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[Intervention Review]

Vitamin B12 for cognition

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ABSTRACT

Background

An association between neuropsychiatric disorders and vitamin B12 deficiency has been recognized since 1849 when pernicious anaemia was first described. It has been suggested that deficiency of vitamin B12 might contribute to age-associated cognitive impairment. Low serum vitamin B12 concentrations are found in more than 10% of older people. A high prevalence of low serum vitamin B12 levels, and other indicators of vitamin B12 deficiency have been reported among people with Alzheimer's disease. A review is needed of trials assessing effects of vitamin B12 supplementation on cognitive function in later life.

Objectives

To examine the effect of B12 supplementation on cognitive function of demented and elderly healthy people in terms of preventing the onset or progression of cognitive impairment or dementia.

Search methods

The trials were identified from a search of the Specialized Register of the Cochrane Dementia and Cognitive Improvement Group on 24 January 2006 using the terms B12, "B 12", B-12, B-complex, "B complex". In addition MEDLINE 1966 to 2006/01-week 3 and EMBASE 1980-2005/12 were searched to pick up studies with healthy volunteers.

Selection criteria

All randomized double-blind trials in which vitamin B12 at any dose was compared with placebo.

Data collection and analysis

Both reviewers applied the selection criteria to assess the quality of the studies. One reviewer (RM) collated and analysed the data. For each outcome measure data were sought on every patient randomized.

Main results

Three trials were included (De La Fourniere 1997; Hvas 2004; Seal 2002). One trial (Hvas 2004) reported follow-up results at 3 months after randomization, 2 months after treatment was completed; the data from this study were not combined with others. People with dementia and low serum vitamin B12 levels were recruited for the studies. The results showed no statistically significant evidence of a treatment effect of vitamin B12 supplementation compared with placebo, on cognitive function.

Authors' conclusions

Evidence of any efficacy of vitamin B12 in improving the cognitive function of people with dementia and low serum B12 levels is insufficient. The included trials (De La Fourniere 1997; Hvas 2004; Seal 2002) were restricted to a small number of patients with Alzheimer's disease and other types of cognitive impairment. No trials involving people without dementia or using other definitions of vitamin B12 deficiency were found.

PLAIN LANGUAGE SUMMARY

No evidence of the efficacy of vitamin B12 supplementation for cognitive function

Vitamin B12 is essential for maintaining normal function of the nervous system, but the relationship between vitamin B12 and cognitive function is not fully understood. From the three studies involving people with dementia or cognitive impairment and low blood levels of vitamin B12 eligible for inclusion in this review there was no statistically significant effect of vitamin B12 supplementation on cognition. The variety of measurement scales used to assess outcomes and uncertainty about diagnostic criteria for vitamin B12 deficiency create difficulties in pooling the results of trials.

BACKGROUND

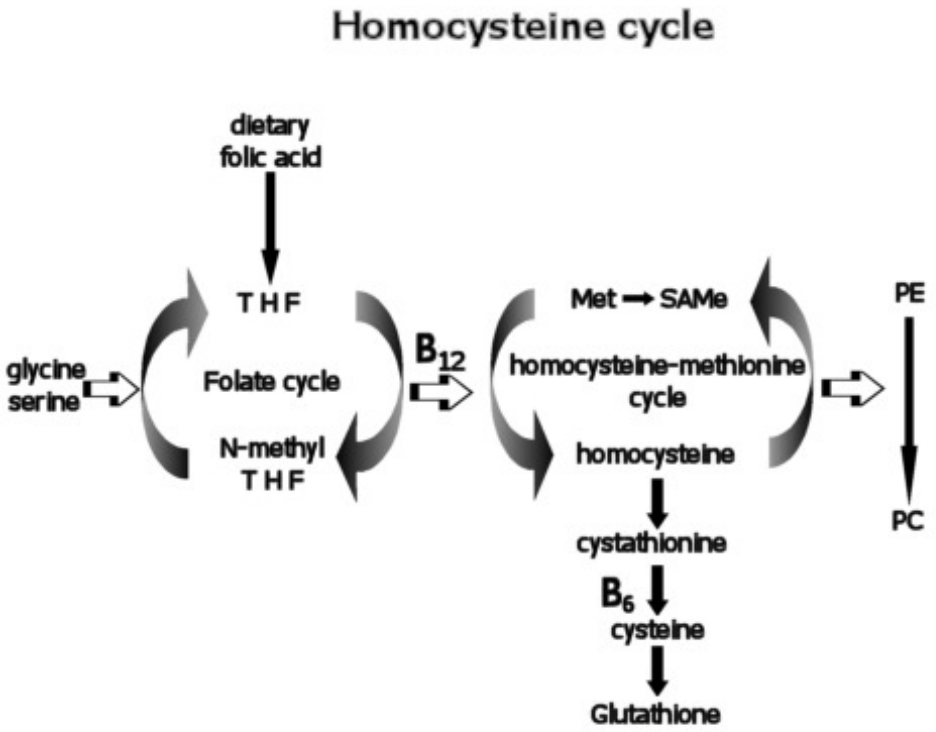
Vitamin B12 is a water-soluble vitamin that is non-toxic in humans, although associated in very high doses with the production of amnesia in chicks (Crowe 1997). Humans are dependent on animal-origin sources to obtain their requirement of B12 from the diet. Although this vitamin is synthesized in the human large bowel by micro-organisms in considerable quantities, it is not absorbed from this site. The recommended daily requirement for adults is 2-5 microgram, and the average adult daily intake from an unrestricted diet is 5-30 microgram, with around 10 to 30% being destroyed by cooking. The body storage of B12, mainly in the liver, is 2-5 mg (Firkin 1989). Vegans are the only population group at risk of developing dietary B12 deficiency (Herbert 1996), but as the absorption of the vitamin may decline with age, the Food Protection Program recommended that older people attain their need of this vitamin from supplements or fortified foods (Kwan 2002).

