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A systematic review of treatments for Mild Cognitive Impairment

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Abstract

Background—More people are presenting with mild cognitive impairment (MCI), frequently a precursor to dementia but we do not know how to reduce deterioration.

Aims—To systematically review Randomised Controlled Trials (RCTs) evaluating effects of any intervention for MCI on cognitive, neuropsychiatric, functional, global outcomes, life quality, or incident dementia.

Methods—We reviewed the 41 studies fitting predetermined criteria, assessed validity using a checklist, calculated standardised outcomes, and prioritised primary outcome findings in placebo-controlled studies.

Results—The strongest evidence was that cholinesterase inhibitors did not reduce incident dementia. Cognition improved in single trials of: a heterogeneous psychological group intervention over 6 months; piribedil, a dopamine agonist over 3 months; and donepezil over 48 weeks. Nicotine improved attention over 6 months. There was equivocal evidence that Huannao Yicong improved cognition and social functioning.

Conclusions—There was no replicated evidence that any intervention was effective. Cholinesterase inhibitors and rofecoxib are ineffective in preventing dementia. Further good quality RCTs are necessary and preliminary evidence suggests these should include trials of psychological group interventions and piribedil.

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All other authors report no conflicts of interest.

Authors' contributions

CC and RL searched for studies and rated study validity; RL translated the Chinese papers; CC drafted the paper; all authors critically revised the draft for important intellectual content and approved the final version for submission.

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INTRODUCTION

Mild cognitive impairment (MCI) is a heterogeneous state between normal aging and early dementia. It has been referred to as objective cognitive complaint for age, in a person with essentially normal functional activities, who does not have dementia[1]. It affects 19% of people aged 65 and over[2]. Around 46% of people with MCI develop dementia within 3 years compared to 3% of the population of the same age[3]. Petersen distinguishes subtypes, depending on whether single or multiple cognitive domains are affected, and whether there is a predominant memory complaint. Amnestic MCI (aMCI), in which memory is affected more often progresses to Alzheimer's disease (AD), while MCI affecting a single non-memory domain may herald Frontotemporal or Lewy Body dementia. A vascular aetiology is more likely in multiple domain MCI[1]. Thus a group of people with MCI may differ from each other, clinically and neuropathologically.

The number of individuals diagnosed with MCI is growing in Western countries as people are encouraged to present early with memory problems to avoid crisis, but we know little about how to treat it. The UK National Institute for Health and Clinical Excellence (NICE) recommends follow-up to ensure dementia is diagnosed and care planned at an early stage, but no specific treatments[4]. Jorm et al[5] calculated that the dementia prevalence would be halved if its onset were delayed for five years. Neuroprotection, treating vascular risk factors or increasing cognitive reserves could theoretically delay dementia, and could be targeted at people with MCI who are at a particularly high risk of developing it. Previous reviews have focussed on specific treatments for MCI. Systematic reviews of Randomised Controlled Trials (RCTs) of all cholinesterase inhibitors[6], donepezil[7] and galantamine[8] concluded there are marginal beneficial effects which are outweighed by the risks of adverse events, including an unexplained increased mortality rate with galantamine. A 2009 Cochrane review found that memory training (specific neuropsychological exercises to improve memory) improved immediate and delayed verbal recall in people with MCI compared to a no-treatment, but not an active control[9]. More recent reviews have included RCT and non-RCT studies and suggested that cognitive interventions may improve memory for specific information, with less evidence that these effects can generalise[10–13].

We aimed to carry out the first systematic review of all types of intervention for MCI, to identify the best current treatment evidence.

METHODS

Search strategy and selection criteria

We searched PubMed (1946-), Web of Science (1900-), Cochrane Systematic Reviews Database (c.1993-), PsycINFO (1880-), CINAHL (1937-) and AMED (1985-) through 10 July 2012 (and updated it 27 January 2013), using the words: "mild cognitive", "cognitive impairment", "benign senescent forgetfulness" OR "age associated cognitive decline" AND treatment AND (controlled trial OR RCT). No limits were applied for language or time published. We searched references of included papers and systematic reviews identified in the search and contacted experts.

We included RCTs evaluating any treatment for MCI which reported as an outcome: cognition (specific domains or global), conversion to dementia; functional, behavioural, quality of life or global measures. We included studies where all participants or a separately analysed subgroup had MCI.

Data extraction

One author (CC) extracted study characteristics (see Tables 1–2). We contacted two authors to request unreported data; and obtained this for one[14] but not the second study[15].

To assess risk of bias, two authors (CC, RL) independently evaluated study validity using questions adapted from the Critical Appraisal Skills Programme (CASP) (http://www.sph.nhs.uk/sph-files/casp-appraisal-tools/rct%20appraisal%20tool.pdf; accessed 24/07/12)

1. Were participants appropriately allocated to intervention and control groups? (Was randomisation independent?)
2. Were patients and clinicians, as far as possible, "masked" to treatment allocation?
3. Were all patients who entered the trial accounted for and an intention to treat analysis used?
4. Were all participants followed up and data collected in the same way?
5. Was a power calculation carried out, based on one of our outcomes of interest?

Disagreements were resolved by consensus between authors.

Analysis

We compared control and intervention groups post-intervention. We prioritised results from placebo-controlled studies that identified one or two primary outcomes, as these were less likely to have reported significant chance findings. For primary outcome results we displayed standardised outcomes in Forest plots (standardised mean differences (SMD), standardised mean change (SMC), hazard ratios (HR) or odds ratio (OR)) for primary outcomes using statsdirect statistical software version 2.7.9 [16]; for some studies where these results were unavailable we calculated SMD or SMC from mean (or mean change), appropriate standard deviations and n for intervention and control groups post-intervention. Our calculations sometimes indicated a significant between group difference where the authors' multivariate calculations did not, or vice versa, and we indicated in the text where this occurred. For all other results we tabulated statistical comparisons between groups, and for the few studies where groups were not directly compared calculated SMD as above. We planned to meta-analyse results where three or more studies with comparable interventions reported comparable outcomes.

Role of funding source

This study was completed by the authors in their capacities as employees of University College London and Johns Hopkins Medicine. These institutions had no role in the study design, collection, analysis and interpretation of data, writing the report, or the decision to submit it for publication.

RESULTS

Figure 1 shows a PRISMA diagram describing the results of our search strategy. We included 41 unique studies and listed excluded studies in Appendix A. Five Chinese studies were translated by RL; the remainder were published in English.

Validity—Table 1 describes the 20 (49%) studies that identified one or two primary outcomes: 16 were placebo-controlled and 13 used intention to treat analyses. Other studies are displayed in Table 2. We rated the overall validity of studies (see methods). 11/20

studies that identified primary outcomes and 5/23 studies that did not had Validity Scores (VS) of 4 or 5, the highest levels of evidence.

Description of studies—Included studies recruited people with MCI via clinics or clinician referrals[17–28], advertisements[24;29–34], screening older populations[21;35–38], care homes[23;39–41], the local Alzheimer's society[34], pre-existing research registers[31;42], a rehabilitation center[43] or a welfare institution.[25] Several did not report the source of participants[11;15;44–52]. Tables 1 and 2 describe funding sources, inclusion criteria, sample sizes, comparators and duration of studies. Figure 2 reports results on all primary outcomes for which standardised outcomes could be calculated; this was not possible for four studies[14;21;51;53] because data was not available or did not approximate the normal distribution, so these results are described in the text. In Table 2, we report statistically significant between group differences from studies without primary outcomes. Non-significant findings for all studies are in Tables 1b and 2b (appendices). The only intervention evaluated in more than two studies was donepezil; three donepezil trials included the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog) at 6 months, but as data were not available from one, we could not meta-analyse these findings.

