ClinicalEvidence

Dementia

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ABSTRACT

INTRODUCTION: Dementia is characterised by chronic, global, non-reversible deterioration in memory, executive function, and personality. Speech and motor function may also be impaired. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of treatments on cognitive symptoms of dementia (Alzheimer's, Lewy body, or vascular)? What are the effects of treatments on behavioural and psychological symptoms of dementia (Alzheimer's, Lewy body, or vascular)? We searched: Medline, Embase, The Cochrane Library, and other important databases up to July 2011 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 49 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review, we present information relating to the effectiveness and safety of the following interventions: acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine), antidepressants (clomipramine, fluoxetine, imipramine, sertraline), antipsychotics (haloperidol, olanzapine, quetiapine, risperidone), aromatherapy, benzodiazepines (diazepam, lorazepam), cognitive behavioural therapy (CBT), cognitive stimulation, exercise, ginkgo biloba, memantine, mood stabilisers (carbamazepine, sodium valproate/valproic acid), music therapy, non-steroidal anti-inflammatory drugs (NSAIDs), omega 3 (fish oil), reminiscence therapy, and statins.

QUESTIONS

INTERVENTIONS

COGNITIVE SYMPTOMS

Likely to be beneficial

Unknown effectiveness

BEHAVIOURAL AND PSYCHOLOGICAL SYMPTOMS

Likely to be beneficial

Trade off between benefits and harms

Unknown effectiveness

Key points

- Dementia is characterised by chronic, global, non-reversible deterioration in memory, executive function, and personality. Speech and motor function may also be impaired.
- Median life expectancy for people with Alzheimer's and Lewy body dementia is about 6 years after diagnosis, although many people may live far longer.
- RCTs of dementia are often not representative of all people with dementia; most are of 6 months' duration or less, not in primary care, and in people with Alzheimer's disease. Few RCTs address vascular dementia, and fewer still Lewy body dementia.
- Some cognitive symptoms of dementia may be improved by acetylcholinesterase inhibitors (donepezil, galantamine, and rivastigmine).

Acetylcholinesterase inhibitors may improve cognitive function and global function scores compared with placebo at 12 to 26 weeks in people with Alzheimer's disease. However, they may be associated with an increase in adverse effects, particularly GI symptoms (anorexia, nausea, vomiting, or diarrhoea).

- We don't know whether cognitive stimulation, music therapy, reminiscence therapy, omega 3 fish oil, statins, or NSAIDs are effective at improving cognitive outcomes in people with cognitive symptoms of dementia, as we found insufficient evidence.
- In people with cognitive symptoms, memantine may modestly improve cognitive function and global function scores in people with Alzheimer's disease over 24 to 28 weeks, and may modestly improve activities of daily living scores in people with moderate to severe Alzheimer's disease.

  Although memantine is associated with a statistically significant increase in cognition scores in some population groups, the clinical importance of some of these results is unclear.
- We found inconsistent evidence on the effects of ginkgo biloba on cognitive outcomes, which varied by the analysis performed.

  We found no evidence that ginkgo biloba improves activities of daily living outcomes, but the available evidence was weak.
- Acetylcholinesterase inhibitors may marginally improve neuropsychiatric symptoms compared with placebo in people with behavioural and psychological symptoms of dementia, but they are also associated with adverse effects.
- We don't know whether antidepressants (clomipramine, fluoxetine, imipramine, sertraline) improve depressive symptoms in people with Alzheimer's disease associated with depression.

  Many RCTs were small and short term, and adverse effects were sparsely reported.
- Memantine may be associated with a small improvement in neuropsychiatric symptoms compared with placebo in people with behavioural and psychological symptoms of dementia, but it is also associated with adverse effects.
- We don't know whether diazepam, lorazepam, aromatherapy, CBT, exercise, carbamazepine, or sodium valproate/valproic acid are effective at improving neuropsychiatric symptoms in people with behavioural and psychological symptoms of dementia, as we found insufficient evidence.
- Some antipsychotics may improve neuropsychiatric symptoms or aggression in people with behavioural and psychological symptoms of dementia, but antipsychotics are also associated with an increased risk of severe adverse events such as stroke, TIA, or death.
- CAUTION: Regulatory bodies have issued alerts that both conventional and atypical antipsychotics are associated with an increased risk of death in older people treated for dementia-related psychosis.

DEFINITION

Dementia is characterised by memory loss (initially of recent events), loss of executive function (such as the ability to make decisions or sequence complex tasks), other cognitive deficits, and changes in personality. This decline must be serious enough to affect social or occupational functioning, and reasonable attempts must be made to exclude other common conditions, such as depression and delirium. **Alzheimer's disease** is a type of dementia characterised by an insidious onset and slow deterioration, and involves impairments in memory, speech, personality, and executive function. It should be diagnosed after other systemic, psychiatric, and neurological causes of dementia have been excluded clinically and by laboratory investigation. **Vascular dementia** is often due to multiple large or small vessel disease. It often presents with a stepwise deterioration in cognitive function with or without language and motor dysfunction. It usually occurs in the presence of vascular risk factors (diabetes, hypertension, arteriosclerosis, and smoking). Characteristically, it has a more sudden onset and stepwise progression than Alzheimer's disease, and often has a patchy picture of cognitive deficits. **Lewy body dementia** is a type of dementia that involves insidious impairment of cognitive function with parkinsonism, visual hallucinations, and fluctuating cognitive abilities. Night-time disturbance is common and there is an increased risk of falls. [1] [2] Careful clinical examination of people with mild to moderate dementia and the use of established diagnostic criteria accurately identifies 70% to 90% of causes confirmed at post mortem. [3] [4] In all types of dementia, people will experience problems with cognitive functioning and are likely to experience behavioural and psychological symptoms of dementia. Where possible, we have divided outcomes into cognitive or behavioural/psychological, although there is often considerable crossover between these outcomes, both clinically and in research. This review deals solely with people with Alzheimer's disease, Lewy body dementia, or vascular dementia.

INCIDENCE/ PREVALENCE

About 6% of people aged >65 years and 30% of people aged >90 years have some form of dementia. [5] Dementia is rare before the age of 60 years. Alzheimer's disease and vascular dementia (including mixed dementia) are each estimated to account for 35% to 50% of dementia, and Lewy body dementia is estimated to account for up to 5% of dementia in older people, varying with geographical, cultural, and racial factors. [1] [5] [6] [7] [8] [9] There are numerous other causes of dementia, all relatively rare, including frontotemporal dementia, alcohol-related dementia, Hunting-

ton's disease, normal pressure hydrocephalus, HIV infection, syphilis, subdural haematoma, and some cerebral tumours.

AETIOLOGY/ RISK FACTORS

Alzheimer's disease: The cause of Alzheimer's disease is unclear. A key pathological process is deposition of abnormal amyloid in the central nervous system. [10] Another early change is abnormal phosphorylation of tau, an intracellular structural protein. This results in apoptosis and neurofibrillary tangles. Disease-modifying agents in development target both processes. Most people with the relatively rare condition of early-onset Alzheimer's disease (before age 60 years) exhibit an autosomal-dominant inheritance due to mutations in presenilin or amyloid precursor protein genes. Several gene mutations (on *APP, PS-1*, and *PS-2* genes) have been identified. Later-onset dementia is sometimes clustered in families, but specific gene mutations have not been identified. Down's syndrome, cardiovascular risks, and lower premorbid intellect may be risk factors for Alzheimer's disease. Alzheimer's disease and vascular pathology frequently co-exist. **Vascular dementia:** Vascular dementia is related to cardiovascular risk factors, such as smoking, arteriosclerosis, hypertension, and diabetes. **Lewy body dementia:** Lewy body dementia is characterised by the presence of Lewy bodies (abnormal intracellular inclusions consisting of alpha-synuclein) in the cortex. Brain acetylcholine activity is reduced in many forms of dementia, and the level of reduction correlates with cognitive impairment. [1] [6]

PROGNOSIS

Alzheimer's disease: Alzheimer's disease usually has an insidious onset with progressive reduction in cerebral function. Diagnosis is difficult in the early stages. Median life expectancy after diagnosis is about 6 years, although many people live far longer. [11] **Vascular dementia:** We found no reliable data on prognosis. **Lewy body dementia:** People with Lewy body dementia have an average life expectancy of about 6 years after diagnosis. [5] Behavioural problems, depression, and psychotic symptoms are common in all types of dementia. [12] [13] Eventually, most people with dementia find it difficult to perform simple tasks without help.

AIMS OF INTERVENTION

To improve cognitive function (memory, orientation, attention, and concentration); to reduce behavioural and psychological symptoms (wandering, aggression, anxiety, depression, and psychosis); to improve quality of life for both the individual and carer, with minimum adverse effects.

