebo or alternative treatments, or comparing different thiamine treatments. Two studies were identified that met the inclusion criteria, but one reported no data that we could analyse, and analysis of the other study was limited by shortcomings in design and in presentation of the results. Therefore no good evidence could be derived from randomised controlled clinical trials to help physicians choose the right dose, frequency, route or duration of thiamine treatment for preventing or treating WKS due to alcohol abuse.

BACKGROUND

Description of the condition

Alcohol abuse is associated with a variety of neuropsychiatric problems, and the Wernicke-Korsakoff syndrome (WKS) is one of the most serious. Wernicke's encephalopathy (WE) is traditionally thought of as a disorder of acute onset characterised by nystagmus, abducent and conjugate gaze palsies, ataxia of gait and a global confusional state, which may occur together or in various combinations (Victor 1989). It is due to deficiency of the B vitamin thiamine (vitamin B_1, also known as *aneurin*). Carl Wernicke first described the disorder in 1881 in three cases, two associated with chronic alcohol dependence and one with persistent vomiting after sulphuric acid poisoning. The symptoms that Wernicke recorded included disturbances of eye movement, ataxia of gait, polyneuropathy and mental changes including apathy, decreased attention span and disorientation in time and space. He noted similar pathological changes in all three cases, in particular numerous punctate haemorrhages in the grey matter around the third and fourth ventricles and the aqueduct of Sylvius. Work by Alexander (1939) and then Jolliffe (1941) established the role of thiamine deficiency in development and potential treatment of the disorder (Lishman 1998).

In 1887 Sergei Korsakoff gave the first comprehensive account of the amnestic syndrome now known as Korsakoff psychosis (KP). He described a range of features including delirium, but the disorder came to be characterised by recent memory loss with confabulation but with relative preservation of other intellectual functions. The two disorders were brought together by Victor and colleagues in 1971 (Victor 1971). WKS is now considered to be a unitary disorder comprising acute WE, which proceeds in a proportion of cases to KP. From a case series of 245 patients, Victor et al concluded that the clinical triad of ophthalmoplegia, ataxia and mental confusion 'needs to be amplified to include the characteristic memory disorder' as well as peripheral neuropathy (Victor 1971).

A major complicating factor is that the pathology of WE may not be associated with the classical clinical triad in up to 90% of patients (Harper 1986). The full triad of symptoms is recognised in just 0.05% of all hospital admissions, whereas the whole population prevalence of WKS based on autopsy studies in Western countries has been estimated at 1% to 2% (Harper 1995; Torvik 1991). Autopsy studies suggest that WE is not a rare disorder, particularly among abusers of alcohol. Therefore it has been suggested that a presumptive diagnosis of WE should be made for any patient with a history of alcohol abuse who may be at risk. This includes anyone showing evidence of ophthalmoplegia, ataxia, acute confusion, memory disturbance, unexplained hypotension, hypothermia, coma or unconsciousness (Cook 2000). Operational criteria for the diagnosis of WE have been proposed (Caine 1997), and although they are not yet widely used, they can help in distinguishing this problem from other potentially coexisting conditions such as alcohol withdrawal or hepatic encephalopathy.

When untreated, WE leads to death in up to 20% of cases (Harper 1979; Harper 1986) or to KP in 85% of survivors (Cook 1998). Up to 25% of the latter group require long-term institutionalisation (Victor 1989). Furthermore, the incidence of KP has been reported to be rising in some parts of the UK (Ramayya 1997). For the reasons already mentioned, it is probable that WE is largely underdiagnosed, and so any published incidence and prevalence figures are likely to represent a considerable underestimation.

Description of the intervention

Chronic alcohol consumption, which is an important but not an exclusive cause of the disorder, does not necessarily result in WE if dietary thiamine intake is adequate (Sechi 2007; NCGCACC 2010). It may lead to thiamine deficiency through several potential mechanisms—genetic predisposition, replacement of vitamin-containing foods by the high calorific value of alcohol, impaired absorption of thiamine from the gut, impairment of storage by the liver, thiamine transport problems, other nutritional deficiencies, decreased phosphorylation to thiamine pyrophosphate and excessive requirements for the metabolism of alcohol (Butterworth 1993; Thomson 2012). Thiamine acts as a coenzyme in the metabolism of glucose and lipids, and, as stores of water-soluble vitamins are limited in the body, deficiency can present within 2 to 3 weeks of cessation of intake (Cook 1998). Oral preparations have been shown to vary in bioavailability (Greb 1998), but in hospital practise, thiamine is usually administered parenterally to patients thought to be at high risk of WKS. Parenteral administration is associated with some risk of anaphylaxis (Thomson 1997).