Findings on primary outcomes in placebo-controlled studies—Cognition improved in small studies of group memory training, cognitive stimulation and reminiscence over 6 months; and piribedil, a dopamine receptor agonist over 3 months[23]. In a large, adequately powered study, donepezil improved cognition compared to placebo with 48 weeks' treatment[15]. Nicotine patches improved attention in a small study of non-smokers over 6 months which was adequately powered to detect a difference on this outcome[21]. Huannao Yicong, a Chinese herbal preparation containing ginseng, demonstrated efficacy on a measure of cognition and social functioning over 8 weeks in a small per protocol, responder analysis, but not when mean scores were compared between groups[28].

The only finding replicated on primary outcome measures involved galantamine[51] (in two studies) and other cholinesterase inhibitors (in two studies[31; 45]) that did not prevent conversion to dementia. In adequately powered trials, conversion to dementia was also not reduced by: vitamin E[45] or Gingko biloba[35]. Rofecoxib, in an adequately powered study increased dementia incidence[49]. Cognitive score was not improved by: 2 years of rivastigmine, or 13 months of the non-steroidal anti-inflammatory drug (NSAID) triflusal [44], or, in underpowered studies, by 6 weeks of computerised cognitive training[18] or DHA (docosahexaenoic acid) and EPA (eicosapentanoic acid) taken for 6 months[29]; or a moderate-intensity walking programme compared to low intensity relaxation, balance and flexibility exercises[54].

Non-pharmacological interventions

Computer-assisted cognitive training (3 studies)—All three studies were probably under-powered so while results were not promising there was insufficient evidence to draw conclusions about its efficacy. Only Barnes et al[18] specified primary outcomes (Validity score (VS)=4). They evaluated a programme that involved distinguishing between similar sounding words and matching sentences with pictures, for 100 minutes daily, 5 days a week. The control group listened to audio books, read an online newspaper and played a computer game. There was no significant difference between groups on the primary outcome, the Repeatable Battery for Assessment of Cognitive Status (RBANS) after 6 weeks (Figure 2). The only significant difference, favouring the intervention was on the delayed memory RBANS subscale (SMD = 0·53, 0·05 to 1·10).

Two studies tested computer-assisted training, but did not specify primary outcomes. Finn et al[55] evaluated a 2 month programme in a higher quality study (VS=4), and Rozzini et al[47] a 9 months programme (VS=3). In both studies, most results were not significant; only results for the visual attention CANTAB (Cambridge Automated Neuropsychiatric Test Assessment Battery) subscale[55] and short story recall[47] favoured the interventions (Table 2).

Summary

- Global cognition did not improve with cognitive training in two trials, in one of which it was a primary outcome, and there were no consistently significant findings on other secondary outcomes. Studies were all underpowered.

Longer term group psychological interventions (2 studies)—Two lower quality studies tested 6 month group interventions. Results were conflicting. Buschert et al[19] (VS=3 and identifying primary outcomes) tested a manualised memory training and cognitive stimulation programme, consisting of 20, 2-hour weekly group sessions comparing 10 people in the intervention group with 12 in the control group. The memory training used mnemonics, calendars, notes and prompts; face-name association and errorless learning. In errorless learning, information was repeated frequently to avoid recall mistakes, with repetitions becoming further apart with successful recalls (spaced retrieval). The programme also included reminiscence, psychomotor and recreational tasks (e.g. playing with balloons), multisensory stimulation and social interaction. Participants did homework, which carers were encouraged to support. The control group met monthly and did paper and pencil exercises. Only participants who attended at least half of sessions were included in analyses. Global cognition, the primary outcome improved in the intervention group in our univariate (Table 1) and the authors' analyses that controlled for baseline score, age and educational status on both primary outcome measures. Montgomery-Asberg Depression rating scale scores were also lower in the intervention compared with control group adjusting for these factors (mean (sd) 0.7 (1.3) for treatment group and 3.8 (6.1) for controls, $F(1,18) = 8.8$, $p < 0.01$).

Troyer et al[24] in a small study (VS=1) evaluated ten, 2-hour sessions, including psychoeducation, recreation, memory training and strategies, relaxation and directing to community resources. The authors found no significant differences between groups post-intervention on several measures of recall (Table 2b).

Summary

- Twenty sessions of memory training, reminiscence, cognitive stimulation, psychomotor recreation and social interaction improved global cognition on a primary outcome in a single, very small, 6-month placebo-controlled trial which did not carry out an intention to treat analysis.
- Ten sessions of memory training, psychoeducation and relaxation did not improve recall on secondary outcomes in one small 6-month trial.

Short term (6 week) psychological group interventions (two studies)—Both studies were lower quality (VS=2) and were underpowered so while neither improved memory there was insufficient evidence to reject this intervention type. Unverzagt et al[14] specified primary outcomes and compared three types of group, 10-session interventions teaching specific cognitive strategies with no treatment. These were: memory training strategies; reasoning training, and processing speed training. Booster training was provided to 60% of participants, approximately 11 months later. Memory training participants did not improve post-intervention, or 1 or 2 years later on the composite memory measure versus

those receiving no treatment (SMD = −0·01, −0·18 to −0·10; p>0.05). Participants receiving the processing speed intervention improved on processing speed (SMD = −1.4, −1·1 to −0·8; p<0·001) and the reasoning group participants improved on reasoning post-intervention (SMD=0.57;p<0·001, and 2 years (SMD=0·28;p<0·05), but not 1 year later (SMD=0·21;p>0·05), compared to those receiving no treatment.

Rapp et al[46] did not specify primary outcomes. They evaluated six, weekly 2-hour groups, of psychoeducation, relaxation, memory strategies (cueing, categorization, chunking, method of loci) and homework. Participants received a manual, which was also sent to the control group who otherwise had no treatment. There were no significant differences between groups on several memory measures, post-intervention or 6 months later.

Summary

- Memory did not improve over 6 weeks in two short-term, underpowered group intervention trials teaching memory strategies, which were not placebo controlled.
- Specific interventions to improve reasoning and processing speed respectively significantly improved these primary outcomes, in an underpowered single, non-placebo controlled trial.

Family psychological interventions (one study)—This lower quality study indicated that a family psychological intervention might improve prospective memory. Kinsella et al[20] (VS=2) compared a course of five, weekly 1.5-hour family intervention groups to a waitlist control. Groups involved problem-solving everyday memory difficulties and practicing possible strategies. Written session material was provided. Results on the primary outcome, an unvalidated (to our knowledge) prospective memory test favoured the intervention 2 weeks and 4 months post-intervention, controlling for baseline scores and age; the SMD for this comparison was not significant in our univariate analysis (Figure 2).

Summary

- Prospective memory improved up to 4 months later in this underpowered trial that was not placebo-controlled, on a non-validated measure but only when baseline memory scores were taken into account.