The absorption of dietary vitamin B12 requires its release from food by gastric acid, the formation of a complex with R-proteins and linkage to intrinsic factor secreted by the stomach. After absorption in the lower small intestine vitamin B12 is transferred to its utilization sites by three carriers, transcobalamin I, II and III. The two active forms of the vitamin are adenosylcobalamin, a major form in the cellular tissues, and methylcobalamin predominating in the plasma. Older people are at risk of developing vitamin B12 deficiency because of loss of intrinsic factor (in Addisonian pernicious anaemia) or through decreased secretion of the gastric acid necessary to release the vitamin from food. Reduction of gastric acid in later life may arise through inflammation of the stomach or from drugs given to combat peptic ulcer, oesophageal regurgitation or dyspepsia. In one survey, although pernicious anaemia was responsible for 50% of the causes of B12 deficiency, it only accounted for 10% of older people with low serum levels of vitamin B12 (Metz 1996).

The two therapeutic forms are cyanocobalamin and hydroxocobalamin, usually given by injection and there is no interference with the actions of other drugs. The absorption of dietary vitamin B12 can be impaired by some medications, such as anti-convulsants, alcohol, potassium products, cimetidine, ranitidine, aminosaliycylic acid and proton pump inhibitors.

Vitamin B12 is required for the methylation of homocysteine (Hcy) to methionine, which is activated into S-adenosyl-methionine that donates its methyl group (CH3) to methyl acceptors such as myelin, neurotransmitters, and membrane phospholipids, essential for maintaining the integrity of the nervous and haematopoietic systems (Figure 1). Insufficiency of vitamin B12 causes disruption of this cycle and intracellular accumulation of homocysteine that is potentially toxic to neurons. Blood levels of homocysteine are also raised by metabolically significant vitamin B12 deficiency. Raised blood levels of homocysteine are a risk factor for vascular disease (Clarke 1991) and a predictive marker for cognitive decline in healthy older people (McCaddon 2001). Elevated serum homocysteine levels are frequently found in healthy older people (Joosten 1997), and vitamin B12 deficiency is suggested as a major cause of elevated homocysteine in elderly populations (Stabler 1997).

Figure 1.



Low serum B12 levels are found in 10 to 15% of people aged over 60 years (Elsborg 1976; Elwood 1971; Gaffney 1957; Kilpatrick 1965). The prevalence varies with sex and ethnic group; the frequency of low serum B12 is higher in Europe than in the United States (Lindenbaum 1994; Pennypacker 1992; Van Asselt 1998), and elderly men are more likely to have low serum B12 than are elderly women. Low serum levels do not however necessarily indicate metabolically significant deficiency of vitamin B12. Not all the vitamin circulating in the blood is in metabolically active form and blood levels do not necessarily reflect intracellular conditions. Criteria for metabolically significant deficiency vary and estimates of its prevalence in older populations vary from 3.0 to 40.5% (Baik 1999).

Most studies prior to 1980 relied on serum vitamin B12 determinations and absorption tests to identify vitamin B12 deficiency. However, subnormal serum cobalamin levels are not specific for cobalamin deficiency (Stabler 1990) and serum and tissue vitamin B12 are insensitive screening tests. In one study, tissue vitamin deficiency was present in only 88% of 94 elderly people with serum vitamin levels <150 pmol/L (Metz 1996). Recently, measuring serum levels of methylmalonic acid (MMA) or total homocysteine (tHcy) have been found useful as biochemical markers of cobalamin deficiency in people with minor or no haematological abnormalities (Marcell 1985; Stabler 1986). In a study of 152 geriatrics outpatients, the prevalence of vitamin B12 deficiency defined by serum B12 level <300pg/ml and levels of (tHcy) elevated to >3 SD, was 14.5% (Pennypacker 1992). In addition, MMA and/or tHcy levels were shown to be necessary in evaluating the benefit of the treatment in terms of low or low-normal cobalamin blood levels (Pennypacker 1992). The conventional lower limit for serum vitamin B12 is 150 pg/ml, but Lindenbaum 1994 reported that deficiency should be suspected when the serum level declines below 300 pg/mL in older people. In summary, accurate diagnosis of vitamin B12 deficiency remains controversial, but low plasma cobalamin concentrations do not necessarily indicate significant deficiency and normal levels do not necessarily exclude it.

Severe vitamin B12 deficiency manifests clinically as a syndrome involving the nervous and/or the haematopoietic systems. It can present with anaemia, polyneuropathy (Table 1), subacute combined degeneration of the spinal cord (Table 1), and various neuropsychiatric problems including cognitive impairment and dementia. The majority of older people with low serum levels of vitamin B12, have no clinical features of deficiency (Matcher 1994),

although half of them have metabolically significant deficiency (Lindenbaum 1994). Neuropsychiatric disorders, in the absence of haematological or metabolical changes, are common features of deficiency in older people. Lindenbaum 1994 found that 40 patients out of 141 with vitamin B12 deficiency exhibited neuropsychiatric abnormalities without anaemia. Associations between vitamin B12 status and cognitive performance in both healthy and impaired people have been reported (Goodwin 1983; La Rue 1997; Riggs 1996). It has been found that patients with low vitamin B12 levels are at enhanced risk of cerebrovascular disease and cognitive decline (Shahar 2001). Poorer memory performance by normal elderly people with low vitamin B12 concentrations has been reported (Goodwin 1983). Such correlations between vitamin B12 and cognition emphasize the need to clarify the role of the vitamin in dementia.

It has been reported that 15% of people with dementia have a potentially treatable cause (Marsden 1972), but the prevalence of reversible dementia is only 1% (Walstra 1997) and vitamin B12 deficiency contributes to only 1% of reversible cases (Clarfield 1988). None the less, the association of vitamin B12 with cognitive impairment makes assay of blood levels a recommended routine investigation in dementia (Wivel 1988). Dementia is common in later life, affecting 10% of people aged over 65 with a prevalence rising to 20% of people over 80 (Jorm 1990). Alzheimer's disease (AD) accounts for more than 70% of cases of dementia, so it is important to identify risk factors for this disease. The prevalence of low serum vitamin B12 levels has been reported to be significantly higher in people with Alzheimer's disease than in people with other types of dementia (Tripathi 2001). It has also been found that serum tHcy levels in patients with Alzheimer's dementia are significantly higher and serum vitamin B12 concentrations significantly lower than in controls (Clarke 1998; McCaddon 2001).