How the intervention might work

This review will focus on WKS in the context of alcohol abuse, as this is by far the most common cause in the developed world, with 30% to 80% of alcohol abusers having clinical or biochemical signs of thiamine deficiency (Thomson 1987). Alcohol also appears to significantly increase the amount of thiamine required to treat the patient successfully compared with individuals in whom thiamine deficiency has a predominantly nutritional cause (Thomson 2008). Despite evidence suggesting a high prevalence of unrecognised neuropathology due to thiamine deficiency, few studies have investigated the therapeutic effects of thiamine in alcohol abusers in a systematic way. Ataxia and eye movement abnormalities have been found to improve rapidly with administration of thiamine (Phillips 1952), but the effects on memory in particular are far from clear. One review of the subject concludes that no formal dose-ranging, placebo-controlled studies have been conducted on the use of parenteral B-complex vitamins (including thiamine) in alcohol abuse before investigators could go on to advocate 'different (treatment) regimens for patients at risk of developing WE and those currently suffering from WE' (Cook 2000).

Why it is important to do this review

Although WKS is reasonably well defined and is known to cause significant mortality and morbidity, the optimal treatment strategy is not clear. The role of thiamine in treating patients with some of the features of WKS has been frequently recorded, but recommendations about dosage and duration of treatment are acknowledged to be arbitrary. Is there clear evidence for the efficacy of thiamine in preventing and treating the features of WKS, and if so, in which form should it be given, at what dose and for how long? Is there a window of opportunity for treatment? This is an update of an earlier Cochrane review, which was originally published in 2004 and was last updated in 2008. This update involved an updated search of the literature and some revisions of background to incorporate developments in the field since the time of the original publication.

OBJECTIVES

- To assess the efficacy of thiamine in preventing and treating the manifestations of WKS due to excess alcohol consumption
- To determine the optimum form, dose and duration of thiamine treatment for this indication

METHODS

Criteria for considering studies for this review

Types of studies

Any randomised trials comparing thiamine with alternative interventions or comparing different thiamine regimens (varying in formulation, dose or duration of administration).

Types of participants

All participants with, or at risk of developing, WKS as the result of any diagnosis of alcohol use disorder or 'alcoholism', including harmful use, abuse and dependence. Participants who developed WKS after thiamine deficiency secondary to causes other than alcohol abuse were excluded.

Types of interventions

- Thiamine or thiamine-containing products at any dose and in any formulation (oral, intramuscular or intravenous).
- Placebo.
- Other interventions or no treatment.

Types of outcome measures

The primary outcome measures of interest included the following:

- Efficacy as measured by change in any of five key domains:
  - Global 'confusion' or delirium (e.g. presence or absence of delirium using the Confusion Assessment Method (CAM)).
  - Neurological symptoms (e.g. presence or absence of nystagmus, gaze palsies or ataxia).
  - Global or domain-specific cognitive measures (e.g. attention, constructional abilities or memory).
  - Functional outcomes (e.g. activities of daily living scales).
  - Death.
- Acceptability of treatment as measured by:
  - Total number of drop-outs
  - Incidence of adverse events and side effects

Search methods for identification of studies

Electronic searches

We searched ALOIS (www.medicine.ox.ac.uk/alois) — the Cochrane Dementia and Cognitive Improvement Group's Specialized Register — on 6 September 2012. The search term used was thiamine OR aneurine.

ALOIS is maintained by the Trials Search Co-ordinator of the Cochrane Dementia and Cognitive Improvement Group and contains studies in the areas of dementia prevention, dementia treatment and cognitive enhancement in healthy individuals. These studies are identified by:

- Monthly searches of a number of major healthcare databases: MEDLINE, EMBASE, CINAHL, PsycINFO and Lilacs.
- Monthly searches of a number of trial registers: ISRCTN; UMIN (Japan's Trial Register); the World Health Organisation (WHO) portal (which covers ClinicalTrials.gov; ISRCTN; the Chinese Clinical Trials Register; the German Clinical Trials Register; the Iranian Registry of Clinical Trials and the Netherlands National Trials Register, plus others).
- Quarterly search of the Cochrane Central Register of Controlled Trials (CENTRAL).
- Six-monthly searches of a number of grey literature sources: ISI Web of Knowledge Conference Proceedings; Index to Theses; Australasian Digital Theses.

To view a list of all sources searched for ALOIS, see About ALOIS on the ALOIS Website.

Details of the search strategies used to retrieve reports of trials from the healthcare databases, CENTRAL and conference proceedings can be viewed in the 'methods used in reviews' section within the editorial information about the Dementia and Cognitive Improvement Group.

Additional searches were performed in many of the sources listed above to cover the time frame from the last searches performed for ALOIS to ensure that the search for the review was as up-to-date and as comprehensive as possible. The search strategies used can be seen in Appendix 1.

The latest search (September 2012) retrieved a total of 563 results.

Searching other resources

Personal communication: Authors of included studies and experts in the field were contacted to find out if they knew of any other published or unpublished randomised controlled trials (RCTs) of thiamine treatment for WKS.

Attempts were made to obtain unpublished trials from the pharmaceutical industry by contacting Link Pharmaceuticals, the manufacturers of Pabrinex (the only thiamine-containing parenteral preparation available in the UK).

Data collection and analysis

Selection of the studies

Two independent review authors (ED and PWB) undertook a systematic examination of all references retrieved by the search. The two review authors independently selected trials assessing the effectiveness of thiamine in participants with or at risk of developing WKS as the result of alcohol abuse.