Individual psychological interventions (one study)—This lower quality study (VS=3) found that an individual psychological intervention did not improve memory. Jean et al[53] evaluated six individual, 45-minute sessions over 3 weeks, focussing on errorless learning of picture-name associations with spaced retrieval (see earlier). In the control condition, the pictures were presented without spaced retrieval. Participants were given written information about memory. The unvalidated primary outcomes evaluated the number of unknown faces (episodic memory) and famous names (semantic memory) matched correctly. There was no significant treatment effects on these measures in mixed linear models (F(2, 35) = 49·390, F(2, 35) = 11·569), or on MMSE.

Summary

- Six individual sessions of errorless learning and spaced retrieval did not improve prospective memory in one placebo-controlled, underpowered study where this was a primary outcome.

Exercise—Exercise has been associated with favourable effects on neuronal survivability and function, neuroinflammation, vascularization, neuroendocrine response to stress, and

brain amyloid burden. It also improves cardiovascular health, which is associated with cognitive health[17].

Group exercise programmes (two studies): Results from two studies comparing year-long, twice-weekly, group based exercise programmes to active control conditions were mixed. In a very high quality study (VS=5), van Uffeln[54] compared a moderate-intensity walking programme to low intensity relaxation, balance and flexibility exercises, and found no significant effect in any cognitive domain, including the primary outcome of immediate word recall (Figure 2A) or in quality of life. In a lower quality study (VS=3; no primary outcomes specified), Suzuki et al[42] compared groups involving circuit training and some outdoor walking to a control group who attended three health promotion classes. The intervention group improved in terms of MMSE score, immediate memory and verbal fluency (Table 2).

Individual exercise programmes (three studies): None of these lower quality studies specified primary outcomes. Busse et al[26] (VS=3) evaluated 9 months of resistance exercises, for one hour twice a week. Scores on a test of every day memory (Rivermead behaviour memory test) improved in the intervention group relative to the no treatment controls, but CAMCog (Cambridge cognition examination) scores and digit span did not.

The remaining two studies had VSs of 2. Baker et al[17] compared cognition in adults exercising less than 90 minutes weekly participating in a 6-month high-intensity aerobic exercise intervention or a stretching and balance exercise control. Each intervention was for 1 hour, 4 days a week. The first 8 sessions, and thereafter one session a week were supervised. Adherence was monitored. Significant between-group effects, favouring intervention, were reported on the Digit Symbol Substitution Test (DSST) (attention and processing speed), trail making test B and verbal fluency (Table 2). For verbal fluency, effects were more apparent for category than letter fluency (letter, P=·20; category, P=·03). Scherder et al[41] compared: assisted walking for 30 minutes, three days a week for 6 weeks; hand and face exercises for the same duration; and a control group, half of whom received additional social visits. The only significant between group differences, all in favour of the interventions, were on the category fluency and trail making tests (Table 2).

Summary

- A very high quality study found that memory, the primary outcome, did not improve with a year long aerobic exercise group compared to a relaxation, balance and flexibility exercise active control group. A lower quality study found that participants in a similar intervention improved on fluency, memory and global cognition relative to a health promotion control.
- The studies of individual exercise studies were low quality and their results were inconsistent. Category fluency and trail-making test scores improved with individual aerobic exercise on secondary outcomes in two studies, of 6 weeks and 6 months duration, but no other cognitive outcomes improved in more than one study.

Pharmacological interventions

Cholinesterase inhibitors (9 studies)—Three large studies compared donepezil 10mg daily to placebo, and results were inconsistent. The highest quality (VS=5) by Doody et al[15] was a 48-week study that included two primary outcome measures: ADAS-Cog, on which results favoured donepezil, and the CDR (Clinical Dementia Rating) on which there was no significant between-group difference (Figure 2). On secondary outcomes, only patient global

assessment differed significantly between groups, in favour of donepezil. The two other large studies were also higher quality (VS=4). Salloway et al[48] carried out a 24-week, adequately powered study there were no significant differences between donepezil and placebo on the primary outcomes, the New York University Paragraph Delayed Recall test or the CGIC (Clinician Global Impression of Change), or on any secondary outcomes except for ADAS-Cog. Petersen et al[45] found no significant difference between groups on conversion to AD, the primary outcome (Figure 2) or any other measures over 3 years.

One small, lower quality study (VS=1) which did not identify primary outcomes found that donepezil and antidepressant treatment improved immediate memory but not other cognitive outcomes, compared with antidepressants alone[27].

Galantamine was investigated in three trials, and results on primary outcomes in the highest quality trials were not significant. Winblad et al[51] evaluated galantamine, titrated to 12mg twice daily in two large, high quality, 24 month, placebo-controlled RCTs (VSs=5). Neither reported a significant effect on the primary outcome, incident dementia (22·9% vs 22·6%, p = 0·15; 25·4% vs 31·2%, p = 0·62). On secondary measures, statistical comparisons favoured galantamine in one of the two studies for global functioning (measured on the CDR) and attention (DSST). In a small, lower quality trial, Koontz et al[22] only reported significant between-group differences on two subscales of the CANTAB, both measuring executive functioning (Table 2).

One high quality study (VS=5), by Feldman et al[31] compared 3–12mg daily of rivastigmine and placebo. There were no significant differences between participants on any measures over 2 years, including the primary outcome, progression to AD (Figure 2).

Finally, Rozzini et al[47] compared people receiving any cholinesterase inhibitor to those taking placebo after 1 year in a lower quality study (VS=2). There were no significant between group differences on any measures (Table 2b - appendix).

Summary

- Incident AD was not reduced in four, higher quality trials where this was the primary outcome – two evaluated galantamine, one donepezil, and one rivastigmine.
- Donepezil improved global cognition in one high quality trial where it was a primary outcome measure, and a second where it was a secondary outcome, but global cognition did not improve in the five other large, high quality trials of cholinesterase inhibitors.
- Donepezil did not improve global functioning in one trial where this was a primary outcome. Galantamine improved global functioning in one trial on a secondary outcome measure.
- Galantamine improved executive functioning and attention on secondary outcome measures in a single trial.
- Donepezil as an adjunct to antidepressants improved immediate memory, also on a secondary outcome.

Piribedil (one study)—Piribedil is a dopamine receptor agonist. Animal models have suggested acetylcholine release in hippocampi and the frontal cortex as a putative mechanism of action. Nagaraja et al[23] evaluated this over 3 months in a higher quality trial (VS=4) with 30 in each group, all with MMSE of 21–25; the primary outcome, response on

MMSE (predefined as a score of 26+), favoured piribedil (Figure 2). Mean MMSE change from baseline also favoured the intervention group (t=2·83, p<0·01). It was well tolerated.

Summary

- Pirbidel improved cognition over 3 months on a primary outcome in one small placebo-controlled study.

Nicotine(one study)—Brain nicotinic receptors are important for cognitive function[21]. Newhouse et al[21] compared transdermal nicotine (titrated to a 15mg patch/day) to placebo in a very high quality study (VS=5 with identified primary outcomes). Attention, measured on the Cognitive Performance Test improved (F=4·89, p =0·031; effect size 0·78) but global functioning on the CGIC did not, on mixed models repeated-measures, analyses of variance. On secondary outcome measures, the treatment group showed less forgetting in between immediate and delayed recall than placebo (F =4·42, p= 0·04), better delayed word recall (F= 5·92, p=0·018) and less anxiety on the older Adult Self Report worries and anxiety subscales (F= 3·48, p =0·04; F=3·14, p=0·05).