OUTCOMES

Primary outcomes are quality of life, time to institutionalisation or death, scales of cognitive function, global assessment of function, functional scores, and behavioural and psychological symptoms. **Cognitive symptoms and global assessment of function:** Comprehensive scales of cognitive function (e.g., Alzheimer's Disease Assessment Scale cognitive subscale [ADAS-cog]: 70-point scale, lower scores indicate better function; [14] Mini Mental State Examination [MMSE]: 30-point scale, lower scores indicate worse function; [15] Clinical Dementia Rating Scale [CDR]: 5-point scale assessing 6 cognitive and functional parameters, higher scores indicate worse function; [16] Alzheimer's Disease Functional Assessment and Change Scale [ADFACS]: 7-point scale, higher scores indicate worse function; [16] and Severe Impairment Battery: 100-point scale used in people with severe Alzheimer's disease, lower scores indicate worse function). [17] It has been suggested that ADAS-cog may be more sensitive than MMSE in assessing dementia, but neither scale directly reflects outcomes important to people with dementia or their carers. Most clinical trials in mild to moderate dementia use the ADAS-cog as the primary outcome for cognition. The ADAS-cog is a 70-point scale; a 2- or 3-point change on this scale is likely to represent only a marginal clinical significance, although the large studies undertaken in dementia have sufficient power to find highly statistically significant differences in what amounts to minimal clinical change. Measures of global state include Clinical Global Impression of Change (CGI-C) with carer input scale and Clinician's Interview Based Impression of Change-Plus (CIBIC-Plus), which provides a rating using a 7-point scale. Gottfries–Brane–Steen (GBS) is a global assessment tool for evaluating dementia symptoms (score ranges from 0 to 156; higher scores indicate worse function). **Functional scores:** These include the Disability Assessment for Dementia (DAD), a 40-item scale assessing 10 domains of function, [18] and the Instrumental Activities of Daily Living Scale, maximum score 14 (lower scores indicate worse function). [19] **Behavioural and psychological symptoms:** Measures of psychiatric symptoms (e.g., Neuropsychiatric Inventory [NPI]: 120-point scale, higher scores indicate greater difficulties; 12-item carer-rated scale: maximum score 144, higher scores indicate greater difficulties; Dementia Mood Assessment Scale and Brief Psychiatric Rating Scale: higher scores indicate greater difficulties; Behavioral Pathology in Alzheimer's Disease Rating (BEHAVE-AD) scale: scores 0–75, higher scores indicate greater difficulties; Behavioural Rating Scale for Geriatric Patients: scale rating 35 aspects of behaviour, score from 0 to 2, higher score indicates worse function). **Quality of life** of the person with dementia or their carer (rarely used in clinical trials). Quality of life and **time to institutionalisation or death** are rarely reported because of the short duration of most trials. [16]

METHODS *Clinical Evidence* search and appraisal July 2011. The following databases were used to identify studies for this systematic review: Medline 1966 to July 2011, Embase 1980 to July 2011, and The Cochrane Database of Systematic Reviews, Issue 2, 2011 (1966 to date of issue). An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs and RCTs in any language, at least single blinded (unless blinding was not possible), and containing 50 or more individuals of whom 80% or more were followed up. Minimum length of follow-up was 12 weeks for drug trials and 6 weeks otherwise to include studies. We excluded all studies described as "open", "open label", or not blinded unless blinding was impossible. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. In addition we did an observational harms search for specific harms as highlighted by the contributor, peer reviewer, and editor. We searched for prospective or retrospective cohort studies (with or without a control group). In addition we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. **Symptom reporting:** Dementia is often considered to have two domains of symptoms: cognitive impairment and non-cognitive symptoms (behavioural and psychological symptoms). We have separated the evidence into these two domains because they are often therapeutic targets at different stages of dementia, and many RCTs focus on one or other domain of symptoms. **Quality issues relating to included RCTs:** In many RCTs, missing data were managed using "last observation carried forward", which does not account for the tendency of people with dementia to deteriorate with time. These RCTs may overestimate the benefit derived from interventions, especially when there are higher withdrawal rates in the intervention arm compared with controls. We found few RCTs in people with types of dementia other than Alzheimer's disease. The authors assessed studies on an individual basis to identify studies that were of sufficient methodological rigour and not subject to obvious bias. Not all systematic reviews identified were reported in each option. For each option, the authors selected the most recent and methodologically sound review and reported this in detail. Older reviews that were superseded by later reviews, or that did not add any further important data above that already presented in included reviews, were not reported. Where a systematic review was included in an option, subsequent RCTs were reported sparingly. **Limitations to generalisability of included RCTs:** Participants in RCTs of treatments for dementia are often not representative of all people with dementia. Few RCTs are conducted in primary care and few are conducted in people with types of dementia other than Alzheimer's disease. Most RCTs are 6 months or less in duration, compared with a disease duration of many years, and most are conducted in mild to moderate dementia. Attrition and methodological difficulties often preclude longer trials in this patient group. This review reports placebo-controlled comparisons. **General reporting:** To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 26). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the *Clinical Evidence* population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **What are the effects of treatments on cognitive symptoms of dementia (Alzheimer's, Lewy body, or vascular)?**

OPTION **ACETYLCHOLINESTERASE INHIBITORS (DONEPEZIL, GALANTAMINE, RIVASTIGMINE) VERSUS PLACEBO IN PEOPLE WITH COGNITIVE SYMPTOMS OF DEMENTIA**

Cognitive symptoms and function (cognitive scores, global scores, activities of daily living scores)
Compared with placebo in people with Alzheimer's disease Acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine) may be more effective at improving cognitive function scores and global function scores in people with Alzheimer's disease (low-quality evidence).

Compared with placebo in people with vascular dementia Acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine) may be marginally more effective at improving cognitive function scores at 6 months in people with vascular dementia, but not global function scores or activities of daily living scores (very low-quality evidence).

Compared with placebo in people with Lewy body dementia We don't know whether rivastigmine is more effective at improving cognitive function scores, global function scores, or activities of daily living scores in people with Lewy body dementia (very low-quality evidence).

Note
Acetylcholinesterase inhibitors may be associated with adverse effects, including GI adverse effects (e.g., nausea, vomiting, diarrhoea, anorexia).

For GRADE evaluation of interventions for dementia, **see table, p 26** .

Benefits:

Acetylcholinesterase inhibitors versus placebo in people with Alzheimer's disease:
We found one systematic review comparing acetylcholinesterase inhibitors as a group versus placebo; [20] one systematic review comparing the acetylcholinesterase inhibitors donepezil, galantamine, and rivastigmine individually versus placebo; [21] one systematic review of rivastigmine versus placebo; [22] and one subsequent RCT comparing galantamine versus placebo. [23] There was widespread overlap of RCTs between the reviews.

The first review (search date 2005; 13 multicentre double-blind RCTs; people with mild, moderate, or severe Alzheimer's disease) included RCTs in which treatment had been given for 6 months or longer, and at the dose recommended as optimal by the manufacturing pharmaceutical company. [20] It performed an intention-to-treat analysis, and where full data were not available, it performed an analysis with the last observation carried forward (LOCF). The review found that people leaving before the end of studies ranged from 16% to 43% in the treatment group and 0% to 30% in the placebo group. The review found that acetylcholinesterase inhibitors significantly improved cognitive outcomes compared with placebo at 6 months or later (Alzheimer's Disease Assessment Scale cognitive subscale [ADAS-cog]: 10 RCTs, 4236 people; WMD –2.4, 95% CI –2.7 to –2.0; Mini Mental State Examination [MMSE]: 9 RCTs, 3118 people; WMD 1.4, 95% CI 1.1 to 1.6). [20] There was significant heterogeneity among RCTs included in both analyses. The review reported that in one analysis (MMSE), this resulted from one RCT (466 people) that found a larger treatment effect than other RCTs. It also found that acetylcholinesterase inhibitors significantly improved global assessment compared with placebo at 6 months (Clinician's Interview-Based Impression of Change-Plus [CIBIC-Plus] scale; number of people improved: 8 RCTs; 428/1755 [24%] with acetylcholinesterase inhibitor *v* 277/1647 [17%] with placebo; OR 1.6, 95% CI 1.3 to 1.9). The review found that acetylcholinesterase inhibitors significantly improved activities of daily living scores compared with placebo at 6 months or later (Progressive Deterioration Scale [scale 0–100]: 5 RCTs [donepezil, rivastigmine], 2188 people; WMD 2.4, 95% CI 1.6 to 3.3; Disability Assessment for Dementia [DAD] scale: 2 RCTs [donepezil, galantamine], 669 people; WMD 4.4, 95% CI 2.0 to 6.8). The review did not provide a subgroup analysis by individual agent versus placebo (see comment below). [20]

The second review (search date 2007; 22 RCTs in people with mild, moderate, or severe Alzheimer's disease) included RCTs of least 12 weeks' duration. [21] It performed an intention-to-treat analysis where data were available. The review found that donepezil, galantamine, and rivastigmine significantly improved cognitive outcomes compared with placebo (ADAS-cog: rivastigmine 6–12 mg: 2 RCTs; WMD –3.1, 95% CI –3.80 to –2.21; donepezil 5 mg or 10 mg: 5 RCTs; WMD –2.67, 95% CI –3.28 to –2.06; galantamine 16–32 mg: 7 RCTs; WMD –2.76, 95% CI –3.17 to –2.34; numbers of people not reported for any of the pooled analyses). [21]

The review also found that donepezil, galantamine, and rivastigmine significantly improved functional outcomes compared with placebo (SMD in functional outcome change from baseline: donepezil 5 mg or 10 mg: 7 RCTs; SMD 0.31, 95% CI 0.21 to 0.40; galantamine 16–32 mg: 4 RCTs; SMD 0.27, 95% CI 0.18 to 0.36; rivastigmine 6–12 mg: 3 RCTs; SMD 0.26, 95% CI 0.11 to 0.40; numbers of people not reported for any of the pooled analyses). [21] There was significant heterogeneity among RCTs included in the rivastigmine comparison.

The review found that rivastigmine and donepezil significantly improved global assessment of change scores compared with placebo at 3 to 6 months (CIBIC-Plus scale: donepezil 5 mg or 10 mg: 3 RCTs; RR 1.88, 95% CI 1.50 to 2.34; rivastigmine 6 mg or 12 mg: 2 RCTs; RR 1.64, 95% CI 1.29 to 2.09), but that galantamine did not significantly improve CIBIC-Plus scores (galantamine 16–32 mg: 4 RCTs; RR 1.15, 95% CI 0.96 to 1.39; numbers of people not reported for any of the pooled analyses). [21]

The review (search sate 2008) of rivastigmine [22] in people with Alzheimer's disease (LOCF analysis for all randomised participants who had at least 1 measurement and an observed cases [OC] analysis for all randomised participants who had an assessment on treatment at the designated times) found that rivastigmine significantly improved cognition scores versus placebo between 18 and 52 weeks. We report data at 26 weeks here (ADAS-cog: rivastigmine 1–4 mg: 3 RCTs, 1293

people; WMD –0.84, 95% CI –1.48 to –0.19; P = 0.011; rivastigmine 6–12 mg: 5 RCTs, 2451 people; WMD –1.99, 95% CI –2.49 to –1.50; P <0.0001). [22] The review found that rivastigmine significantly improved MMSE scores at 26 to 52 weeks compared with placebo (MMSE change from baseline, 26 weeks: rivastigmine 1–4 mg: 1297 people, 3 RCTs; WMD 0.43, 95% CI 0.08 to 0.78; P = 0.015; rivastigmine 6–12 mg: 4 RCTs, 2458 people; WMD 0.82, 95% CI 0.56 to 1.08; P <0.0001). The review also reported significant heterogeneity between trials.