Several hypotheses have been advanced to explain the high frequency of low vitamin B12 levels in demented older people. Poor diet is one suggestion, but its effects would be unlikely to become apparent in less than one or two decades, given the very low daily intake required and the body storage of the vitamin. Transcobalamin II, responsible for the carriage of 15% to 20% of vitamin B12, has been reported to be low in old age. This raises the possibility of an age-associated defect of cobalamin delivery into the tissues (Marcus 1987). Low vitamin B12 levels in elderly and demented people might be due to malabsorption consequent on the atrophic gastritis with hypochlorhydria (Table 1) common among older people. Another hypothesis is that patients with Alzheimer's disease have inactive analogue forms of vitamin B12 in their serum (McCaddon 2001). It has been suggested that one-carbon metabolism, in which vitamin B12 is involved, might be compromised by deposition of amyloid, one of the characteristic features of Alzheimer's disease (Regland 1999). Another hypothesis is that Alzheimer's disease may cause dysfunction in the ability to use vitamin B12 by affecting cellular function so as to reduce vitamin B12 absorption, storage, utilization and or excretion (Levitt 1992).

Some intervention studies examined the relationship between the vitamin status and the cognitive function on healthy and demented people. One study of cognitively unimpaired community-dwelling old people with low serum vitamin B12 levels measured cognitive and cerebral function before and after supplementation with vitamin B12. There were improvements in function and the increase in scores on a verbal word learning test were substantial (van Asselt 2001).

Several observational, non-randomized or confounded studies of effects of vitamin B12 on people with dementia have been published. Despite suggestions that supplementation may improve language and frontal lobe function in patients with cognitive impairment and low serum vitamin B12 level, no changes were found in the MMSE (Eastley 2000). Ikeda 1992 reported a correlation between cognitive function and the levels of vitamin B12 in the cerebrospinal fluid in Alzheimer's patients treated with intravenous vitamin B12. Carmel 1995 observed improvements in blood homocysteine and haemoglobin levels, neuropsychiatric symptoms, electroencephalographic abnormalities in 13 patients with Alzheimer's disease and low serum B12 after supplementation, but there was no improvement in cognitive function. Takao 2001has reported that bright light therapy accompanied by vitamin B12 supplementation improved circadian rhythm disturbances and cognitive state of patients in the early stages of Alzheimer's disease.

Other studies have found no benefit from vitamin B12 supplementation in terms of cognitive function or delay in deterioration for patients with dementia and low serum vitamin B12 levels when assessed against a matching group (Eastley 2000). Teunisse 1996a found no effect over six months of vitamin B12 supplementation on the severity of cognitive decline in a comparison of treated and untreated groups of people with Alzheimer's disease. Levitt 1992 described two patients with Alzheimer's disease and low serum vitamin B12 levels whose cognitive performance continued to decline despite their serum vitamin B12 levels returning to normal after supplementation. Observing a group of people with vitamin B12 deficiency without measurement of cognitive function, Hughes 1970 concluded that vitamin B12 replacement therapy was no better than placebo in terms of responses to a self - report questionnaire and psychiatric assessment. Nagga 2002 observed the effect of a year of cobalamin supplementation on 23 patients with cognitive impairment and newly diagnosed cobalamin deficiency. There was no beneficial effect from cobalamin supplementation on cognition or on electroencephalography (EEG); 14 patients deteriorated in their MMSE scores and 17 showed an increase in EEG abnormalities. It has been suggested that there is a time-limited window of less than one year during which vitamin B12 treatment is effective for patients with cognitive impairment and with low serum vitamin B12 (Abyad 2002; Martin 1992). If this is so, early detection and treatment will be essential to the reversibility of cognitive impairment attributable to vitamin B12

deficiency.

Some researchers have challenged the existence of a reversible dementia due to vitamin B12 deficiency (Byrne 1987; Hector 1988), and few cases of reversible dementia attributed to deficiency of vitamin B12 have been reported in the literature in which supplementation has produced complete recovery. In one series of 18 patients with vitamin B12 deficiency and cognitive impairment, eight with global dementia, eleven patients showed complete recovery after vitamin B12 replacement (Healton 1991). The Synonym Learning tests returned to normal in 9 of 12 patients with pernicious anaemia after treatment, the earliest changes were observed 20 hours from the intervention (Shulman 1967). Among 152 moderately to severely demented patients who met criteria of global cognitive impairment, one patient had dementia attributed to vitamin B12 deficiency, but the duration of the disease and the result of treatment were not reported (Erkinjuntti 1986). The vitamin B12 replacement therapy was associated with temporary improvement in cognitive performance in two patients with Alzheimer's disease and low serum vitamin B12 levels, but there was no benefit observable in a one-year follow-up evaluation (Larson 1985). However, in some of these cases (Healton 1991; Larson 1985) there was no neuropsychiatric assessment or use of standardized diagnostic criteria for dementia.

It is necessary to know whether low vitamin B12 levels are a cause or a consequence of Alzheimer's disease. Untreated deficiency in asymptomatic old people might cause impairment of cognitive function that becomes irreversible (Martin 1992). Conversely, people with Alzheimer's disease and low vitamin B12 levels may be more severely demented and have suffered from dementia and reduced nutrition for a longer time than patients with normal serum levels (Meins 2000).

In considering the significance of vitamin B12 deficiency in later life, a central concern is how deficiency should be defined. Traditionally, the necessary intake of a vitamin is determined with regard to preventing the deficiency disease specific to lack of the vitamin. Until recently the specific deficiency disease for vitamin B12 has been pernicious anaemia; should hyperhomocysteinaemia, where not due to folic acid deficiency or renal failure, now be regarded as indicating mild or incipient vitamin B12 deficiency? The issue has ethical implications for the design of controlled trials; it would not be ethical to leave people with pernicious anaemia or subacute combined degeneration of the spinal cord untreated in a control group, would it now be unethical for people with high homocysteine levels to be allocated to a control group? One issue is that the original evidence for a relationship between homocysteine and vascular disease and dementia was derived from observational studies; whether the relationship is causative can only be resolved by intervention studies. There also remains a possibility that vitamin B12 has benefits for brain function not mediated through homocysteine metabolism. Clearly, the ethical situation will change as science advances.