Summary

- Nicotine patches improved attention, but not global functioning, over 6 months on primary outcomes in one, high quality study. Delayed recall and self-reported anxiety improved on secondary outcomes.

Huannao Yicong (one study)—Li et al[28] evaluated this Chinese medicinal compound, which includes ginseng in a study that identified primary outcomes but was low quality (VS=0). Increases or changes in hippocampal mitochondria have been proposed as mechanisms of action. Over 2 months, comparisons favoured the intervention on the primary outcome, response (improvement of 6+ points) on the Cognitive Effect Index (CEI), which comprised the MMSE, Cognitive Capacity Screening Examination (CCSE) and Social Functioning scale (SF-36). We found that the mean difference in CEI scores between groups post-treatment was not significant (Table 1). The analyses excluded people who did not take their medication.

Summary

- Results in one, low quality trial were equivocal: more participants taking Huannao Yicong than placebo responded on a cognition and social functioning measure, but the mean difference between groups on this measure was not significant.

Gingko biloba (two studies)—Results from these studies were inconsistent, but the highest quality trials suggested it is ineffective. Proposed mechanisms of action of Gingko biloba include increasing brain blood supply, reducing blood viscosity, modifying neurotransmitter systems, and reducing oxygen free radical density[56]. In a very high quality study (VS=5), deKosky et al[35;57] found that 240mg daily, taken for a median of 6·1 years, did not reduce incident dementia or AD. In a lower quality (VS=3), 6-month study which was not placebo controlled, Zhao et al[25] reported that participants prescribed 56·7mg daily Gingko biloba performed better than those receiving no treatment on nonsense picture recognition and logical memory tests (Figure 2).

Summary

- On primary outcomes, 240mg daily Gingko biloba did not reduce incident dementia in a very high quality trial over 6 years; while 56·7mg daily improved cognition in a second trial compared with usual treatment.

NSAIDs (two studies)—NSAIDs reduce brain neurotoxic inflammatory responses, so could improve cognition[58]. Thal et al[49], in a very high quality large study (VS=5) found significantly more incident cases of AD over 4 years in participants randomised to 25mg daily of rofecoxib (a COX-2 inhibitor) than those taking placebo (Figure 2). There was no significant difference between groups on secondary outcomes. In 2003, rofecoxib was withdrawn due to cerebrovascular and cardiovascular side effects.

Gomez-Isla et al[44] evaluated 900mg a day of triflusal, a COX-1 and COX-2 inhibitor in a lower quality study (VS=3), which was terminated early. It found no significant difference between groups on the primary cognitive outcome, ADAS-Cog (Figure 2). The only significant finding on secondary outcomes was a lower rate of conversion to AD in the intervention group (HR = 2·10; 1·10 to 4·01; P=0·024).

Summary

- Rofecoxib *increased* incident cases of AD in one very high quality study on a primary outcome.
- One trial of triflusal reported no significant effect on cognition on a primary outcome measure, although it was associated with a reduced risk of conversion to AD on a secondary outcome.

B vitamins (two studies)—Higher homocysteine plasma concentrations are associated with cognitive impairment; levels are decreased by B vitamins. Two placebo-controlled trials investigated the effectiveness of B vitamins (folic acid, B12 and B6). In a very high quality study (VS=5 and primary outcome identified), van Uffelen[38] found no significant difference on the primary outcome of immediate memory over 6 months. On secondary outcomes, the group taking vitamins performed better than placebo group on the DSST (attention and processing speed; longitudinal regression, coefficient not given, p=0.02). De Jager et al[30] found in a lower quality (VS=3), 2 year study that executive functioning improved relative to placebo (Table 2).

Summary

- Immediate memory did not improve in a high quality study in which this was primary outcome. Out of numerous secondary measures, attention improved in one trial and executive functioning in another, so results were inconsistent.

Vitamin E (two studies)—One large, higher quality trial (VS=4) reported by Petersen et al[45] found no significant treatment effect of vitamin E (2000IU) on the primary outcome measure, progression to AD or on a range of secondary outcomes over 3 years. Zhou et al[50] reported in a lower quality study (VS=1) that participants receiving vitamin E 500mg daily improved versus placebo on picture recognition (Table 2).

Summary

- Vitamin E did not reduce incident dementia in one high quality study on a primary outcome.
- In a lower quality study 500mg daily was associated with improvement in picture recognition, a secondary outcome.

Omega-3 Polyunsaturated fatty acids (PUFA) (two studies)—DHA (docosahexaenoic acid) and EPA (eicosapentanoic acid) are dietary PUFA, which have structural and functional roles in the brain. Both these studies had VS of 3. Chiu et al[29]

found that, as primary outcomes, ADAS-Cog improved over 6 months in people taking 1080mg EPA and 720mg DHA versus placebo after adjusting for age, gender, and education, but no differences were reported on the CIBIC-plus (global functioning). When we calculated SMD for ADAS-Cog at follow-up between groups, there were no significant differences (Table 1).

Sinn et al[34] in a small study compared groups receiving EPA-rich fish oil (1670mg EPA and 160mg DHA), and DHA-rich fish oil (1550mg DHA and 400mg EPA) to placebo. Using a linear mixed model analysis, letter fluency scores significantly improved over 6 months in the DHA group versus placebo, and depressive symptoms, measured using the Geriatric Depression Score were reduced in both groups (Table 2).

Summary

- Cognition improved on a primary outcome in one study, but only after adjusting for age, gender and education.
- Verbal fluency improved with DHA-rich fish oil and depressive symptoms were reduced by DHA and EPA-rich oil after 6 months in a single small study on secondary outcome measures.

Interventions evaluated in single trials without primary outcomes (Table 2)

Ten different interventions have been evaluated in single trials, not specifying one or two primary outcomes. Three were higher quality trials (VSs 4+). These found that: Transcutaneous Electrical Nerve Stimulation (TENS) treatment reduced ADL impairment and depression over 6 weeks in the only trial we reviewed that did not measure cognition[39]; and that in 3 month trials, memantine improved information processing speed but not cognition[52]; and a nutritional supplement composed of: DHA 720mg, EPA 286mg, vitamin E 16 mg, soy phospholipids 160mg, tryptophan 95mg and melatonin 5mg[40] improved cognition. Fluoxetine[43], Shenyin oral liquid[50], Ginseng[37], Wuzi Yanzong[36], grape juice[32] Green tea[33] and lithium[59] were ineffective in single, lower quality trials.

Discussion

Our most striking finding is the lack of good quality evidence except in the pharmacological trials. These enable us to more confidently reject cholinesterase inhibitors as useful in preventing conversion of MCI to dementia, and confirm NICE guidance that cholinesterase inhibitors should not be prescribed clinically for MCI[4]. The only non-pharmacological intervention for which we found preliminary evidence, in a single, placebo-controlled trial on co-primary outcomes was a heterogeneous group programme of memory training, reminiscence and cognitive stimulation, recreation and social interaction, which improved cognition over 6 months. There was equivocal evidence that a group intervention for families might improve prospective memory from a trial that was not placebo-controlled. We also found replicated evidence on secondary outcomes that category fluency improved with individual aerobic exercise programmes, of 6 weeks and 6 months duration, and delayed recall improved in two studies evaluating computerised cognitive training programmes. These latter studies had multiple secondary outcomes, thus increasing the possibility of a chance finding and the clinical benefit of isolated improvements in these domains is unclear. Most studies were underpowered and lack of evidence of efficacy is not evidence of lack of efficacy.