Data collection

Both review authors (ED and PWB) independently extracted the data. Any disagreement was discussed and the decisions documented. Where necessary, attempts were made to contact the authors of the studies to help resolve the issue.

For dichotomous outcomes, we extracted the number of participants experiencing the event and the total number of participants in each arm of the trial. For continuous outcomes, we extracted the arithmetic mean and standard deviation (SD) in each arm of the trial, as well as the total number in each group. If final

means and SDs were not reported, we extracted the mean and SD of change from baseline where available.

The baseline assessment was defined as the latest available assessment before randomisation, but no longer than two months before.

For each outcome measure, data were sought on every patient assessed. To allow an intention-to-treat analysis, the data were sought irrespective of compliance and whether or not the patient was subsequently deemed ineligible or otherwise excluded from treatment or follow-up. If intention-to-treat data were not available in the publications, "on-treatment" or the data of those who completed the trial were sought and were indicated as such.

Assessment of risk of bias in included studies

The assessment of bias took into account the adequacy of random sequence generation, allocation concealment, blinding, completeness of outcome data, selective outcome reporting, and any other potential sources of bias according to the Cochrane risk of bias tool (Higgins 2011).

Risk of bias of the included studies was assessed under the following headings:

- Sequence generation.
- Allocation concealment.
- Blinding.
- Incomplete outcome data.
- Selective outcome reporting.
- Other biases.

Rating scales

A wide range of rating scales are available to measure the various aspects of global and domain-specific cognitive function (especially memory). These scales vary in quality, and many are poorly validated in this population (i.e. heavy drinkers). The review authors included data generated by the use of unpublished rating scales or scales without established reliability and validity but where relevant commented on their shortcomings.

Measures of treatment effect

The outcomes measured in clinical trials of dementia and cognitive impairment often arise from ordinal rating scales. When the rating scales used in the trials had a reasonably large number of categories (more than 10), the data would have been treated as continuous outcomes arising from a normal distribution.

We expressed the results as odds ratio (OR) with 95% confidence interval (CI) for dichotomous outcomes, and as mean difference (MD) and standardised mean difference (SMD) with 95% CI for continuous outcomes. We planned to use the MD when pooled trials used the same rating scale or test, and the SMD (i.e. the absolute MD divided by the standard deviation (SD)) when different rating scales were used. The available data did not permit meta-analytical methods of data synthesis.

Unit of analysis issues

We intended to deal with any unit of analysis issues using guidance provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011)

.

Data analysis and assessment of heterogeneity

Overall estimates of the treatment difference were to be presented. In all cases, the overall estimate from a fixed-effect model would have been presented and a test for heterogeneity using a standard Chi^2 statistic or the I^2 statistic performed. If significant heterogeneity had been noted, a random-effects model would have been presented. If evidence of heterogeneity of the treatment effect between trials had been found, then either only homogeneous results were to be pooled, or a random-effects model would have been used (in which case the CIs would have been broader than those of a fixed-effect model).

Subgroup analysis

Depending on availability of data, we planned the following patient subgroup analyses:

- Heavy alcohol consumption and at risk for WKS
- Diagnosis of WE
- Diagnosis of KP

If possible, we also aimed to analyse data by the following:

- Time to outcome measure - short-term (up to one month), medium term (one month up to six months) and long-term (longer than six months).
- Route of administration of thiamine.
- Type of thiamine-containing preparation.
- Dose of thiamine.
- Duration of treatment.

RESULTS

Description of studies

Results of the search

The Cochrane Dementia and Cognitive Improvement Group trials register is the most comprehensive of its kind, and yet only two trials were found. A review of the reference lists of these articles and of other descriptive reviews of the management of WKS, as well as discussion with experts in the field, yielded no further controlled trials. Link Pharmaceuticals, the manufacturer of a commonly prescribed vitamin preparation containing thiamine, reported that the company had no records of relevant, randomised controlled trials on file. An author of one trial (Ambrose 2001) was unable to furnish additional data, and attempts to contact an author of the other trial (Nichols unpublished) were unsuccessful.

Included studies

We identified two studies that met the inclusion criteria for the review (Ambrose 2001; Nichols unpublished), one of which was unpublished. These studies involved a total of 177 participants, and both were randomised double-blind, placebo-controlled trials. However, one study (Nichols unpublished) was very small (n = 8) and contained insufficient data for quantitative analysis.

Both studies involved participants with a history of chronic alcohol use. In Ambrose 2001, participants were recruited by consecutive admissions to a 12-bed detoxification unit with 24-hour nursing cover. Participants had a mean age of 42 years, had been drinking

for an average of 17 years and had consumed a mean of 303 g of alcohol per day at the time of admission. All conformed to a *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* diagnosis of alcohol dependence but did not have the triad of acute symptoms associated with WKS. In Nichols unpublished, participants were described as having a history of chronic alcohol abuse, but no information was given about the length or level of drinking history or how participants were recruited. All participants had evidence of baseline neuropsychological memory impairment, as defined by a Buschke Selective Reminding Test (Consistent Long-Term Recall and Delayed Recall (CLTR)) score of less than 90. No other indication of the manifestations of WKS was given.