Therefore, the central question is whether degrees of vitamin B12 deficiency insufficient to manifest as megaloblastic anaemia or neurological disorder cause cognitive impairment and dementia, the answer may depend on how vitamin B12 deficiency is defined. In the absence of overt neurological signs it may be defined simply in terms of low blood levels of vitamin B12, or as low blood levels of vitamin B12 plus evidence of metabolically significant deficiency in the form of raised blood homocysteine or methlymalonic acid. A third possibility, arising in a public health context, is whether giving vitamin B12 to people without knowledge of their blood biochemistry will reduce the incidence or severity of cognitive impairment and dementia in a population.

In this review of vitamin B12 as a possible means for preventing or retarding the progression of cognitive impairment in healthy people and in people with dementia, particular attention needs to be paid to the eligibility criteria for participants in trials in order to determine which of the these situations in being investigated.

OBJECTIVES

To estimate the effect of vitamin B12 on cognitive function of healthy elderly people and of people with dementia.

METHODS

Criteria for considering studies for this review

Types of studies

The review aims to include all randomized placebo-controlled double-blind trials of the effects of vitamin B12 on cognitive function at any dose or by any route of administration. Trials in which combinations of folic acid and B12 were administrated were excluded, as they are the subject of another Cochrane review (Malouf 2003a). The review also discusses case-control studies of the relationship between vitamin B12 and cognitive impairment or dementia.

Types of participants

Elderly healthy people and patients at any stage or type of cognitive impairment with or without vitamin B12 deficiency as defined by the trialists.

Types of interventions

Vitamin B12 at any dosage or route of administration compared with placebo.

Types of outcome measures

Cognitive function measures.

Search methods for identification of studies

Trials were identified from a search of the Specialized Register of the Cochrane Dementia and Cognitive Improvement Group on 24 January 2006 using the terms using the terms B12, "B 12", B-12, B-complex, "B complex"
The Specialized Register at that time contained records from the following databases:

- CENTRAL: July 2005 (issue 3);
- MEDLINE: 1966 to 2005/08, week 2;
- EMBASE: 1980 to 2005/08, week 2;
- PsycINFO: 1887 to 2005/07;
- CINAHL: 1982 to 2004/07;
- SIGLE (Grey Literature in Europe): 1980 to 2004/06;
- 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 March 2003;
- Dissertation Abstract (USA): 1861 to March 2003;
- http://clinicalstudies.info.nih.gov/;
- National Research Register (issue 3/2005);
- ClinicalTrials.gov: last searched 1 January 2006;
- LILACS: Latin American and Caribbean Health Science Literature: last searched April 2003;
- http://www.forestclinicaltrials.com/: last searched 1 September 2005;
- ClinicalStudyResults.org: last searched 1 September 2005;
- http://www.lillytrials.com/index.shtml: last searched 28 August 2005;
- ISRCTN Register: last searched 1 September 2005;
- IPFMA Clinical trials Register: www.ifpma.org/clinicaltrials.html: last searched September 2005.

The search strategies used to identify relevant records in MEDLINE, EMBASE, PsycINFO, CINAHL and LILACS can be found in the Group's module.

MEDLINE 1966 to 2006/01-week 3 and EMBASE 1980-2005/12 were searched using the same terms to pick up studies with healthy volunteers. The following search strategies were used:
MEDLINE:
#1 B12 or "B 12" or B-12 or B-complex or "B complex"
#2 explode "Vitamin-B-12"/ all subheadings
#3 #1 or #2
#4 random* or placebo* or "double blind*" or double-blind*
#5 #3 and #4
#6 #5 and (cognit* or MMSE or ADAS-cog)
EMBASE:
#1 "cyanocobalamin"/ all subheadings
#2 B12 or "B 12" or B-12 or B-complex or "B complex"
#3 5#1 or #2
#4 random* or placebo* or "double blind*" or double-blind*
#5 #3 and #4
#6 #5 and (cognit* or MMSE or ADAS-cog)
The internet was searched using the super search engine Copernic using the term "B12 cognition trial".
Reference lists of retrieved articles were examined for additional trials. Books concerning vitamin B12 and cognition were hand-searched for additional trials.

Data collection and analysis

SELECTION OF STUDIES
Abstracts of the references retrieved by the search were read by one reviewer who discarded those that were clearly not eligible for inclusion. Both reviewers studied the full text of the remaining references and independently selected studies for inclusion. Any disparities were resolved by discussion to arrive at a final list of included studies.
QUALITY ASSESSMENT
The reviewers (RM and AAS) assessed the methodological quality of each trial using Cochrane Collaboration guidelines (Mulrow 1997):

- In category A (adequate), the report describes allocation of treatment by: (i) some forms of centralized randomized scheme, such as having to provide details of an enrolled participant to an office by telephone to receive the treatment group allocation; (ii) some form of randomization scheme controlled by a pharmacy; (iii) numbered or coded containers, as in a pharmaceutical trial in which capsules from identical-looking numbered bottles are administrated sequentially to enrolled participants; (iv) an on-site or coded computer system, provided that the allocations were in a locked, unreadable file that could be accessed only after inputting the characteristics of an enrolled participants; or (v) if assignment envelopes were used, the report should at least specify that they were sequentially numbered, sealed, and opaque; (vi) other combinations of described elements of the process that provide assurance of adequate concealment.

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

- In Category C (inadequate) reports describe allocation of treatment by: (i) alternation; (ii) reference to case record numbers, dates of birth, day of week, or any such approach; (iii) any allocation procedure that is transparent before assignment, such as an open list of random numbers or assignments.
Empirical research has shown that lack of adequate allocation concealment is associated with bias. Trials with unclear concealment measures have been shown liable to yield more pronounced estimates of treatment effects than trials that have adequate measure to conceal allocation schedules, but the effect

is less pronounced than inadequately concealed trials (Chalmers 1983; Schulz 1995). Trials are to be considered if they conform to categories A or B, but those falling in category C are excluded. Other aspects of trial quality were not assessed by a scoring system but details of blinding, appropriateness of methods and the number of patients lost to follow-up were to be be noted.