In pharmacological studies, donepezil improved cognition over a year in two trials, one on a primary outcome, but in general the evidence from seven studies of cholinesterase inhibitors was not promising. The strongest evidence we found was that cholinesterase

inhibitors[31;51;45] did not reduce the incidence of dementia. Given the safety concerns around the use of cholinesterase inhibitors in MCI[8], we think that trials of alternative therapeutic agents are now needed.

Piribedil, a dopamine agonist was effective on a cognitive primary outcome in one study. However, the criteria for MCI were not strict and the authors acknowledge that some of the participants may have had dementia. Nicotine patches improved attention on a primary outcome over 6 months, and also verbal recall on a secondary outcome; and we found equivocal evidence that Huannao Yicong, a Chinese herbal preparation, may improve cognition and social functioning.

It is disappointing that we did not find stronger evidence of efficacy, but nonetheless some of the interventions included warrant further investigation. It is unclear why there have been no further trials of Piribedil in MCI since the positive trial reported in 2001; a trial of Piribedil in people with Parkinson's disease has not yet reported (NCT01007864). The effectiveness of Huannao Yicong in one trial, albeit of low validity, could indicate that further exploration of Chinese Medicine treatments of MCI may be fruitful. There was limited evidence that exercise therapies improved executive functioning. Resistance training, walking and aerobic exercises may well differ in their effects, and given the positive impact of exercise on general health this would also be an interesting area for future study.

Limitations

This is one of the first comprehensive reviews of all treatments evaluated for MCI. Methodological challenges for MCI trial include deciding inclusion criteria. Nearly two-thirds of studies used Petersen criteria. Some of the studies only included participants with aMCI while others included other subtypes so even within those using Petersen criteria, target groups were heterogeneous. Some people with MCI have prodromal Alzheimer's Disease or will progress to vascular or other subtypes of dementia. Only two- thirds of people with MCI progress to dementia in their lifetime[60], limiting the power of secondary prevention studies that recruit MCI populations. The heterogeneity and instability of the MCI diagnosis militate against finding positive results in MCI trials. It is interesting that while in the trial reported by Petersen et al[45], vitamin E did not prevent AD in people with aMCI overall, it was effective at doing so among carriers of one or more apolipoprotein Eε4 alleles, perhaps because this is a more homogenous group, more likely to have prodromal AD. Availability of biomarkers may enable future trials to recruit participants according to disease process rather than clinical deficits. For example, trials of pharmacological agents targeting people with early AD may recruit people with aMCI and probable AD[61]. Biomarkers may also allow participants to be recruited earlier in the disease process, at the stage of subjective memory impairment which usually precedes MCI. By the time MCI develops the pathological process may be too advanced for treatments to be preventative, perhaps because the brain is by this point very vulnerable to other comorbidities which lead to a dementia, even though progression of the original pathology is halted. A second challenge is deciding on a primary outcome. "Conversion" trials are difficult to power adequately as only 10% of people with MCI convert every year to dementia, and this rate seems to be lower in RCTs[31]. Incident dementia is often the primary outcome as dementia prevention is a clear goal, but Schneider has suggested it is a problematic endpoint because many participants would be on the cusp of dementia and dementia onset is influenced by numerous biological and environmental factors[61]. We prioritised placebo-controlled trials, because this evidence is most directly applicable to current practice. There are no evidence-based interventions for MCI and most people with it receive no active treatment. We included a broad range of clinical outcomes, but excluded studies evaluating subjective experiences of memory or biological markers. We included papers in all languages, but only searched English language databases. We planned to meta-analyse findings from three or

more studies, but in practice only donepezil was evaluated in more than two studies, and this could not be meta-analysed as required data was unavailable from one study.

Conclusions

There is no evidence, replicated on primary outcomes that any intervention is effective for MCI on the outcomes studied. Results for cholinesterase inhibitors in MCI, the most widely studied intervention, are unpromising. More high quality randomised controlled trials are urgently needed. This review would support further trials of a heterogeneous group psychological intervention, and a dopamine agonist as interventions targeting cognition.

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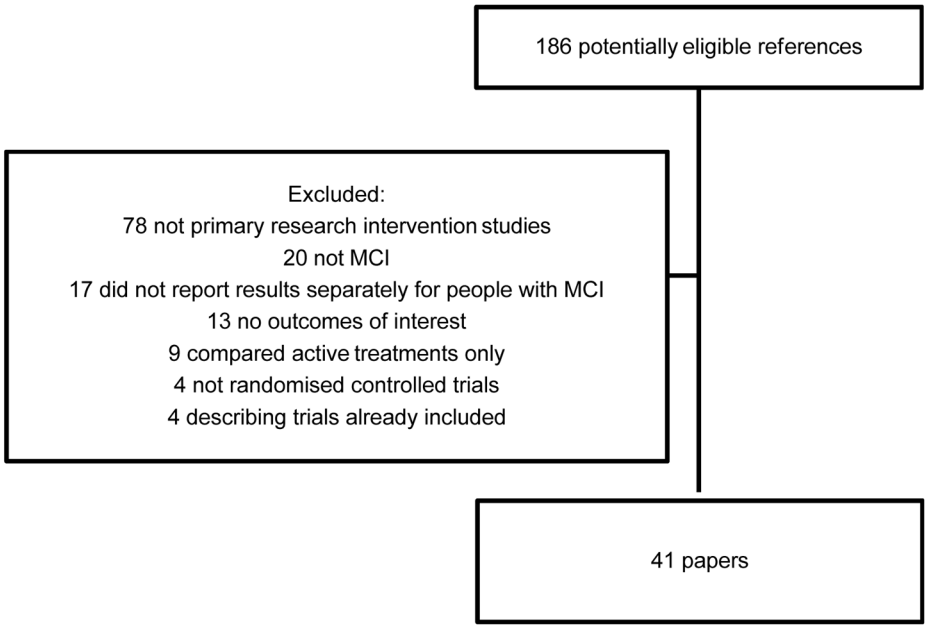