Ambrose 2001 compared five doses of intramuscular thiamine hydrochloride (5, 20, 50, 100 and 200 mg) given once per day for two consecutive days. Nichols unpublished compared 5 g per day of oral thiamine hydrochloride with a lactose placebo given for a period of two weeks.

In Ambrose 2001, participants were assessed individually on day 3 of treatment on the delayed alternation test by a psychologist blind to treatment allocation. Their blood alcohol levels were recorded as zero. Nichols unpublished used a more extensive battery of cognitive measures at baseline and after two weeks of treatment. These included the Buschke Selective Reminding Test (CLTR), the Halstead Category Test, the MCG Complex Figure Test and the Controlled Oral Word Association Test (COWA).

Excluded studies

One study was excluded (Peters 2006). This study investigates different outcome measures involving polyneuropathy, not WKS.

Risk of bias in included studies

Allocation

Neither of the two included studies reported the method used to generate random allocation.

In Ambrose 2001, 43 studies in the initial sample did not complete treatment and assessment, and the final treatment groups differed in age and average daily ethanol consumption. Therefore data from 19 participants were removed to equate treatment group means on the background variables of age, education and drinking history. The authors do not make clear how the 19 cases were selected, although they comment that this was done without regard for treatment outcome data.

Blinding

Both studies were described as double blind, but neither described precautions taken to minimise detection bias.

Incomplete outcome data

In Ambrose 2001, 43 participants did not complete treatment, but it is not clear whether the rate of non-completion was different in each of the five treatment groups.

Effects of interventions

The Cochrane Dementia and Cognitive Improvement Group trials register is the most comprehensive of its kind, and yet only two trials were found. A review of the reference lists of these articles and of other descriptive reviews of the management of WKS, as well as discussion with experts in the field, yielded no further controlled trials. Link Pharmaceuticals, manufacturer of a commonly prescribed vitamin preparation containing thiamine, reported that the company had no records of relevant, randomised controlled trials on file. An author of one trial (Ambrose 2001) was unable to furnish additional data, and attempts to contact an author of the other trial (Nichols unpublished) were unsuccessful.

The two studies that met the inclusion criteria differed in terms of the group of participants recruited. One study (Ambrose 2001) set out to investigate the therapeutic effects of thiamine in a sample of alcohol-dependent people without the clinical triad of acute WKS, whereas the other study (Nichols unpublished) assessed the cognitive effects of thiamine in participants with memory impairment associated with chronic alcohol abuse. Both studies described measures of cognitive impairment as the main outcome but used very different approaches to measurement.

The unpublished study (Nichols unpublished) contained insufficient data for full analysis and will not be included in the following sections.

Primary Outcomes

Global 'confusion' or delirium

Not reported.

Neurological symptoms (e.g. presence or absence of nystagmus, gaze palsies or ataxia)

Not reported.

Global or domain-specific cognitive measures

Learning and memory

Ambrose 2001 found a significant difference between dosage groups in the number of trials taken to reach criteria on a delayed alternation test. A planned comparison between the 200-mg group and the mean of the other dosage groups was significant. After measuring the results presented in a graph, we compared the lowest dose (5 mg/day) with each of the other four doses. A significant difference favoured 200 mg/day compared with the 5-mg/day dose in the number of trials taken to reach criteria on a delayed alternation test (MD -17.90, 95% CI -35.4 to -0.40, P = 0.04). No significant differences were observed when the other doses were compared with 5 mg/day.

Functional outcomes

Not reported.

Death

No deaths were reported in Ambrose 2001.

Total number of drop-outs

Ambrose 2001 recruited 169 participants from consecutive admissions to a detoxification unit, but 43 of the initial sample did not complete treatment and assessment. The authors report that analyses of variance revealed no difference between participants who did and those who did not complete the final assessment with respect to age, education, years of problem drinking, typical daily consumption of ethanol and Mini-Mental State score. However, no

record identifies the reasons why these participants left the study, or to which treatment group they belonged.

Incidence of adverse effects

Adverse effects were not recorded in Ambrose 2001.

Overall

Ambrose 2001 investigators comment that in view of the relatively small size of each treatment group, the high rate of non-completion and the short duration of thiamine treatment, the results should be treated as preliminary.

DISCUSSION

Although the use of thiamine or thiamine-containing products for prophylaxis against and treatment of WKS in individuals who misuse alcohol is well established, only two small randomised controlled trials were identified by our search. Both studies selected different groups of participants within the WKS spectrum and adopted very different treatment strategies, and so it was not possible to combine data. Furthermore considerable methodological shortcomings were noted in both studies.

Ambrose et al (Ambrose 2001) used the results of the delayed alternation test (Freedman 1986) as the main outcome measure of working memory. However, because little information about the reliability of this test in humans is available, there is reason to doubt whether it has undergone adequate psychometric evaluation for the task. Furthermore, although we have extracted data from this study to compare higher doses of thiamine with the 5-mg/day dose, it should be noted that 19 participants were removed from the analyses to balance the baseline characteristics of the treatment groups. No report has described how this was done, and it would be very difficult in practise. It is an unnecessary procedure, and a better approach would have been to carry out an analysis of covariance with the relevant baseline characteristics as covariates. Assessment of further outcomes that covers other aspects of the syndrome, in addition to the one chosen, would have been desirable.