DATA COLLECTION

Data were extracted from the published reports. The summary statistics required for each trial and each outcome for continuous data were the mean change from baseline, the standard error of the mean change, and the number of patients for each treatment group at each assessment. Where changes from baseline were not reported, the mean, standard deviation and the number of patients for each treatment group at each time point were extracted. The baseline assessment is defined as the latest available assessment prior to randomization, 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, 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 extracted and indicated as such.

DATA ANALYSIS

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

Summary statistics (n, mean and standard deviation) were required for each assessment time for each treatment group in each trial for change from baseline.

The meta-analysis requires the combination of data from the trials that may not use the same rating scale to assess an outcome. The measure of the treatment difference for any outcome is the weighted mean difference, which is the weighted average of the individual trial estimates, where the pooled trials use the same rating scale or test, or the standardised mean difference, which is the absolute mean difference, where they used different rating scales or tests.

The duration of trials may vary considerably. If the range is considered too great to combine all trials into one meta-analysis it is divided into smaller time periods and a separate meta-analysis conducted for each period.

Overall estimates of the treatment difference have been presented. In all cases the overall estimate from a fixed effects model are presented and a test for heterogeneity using a standard chi-square statistic performed. If there is significant heterogeneity a random effects model is presented.

If a test of heterogeneity is negative then a weighted estimate of the typical treatment effect across trials, is calculated. If, however, there is evidence of heterogeneity of the treatment effect between trials then either only homogeneous results are pooled, or a random-effects model used (in which case the confidence intervals are broader than those of a fixed-effects model).

RESULTS

Description of studies

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

Two studies, Seal 2002 and De La Fourniere 1997, fulfilled randomization criteria for category A or B as defined above. Both enrolled older people with dementia and low blood levels of vitamin B12. The treatment period varied from one month to five months, and the trials also differed in dose, the method of intervention and the definition of low serum vitamin B12 deficiency. As cognitive function outcome scales, the trials used the Mini Mental State Examination (MMSE) (Folstein 1975) and the cognitive part of the Alzheimer's Disease Assessment Scale (ADAS-Cog). The Mini-Mental State Examination tests orientation, memory, language and other cognitive functions, the score ranging from 0, severely demented, to 30, normal function. The ADAS-Cog comprises eleven subtests assessing spoken language, comprehension of spoken language, naming objects, following orders, orientation, word recall, ward recognition, recall of instruction test, drawing construction and ideational praxis (Rosen 1984). The score range of the ADAS-Cog is from 0-70 with higher scores indicating greater impairment.

The primary aim of Seal 2002 was to determine the minimum oral daily dose of vitamin B12 required to maintain the serum level of vitamin B12 within a normal range in older people. A three-group design was comprised of placebo and two treatment groups receiving either 10 microgram or 50 microgram of oral cyanocobalamin daily for one month. Thirty-one inpatients were recruited from two centres in Australia with low serum vitamin B12 levels defined as between 100 and 150 pmol/L. Additional inclusion criteria were that patients should not be taking any treatment containing vitamin B12 and there should be no history of malabsorption disorders, pernicious anaemia or neurological disorder other than stroke. Participants were moderately to severely demented as defined by the MMSE. The majority were resident in the community. Their daily intakes of vitamin B12 were estimated and assessments of serum vitamin B12, folate, and homocysteine levels and MMSE measurements were conducted at baseline and one month after enrolment. The primary outcome was the vitamin B12 serum level after treatment to any of three endpoints, normalized serum vitamin B12 levels, normalized homocysteine levels, and the change in MMSE score. The biochemical results were calculated as percentage changes from baseline at endpoint

for each group of patients while the performance on the MMSE was calculated as an absolute change.

In the De La Fourniere 1997 study, eleven community-dwelling inpatients were enrolled from nine centres in France; all participants had a diagnosis of Alzheimer's disease according to DSM III of moderate severity (MMSE scores 11-23). The other criteria for inclusion were low serum vitamin B12 levels, defined for this trial as below 240 pg/ml, and normal serum folate levels. Five patients were randomly assigned to the treatment group and received injections of vitamin B12 1000 microgram daily for 5 days and then one injection each month for 5 months; the remaining six patients received placebo injections. The ADAS-Cog was used to assess cognitive function.

2006 update:

One randomized placebo controlled-trial was found in the new search (Hvas 2004). This study tested the effect of vitamin B12 treatment on cognitive function and symptoms of depression in patients with vitamin B12 deficiency who had not been previously treated with this vitamin. One hundred and forty participants were involved in this trial with early stages of vitamin B12 deficiency defined as increase in plasma methylmalonic acid (0.40-2.00 mcmol/l). Each participant was randomized to receive an injection of 1 mg of vitamin B12 (cyanocobalamin) or placebo weekly for 4 weeks. Patients were assessed at baseline and 3 months later, 2 months after treatment was completed. Three batteries were included to assess the cognitive function: the Cambridge Cognitive Examination (CAMCOG) (Roth 1986), the Mini-Mental State Examination (MMSE) (Folstein 1975) and the 12-words learning test (Nielsen 1995). The major Depression Inventory (MDI) (Bech 2001) was used to assess depression severity. The CAMCOG is a scale assessing a broad range of cognitive function (orientation, language, memory, concentration, practice, calculation, abstract thinking, perception) and consists of 60 items with a maximum score of 107. The MMSE evaluates cognition in five areas: orientation, immediate recall, attention and calculation, delayed recall, and language. The score may vary between 30 (normal) and 0 (severe impairment). The 12-words learning test is a sensitive test to examine short-term memory, immediate recall and delayed recall after 15 minutes.

At baseline 78 patients had a total score below 90 on CAMCOG, and 40 participants had a MMSE score below 25. The mean MMSE was 26.5 points.

Risk of bias in included studies

In the included studies the patients were assigned randomly, and both participants and researchers were blinded to the supplementation. There must be some doubt about the effectiveness of blinding in De La Fourniere 1997 owing to difficulty in manufacturing pink placebo injections to match those of vitamin B12. Six participants were reported to have dropped out from both Seal 2002, and Hvas 2004.

Effects of interventions

Meta-analysis revealed no benefit from vitamin B12 supplementation on cognitive function of people with low serum vitamin B12 levels..