Figure 1.
Details of search strategy

Figure 2A

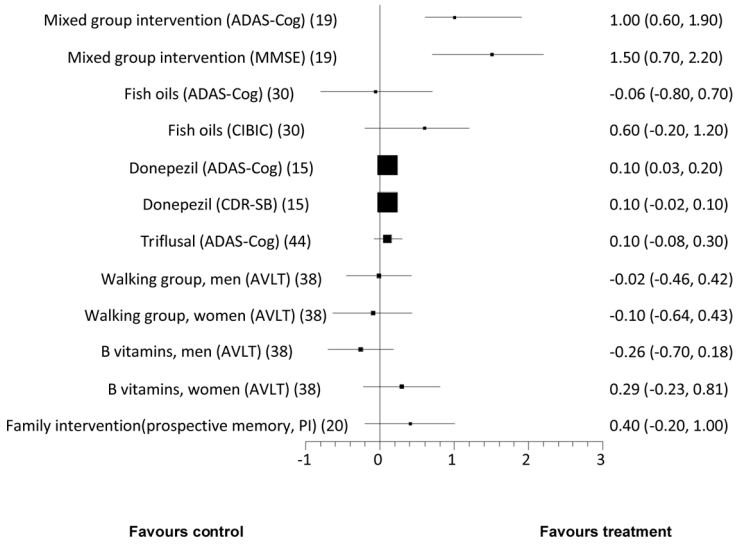

Figure 2B

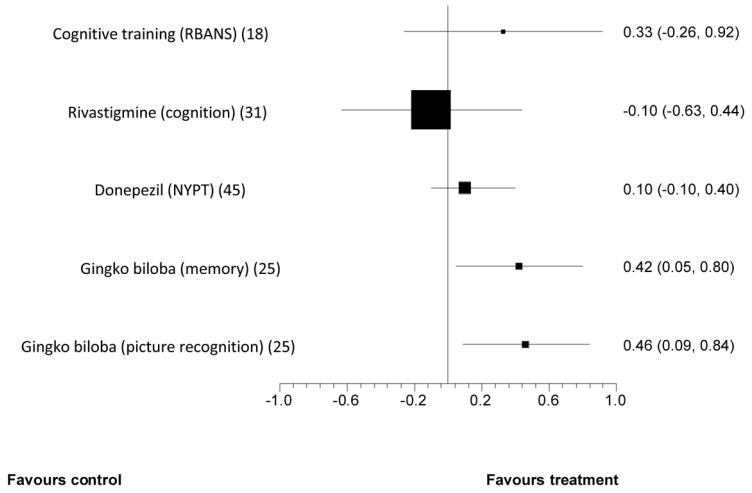

Figure 2C

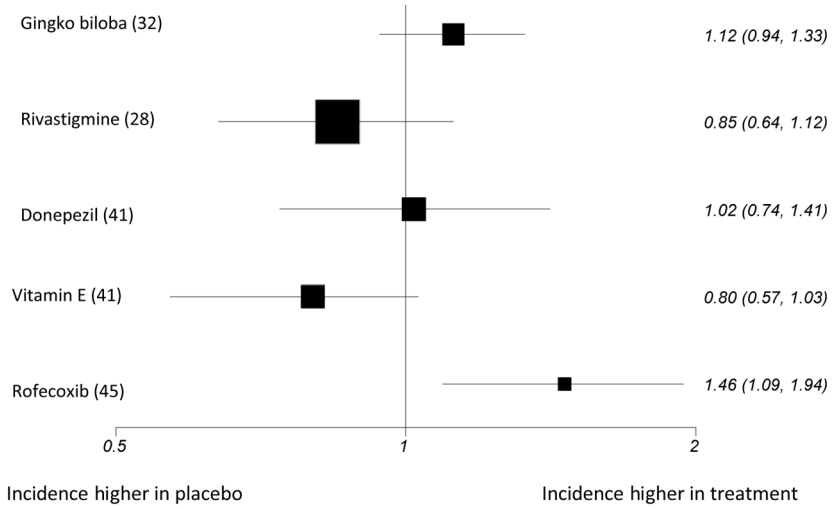

Figure 2D

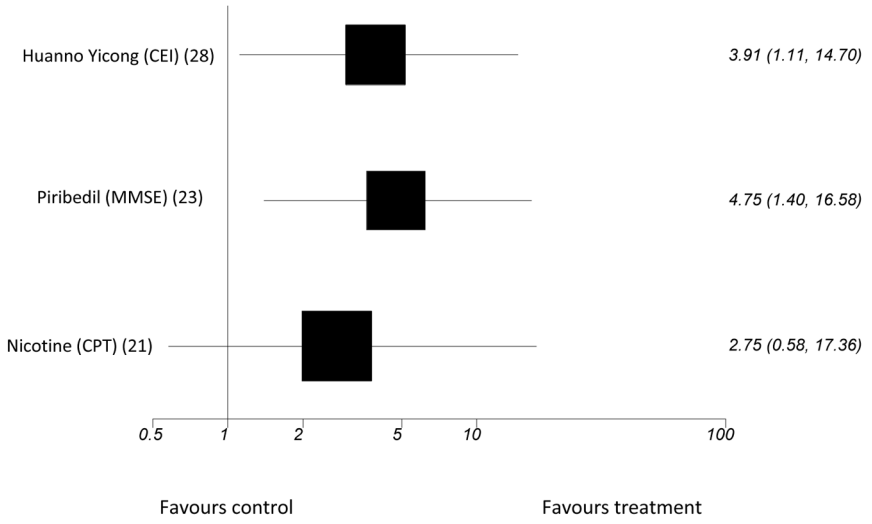

Figure 2.

Forest plots showing between group comparisons for standardised primary outcomes post-intervention for all studies citing one or two primary outcomes(see text for study duration)[1]

Figure 2A: Studies with outcomes expressed as Standardised Mean Difference (with 95% confidence intervals)

Figure 2B: Studies with outcomes expressed as Standardised Mean Change from baseline (with 95% confidence intervals)

Figure 2C: Studies reporting Hazard Ratios (95% confidence intervals) for incident dementia or Alzheimer's disease (log scale)

Figure 2D: Studies for which outcomes expressed as odds ratio for response (95% Confidence intervals) (log scale)

See Table 1 for key to abbreviations

Table 1

Characteristics and validity of studies specifying one or two primary efficacy outcomes

Study	Support sources	Inclusion criteria	Treatment	n	Control	n	Duration	Primary outcome	Validity***				
									1	2	3	4	5
Barnes[18]	Posit Science, Gov (USA)	cognitive complaint in >1 domain and no dementia	Computerised, cognitive training	22	Audio books, online news, computer game	25	6 weeks	RBANS total score	y	y	y	y	n
Buschert[19]	None declared	Age 50+, aMCI*	20 × 2 hour group memory training & cognitive stimulation	10	Monthly groups 1-hour sessions doing paper and pencil exercises	12	6 months	ADAS Cog	y	y	n	y	n
								MMSE					
Chiu[29]	Gov (Taiwan)	aMCI*	1080mg EPA and 720mg DHA	14	Olive oil	9	6 months	ADAS Cog	y	y	n	y	n
								CIBIC					
DeKosky[35]	NCCAM Schwabe Pharmaceuticals	Age 75+ ; MCI**	Ginkgo biloba 120mg bd	256	Placebo	226	6 years	Incident dementia	y	y	y	y	y
Doody[15]	Eisai Pfizer	Age 45–90, MCI*, daily contact with informant	Donepezil	379	Placebo	378	48 weeks	ADAS Cog	y	y	y	y	y
								CDR-SB					
Feldman[31]	Novartis	CDR= 0·5,< 9 New York University delayed paragraph recall score, no dementia	Rivastigmine	508	Placebo	510	2 years	Cognitive test battery	y	y	y	y	y
								Incident AD					
Gomez-Isla[44]	J. Uriach y Compania S.A.	SuMC, MMSE >23, recall test > 1.5 SD below expected & no dementia	Triflusal	129	Placebo	128	13 months	ADAS-Cog	n	y	y	y	n
Jean[53]	Gov (Canada) & Alzheimer society	aMCI*	2 × weekly individual errorless learning sessions	11	Errorful learning and psycho-education	11	3 weeks	Episodic & semantic recall	n	y	n	y	y
Kinsella[20]	Alzheimer's Australia, Hospital & University grant	aMCI*	Five, weekly 1.5-hour family memory strategy interventions	22	Waitlist	22	5 weeks	Prospective memory	n	y	n	y	n
Li[28]	Not stated	MCI*; aged 60–80 SuMC, GDS level 2–3 or CDR 0·5; no ADL imp; MMSE 24–27	3 Huannao Yicong capsules 3× daily	31	Placebo (hydergin)	31	2 months	Cognitive effect Index	n	n	n	n	n
Nagaraja[23]	Gov (India) Serdia Pharmaceuticals	SuMC, no dementia, aged 60+ and MMSE 21–25	Piribedil 50mg od	30	Placebo	30	3 months	MMSE (responder)	n	y	y	y	y
Newhouse[21]	Gov (USA), Pfizer	aMCI*, non-smoker	15mg/day nicotine patch	39	Placebo	35	6 months	CPT	y	y	y	y	y
								MCI-CGIC					
Petersen[45]	Eisai, Pfizer Gov body (USA)	age 55–90; aMCI*, CDR 0·5; MMSE 24–30; memory recall 1·5–2·0 sd below norm	donepezil titrated to 10mg	257	Placebo	259	3 years	Incident AD	y	y	y	y	n
			2000IU vitamin E	253									
Salloway[48]	Eisai, Pfizer	Aged 55–90, SuMC, MMSE 24+, CDR 0·5	Donepezil titrated to 10mg	133	Placebo	137	24 weeks	NYPDRT	n	y	y	y	y
								MCI-CGIC					