We found one subsequent RCT comparing galantamine (8–24 mg; 87% of people in the galantamine group received 24 mg/day) versus placebo for 6 months in people with severe Alzheimer's disease (407 people with MMSE 5–12; multicentre trial). [23] The main outcome measures were the Self-Impairment Battery (SIB) and composite 7-item Minimum Data Set Activities of Daily Living (MDS-ADL) self-performance scale. The RCT found that galantamine significantly improved SIB scores compared with placebo (completer analysis; 311/407 [76%] people; between-group mean difference 4.36, 95% CI 1.3 to 7.5; P = 0.006; LOCF analysis, 364/407 [89%] people; between-group mean difference 5.02, 95% CI 2.17 to 7.86; P = 0.0006). However, the RCT found no significant difference between groups in MDS-ADL self-performance scale (LOCF analysis; between-group mean difference –0.50, 95% CI –1.39 to +0.39, P = 0.394). [23]

Acetylcholinesterase inhibitors versus placebo in people with vascular dementia:
We found one systematic review [24] and three subsequent RCTs. [25] [26] [27]

The review (search date 2006, 6 RCTs, vascular dementia of mild–moderate severity; 24–28 weeks' duration) included both published and unpublished RCTs and pooled data by individual agents, rather than by acetylcholinesterase inhibitors as a group. [24] One RCT of galantamine also included people with Alzheimer's and vascular disease, from which subgroup data for those people with vascular dementia were extracted. Reporting of allocation concealment and randomisation method varied among RCTs, and some were of poor quality. It found that donepezil, galantamine, and rivastigmine all significantly improved cognition scores compared with placebo (ADAS-cog: donepezil 10 mg: 2 RCTs, 763 people; WMD –2.2, 95% CI –3.0 to –1.4; galantamine 24 mg: 2 RCTs, 966 people; WMD –1.6, 95% CI –2.4 to –0.8; rivastigmine 12 mg: 1 RCT, 368 people; WMD –1.10, 95% CI –2.15 to –0.05). [24] However, it found no significant difference between groups in global outcomes (CIBIC-Plus or Clinical Global Impression of Change [CGI-C; improvement or no change]: donepezil 10 mg: 2 RCTs, 785 people; OR 1.2, 95% CI 0.9 to 1.6; galantamine 24 mg: 2 RCTs, 943 people; OR 1.1, 95% CI 0.8 to 1.42; rivastigmine 12 mg: 1 RCT, 649 people; OR 1.0, 95% CI 0.8 to 1.4). It found that donepezil 10 mg significantly improved activities of daily living scores compared with placebo, but not donepezil 5 mg (Alzheimer's Disease Functional Assessment and Change Scale [ADFACS]: donepezil 10 mg: –0.95, 95% CI –1.74 to +0.16; donepezil 5 mg: –0.73, 95% CI –1.53 to +0.07; no further details reported). It also found no significant difference between groups in activities of daily living scores for galantamine or rivastigmine (Alzheimer's Disease Co-operative Study-Activities of Daily Living [ADCS-ADL]/DAD: galantamine: –0.04, 95% CI –0.27 to +0.20; ADCS-ADL: rivastigmine: –0.05, 95% CI –0.20 to +0.09; no further details reported). [24] The review concluded that the acetylcholinesterase inhibitors produced small benefits in cognition of uncertain clinical significance and that more specific patient-level information was needed on treatment responses across different types and severities of vascular dementia.

The first subsequent RCT [25] (974 people with probable and possible vascular dementia, LOCF analysis) compared donepezil 5 mg versus placebo (2:1 ratio) for 24 weeks. It found that donepezil significantly improved Vascular-Alzheimer's Disease Assessment Scale cognitive subscale scores (V-ADAS-cog) at 24 weeks (between-group mean difference –0.707, 95% CI –1.40 to –0.02; P = 0.046) and MMSE scores (mean difference 0.472, 95% CI 0.05 to 0.89; P = 0.03) compared with placebo. The RCT found no significant difference between groups in CIBIC-Plus scores at 24 weeks (LOCF analysis; P = 0.23). [25]

The second subsequent RCT [26] compared galantamine 24 mg daily versus placebo for 6 months in 285 people with Alzheimer's disease with cerebrovascular disease. In total, 239/285 (84%) people completed treatment and were included in the completer analysis. The RCT found that galantamine improved cognitive abilities compared with placebo as measured by ADAS-cog (proportion of people whose scores improved by at least 4: 51/152 [34%] with galantamine *v* 15/87 [17%] with placebo; P = 0.003) and CIBIC-Plus (proportion of people stable or improved: 116/155 [75%] with galantamine *v* 45/84 [54%] with placebo; P = 0.0006).

The third subsequent RCT [27] compared rivastigmine (3–12 mg/day, mean 9.6 mg) versus placebo in 710 people with probable vascular dementia for 24 weeks. In total, 572/710 (81%) people completed treatment. The RCT found that rivastigmine improved Vascular Dementia Assessment Scale (VaDAS) scores at 24 weeks compared with placebo (intention-to-treat analysis for all results, mean between-group difference –1.3; P = 0.028; CI not reported), and MMSE scores (mean between-group difference 0.6; P = 0.007; CI not reported). However, the RCT found that rivastigmine

did not improve global functioning (ADCS-CGIC) scores (mean between-group difference 0.1; reported as not significant) or activities of daily living (ADCS-ADL) scores (between-group mean difference 0.6; reported as not significant).

Acetylcholinesterase inhibitors versus placebo in people with Lewy body dementia:
We found one systematic review (search date 2006), which found one RCT (120 people) comparing rivastigmine versus placebo for 20 weeks. [28] The review found that rivastigmine significantly improved activities of daily living scores compared with placebo (activities of daily living, power of attention: 83 people in analysis; SMD –0.52, 95% CI –0.96 to –0.08). It found no significant difference between groups in cognitive outcomes or global functioning (MMSE: difference in change score favouring drug: absolute numbers not reported; P = 0.72; Clinical Global Change Scale [CGC]-Plus: good, moderate, or minimal improvement: P = 0.085; absolute numbers not reported). However, the activities of daily living analysis was based on 83/120 (69%) people, which is below the minimum follow-up of 80% for this review. [28]

Harms:

Acetylcholinesterase inhibitors versus placebo in people with Alzheimer's disease:
The first review found that acetylcholinesterase inhibitors significantly increased the proportion of people who withdrew before the end of treatment (withdrawal before the end of treatment: 13 RCTs; 778/2672 [29%] with acetylcholinesterase inhibitors *v* 453/2471 [18%] with placebo; OR 1.8, 95% CI 1.5 to 2.0; withdrawal before the end of treatment because of adverse effect: 13 RCTs; 488/2672 [18%] with acetylcholinesterase inhibitors *v* 209/2471 [8%] with placebo; OR 2.3, 95% CI 2.0 to 2.8). [20] It found that during treatment for 6 months or more, compared with placebo, acetylcholinesterase inhibitors significantly increased the proportion of people with at least one adverse effect of: abdominal pain, anorexia, diarrhoea, dizziness, fatigue, headache, insomnia, nausea, tremor, vomiting, or weight loss (abdominal pain: 7 RCTs, 2703 people; OR 2.0, 95% CI 1.5 to 2.6; anorexia: 10 RCTs, 4419 people; OR 3.8, 95% CI 2.9 to 4.9; diarrhoea: 13 RCTs, 5173 people; OR 1.9, 95% CI 1.6 to 2.3; dizziness: 12 RCTs, 4583 people; OR 2.0, 95% CI 1.6 to 2.4; fatigue: 1 RCT, 319 people; OR 4.4, 95% CI 1.2 to 15.9; headache: 9 RCTs, 3686 people; OR 1.6, 95% CI 1.3 to 1.9; insomnia: 7 RCTs, 2905 people; OR 1.5, 95% CI 1.1 to 2.0; nausea: 13 RCTs, 5089 people; OR 4.9, 95% CI 4.1 to 5.7; tremor: 2 RCTs, 633 people; OR 6.8, 95% CI 2.0 to 23.4; vomiting: 11 RCTs, 4703 people; OR 4.8, 95% CI 3.9 to 5.9; weight loss: 4 RCTs, 1358 people; OR 3.0, 95% CI 1.9 to 4.8). It found no significant difference between groups in abnormal gait, accidental injury, agitation, anxiety, arthralgia, back pain, confusion, conjunctivitis, constipation, cough, depression, ecchymosis, fever, fracture, hostility, infection, pain, rash, skin ulcer, respiratory tract infection, or urinary tract infection. [20]

The review comparing individual acetylcholinesterase inhibitors versus placebo [21] found an overall withdrawal rate of 26% (95% CI 21% to 31%) among people in the active treatment groups of the trials, approximately 50% of whom withdrew because of adverse events. For donepezil, a total of 24% of people withdrew from treatment, 11% because of adverse events. For galantamine the figures were 27% and 14%, and for rivastigmine 28% and 21%. The frequency of adverse events was lowest for donepezil and highest for rivastigmine. The pooled relative risks for withdrawal were, for donepezil: 1.1 (95% CI 0.9 to 1.3); for galantamine: 1.6 (95% CI 1.3 to 1.9); and for rivastigmine: 2.3 (95% CI 1.8 to 2.9); the relative risk for placebo was not reported. The pooled relative risks for withdrawals owing to adverse events were, for donepezil: 1.3 (95% CI 0.9 to 1.8); for galantamine: 2.0 (95% CI 1.4 to 2.8); and for rivastigmine: 3.6 (95% CI 2.6 to 5.1). The most common adverse effects reported were nausea, vomiting, diarrhoea, dizziness, and weight loss. With the exception of diarrhoea, adverse effects were proportionately lowest for donepezil and highest for rivastigmine (nausea: 11% with donepezil, 24% with galantamine, and 44% with rivastigmine; vomiting: 7% with donepezil, 14% with galantamine, and 30% with rivastigmine, respectively; dizziness: 8% with donepezil, 10% with galantamine, and 22% with rivastigmine; weight loss: 7% with donepezil, 10% with galantamine, and 11% with rivastigmine; diarrhoea: 12% with donepezil, 8% with galantamine, and 13% with rivastigmine).