Nichols et al (Nichols unpublished) used a wider range of neuropsychological tests, but their results were undermined by the small number of participants and limited reporting of data. Participants in the group treated with thiamine 5 g/day taken orally showed significant improvement on the Buschke CLTR and Delayed Recall when compared with baseline, but not on the COWA or MCG-D. Participants in the placebo group failed to show improvement on any measures. However, the article does not report the number of participants in each group, thus preventing quantitative analysis. The review was limited by inability to contact the authors to discuss this further.

AUTHORS' CONCLUSIONS

Implications for practice

WKS is a fairly common condition, and effective recognition and treatment of this disorder have important human and economic consequences. The use of thiamine in the treatment of acute WKS is well established and is supported by a series of published case reports (Cook 1998; Victor 1989; NCGCACC 2010). Such reports provide evidence of thiamine treatment bringing about rapid resolution of the ataxia and ophthalmoplegia (Phillips 1952; Wood 1995) and slow but significant improvement in the severity of nystagmus (Wood 1995). The global confusional state also appears to improve rapidly within hours of thiamine treatment (Wood 1995), but other issues remain unresolved. Impairment of memory and learning responds more slowly and often incompletely, suggesting a different mechanism of effect. The two studies included in this review suggest a role for thiamine in treating memory and learning impairments, but neither answers the questions posed in the introduction to this review.

Available evidence from RCTs is insufficient to guide clinicians in the dose, frequency, route or duration of thiamine treatment for prophylaxis against or treatment of established WKS due to alcohol abuse. Current recommendations for best practise continue to be found in guided extrapolations from basic science and case reports (Thomson 2006; NCGCACC 2010).

Implications for research

When the weight of evidence from clinical experience and case studies is considered, placebo-controlled trials of thiamine treatment in newly diagnosed WE are not ethically justifiable. However, it would be scientifically and ethically sound to randomly assign participants with established WKS to different parenteral dosing regimens for differing time periods, perhaps as part of a single trial in which a factorial design is used. The issue of prophylaxis for those at risk of developing WKS is less clear. In preparing evidence for the National Institute for Health and Clinical Excellence, an expert group of the National Clinical Guideline Centre for Acute and Chronic Conditions divided participants into groups at low and high risk of developing WE (NCGCACC 2010). The low-risk group was defined as 'people who are alcohol dependent but otherwise eating a normal diet and with no other alcohol-related problems'. Based on a systematic review of available evidence, the group noted that it could not recommend widespread use of thiamine in this group. Therefore it would be justified to randomly assign those at high risk of developing WE in a similar study with a factorial design, including an oral thiamine treatment arm and probably involving high doses. The high-risk group consists of people undertaking medically assisted withdrawal from alcohol (planned or unplanned) and those with alcohol-related liver disease, acute alcohol withdrawal, malnourishment or risk of malnourishment (i.e. weight loss in past year, reduced body mass index (BMI), loss of appetite, nausea and vomiting), acute illness or alcohol-related co-morbidity requiring hospitalisation (NCGCACC 2010).

When such trials are designed, how the diagnosis of WKS is to be made should be clearly stated. The Ambrose 2001 study focuses on a group without the classical triad of symptoms of WKS, but post-mortem and other data suggest that a much broader diagnostic strategy should be adopted (Cook 1998; Cook 2000; Caine 1997). Nichols unpublished describes a group with a history of chronic alcohol abuse and evidence of neuropsychological memory impairment but does not describe the presence or absence of other symptoms of WKS.

Consideration must also be given to the best way of measuring outcomes in WKS, but no consensus has been reached in this area. This review has focused on memory impairment, mainly because it seems clear that WKS is caused by a deficiency of thiamine (Victor 1989), and study participants with non—alcohol-induced WKS have

been reported to have a relatively pure amnestic syndrome (Becker 1990). Memory impairment and the neurological manifestations of WKS are the problems most likely to respond to thiamine therapy. Evidence that the broader range of visuospatial and executive functions impaired by alcohol are caused by thiamine deficiency is less clear, although this remains a possibility (Bowden 1990). If the focus is to be on memory impairment, the ideal cognitive battery should be sensitive to the impairment of consciousness associated with WE and to the learning and retrograde memory deficits associated with KP, as both are related to the thiamine deficiency state that treatment aims to correct. This battery ideally would be less sensitive to the enduring cognitive abnormalities arising more directly from chronic alcohol abuse, such as executive and visuospatial deficits, but would take into account that these abnormalities are also likely to be encountered in WE.