Study	Support sources	Inclusion criteria	Treatment	n	Control	n	Duration	Primary outcome	Validity***				
									1	2	3	4	5
Thal[49]	Merck Research Laboratories	age 65+, SuMC, MMSE>23, CDR=0·5, BDRS<3.5, AVLT<38	Rofecoxib 25mg od	129	Placebo	128	<4 years	Incident AD	y	y	y	y	y
Unverzagt[14]	Gov (USA)	AVLT 1.5 SD below predicted score, no dementia	10 × 1 hour group: memory training	49	No treatment	52	6 weeks, booster at 11 months	Memory, reasoning and speed composite Measures[1]	n	y	n	y	n
			Reasoning training	39									
			Speed training	53									
van Uffelen[38;54]	(Viatris; Gov, (Netherlands)	MCI*	folic acid (5mg), vitamins B12 (0·4mg) & B6 (50mg)	78	Placebo	74	1 year	AVLT 1–5 words	y	y	y	y	y
			2×weekly, group walking	77	activities	75		AVLT 6 words					
Winblad[51]	Janssen-Cilag Johnson&Johnson	CDR=0·5, memory score > 0·5; age 50+	Galantamine 16–24mg od	494	Placebo	496	2 years	Incident dementia	y	y	y	y	y
				532		526							
Zhao[25]	Gov (China)	60–85, SMC, aMCI *	Ginkgo biloba	60	Usual treatment	60	6 months	Memory test	y	n	n	y	y
								NPR					

[1] Composite outcome measures tested: memory [mean Rey Auditory Verbal Learning Test, Hopkins Verbal learning Test, and Rivermead Behavioral Memory Test z-scores], reasoning [mean Letter Series, Letter Sets, and Word Series tests], and processing speed [mean Useful Field of View task scores].

* diagnosed according to Petersen criteria;

** defined by International working group guidelines;

*** see method – numbers refer to questions asked about validity;

AD= Alzheimer's disease; ADASCog =Alzheimer's Disease Assessment Scale-cognitive subscale; aMCI=amnestic mild cognitive impairment; AVLT = Rey Auditory Verbal Learning Test; BDRS=Blessed dementia rating score ; CDR-SB= clinical dementia rating stage (sum of boxes); ChEI= cholinesterase inhibitors; CIBIC= Clinician's Interview-Based Impression of Change; CPT=Connors continuous performance test (reaction time standard error change/interstimulus intervals) ; DHA= docosahexaenoic acid; EPA=eicosapentanoic acid; GDS= Global deterioration scale; Gov = National government supported funding source; MCI= Mild Cognitive impairment; MMSE=Mini Mental State Examination;NCCAM= National Center for Complementary and Alternative Medicine; NPR=nonsense picture recognition; NYPDRT=New York University Paragraph Delayed Recall test ; RBANS= Repeatable Battery for Assessment of Cognitive Status; SD=Standard deviation; SuMC=Subjective memory complaint

Table 2

Characteristics and validity of studies that do not specify one or two primary efficacy outcomes meeting inclusion criteria for this review, with number of outcomes and significant results

Study (support source)	Inclusion criteria	Treatment	n	Control	n	Duration	Measures on which control and intervention groups differed significantly; post-intervention mean (sd) and statistical comparisons				Validity (answers to questions 1–5 in method)				
								Intervention	Control		1	2	3	4	5
Baker[17] (Gov, USA)	aMCI*; sedentary adults	1 hour, individual, high intensity aerobic exercise, 4 days a week	23	Stretching control	19	6 months	DSST	n/a	n/a	F=4·18; P=·05	n	y	n	y	n
							Verbal fluency	n/a	n/a	F=4·87; P=·04					
							Trail making test B	n/a	n/a	F=4.58; P=.04					
Busse[26] (not stated)	MCI*; sedentary adults	1 hour, twice a week of resistance training	14	No treatment	17	9 months	Rivermead memory behavioural test	18.9	15.33	ANOVA (group/time): p=0.021	y	n	y	y	n
$De Jager[30](Gov, UK; Charities)	Aged 70+; MCI*	0·8mg folic acid, 0·5mg vitamin B12 and 20mg vitamin B6	110	Placebo	113	2 years	CDT correctly performed	Low H[1]: 13.5(1.7) High H: 12.6(1.9)	Low H: 13.0(1.7) High H: 12.3(2.4)	OR=1·3, p=0·015	y	y	y	y	n
Ferris[52] (Forest research institute)	Aged 50–79; MMSE 27+; AAMI diagnosis**	Memantine 20mg	30	placebo	30	3 months	Cogscreen symbol digit accuracy	n/a	n/a	F=2.86, 0.05	y	y	y	y	y
Finn[55] (LumosityInc.)	Aged 60+; MCI diagnosis, MMSE<24	30 computerised cognitive training sessions, each with 4–5 exercises	12	Waitlist	13	8 weeks	Visual sustained attention (CANTAB)	0.90 (0.05)	0.79 (0.13)	F=11·95, p=0·004	y	y	n	y	n
Forlenza[59](Gov, Brazil; Charities)	aged 60+; Mayo clinic aMCI criteria	Lithium	21	Placebo	20	1 year					n	y	n	y	n
Fu[36] (Peking University; Gov, China)	MCI*, MMSE 24–27; no ChEI	Wuzi Yanzong granules 4·5g sachet as a drink, twice a day	18	Placebo	18	3 months	Memory quotient	15·83 (17·54)	5·17 (13·5)	p<0·05	n	y	y	y	n
Koontz[22](Janssen)	MCI*, MMSE >25	Galantamine titrated to 12mg bd	8	Placebo	11	16 weeks	Problem solving (CANTAB)	8·3 (1·89)	7·0 (1·41)	p=0·023	n	y	n	y	n
							Pattern recognition memory	2449 (807)	2239(690)	p=0·001					
Krikorian[32](Welch food)	SuMC & CDR “mild”	grape juice 444–621ml/d	5	Placebo	7	12 weeks	CVLT	38.6	33.2	F= 5·55; P=0·04	n	y	y	y	n
Luijpen[39](Gov, Netherland)	MCI*, living in care home	TENS 30 minutes a day 5 days a week for 6 weeks	17	Placebo	17	6 weeks	GDS	7.35 (3.22)	11.82 (6.79)	F= 4·35 p= 0·02	y	y	y	y	n
							GARS	39.35 (10.14)	45.41 (13.71)	F=3·90, p=0·03					
Mowla[43](none stated)	MCI* and HDS <10	Fluoxetine titrated to 20mg	23	Placebo	21	8 weeks	MMSE	27.0 (1.5)	24.1 ±1.5	MWU, p=0.003	n	y	n	y	n
							Immediate memory (WMS)	10.8(4.9)	7.62 (4.7)	MWU p=0.015					
							Delayed memory (WMS)	9.28(5.1)	5.95(4.3)	MWU p=0.008					
Park[33] (LG)	aged 40–75; GLDS 2/3; MMSE 21–26; SuMC	green tea extract and L-theanine	45	Placebo	46	16 weeks					n	y	y	y	n