In Seal 2002 performance in the MMSE did not differ between the 50 mcg treatment and the placebo groups (MD -0.60 95% CI -3.06 to 1.86, p=0.63) or between the 10 mcg treatment and placebo groups (MD -1.60 5% CI -3.99 to 0.79, p=0.19). In De La Fourniere 1997 placebo and treatment groups did not differ significantly in changes in ADAS-Cog scores (MD 0.04 95% CI -5.95 to 6.03, p=0.99).

No adverse effects were reported in either trial. Seal 2002 noted that 6 of the 31 participants did not complete the study: one patient in the placebo group was excluded because he showed a 75% increase in his serum vitamin B12 level, and 5 were excluded because it was assumed that they would not benefit from small oral doses of vitamin B12. In De La Fourniere 1997 all patients completed the protocol.

The results from Hvas 2004 were not combined with other studies as the data were taken at 3 months after randomization (the trial lasted for only 4 weeks). The follow-up results did not show significant difference between treatment and placebo groups in changes from baseline in cognition function as assessed by the CAMCOG, MMSE, 12-words learning test immediate recall scores (MD -0.6 95% CI -2.2 to 0.9; P=0.43); (MD 0.1 95%CI -0.6 to 0.8, P= 0.70); and (MD -0.2 95%CI -0.7 to 0.3, P=0.42) respectively. The was benefit in favour of placebo for the 12-words delayed recall (MD -0.50, 95% CI -1.0 to 0.0, p=0.05). No significant difference was found in the Major Depression Inventory test between the groups (MD -1.5 95% -3.8 to 0.7; P=0.18). No adverse effects were described in this trial. Six participants did not complete the study: five in the treatment group and one in the placebo. The reasons for dropping out were not specified.

DISCUSSION

In Seal 2002 a daily oral dose of 50 mcg of vitamin B12 significantly increased the average serum levels of older people with initially low values. Selection for the study had, however, excluded anyone with a history of intestinal malabsorption or intrinsic factor deficiency (pernicious anaemia). This finding cannot therefore be extrapolated to the general population.

There was no evidence from the studies that vitamin B12 supplementation had any effect on cognitive function in the short term. Seal 2002 only lasted for a month and

De La Fourniere 1997 stopped after 5 months because no difference in ADAS-Cog scores was emerging between the placebo and the treatment groups. Much bigger numbers would be needed to detect anything but a very large effect.

The follow-up data after 3 months of Hvas 2004, showed no significant difference between the treatment and placebo group for measurement of cognitive function, with one significant difference in the 12-words learning test after 15 minutes in favour of the placebo group.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence of any effect of vitamin B12 therapy on cognitive function of older people with low serum vitamin B12 levels and dementia.

Implications for research

Large randomized trials are required to evaluate the value of vitamin B12 for improving cognitive function and preventing or retarding cognitive decline in normal and demented older people. Trials need to use established and validated diagnostic criteria and measures of cognitive function and to be long enough to detect trends.

ACKNOWLEDGEMENTS

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

De La Fourniere 1997

Methods	Randomized double-blind placebo-controlled trial
Participants	Country: France Number: 11 randomized No drop outs
Interventions	1. Placebo 2. 5 injections of 1000 microgram of vitamin B12 per day for 5 days then one injection per month for 5 months
Outcomes	ADAS
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Hvas 2004

Methods	Randomized double-blind placebo-controlled trial
Participants	Country: Denmark Number: 140 randomized Mean age in the treatment: 75 years Mean age in the placebo group: 74 years 5 patients dropped out in the treatment group 1 patient dropped out in the placebo group
Interventions	1.Placebo 2. 1 mg of cyanocobalamin weekly for 4 weeks
Outcomes	1.CAMCOG 2. MMSE 3.12-words learning test 4. MDI 5. P-MMA
Notes	

Risk of bias

Hvas 2004 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Seal 2002

Methods	Randomized double-blind placebo-controlled trial
Participants	Country: Australia Number: 31 randomized Age: mean 81.4 years Inclusion Criteria: serum B12 level < 150 pmol/L , the majority living at home Exclusion criteria: Pernicious anaemia, history of malabsorption, vitamin B12 treatment or supplementation 6: dropped-out
Interventions	1. Placebo 2. Oral cyanocobalamin in two doses: 10 and 50 microgram daily for 1 month
Outcomes	MMSE Serum vitamin B12/folate/Hcy
Notes	3 people had diabetes mellitus type II

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

MMSE: Mini Mental State Examination
ADAS: Alzheimer's Disease Assessment Scale
CAMCOG: Cambridge Cognitive Examination
MDI: Major Depression Inventory
P-MMA: Plasma Methylmalonic Acid

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

Study	Reason for exclusion
Abyad 2002	Single-blind
Eastley 2000	No intervention in the control group
Hughes 1970	No measure of cognitive function
Kwok 1998	No intervention in the control group
Martin 1992	No control group
Nagga 2002	No control group
Takao 2001	Not clear whether randomized
Teunisse 1996	No randomization

DATA AND ANALYSES

Comparison 1. vitamin B12 supplementation versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ADAS-Cog (change from baseline at 5 months)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 10 mg dose in 5 months	1	11	Mean Difference (IV, Fixed, 95% CI)	0.04 [-5.95, 6.03]
2 MMSE (change from baseline at 4 weeks)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 10 microg/day for four weeks	1	17	Mean Difference (IV, Fixed, 95% CI)	-1.6 [-3.99, 0.79]
2.2 50 microg/day for four weeks	1	18	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-3.06, 1.86]
3 CAMCOG (change from baseline) in 3 months follow-up from baseline	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 1mg dose weekly for 4 weeks	1	134	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-2.15, 0.95]
4 MMSE (change from baseline) in 3 months follow-up from baseline	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 1mg dose weekly for 4 weeks	1	134	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.59, 0.79]
5 12 words learning test, immediate recall, (change from baseline) in 3 months follow-up from baseline	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 1mg dose weekly for 4 weeks	1	134	Mean Difference (IV, Fixed, 95% CI)	-0.2 [-0.69, 0.29]
6 12 words learning test, 15 min delayed recall (change from baseline) in 3 months follow-up from baseline	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 1mg dose weekly for 4 weeks	1	134	Mean Difference (IV, Fixed, 95% CI)	-0.50 [-1.01, 0.01]
7 Major Depression Inventory (change from baseline) in 3 months follow-up from baseline	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 1mg dose weekly for 4 weeks	1	134	Mean Difference (IV, Fixed, 95% CI)	-1.6 [-3.75, 0.55]

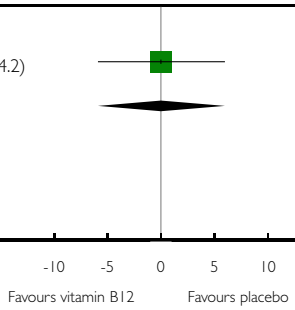
Analysis 1.1. Comparison 1 vitamin B12 supplementation versus placebo, Outcome 1 ADAS-Cog (change from baseline at 5 months).