One barrier to effective treatment and prophylaxis appears to be concern about the risks of anaphylaxis when thiamine-containing preparations are administered parenterally (Thomson 1997). Therefore more research is needed to explore the potential clinical benefits of the reported increased bioavailability of lipid-soluble oral thiamine derivatives (Greb 1998) and to clarify the most useful measures of thiamine sufficiency and biological endpoints of treatment. A further important issue involves the timing of administration of thiamine relative to the course of alcohol abuse or dependence. Administration of thiamine treatment to patients experiencing alcohol withdrawal may also be influenced by other factors such as magnesium depletion (McLean 1999), N-methyl-d-aspartate (NMDA) receptor up-regulation or liver impairment, all of which may alter thiamine metabolism and utilization.

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We are grateful to Bill Perberdy, the consumer editor, for constructive comments.

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CHARACTERISTICS OF STUDIES

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

Ambrose 2001

Methods	5-Group randomised clinical trial. All participants (including outcome assessors) were blind to treatment dose.
Participants	Recruited from consecutive admissions to 12-bed detoxification unit. N = 169. All conformed to a DSM-IV diagnosis of alcohol dependence but did not have the triad of acute symptoms of WKS. Mean age = 42 years. Sex = not specified.
Interventions	• 5 mg of thiamine hydrochloride intramuscularly once per day for two consecutive days. • 20 mg of thiamine hydrochloride intramuscularly once per day for two consecutive days. • 50 mg of thiamine hydrochloride intramuscularly once per day for two consecutive days. • 100 mg of thiamine hydrochloride intramuscularly once per day for two consecutive days. • 200 mg of thiamine hydrochloride intramuscularly once per day for two consecutive days.
Outcomes	All participants were assessed individually on delayed alternation by a psychologist on the third day of admission.
Notes	Participants were randomly assigned as they began a 4- to 5-day alcohol withdrawal regimen. All participants were administered a reducing schedule of oral diazepam. 43 of the initial sample did not complete treatment and assessment. As the final treatment groups differed in age and average daily ethanol consumption, 19 participants were removed to equate treatment group means on the back-

Ambrose 2001 *(Continued)*

	ground variables of age, education and drinking history. No record describes how the cases to be removed were selected.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Participants were assigned randomly in equal numbers to one of five treatment groups". No other information provided.
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Insufficient information provided.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"On the third day of admission, all subjects were assessed individually on delayed alternation (DA) by a psychologist blind to the treatment condition".
Incomplete outcome data (attrition bias) All outcomes	High risk	"43 of the initial sample did not complete treatment and assessment, and the final treatment groups differed in age and average daily ethanol consumption. Therefore, data from 19 participants were removed to equate treatment group means on the background variables of age, education and drinking history without regard to background data".
Selective reporting (reporting bias)	Unclear risk	No pre-specified analyses described in the report.

Nichols unpublished

Methods	A double-blind placebo-controlled trial.
Participants	N = 8. History of chronic alcohol abuse and baseline evidence of neuropsychological memory impairment (Buschke CLTR < 90).
Interventions	2-Week double-blind phase. Group 1: thiamine hydrochloride 5 g/day orally. Group 2: lactose placebo.
Outcomes	Cognitive measures at baseline and at 2 weeks: Buschke Consistent Long-Term Recall (CLTR) and Selective Reminding Test (SRT), Halstead Category Test, MCG Complex Figure Test, Controlled Oral Word Association Test (COWA).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Subjects were randomised into a two-week double-blind phase, receiving either thiamine hydrochloride 5 g/day (Group 1) or lactose placebo (Group 2)".
Allocation concealment (selection bias)	Unclear risk	No information provided.

Nichols unpublished *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information provided.
Selective reporting (reporting bias)	Unclear risk	No information provided. Quote: "Cognitive measures included the Buschke Selective Reminding Test, the Halstead Category Test, an MCG Complex Figure Test, and the Controlled Oral Word Association Test".