Study (support source)	Inclusion criteria	Treatment	n	Control	n	Duration	Measures on which control and intervention groups differed significantly; post-intervention mean (sd) and statistical comparisons				Validity (answers to questions 1–5 in method)				
								Intervention	Control		1	2	3	4	5
Pelton[27]	Aged 50+, depression or memory clinic out-patients; SuMC, NPT >1SD below normal; MMSE>19; no ADL impairment	Antidepressant + donepezil	12	Antidepressant + placebo	9	12 weeks	Buschke Selective Reminding Test immediate recall	37.8 (10.9)	39.0 (12.0)	ANOVA: F=3.0, p=0.05	y	y	y	y	n
Rapp[46](none stated)	MCI*	6, weekly 2 hour groups, psycho-education, memory skills & homework	9	Given manual	10	6 weeks					n	y	n	y	n
Rondanelli[40](none stated)	MCI*, MMSE 24+	Nutritional supplement (see text)	11	Placebo	14	12 weeks	MMSE	−2·07[c]	1·01[c]	p=0·0011	y	y	y	y	n
Rozzini[47] (not stated)	Aged 63–78, MCI*, living independently, GDS<5	Neuropsychological training + ChEI	15	ChEI	22	9 months	Short story recall	11.0 (3.5)	8.3 (3.5)	t=2·3, p=0·03	n	y	n	y	n
		ChEI	22	No treatment											
Scherder[41] (Gov, Netherlands)	MCI* and abbreviated MMSE score of 7+	Half hour assisted walk, 3× a day/6 weeks	15	Half had additional social visit	15	6 weeks	category fluency	24.80 (11.37)	20.27 (9.51)	F=5·02; p=0·02	n	y	n	y	n
		hand and face exercises, same duration	13				category fluency	25.69 (8.14)	20.27 (9.51)	F=3·27; p=0·04					
							Trail making	273.15 (139.85)	253.73 (150.03)	F=5·03; p=0·02					
Sinn[34] (Gov, Australia; Novasel)	MMSE 22+, SuMC, normal daily functioning	EPA-rich fish oil	17	Vegetable oil	15	6 months	GDS	n/a	n/a	LMM: t=2·2, p=0·04	n	y	y	y	n
		DHA-rich fish oil	18					n/a	n/a	LMM: t=2·6, p<0·01					
							Letter fluency	n/a	n/a	LMM: t=2·1, p=0·04					
Suzuki[42] (Gov, Japan)	Aged 65+, aMCI*	multicomponent exercise group 90mins, 2days/week	25	Educational group	25	1 year	MMSE	n/a	n/a	LMM: F=3.4, p=0.04	y	n	y	y	n
							WMS-LM I	n/a	n/a	LMM: F=3.9, p=0.03					
							Verbal fluency	n/a	n/a	LMM: F=4.1, p=0.02					
Tian[37] (Gov, China)	MCI*, SuMC, age 45–70 CDR <1; MMSE 25+	Ginseng	30	Placebo	15	12 weeks	Cognitive score	5.3[c]	6.2[c]	p<0·05	n	n	n	n	n
							Verbal subscale	18·6[c]	−6·0[c]	p<0·05					
Troyer[24] **	aMCI*	10× 2 hour relaxation and memory strategy groups	24	Waitlist	24	6 months					n	n	y	n	n
Pelton[27] (Gov, USA; Pfizer, Inc. & Esai, Inc.)	aMCI*	10× 2 hour relaxation and memory strategy groups	24	Waitlist	24	6 months					n	n	y	n	n
Zhou[50] (Gov, China)	MCI*; SuMC, MMSE 24–27, aged < 80, HDS<18	Shenyin oral liquid 10ml bd	42	Placebo	37	1 year	CDT	1·25 (1·13)	0·26 (1·1)	p<0·001	n	n	n	y	n
							Picture recognition	5.15 (4·7)	0·63 (5·0)	p<0·05					

Study (support source)	Inclusion criteria	Treatment	n	Control	n	Duration	Measures on which control and intervention groups differed significantly; post-intervention mean (sd) and statistical comparisons				Validity (answers to questions 1–5 in method)				
								Intervention	Control		1	2	3	4	5
		vitamin E tablets 500mg	38					3·68 (6·51)	0·63(4·99)	p<0·05					

[1]Summary statistics are given by median split of homocysteine levels; high H indicates value for those scoring above this cut point, Low H for those scoring below

[*]diagnosed according to Petersen criteria [1];

[**]Charity, Dejardins Financial & Richter Usher & Vineberg

[***]AAMI diagnosed using Crook criteria;

aMCI=amnestic mild cognitive impairment; AVLT = Rey Auditory Verbal Learning Test; C=mean change rather than mean post-intervention displayed; CANTAB=Cambridge Automated Neuropsychiatric Test Assessment Battery; CDT=Clock drawing test; ChEI= cholinesterase inhibitor; DSST=Digit Symbol Substitution Test EL= eligible for inclusion in this review; CVLT=California verbal learning test; F= MANOVA statistic; GDS=Geriatric Depression Scale; GLDS: Global deterioration scale; GARS=Groninger Activity Restriction Scale; Gov = National government supported funding source; HDS=Hamilton depression score; LG=LG Household & Health Care, Ltd LMM=Linear Mixed Model; M=Mean; MC=Mean change, baseline to follow-up; MD= Mean difference between groups at follow-up; MCI= mild cognitive impairment; MMSE=Minim mental state examination; n/a= not available; NPT= Neuropsychological testing battery; SD=Standard deviation; SuMC=Subjective memory complaint; TCPR=time to correct pattern recognition; OR = odds ratio; WMS=Wechsler Memory Scale III; WMS-LM; Logical Memory subtest of the Wechsler memory scale-revised