The systematic review of rivastigmine [22] found that, in people taking rivastigmine 1 mg to 4 mg, the proportion withdrawing from treatment was not significantly greater than with placebo (proportion of people who withdrew: 3 RCTs; 113/644 [17.5%] with rivastigmine 1–4 mg *v* 113/646 [17.5%] with placebo; OR 1.01, 95% CI 0.75 to 1.34; P = 0.97), whereas, in people taking 6 mg to 12 mg, the withdrawal rate was significantly higher (withdrawals: 6 RCTs; 448/1458 [31%] with rivastigmine 6–12 mg *v* 194/1243 [16%] with placebo; OR 2.19, 95% CI 1.83 to 2.63; P <0.0001). At 26 weeks, frequency of adverse events was not significantly higher in people taking the lower dose of rivastigmine than in people taking placebo (total number of adverse events/number of people: 3 RCTs; 509/644 [79%] with lower-dose rivastigmine *v* 518/646 [80%] with placebo; OR 0.94, 95% CI 0.71 to 1.23; P = 0.63), but it was significantly higher in people taking the higher dose than in people taking placebo (6 RCTs; 1242/1450 [86%] with higher-dose rivastigmine *v* 901/1276 [71%] with placebo; OR 2.49, 95% CI 2.05 to 3.02; P <0.0001). A significantly greater proportion of people withdrew because of adverse events with higher-dose rivastigmine than with placebo (5 RCTs;

291/1453 [20%] with higher-dose rivastigmine *v* 94/1276 [7%] with placebo; OR 2.73, 95% CI 2.19 to 3.41; P <0.0001). The most commonly reported adverse events were nausea (586/1450 [40%] with higher-dose rivastigmine *v* 122/1276 [10%] with placebo; OR 5.36, 95% CI 4.50 to 6.40; P <0.0001; 119/644 [18%] with lower-dose rivastigmine *v* 74/646 [11%] with placebo; OR 1.74, 95% CI 1.28 to 2.36; P = 0.0004), vomiting (394/1450 [27%] with higher-dose rivastigmine *v* 63/1276 [5%] with placebo; OR 5.15, 95% CI 4.20 to 6.32; P <0.0001; 56/644 [9%] with lower-dose rivastigmine *v* 35/646 [5%] with placebo; OR 1.65, 95% CI 1.08 to 2.52; P = 0.022), dizziness (252/1346 [19%] with higher-dose rivastigmine *v* 102/1170 [9%] with placebo; OR 2.24, 95% CI 1.78 to 2.82; P <0.0001; no significant difference for lower dose *v* placebo; P = 0.17), and anorexia (5 RCTs; 182/1156 [16%] for higher-dose rivastigmine *v* 29/974 [3%] with placebo; OR 4.46, 95% CI 3.34 to 5.95; P <0.0001; 44/644 [7%] with lower-dose rivastigmine *v* 21/646 [3%] with placebo; OR 2.13, 95% CI 1.29 to 3.52; P = 0.003). Decreased appetite, nausea, vomiting, dizziness, and asthenia were significantly more common with rivastigmine capsule than with patch.

In the RCT comparing galantamine versus placebo, [23] 15% of people in the galantamine group and 16% in the placebo group withdrew from treatment because of adverse events (absolute numbers and significance assessment not reported). The most common adverse events reported were urinary tract infections, diarrhoea, nausea, and falls (urinary tract infections: 17% with galantamine *v* 22% with placebo; vomiting: 16% with galantamine *v* 15% with placebo; diarrhoea: 27% with galantamine *v* 37% with placebo; nausea: 25% with galantamine *v* 13% with placebo; falls: 24% with galantamine *v* 22% with placebo; significance not assessed for any outcome). Abnormally low heart rate was noted in 7% of people taking galantamine and in 4% of people taking placebo. Reduction in heart rate was significantly higher in the galantamine group (–2.7 beats per minute [bpm], 95% CI –4.5 bpm to –0.9 bpm) compared with the placebo group (+0.9 bpm, 95% CI –0.9 bpm to +2.7 bpm; P = 0.002 for between-group comparison). QT prolongation was reported in 4% of people in each group, and atrial fibrillation in 2% in each group. A significantly smaller proportion of people died in the galantamine group than in the placebo group (4% with galantamine *v* 11% with placebo; P = 0.012; absolute numbers not reported).

We found one systematic review reporting on mortality risk in people with Alzheimer's disease, Alzheimer's disease plus CVD, or vascular dementia treated with galantamine (search date 2006, 6502 people, 12 RCTs of up to 6 months' duration). [29] The review included several RCTs reported elsewhere in this *Clinical Evidence* review. It found an overall death rate in both groups combined of 1.1%, with no significance in mortality between groups (deaths: 37/4116 [0.9%] with galantamine *v* 33/2386 [1.4%] with placebo; OR 0.67, 95% CI 0.41 to 1.10).

Acetylcholinesterase inhibitors versus placebo in people with vascular dementia:
The review found that rates of discontinuation for adverse effects were significantly higher in the acetylcholinesterase inhibitor groups compared with placebo (donepezil 10 mg: OR 2.1, 95% CI 1.4 to 3.2; galantamine: OR 2.4, 95%, CI 1.7 to 3.5; rivastigmine: OR 2.7, 95% CI 1.5 to 4.6). [24] It reported that in one RCT, the risk of death was significantly higher with donepezil (11/678 [2%] with donepezil *v* 0/326 [0%] with placebo; OR 4.6, 95% CI 1.3 to 16.1). After pooling data from all three RCTs of donepezil, the review found no significant difference between groups in death (OR 1.4, 95% CI 0.7 to 3.0). The RCTs were heterogeneous for this outcome, possibly because of a high death rate (3.5%) in the placebo arm of one RCT. [24] The review found that adverse effects were inconsistently reported and numbers were low, although the acetylcholinesterase inhibitors were broadly associated with a significantly increased risk of GI events (such as nausea, vomiting, diarrhoea, and anorexia). [24]

One subsequent RCT assessing donepezil [25] reported that 113/648 (17%) people withdrew from treatment in the donepezil group compared with 43/326 (13%) in the placebo group, and that withdrawals because of adverse events were 71/648 (11%) people with donepezil and 18/326 (6%) with placebo. The trial reported a similar incidence of overall adverse effects between groups (81% with donepezil *v* 78% with placebo). Commonly reported adverse effects included nausea, anorexia, abdominal pain, diarrhoea, abnormal dreams, hypertonia, and leg cramps, with most transient and mild to moderate in severity. Among adverse events assessed as probably/possibly related to the study drug, diarrhoea and nausea were more common with donepezil than with placebo (diarrhoea: 8% with donepezil *v* 3% with placebo; nausea: 7% with donepezil *v* 2% with placebo; absolute numbers not reported). The RCT found no significant difference between groups in the proportion of people with at least one serious adverse event (7% with donepezil *v* 6% with placebo; P = 0.77), and no clinically meaningful changes in blood pressure or ECG in either group. Eleven people in the donepezil group and no people in the placebo group died during the trial, with 3/11 (27%) deaths in the donepezil group assessed as possibly related to donepezil. [25]

One subsequent RCT assessing galantamine [26] reported that 13% of people taking galantamine and 5% of people taking placebo withdrew from treatment, most because of adverse events. The most commonly reported adverse events were nausea, vomiting, and dizziness (nausea: 20% with

galantamine *v* 10% with placebo; vomiting: 12% with galantamine *v* 5% with placebo; dizziness: 12% with galantamine *v* 7% with placebo; absolute numbers not reported; significance not assessed). Most adverse events were of mild to moderate severity. Death rate was similar in both groups. Two people taking galantamine and one person taking placebo died. [26]

One subsequent RCT [27] assessing rivastigmine reported that 8/365 (2%) people randomised died in the rivastigmine group compared with 4/345 (1%) in the placebo group. In total, 90/365 (25%) people withdrew from treatment with rivastigmine compared with 48/345 (14%) with placebo. Withdrawals because of adverse effects were 49/365 (13%) with rivastigmine compared with 19/345 (6%) with placebo. The most commonly reported adverse effects were nausea (96/363 [26%] with rivastigmine *v* 13/344 [4%] with placebo), vomiting (80/363 [22%] with rivastigmine v 8/344 [2%] with placebo), diarrhoea (33/363 [9%] with rivastigmine *v* 17/344 [4%] with placebo), dizziness (29/363 [8%] with rivastigmine *v* 17/344 [5%] with placebo), falls (24/363 [7%] with rivastigmine *v* 17/344 [5%] with placebo), hypertension (20/363 [6%] with rivastigmine *v* 10/344 [3%] with placebo), headache (19/363 [5%] with rivastigmine *v* 10/344 [3%] with placebo), and anorexia (19/363 [5%] with rivastigmine *v* 6/344 [2%] with placebo). On ECG, people in the rivastigmine group showed a decrease in ventricular rate of –1.4 bpm compared with an increase of 1.1 bpm in the placebo group. Both groups showed slight increases in QT intervals for heart rate. Mean weight reduction was 1.0 kg with rivastigmine and 0.2 kg with placebo.