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

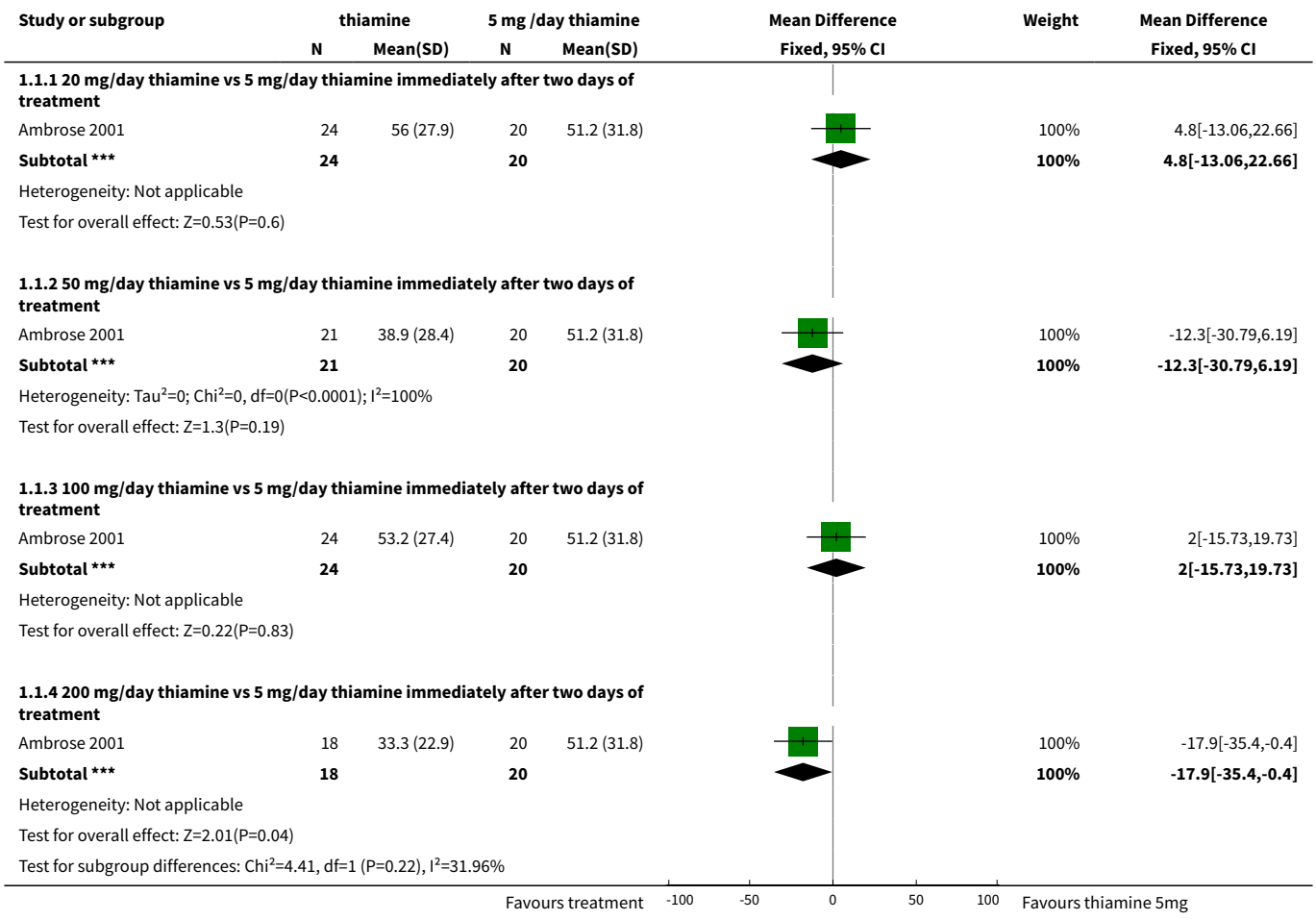
Study	Reason for exclusion
Peters 2006	Investigates different outcome measures involving polyneuropathy, not WKS.

DATA AND ANALYSES

Comparison 1. Thiamine (any dose) vs thiamine 5mg/day

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 performance on a delayed alternation test	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 20 mg/day thiamine vs 5 mg/day thiamine immediately after two days of treatment	1	44	Mean Difference (IV, Fixed, 95% CI)	4.80 [-13.06, 22.66]
1.2 50 mg/day thiamine vs 5 mg/day thiamine immediately after two days of treatment	1	41	Mean Difference (IV, Fixed, 95% CI)	-12.30 [-30.79, 6.19]
1.3 100 mg/day thiamine vs 5 mg/day thiamine immediately after two days of treatment	1	44	Mean Difference (IV, Fixed, 95% CI)	2.0 [-15.73, 19.73]
1.4 200 mg/day thiamine vs 5 mg/day thiamine immediately after two days of treatment	1	38	Mean Difference (IV, Fixed, 95% CI)	-17.90 [-35.40, -0.40]

Analysis 1.1. Comparison 1 Thiamine (any dose) vs thiamine 5mg/day, Outcome 1 performance on a delayed alternation test.



APPENDICES

Appendix 1. Update search: September 2012

Source	Search strategy	Hits retrieved
1. ALOIS (www.medicine.ox.ac.uk/alois)	thiamine OR aneurine	8 (all dates)
2. MEDLINE In-process and other non-indexed citations and MEDLINE 1950-present (Ovid SP)	1. Thiamine/ 2. thiamin*.ti,ab. 3. aneurin*.ti,ab. 4. or/1-3	249

(Continued)

	5. alcohol.ti,ab. 6. alcoholic.ti,ab. 7. alcoholism.ti,ab. 8. Wernicke-Korsakoff*.ti,ab. 9. Wernicke Encephalopathy/ 10. Korsakoff Syndrome/ 11. Alcohol Amnestic Disorder/ 12. Alcoholism/ 13. wernicke* encephalopathy.ti,ab. 14. or/5-13 15. 4 and 14 16. (2008* or 2009* or 2010* or 2011* or 2012*).ed. 17. 15 and 16	
3. EMBASE 1974-2012 September 05 (Ovid SP)	1. exp thiamine/ 2. thiamin*.ti,ab. 3. aneurin*.ti,ab. 4. or/1-3 5. alcohol.ti,ab. 6. alcoholic.ti,ab. 7. alcoholism.ti,ab. 8. Wernicke-Korsakoff*.ti,ab. 9. exp Wernicke encephalopathy/ 10. exp Korsakoff psychosis/ 11. (alcohol* adj3 disorder*).ti,ab. 12. alcoholism/ 13. wernicke* encephalopathy.ti,ab. 14. or/5-13 15. 4 and 14 16. trial.ti,ab. 17. randomized controlled trial/ 18. controlled clinical trial/ 19. randomly.ab. 20. groups.ab.	45