Review: Vitamin B12 for cognition

Comparison: 1 vitamin B12 supplementation versus placebo

Outcome: 1 ADAS-Cog (change from baseline at 5 months)

Study or subgroup	Vitamin B12 N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 10 mg dose in 5 months							
De La Fourniere 1997	6	1.12 (5.9)	5	1.08 (4.2)		100.0 %	0.04 [-5.95, 6.03]
Subtotal (95% CI)	**6**		**5**			**100.0 %**	**0.04 [-5.95, 6.03]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.01 (P = 0.99)							
Test for subgroup differences: Not applicable							



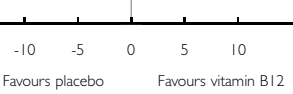
Analysis 1.2. Comparison 1 vitamin B12 supplementation versus placebo, Outcome 2 MMSE (change from baseline at 4 weeks).

Review: Vitamin B12 for cognition

Comparison: 1 vitamin B12 supplementation versus placebo

Outcome: 2 MMSE (change from baseline at 4 weeks)

Study or subgroup	Vitamin B12 N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 10 microg/day for four weeks							
Seal 2002	9	0 (2.9)	8	1.6 (2.1)		100.0 %	-1.60 [-3.99, 0.79]
Subtotal (95% CI)	**9**		**8**			**100.0 %**	**-1.60 [-3.99, 0.79]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.31 (P = 0.19)							
2 50 microg/day for four weeks							
Seal 2002	10	1 (3.2)	8	1.6 (2.1)		100.0 %	-0.60 [-3.06, 1.86]
Subtotal (95% CI)	**10**		**8**			**100.0 %**	**-0.60 [-3.06, 1.86]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.48 (P = 0.63)							
Test for subgroup differences: Chi^2 = 0.33, df = 1 (P = 0.57), I^2 =0.0%							

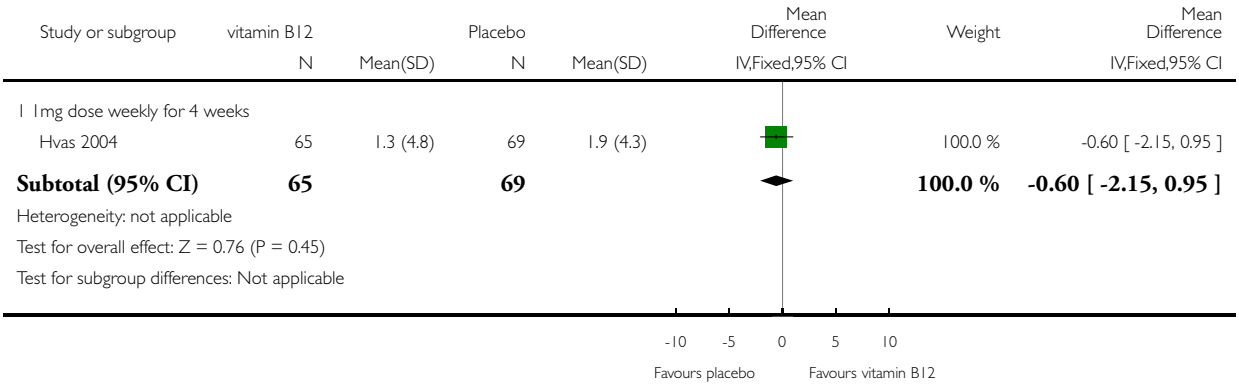


Analysis 1.3. Comparison 1 vitamin B12 supplementation versus placebo, Outcome 3 CAMCOG (change from baseline) in 3 months follow-up from baseline.

Review: Vitamin B12 for cognition

Comparison: 1 vitamin B12 supplementation versus placebo

Outcome: 3 CAMCOG (change from baseline) in 3 months follow-up from baseline

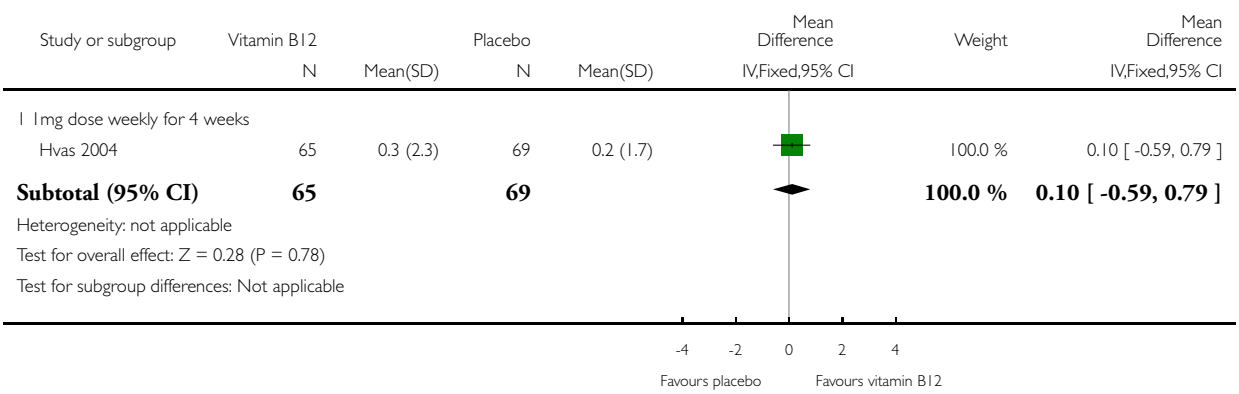


Analysis 1.4. Comparison 1 vitamin B12 supplementation versus placebo, Outcome 4 MMSE (change from baseline) in 3 months follow-up from baseline.