Acetylcholinesterase inhibitors versus placebo in people with Lewy body dementia:
The review found that rivastigmine significantly increased the risk of any adverse event compared with placebo (120 people; NNH 7, 95% CI 4 to 34). [28]

Comment: The meta-analyses were quite restrictive in study selection; the authors of the systematic reviews raise concerns about the quality and reporting of many trials. The overall effect size of <3 points on the ADAS-cog is barely clinically significant, although this represents an average, and some people derive significant clinical benefit. More studies are needed on people with vascular and Lewy body dementia.

OPTION GINKGO BILOBA VERSUS PLACEBO IN PEOPLE WITH COGNITIVE SYMPTOMS OF DEMENTIA

Cognitive symptoms and function (cognitive scores, global scores, activities of daily living scores)
Compared with placebo We don't know whether ginkgo biloba is more effective at improving cognitive function scores or global function scores at 22 to 28 weeks in people with Alzheimer's disease and multiple infarct dementia, as results were inconsistent, varied by the exact analysis performed, and evidence was weak. Ginkgo biloba may be no more effective than placebo at improving activities of daily living scores (very low-quality evidence).

For GRADE evaluation of interventions for dementia, see table, p 26 .

Benefits:

Ginkgo biloba versus placebo:
We found three systematic reviews. [30] [31] [32] The first two reviews [30] [31] included RCTs in any type of dementia or mild cognitive impairment, while the third review [32] included RCTs in people with Alzheimer's disease. There was an overlap of included RCTs between reviews — the first review [30] included almost all the RCTs reported by the other two. [31] [32] The third review did not conduct a meta-analysis owing to heterogeneity among RCTs (see comment). [32]

The first review (search date 2007) [30] included RCTs in which any strength of ginkgo biloba was used (dose varied from 80 mg to 600 mg), and of any duration. Among the 36 RCTs identified, only 9 RCTs were of at least 6 months' duration. The review did not separately analyse data by type of dementia, but performed a meta-analysis for all RCTs. It noted that some RCTs included people with any type of dementia or cognitive impairment, although others were more selective and applied appropriate diagnostic criteria. Several rating scales or sub-tests of rating scale were used to assess cognition. The review performed multiple analyses by dose, length of treatment, and outcome measure. We have selectively reported outcomes at longer term (22–28 weeks) assessed by our outcome measures of choice.

The review found no significant difference between ginkgo biloba and placebo in cognitive outcomes measured by Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog) score at 22 to 26 weeks (ginkgo biloba any dose: 3 RCTs, number of people not reported; treatment effect –0.03, 95% CI –0.77 to +0.71; P = 0.93). [30] There was significant heterogeneity among RCTs. However, the review found that ginkgo biloba (varied doses) improved cognition scores compared with placebo in a meta-analysis of 4 RCTs that used the Syndrom Kurztest (SKT) as the outcome measure (4 RCTs, 775 people; mean difference –3.57, 95% CI –3.94 to –3.20; P <0.0001). [30] There was significant heterogeneity among RCTs.

The review found that ginkgo biloba significantly improved global improvement compared with placebo at 24 to 26 weeks, but only at doses above 200 mg daily (Clinical Global Impression of Change [CGI-C] improved or unchanged compared with baseline: doses <200 mg/day: 2 RCTs [mainly Alzheimer's disease, also multiple infarct dementia], 652 people; OR 1.25, 95% CI 0.91 to 1.70; P = 0.17; doses >200 mg/day: 2 RCTs [mainly Alzheimer's disease, also multiple infarct dementia], 549 people; OR 1.8, 95% CI 1.22 to 2.65; P = 0.003). [30] The review found no significant difference between groups in activities of daily living scores at 22 to 24 weeks, whether at all doses (variety of measures, any dose, 4 RCTs [mainly Alzheimer's disease, also multiple infarct dementia, other dementias, and cognitive impairment], 1111 people; SMD –0.12, 95% CI –0.24 to 0; P = 0.057) or with high-dose ginkgo biloba (>200 mg/day; 3 RCTs [mainly Alzheimer's disease, also multiple infarct dementia, other dementias, and cognitive impairment], 632 people; SMD –0.07, 95% CI –0.22 to +0.09; P = 0.39). However, these data excluded one RCT that introduced heterogeneity owing to an extreme result; and some measures reported by RCTs ostensibly as "activities of daily living" assessed additional areas such as cognition, social, and mood items. [30]

In the second systematic review (search date 2008, 9 RCTs), 3 RCTs assessed cognition using ADAS-cog, 5 used SKT, and one used both outcome measures. [31] The review noted that, in some included RCTs, the method of allocation concealment and blinding was unclear. The review combined RCTs reporting ADAS-cog and SKT in its meta-analysis. Included RCTs were of at least 12 weeks' treatment; analysis was by last observation carried forward (LOCF). It found that ginkgo biloba significantly improved cognitive function compared with placebo (7 RCTs, 1752 people; SMD –0.58, 95% CI –1.14 to –0.01; P = 0.04). [31] However, there was significant heterogeneity among RCTs. The review found no significant difference between groups in activities of daily living scores (6 RCTs, 1736 people; SMD –0.32, 95% CI –0.66 to +0.03; P = 0.08). Again, there was significant heterogeneity between RCTs. [31]

Harms:

Ginkgo biloba versus placebo:
The first review found no significant difference between ginkgo biloba and placebo in the proportion of people with adverse effects at 12 or 24 weeks (12 weeks: 11 RCTs, 1062 people; OR 0.93, 95% CI 0.63 to 1.38; P = 0.71; 24 weeks: dose <200 mg/day: 5 RCTs, 969 people; OR 0.88, 95% CI 0.66 to 1.17; P = 0.38; dose >200 mg/day: 2 RCTs, 744 people; OR 0.71, 95% CI 0.49 to 1.01; P = 0.055). [30]

The second review reported no difference between ginkgo biloba and placebo in incidence of adverse effects (no further data reported). Between 1% and 6% of people withdrew from treatment with ginkgo biloba compared with 0% to 8% with placebo. [31]

The third systematic review reported that proportionately more people withdrew from active treatment compared with placebo, but that there was no indication that ginkgo biloba had caused harm (no data reported). [32]

Comment:

Many earlier studies were of poor methodological quality, and there was significant clinical and statistical heterogeneity between RCTs. [30] With regard to all included studies and analyses, the Cochrane review noted that positive effects with ginkgo biloba found in several earlier smaller studies had not been confirmed in more recent trials; it was unable to exclude the possibility of publication bias; and the evidence that ginkgo biloba has predictable and clinically significant benefit for people with dementia or cognitive impairment was inconsistent and unconvincing. [30]

Like the first two reviews, the third systematic review (6 RCTs, search date 2007, 739 people with Alzheimer's disease, ginkgo biloba 120–240 mg, duration 22–26 weeks) [32] found significant heterogeneity between trials, to the extent that it did not conduct a meta-analysis and, although some included trials showed evidence of benefit in cognitive outcomes in people taking high-dose ginkgo biloba, the authors concluded that it was not possible to estimate an effect size. The review also noted that the results were dominated by two studies not conducted in "the healthcare setting of a Western country". [32]

OPTION MEMANTINE VERSUS PLACEBO IN PEOPLE WITH COGNITIVE SYMPTOMS OF DEMENTIA

Cognitive symptoms and function (cognitive scores, global scores, activities of daily living scores)
Compared with placebo in people with Alzheimer's disease Memantine may be marginally more effective at improving cognitive function scores and global function scores at 24 to 28 weeks in people with Alzheimer's disease. Memantine may be marginally more effective at improving activities of daily living scores in people with moderate to severe Alzheimer's disease, but not in people with mild to moderate Alzheimer's disease (very low-quality evidence).

Compared with placebo in people with vascular dementia Memantine may be marginally more effective at improving cognitive function scores at 28 weeks in people with vascular dementia, but not global function scores or activities of daily living scores (low-quality evidence).

Compared with placebo in people with Lewy body dementia We don't know whether memantine is more effective at improving outcomes in people with Lewy body dementia as we found insufficient evidence from one small RCT (very low-quality evidence).

Note
Although studies found a statistical improvement in scores with memantine for some outcomes, the clinical importance of some of these improvements is unclear.

For GRADE evaluation of interventions for dementia, **see table, p 26** **.**

Benefits:

Memantine versus placebo in people with Alzheimer's disease:
We found three systematic reviews, which pooled data, but which used different inclusion criteria and performed different analyses. [33] [34] [35]

The first review (search date 2006) included double-blind RCTs of any length and memantine dose, and included unpublished data. [33] In people with moderate to severe Alzheimer's disease, it found that memantine 20 mg daily significantly improved cognitive and global outcomes compared with placebo at 24 to 28 weeks, although the effects were small (Severe Impairment Battery [100-point scale]: 3 RCTs, 976 people; WMD 3.0, 95% CI 1.7 to 4.3; Clinician's Interview-Based Impression of Change-Plus [CIBIC-Plus] scale: 3 RCTs, 964 people; WMD 0.3, 95% CI 0.2 to 0.4). [33] The RCTs in the cognitive result were heterogeneous, which was due to widely differing results in two RCTs. [33] The review found that memantine significantly improved activities of daily living scores at 24 to 28 weeks (Alzheimer's Disease Cooperative Study-Activities of Daily Living scale for severe Alzheimer's Disease [ADCS-ADL-sev19] [54-point scale]: 3 RCTs, 978 people; WMD 1.3, 95% CI 0.4 to 2.1). In people with mild to moderate Alzheimer's disease, the review found a significant improvement with memantine 20 mg daily in cognition scores and global outcomes at 24 weeks compared with placebo (Alzheimer's Disease Assessment Scale cognitive subscale [ADAS-cog]: 3 RCTs, 1379 people; WMD 0.99, 95% CI 0.21 to 1.78; CIBIC-Plus: 3 RCTs, 1381 people; WMD 0.13, 95% CI 0.01 to 0.25). It found no significant difference between groups in activities of daily living scores (ADCS-ADL23: 3 RCTs, 1371 people; WMD +0.2, 95% CI –0.9 to +1.27).