(Continued)

	21. placebo.ab. 22. (RCT or CCT).ti,ab. 23. or/16-22 24. 15 and 23 25. (2008* or 2009* or 2010* or 2011* or 2012*).em. 26. 24 and 25	
4. PSYCINFO 1806-July week 1 2012 (Ovid SP)	1. exp Encephalopathies/ or exp Wernicke's Syndrome/ or exp Korsakoffs Psychosis/ or exp Alcoholism/ 2. wernicke* encephalopathy.ti,ab. 3. Wernicke-Korsakoff*.ti,ab. 4. alcoholism.ti,ab. 5. alcoholic.ti,ab. 6. alcohol.ti,ab. 7. or/1-6 8. Thiamin*.ti,ab. 9. aneurin*.ti,ab. 10. or/8-9 11. 7 and 10 12. (2008* or 2009* or 2010* or 2011* or 2012*).up. 13. 11 and 12	94
5. CINAHL (EBSCOhost)		80
6. Web of Science and conference proceedings	Topic=(thiamin* OR aneurin*) AND Topic=(alcohol OR alcoholic OR alcoholism OR "wernicke-Korsakoff*" OR "wernicke* encephalopathy" OR korsakoff*) AND Topic=(randomly OR placebo OR groups OR trial OR RCT OR randomized OR randomised OR "double-blind*" OR "single-blind*" OR CCT OR "cross-over" OR crossover) AND Year Published=(2008-2012) Timespan=All Years. Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH. Lemmatization=On	49
7. LILACS (BIREME)	thiamine OR aneurine OR aneurin OR thiamin [Words] and alcohol OR alcoholic OR alcoholism OR korsakoff OR wernicke OR wernickes [Words]	33
8. CENTRAL (*The Cochrane Library*) (Issue 2 of 4, 2012)	#1 MeSH descriptor Thiamine explode all trees #2 thiamin*	2

(Continued)

	#3 aneurin* #4 (#1 OR #2 OR #3) #5 alcohol #6 alcoholic #7 alcoholism #8 Wernicke-Korsakoff* #9 MeSH descriptor Wernicke Encephalopathy explode all trees #10 MeSH descriptor Korsakoff Syndrome explode all trees #11 MeSH descriptor Alcohol Amnestic Disorder explode all trees #12 MeSH descriptor Alcoholism explode all trees #13 "wernicke* encephalopathy" #14 (#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13), from 2008 to 2012 #15 (#4 AND #14), from 2008 to 2012	
9. Clinicaltrials.gov (www.clinicaltrials.gov)	Interventional Studies | korsakoff OR alcohol OR alcohlism OR alcoholic OR wernicke OR wernickes | thiamine OR aneurine	3
10. ICTRP Search Portal (http://apps.who.int/trialsearch) [includes: Australian New Zealand Clinical Trials Registry; ClinicalTrilas.gov; ISRCTN; Chinese Clinical Trial Registry; Clinical Trials Registry – India; Clinical Research Information Service – Republic of Korea; German Clinical Trials Register; Iranian Registry of Clinical Trials; Japan Primary Registries Network; Pan African Clinical Trial Registry; Sri Lanka Clinical Trials Registry; The Netherlands National Trial Register]	Recruitment status: ALL | korsakoff OR alcohol OR alcohlism OR alcoholic OR wernicke OR wernickes | thiamine OR aneurine	5
TOTAL before de-duplication and first assess		563
TOTAL after de-dupe and first assess		19

WHAT'S NEW

Date	Event	Description
25 June 2013	New citation required but conclusions have not changed	No new studies were retrieved, no change to conclusions. The background and research recommendations were updated to reflect new basic science and clinical findings.

Date	Event	Description
6 September 2012	New search has been performed	An update search was conducted on 06/09/2012.

HISTORY

Protocol first published: Issue 1, 2003
Review first published: Issue 1, 2004

Date	Event	Description
19 May 2008	Amended	Converted to new review format.
19 May 2008	New search has been performed	An update search was conducted on 22/01/2008. One possible study was retrieved, that was excluded.
24 August 2005	New search has been performed	An update search was conducted, which retrieved no new studies for inclusion
16 November 2003	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

ED: all correspondence, drafting of protocol, search for trials, obtaining copies of trial reports, selection of trials for inclusion, data extraction, data entry, data interpretation.
PWB: drafting of protocol, selection of trials for inclusion, extraction of data, interpretation of data.
RC, TK and SG: obtaining copies of trial reports, data entry, interpretation of data.

Contact editor: J Grimley Evans.
Consumer editor: Bill Perberdy.
This review has been peer-reviewed anonymously.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Birmingham and Solihull Mental Health NHS Foundation Trust, UK.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Korsakoff Syndrome [*drug therapy]; Randomized Controlled Trials as Topic; Thiamine [administration & dosage] [*therapeutic use]

MeSH check words

Humans