Review: Vitamin B12 for cognition

Comparison: 1 vitamin B12 supplementation versus placebo

Outcome: 4 MMSE (change from baseline) in 3 months follow-up from baseline

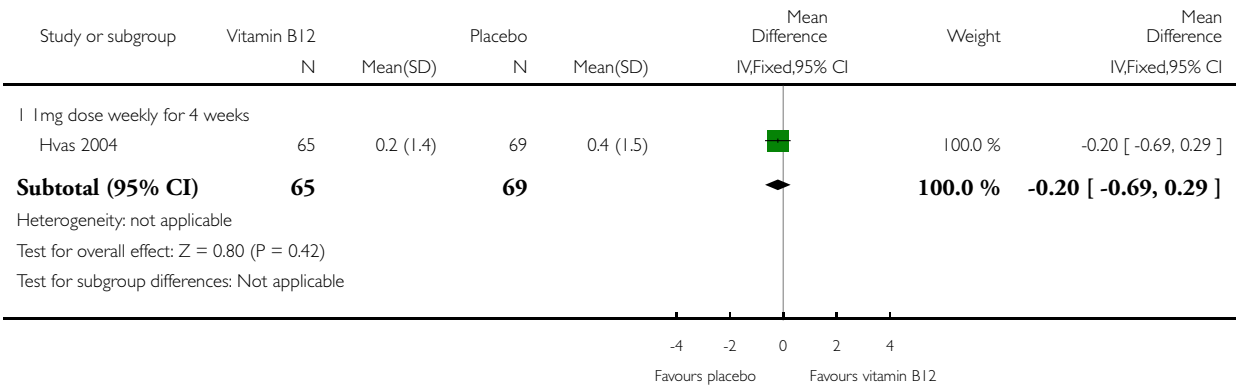


Analysis 1.5. Comparison 1 vitamin B12 supplementation versus placebo, Outcome 5 12 words learning test, immediate recall, (change from baseline) in 3 months follow-up from baseline.

Review: Vitamin B12 for cognition

Comparison: 1 vitamin B12 supplementation versus placebo

Outcome: 5 12 words learning test, immediate recall, (change from baseline) in 3 months follow-up from baseline



Analysis 1.6. Comparison 1 vitamin B12 supplementation versus placebo, Outcome 6 12 words learning test, 15 min delayed recall (change from baseline) in 3 months follow-up from baseline.

Review: Vitamin B12 for cognition

Comparison: 1 vitamin B12 supplementation versus placebo

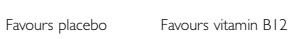
Outcome: 6 12 words learning test, 15 min delayed recall (change from baseline) in 3 months follow-up from baseline

Study or subgroup	Vitamin B12 N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 1mg dose weekly for 4 weeks							
Hvas 2004	65	0.2 (1.3)	69	0.7 (1.7)		100.0 %	-0.50 [-1.01, 0.01]
Subtotal (95% CI)	**65**		**69**			**100.0 %**	**-0.50 [-1.01, 0.01]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.92 (P = 0.055)

Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1 vitamin B12 supplementation versus placebo, Outcome 7 Major Depression Inventory (change from baseline) in 3 months follow-up from baseline.

Review: Vitamin B12 for cognition

Comparison: 1 vitamin B12 supplementation versus placebo

Outcome: 7 Major Depression Inventory (change from baseline) in 3 months follow-up from baseline

Study or subgroup	Vitamin B12 N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 1mg dose weekly for 4 weeks							
Hvas 2004	65	-1.8 (5.9)	69	-0.2 (6.8)		100.0 %	-1.60 [-3.75, 0.55]
Subtotal (95% CI)	**65**		**69**			**100.0 %**	**-1.60 [-3.75, 0.55]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.46 (P = 0.15)

Test for subgroup differences: Not applicable

ADDITIONAL TABLES

Table 1. Glossary

Term	Defination
Haemopothoietic system	The system that is responsible for production of the blood cells, which includes the bone marrow, liver, spleen, lymph nodes and thymus
Polyneuropathy	A generalized disturbance in peripheral nerves which could be acute (beginning suddenly) or chronic (developing gradually). The commonest type which involves both sensory and motor nerves
Subacute combined degeneration of the spinal cord	A progressive disorder that is due to vitamin B12 deficiency and produces weakness, tingling and other abnormal sensations
Hyperhomocysteine	A raised level in the plasma concentration of the homocysteine (a sulphur-amino acid)
Hypochlorhydria	A decline in the secretion of the hydrochloric acid (Hcl), that is secreted from the parietal cells in the stomach

WHAT'S NEW

Last assessed as up-to-date: 23 January 2006.

Date	Event	Description
7 November 2008	Amended	Converted to new review format.

HISTORY

Review first published: Issue 3, 2003

Date	Event	Description
23 May 2006	New search has been performed	Update 2006: One randomized double-blind controlled trial (Hvas 2004) was found in the new search. This trial was performed on elderly with cognitive impairment and vitamin B12 deficiency. No data was available at the end of the treatment period, however, the follow-up results at three months did not show any efficacy of B12 treatment on cognitive function
25 May 2003	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Reem Malouf: selecting trials for inclusion/exclusion, extracting and interpreting data for review, drafting and updating review versions. Moreover, she is responsible for all correspondence related to this review.

Almudena Areosa Sastre: selection of trials to be included for review, extracting and interpreting data, and assisting in drafting the review.

Original search and update searches: Dymphna Hermans

Contact editor: Jacqueline Birks

Consumer editor: Angela Clayton-Turner

This review has been peer reviewed anonymously

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- Division of Clinical Geratology, Nuffield Department of Clinical Medicine, University of Oxford, UK.
- NHS R&D, UK.

External sources

- No sources of support supplied

NOTES

August 2003: The comments of the consumer editor have been dealt with: additional table 2 (Glossary) has been added as well an additional graph (Homocysteine cycle).

INDEX TERMS

Medical Subject Headings (MeSH)

*Psychotherapy; Depression [etiology; *therapy]; Heart Defects, Congenital [*psychology]

MeSH check words

Adolescent; Adult; Humans