The second review (search date 2004) included double-blind RCTs of at least 6 months' duration in people with Alzheimer's disease only. [34] It included two published RCTs, one RCT presented as a poster, and three unpublished RCTs (information on file). Five RCTs used memantine 20 mg daily and one RCT used 40 mg daily. Overall, in people with mild to severe Alzheimer's disease, it found that memantine significantly improved cognition scores, global scores, and activities of daily living scores compared with placebo (cognition: 6 RCTs, 2255 people; SMD –0.21, 95% CI –0.34 to –0.08; global status: 6 RCTs, 2245 people; SMD –0.19, 95% CI –0.27 to –0.10; activities of daily living: 6 RCTs, 2249 people; SMD –0.10, 95% CI –0.18 to –0.01). [34] The analysis for cognition score was heterogeneous, which was due to the most positive outlier RCT (247 people). [34] All analyses were based on intention to treat, with last observation carried forward (LOCF).

The third review, in people with moderate to severe Alzheimer's disease (6 RCTs, search date not reported), [35] found that memantine 20 mg significantly improved cognition scores as measured by ADAS-cog compared with placebo at 24 weeks (6 RCTs, 821 people assessed by ADAS-cog; results presented graphically; mean change in ADAS-cog in people with moderate Alzheimer's disease, P <0.01, analysis by LOCF and observed cases [OC]). Subscale analysis also showed significant improvement in ideational praxis (P <0.05), orientation (P <0.01), comprehension (P <0.05), and remembering test instructions (P <0.05). The analysis also found that Self-Impairment Battery (SIB) scores were significantly better with memantine compared with placebo at 24 weeks (6 RCTs, 976 people; results presented graphically; P <0.001). [35]

Memantine versus placebo in people with vascular dementia:
In people with vascular dementia, the first review [33] found that memantine 20 mg daily produced a small but significant improvement in cognition at 28 weeks (ADAS-cog: 2 RCTs, 815 people; WMD 1.8, 95% CI 0.9 to 2.8). It found no significant difference between groups in global outcomes or activities of daily living (Clinical Global Impression [CGI]: 2 RCTs, 775 people; WMD +0.03, 95% CI –0.13 to +0.19; Nurses' Observation Scale for Geriatric Patients [NOSGER] self-care subscale: 2 RCTs, 542 people; WMD +0.12, 95% CI –0.43 to +0.67). All analyses were based on intention to treat with the LOCF. [33]

Memantine versus placebo in people with Lewy body dementia:
We found one RCT comparing memantine versus placebo in people with Lewy body dementia or Parkinson's disease dementia. [36] We report the data from the subgroup of 75 people with moderate Lewy body dementia. The subgroup analysis found that, at 24 weeks, memantine 20 mg significantly improved cognition scores compared with placebo as measured by ADCS-Clinical Global Impression of Change (ADCS-CGIC) scale (LOCF analysis, ADCS-CGIC change from baseline: 3.3 with me-

mantine *v* 3.9 with placebo; mean difference –0.6; P = 0.023). It found no significant difference between groups in activities of daily living scores as measured by ADCS (mean difference 1.7; P = 0.57). [36]

Harms:

Memantine versus placebo in people with Alzheimer's disease:
The first review reported adverse effects by different population groups rather than overall figures. [33] It reported that memantine was "well tolerated", and found no significant difference between memantine and placebo in people with at least one adverse effect, or between groups in falls or depression. [33] One RCT found that memantine significantly increased somnolence (14/201 [7%] with memantine *v* 2/202 [1%] with placebo; OR 7.5, 95% CI 1.7 to 33.3). [33]

The second review found no significant difference between memantine and placebo in treatment discontinuation caused by adverse effects (P = 0.86), in people having any adverse effect (P = 0.42), or in people having a serious adverse effect (P = 0.89). [34] It found that, compared with placebo, memantine significantly increased constipation, somnolence, vomiting, hypertension, and abnormal gait (constipation: 3.6% with memantine *v* 2.5% with placebo; OR 1.62, 95% CI 1.01 to 2.60; somnolence: 3.8% with memantine *v* 2.3% with placebo; OR 1.81, 95% CI 1.13 to 2.90; vomiting: 3.3% with memantine *v* 2.1% with placebo; OR 1.77, 95% CI 1.07 to 2.94; hypertension: 4.3% with memantine *v* 2.9% with placebo; OR 1.60, 95% CI 1.03 to 2.47; abnormal gait: 3.2% with memantine *v* 2.1% with placebo; OR 1.70, 95% CI 1.02 to 2.83). [34]

We found one pooled analysis of 6 RCTs reporting on the tolerability and safety of memantine 10 mg to 20 mg. [37] The analysis reported the same 6 RCTs reported by the third review of memantine versus placebo in people with Alzheimer's disease. [35] The analysis (2311 people taking memantine or placebo for 24–26 weeks) reported that the proportion of people who withdrew from treatment because of adverse events was similar in both arms (111/1242 [9%] with memantine *v* 105/1069 [10%] with placebo). [37] The proportion of people with at least one treatment-emergent adverse event was also similar between groups (710/1242 [57%] with memantine *v* 619/1069 [58%] with placebo). The most frequently reported adverse events included agitation, falls, dizziness, accidental injury, influenza-like symptoms, headache, and diarrhoea (agitation: 93/1242 [7%] with memantine *v* 128/1069 [12%] with placebo; falls: 84/1242 [6.8%] with memantine *v* 76/1069 [7.1%] with placebo; dizziness: 78/1242 [6.3%] with memantine *v* 61/1069 [5.7%] with placebo; accidental injury: 74/1242 [6%] with memantine *v* 77/1069 [7%] with placebo; influenza-like symptoms: 74/1242 [6.0%] with memantine *v* 62/1069 [5.8%] with placebo; headache: 64/1242 [5%] with memantine *v* 40/1069 [4%] with placebo; diarrhoea: 62/1242 [5%] with memantine *v* 60/1069 [6%] with placebo). A similar proportion of people died in each arm (deaths: 17/1242 [1.4%] *v* 15/1069 [1.4%]), and there was no significant difference between groups in QTc (0.5 ms with memantine *v* 2.1 ms with placebo; mean difference –1.6 ms, 95% CI –3.3 ms to 0 ms). [37]

Memantine versus placebo in people with Lewy body dementia:
The RCT [36] reported that 18/34 (53%) people in the memantine group had adverse effects compared with 17/41 (41%) in the placebo group. The most commonly reported adverse effects were falls, somnolence, viral gastroenteritis, and pain (falls: 2/34 [6%] with memantine *v* 3/41 [7%] with placebo; somnolence: 3/34 [9%] with memantine *v* 0/41 [0%] with placebo; viral gastroenteritis: 2/34 [6%] with memantine *v* 0/41 [0%] with placebo; pain in extremity: 2/34 [6%] with memantine *v* 0/41 [0%] with placebo).

Comment:

Memantine seems to be well tolerated. Although reviews report statistically significant results, the effect size is small, and at best confers only minimal clinically meaningful benefit on the treatment of cognitive symptoms of dementia. In Lewy body dementia memantine is well tolerated, but results have shown only mild benefit and are not promising at present.

OPTION NON-PHARMACOLOGICAL INTERVENTIONS (COGNITIVE STIMULATION, MUSIC THERAPY, REMINISCENCE THERAPY) VERSUS PLACEBO IN PEOPLE WITH COGNITIVE SYMPTOMS OF DEMENTIA

Cognitive symptoms and function (cognitive scores, global scores, activities of daily living scores)
Reminiscence therapy compared with placebo or no treatment Reminiscence therapy may be more effective than placebo at improving cognition function scores at 4 to 6 weeks in people with dementia (type and severity unspecified), but we don't know about the longer term (very low-quality evidence).

Cognitive stimulation compared with placebo or no treatment Cognitive training in small groups 2 to 7 times a week for 1 to 25 days, and group cognitive stimulation 2 to 5 times a week for 4 to 24 weeks may be more effective than no treatment at improving measures of cognitive function. However, evidence was weak (very low-quality evidence).

Note

We found no direct information from RCTs about music therapy in the treatment of people with cognitive symptoms of dementia (Alzheimer's, Lewy body, or vascular).

For GRADE evaluation of interventions for dementia, **see table, p 26 .**

Benefits:

Reminiscence therapy versus placebo or no treatment:
We found one systematic review of reminiscence therapy (search date 2004, 4 RCTs; 144 people with evaluable data; therapy for 4–18 weeks for 1–5 times/week). [38] The RCTs in the meta-analysis provided incomplete data on the type or severity of dementia. The review found that reminiscence therapy improved cognition compared with no reminiscence therapy at 4 to 6 weeks (3 RCTs, 93 people; SMD 0.50, 95% CI 0.07 to 0.92; P = 0.02). The review noted that each RCT included a different type of reminiscence therapy, and that included RCTs had important methodological weaknesses. [38] None of the individual RCTs met our inclusion criteria for this review. The primary studies lacked adequate controls, had potential for bias, used diverse interventions, and used inadequate outcome measures.

Music therapy versus placebo or no treatment:
We found one systematic review (search date 2007) [39] of music therapy, which found no RCTs of sufficient quality.

Cognitive stimulation versus placebo or no treatment:
We found one systematic review (search date 2008) [40] of cognitive training including mental imagery. The review found that strategies to improve verbal learning and other cognitive functions in a small group setting significantly improved cognition compared with no training (3 RCTs, 67 people; therapy for 45–90 minutes 2–7 times/week for 1–25 days; effect size 0.59, 95% CI 0.05 to 1.14). The effect size was classed as "moderate". However, the sample size was small. [40]

The review found that group cognitive stimulation sessions (themed activities to orientate and actively stimulate cognition through association and categorisation) showed significant improvement in measures of attention, memory, orientation, language, and general cognition compared with no treatment (7 RCTs, 270 people; 30–60 minutes 2–5 times/week for 4–24 weeks; effect size 0.44, 95% CI 0.20 to 0.70). The effect size was classed as "mild". [40]

Harms:

Reminiscence therapy versus placebo or no treatment:
The review did not report on harms. [38]

Music therapy versus placebo or no treatment:
We found no RCTs.

Cognitive stimulation versus placebo or no treatment:
The review did not report on harms. [40]

Comment: None.

OPTION OMEGA 3 (FISH OIL) VERSUS PLACEBO IN PEOPLE WITH COGNITIVE SYMPTOMS OF DEMENTIA

Cognitive symptoms and function (cognitive scores, global scores, activities of daily living scores)
Compared with placebo Omega 3 fish oil (docosahexaenoic acid plus eicosapentaenoic acid) may be no more effective at improving cognitive or global function scores at 6 months in people with mild to moderate Alzheimer's disease (low-quality evidence).

For GRADE evaluation of interventions for dementia, **see table, p 26 .**

Benefits:

Omega 3 (fish oil) versus placebo:
We found one systematic review (search date 2008, 4 RCTs) [41] reporting on the effect of long-chain omega-3 fatty acids. The review did not pool data. Two RCTs met our inclusion criteria. The first RCT (174 people with mild to moderate Alzheimer's disease), [42] comparing docosahexaenoic acid (DHA) plus eicosapentaenoic acid (EPA) versus placebo, found no significant difference between groups in cognitive or global outcomes at 6 months (Mini Mental State Examination [MMSE] mean score [0–30 points]: 22.8 with active intervention *v* 22.4 with placebo; Alzheimer's Disease Assessment Scale cognitive subscale [ADAS-cog] mean score [0–85 points]: 27.7 with active intervention *v* 28.3 with placebo; Clinical Dementia Rating [CDR] scale, mean global score [0–3 points]: 1.1 with active intervention *v* 1.1 with placebo; all reported as not significant; P values not reported). [42] The RCT found a statistically significant benefit for omega-3 fatty acids in a subgroup of people with very mild Alzheimer's disease (32 people MMSE >27; P = 0.01). [41]

The second RCT in the review (302 people with mild dementia, MMSE score >21), [41] which compared DHA-EPA 400 mg or 1800 mg versus placebo for 26 weeks, found no significant difference in cognitive function between either dose of DHA-EPA and placebo, as measured by a variety of tests including word learning, Wechsler's digit span, trail making test versions A and B, Stroop colour–word test, and verbal fluency test. [41]

Harms:

Omega 3 fish oil versus placebo:
The first RCT reported in the review found that the fatty acid preparation was "well tolerated and safe". [42] Reasons given for withdrawing from treatment were: diarrhoea (9 people), dysphagia (9), new serious somatic disease (10), non-compliance (1), and withdrawal of informed consent (1) (numbers in individual groups and statistical analysis between groups not reported). [42]

The systematic review did not report on harms. [41]

Comment:

Although we found a few studies looking at prevention of dementia using omega 3 fish oil, there is a need for more studies on treatment of established dementia. Clinical trials have failed to detect any beneficial effect for DHA-EPA for secondary prevention or treatment of Alzheimer's disease.

OPTION STATINS VERSUS PLACEBO IN PEOPLE WITH COGNITIVE SYMPTOMS OF DEMENTIA

Cognitive symptoms and function (cognitive scores, global scores, activities of daily living scores)
Compared with placebo Statins may be no more effective at improving cognitive function scores or global functioning scores at 6–12 months in people with mild to moderate Alzheimer's disease (low-quality evidence).

For GRADE evaluation of interventions for dementia, see table, p 26 .

Benefits:

Statins versus placebo:
We found one systematic review (search date 2008, 3 RCTs) [43] of statins for treatment of mild to moderate Alzheimer's disease. Treatment was given for 24 to 26 weeks with statin at the recommended dose. The review found no significant difference in Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog) between statins and placebo (3 RCTs, analysis by last observation carried forward [LOCF], 704 people; mean difference –1.1, 95% CI –3.99 to +1.75; P = 0.44). [43] Heterogeneity between trials approached significance (P = 0.05). The review also found no significant difference between groups in Mini Mental State Examination (MMSE) at 12 months (3 RCTs, analysis by LOCF; mean difference –1.53, 95% CI –3.28 to +0.21; P = 0.085), or in global functioning measured by Clinical Global Impression of Change (CGIC) scale at 6 or 12 months (6 months: 1 RCT, 564 people; mean difference +0.03, 95% CI –0.11 to +0.18; 12 months: 1 RCT, 505 people; mean difference –0.03, 95% CI –0.2 to +0.13; P = 0.68). [43] The review reported no difference in quality of life between groups as measured by several scales, including Caregiver Burden Questionnaire and Patient Health Resources Utilization (2 RCTs, no further data reported). [43]

Harms:

Statins versus placebo:
The review reported that the incidence of adverse effects was low. [43] There was no significant difference between groups in the proportion of people who withdrew from treatment because of adverse effects (2 RCTs, 683 people; 8/338 [2%] with statins *v* 3/345 [1%] with placebo; OR 2.45, 95% CI 0.69 to 8.62; P = 0.16). Liver enzymes were elevated in 2.6% of people taking statins in one RCT. Overall, rates of adverse events were similar in both groups. Serious adverse events in the statin group included hepatitis, acute renal failure/rhabdomyolysis/pancreatitis, GI haemorrhage, and abdominal pain/nausea/chest discomfort. [43]

Comment:

Statins may be useful in prevention of dementia as they modify known risk factors for dementia. However, we found no evidence of benefit in the studies we identified on treatment. More evidence is needed, and prevention trials are difficult.

OPTION NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS) VERSUS PLACEBO IN PEOPLE WITH COGNITIVE SYMPTOMS OF DEMENTIA

Cognitive symptoms and function (cognitive scores, global scores, activities of daily living scores)
Compared with placebo Naproxen, celecoxib, and ibuprofen may be no more effective at improving cognitive function scores or global function scores at 1 year in people with mild to moderate Alzheimer's disease, and naproxen may be no more effective at improving activities of daily living scores at 1 year (low-quality evidence).

Note
We found no direct evidence from RCTs on NSAIDs other than naproxen, celecoxib, and ibuprofen.

For GRADE evaluation of interventions for dementia, see table, p 26 .

Benefits:

NSAIDs versus placebo:
We found one systematic review of aspirin (search date 2008) in people with vascular dementia, [44] one of ibuprofen (search date 2002) in Alzheimer's disease, [45] and one on indometacin (indomethacin; search date 2004) [46] in Alzheimer's disease, none of which found any RCTs of sufficient quality. We found one RCT of naproxen, [47] one RCT of celecoxib, [48] and one RCT of ibuprofen [49] of sufficient quality.

The first RCT (351 people; mild to moderate Alzheimer's disease) compared three treatments: rofecoxib (122 people), naproxen (118 people), and placebo (111 people). [47] We have not reported any results on rofecoxib as the drug has been withdrawn. The RCT found no significant difference between naproxen and placebo in cognitive scores, global symptom scores, activities of daily living, or quality of life at 1 year (cognitive scores measured by Alzheimer's Disease Assessment Scale cognitive subscale [ADAS-cog]: P = 0.96; global symptom scores measured by Clinical Dementia Rating Scale Sum of Boxes [CDR-SOB]: P = 0.89; activities of daily living measured by Alzheimer's Disease Cooperative Study-Activities of Daily Living [ADCS-ADL] scale: P = 0.14; quality of life measured by Quality of Life–Alzheimer's Disease [QOL-AD]: P = 0.93). [47]

The second RCT (425 people with mild to moderate Alzheimer's disease) compared celecoxib twice daily versus placebo over 52 weeks. [48] The RCT found no significant differences between groups in cognitive outcomes or global outcomes at 1 year (ADAS-cog: P = 0.54; Clinician's Interview Based Impression of Change-Plus [CIBIC-Plus] scores: P = 0.45). [48]

The third RCT, [49] which assessed the effects of ibuprofen in people with mild to moderate Alzheimer's disease, found no significant difference at 1 year between ibuprofen and placebo in change from baseline in ADAS-cog (132 people, 400 mg ibuprofen twice daily, analysis by last observation carried forward; –3.0 with ibuprofen *v* –3.1 with placebo; mean difference 0.1, CIs not reported; P = 0.95), Mini Mental State Examination (MMSE; 2.1 with ibuprofen *v* 2.7 with placebo; mean difference –0.6; P = 0.29), Geriatric Depression Scale (GDS; +0.2 with ibuprofen *v* –0.1 with placebo; mean difference +0.4; P = 0.55), or CIBIC-Plus (4.0 with ibuprofen *v* 3.9 with placebo; mean difference 0.1; P = 0.74). In total, 97/132 (73%) people completed treatment.

Harms:

NSAIDs versus placebo:
The first RCT found that naproxen significantly increased the proportion of people with hypertension compared with placebo (5% with naproxen *v* 0% with placebo; P =0.03). [47] It found that proportionately more people had fatigue, dizziness, and dry mouth with naproxen than with placebo, although differences between groups were not significant (P = 0.06 for all comparisons). [47]

The second RCT found that, compared with placebo, celecoxib significantly increased dyspnoea, dyspepsia, and urinary incontinence (dyspnoea: 4% with celecoxib *v* 0% with placebo; dyspepsia: 3% with celecoxib *v* 0% with placebo; urinary incontinence: 3% with celecoxib *v* 0% with placebo; all comparisons, P <0.05), although more people had hernia with placebo than with celecoxib (0% with celecoxib *v* 2% with placebo; P <0.05). [48] In total, 73 (26%) people with celecoxib and 32 (23%) people with placebo experienced serious adverse effects (statistical analysis between groups not reported). The RCT reported that the most frequently reported serious adverse effects were confusion, urinary tract infection, accidental fracture, pneumonia, cardiac failure, cerebrovascular disorder, and respite care (statistical analysis between groups not reported). [48]

The third RCT did not report in detail on adverse effects, although it reported that most adverse events were gastrointestinal and occurred more frequently in the placebo group (GI events: 3/66 [5%] with ibuprofen *v* 8/66 [12%] with placebo). Withdrawal rates were similar between groups. [49]

General:
The use of NSAIDs has been linked to an increased risk of myocardial infarction and stroke, and safety warnings have been issued about the use of celecoxib, etoricoxib, valdecoxib, and naproxen (see *Clinical Evidence* review on NSAIDs).

Comment:

None.

QUESTION What are the effects of treatments on behavioural and psychological symptoms of dementia (Alzheimer's, Lewy body, or vascular)?

OPTION ACETYLCHOLINESTERASE INHIBITORS (DONEPEZIL, GALANTAMINE, RIVASTIGMINE) VERSUS PLACEBO IN PEOPLE WITH BEHAVIOURAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

Behavioural and psychological symptoms

Compared with placebo Acetylcholinesterase inhibitors (donepezil and galantamine) may be marginally more effective at improving neuropsychiatric symptoms (measured by Neuropsychiatric Inventory [NPI] scores) in people with Alzheimer's disease and vascular dementia. We don't know whether rivastigmine is more effective at improving neuropsychiatric symptoms (measured by NPI) in people with Lewy body dementia (very low-quality evidence).

Note
Acetylcholinesterase inhibitors may be associated with adverse effects, including GI adverse effects (e.g., nausea, vomiting, diarrhoea, anorexia).

For GRADE evaluation of interventions for dementia, **see table, p 26 .**

Benefits:

Acetylcholinesterase inhibitors versus placebo:
We found 4 systematic reviews. [20] [28] [21] [50] There was some overlap of reporting among the reviews; however, they had different inclusion criteria and performed different analyses. We found two subsequent RCTs. [51] [26] The fourth review [50] did not perform a meta-analysis, so we have reported the two included RCTs [52] [53] separately.

The first review (search date 2005; double-blind RCTs in people with mild, moderate, or severe Alzheimer's disease) included RCTs in which treatment had been given for 6 months or longer, and at the dose recommended as optimal by the manufacturing pharmaceutical company. [20] It pooled data on acetylcholinesterase inhibitors as a group, and performed an intention-to-treat analysis with the last observation carried forward. All the RCTs in the analysis had been published. The review found that acetylcholinesterase inhibitors significantly improved neuropsychiatric symptoms compared with placebo at 26 weeks (measured by Neuropsychiatric Inventory [NPI]: 3 RCTs [2 RCTs of donepezil; 1 RCT of galantamine]; 1005 people; WMD –2.4, 95% CI –4.1 to –0.8). [20]

The second systematic review (search date 2006) examined acetylcholinesterase inhibitors in people with behavioural and psychological (non-cognitive) symptoms of dementia, and pooled results both by individual agent and by acetylcholinesterase inhibitors as a group. [28] It included RCTs of any treatment duration and dose, and also included unpublished RCTs. In people with Alzheimer's disease, the review found that donepezil significantly reduced neuropsychiatric symptoms compared with placebo (measured by NPI: 4 RCTs [treatment length 12–52 weeks]; 866 people; SMD –0.3, 95% CI –0.5 to –0.2). One RCT, which was an outlier in terms of treatment effect and introduced heterogeneity, was excluded from this analysis. In people with Alzheimer's disease, it found that galantamine reduced neuropsychiatric symptoms compared with placebo, although the result was of borderline significance (measured by NPI: 2 RCTs [12–21 weeks' duration]; 889 people; SMD –0.13, 95% CI –0.27 to 0; P = 0.05). The review found two RCTs of donepezil and one RCT of galantamine versus placebo in people with vascular dementia. The review found that acetylcholinesterase inhibitors significantly reduced neuropsychiatric symptoms compared with placebo in people with vascular dementia (measured by NPI: SMD –0.21, 95% CI –0.41 to –0.01; RCTs included in the analysis and absolute numbers not reported). The review found one RCT (120 people; 20 weeks' duration) of rivastigmine versus placebo in people with Lewy body dementia. It found that rivastigmine was associated with a reduction in neuropsychiatric symptoms compared with placebo, but differences between groups did not reach significance (measured by NPI: 1 RCT, 100 people; SMD –0.28, 95% CI –0.67 to +0.12). [28]

The third review (search date 2007; [21] 22 RCTs in people with mild, moderate, or severe Alzheimer's disease) included RCTs in which treatment had been given for at least 12 weeks and at the dose recommended as optimal by the manufacturing pharmaceutical company. It found that donepezil and galantamine significantly improved NPI scores from baseline compared with placebo at 3 to 6 months (donepezil 5–10 mg: 4 RCTs, number of people not reported; WMD –4.3, 95% CI –5.95 to –2.65; galantamine 16–32 mg: 3 RCTs, number of people not reported; WMD –1.44, 95% CI –2.39 to –0.48).

The first RCT [52] included in the fourth review [50] of donepezil versus placebo (272 people with Alzheimer's disease and clinically significant agitation; 12 weeks' duration) found no significant difference between groups in neuropsychiatric symptoms as measured by the Cohen-Mansfield Agitation Inventory (CMAI) or the NPI at 12 weeks (CMAI: difference between groups in reduction in scores from baseline –0.06, 95% CI –4.35 to +4.22; P = 0.98; NPI: difference between groups in reduction in scores from baseline –0.13, 95 CI –4.06 to +3.80; P = 0.95). [52]

The second RCT [53] included in the fourth review [50] and the two subsequent RCTs [51] [26] were designed primarily to examine the effects of acetylcholinesterase inhibitors on cognition. However, they also reported on neuropsychiatric symptoms. The second RCT [53] included in the fourth review (343 people with severe Alzheimer's disease) [50] found no significant difference between donepezil and placebo in neuropsychiatric symptoms measured by the NPI at 24 weeks (P = 0.46). [53]

The first subsequent RCT (788 people with vascular dementia) found similar changes in neuropsychiatric symptoms measured by NPI at 26 weeks (mean change: +0.6 with galantamine *v* –1.2 with placebo; reported as no significant difference; P value not reported). [51] These two RCTs may not have been adequately powered to recognise a clinically important difference between groups in neuropsychiatric symptoms. [53] [51]

The second subsequent RCT [26] compared galantamine 24 mg daily versus placebo for 6 months in 285 people with Alzheimer's disease with cerebrovascular disease. In total, 239/285 (84%) people completed treatment and were included in the completer analysis. The RCT found no significant difference between groups in change in mean NPI scores (P = 0.12).

Harms:

Acetylcholinesterase inhibitors versus placebo:
See harms of acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine) versus placebo in people with cognitive symptoms of dementia, p 4 .

In addition, the second review found that acetylcholinesterase inhibitors in vascular dementia significantly increased people leaving the study early because of adverse effects (NNH 10, 95% CI 8 to 15). [28]

The first RCT included in the fourth review reported that adverse effects were similar between groups (statistical analysis between groups not reported). [52]

The second RCT included in the fourth review reported that most adverse effects were rated as mild or moderate. [53] The most common adverse effects were: diarrhoea, anorexia, nausea, agitation, and vomiting (diarrhoea: 10% with donepezil *v* 4% with placebo; anorexia: 7% with donepezil *v* 4% with placebo; nausea: 7% with donepezil *v* 2% with placebo; agitation: 6.3% with donepezil *v* 6.0% with placebo; vomiting: 6% with donepezil *v* 2% with placebo; statistical analysis between groups not reported). [53]

The first subsequent RCT reported that most adverse effects were mild to moderate in severity. [51] Adverse effects led to treatment discontinuation in 50/396 (13%) people with galantamine and 25/390 (6%) with placebo (statistical analysis between groups not reported). [51]

Comment:

Many of the studies were primarily designed to measure cognition so they included people without clinically significant behavioural or psychological symptoms of dementia. The fourth review (search date 2008; 14 RCTs in people with possible/probable Alzheimer's disease) [50] did not perform a meta-analysis. It concluded that, although the evidence was limited (only 3/14 trials in the review found a statistically significant difference in NPI scores), in the absence of alternative safe and effective management options, acetylcholinesterase inhibitors were an appropriate pharmacological strategy for the management of behavioural and psychological symptoms of dementia.

OPTION ANTIPSYCHOTIC MEDICATIONS (HALOPERIDOL, OLANZAPINE, QUETIAPINE, RISPERIDONE) VERSUS PLACEBO IN PEOPLE WITH BEHAVIOURAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

Behavioural and psychological symptoms

Compared with placebo Risperidone may be more effective at reducing neuropsychiatric symptoms (measured by Neuropsychiatric Inventory [NPI] or Behavioral Pathology in Alzheimer's Disease Rating [BEHAVE-AD] scale) at 6 to 12 weeks in people with Alzheimer's disease, and haloperidol may be more effective at reducing aggression in people with Alzheimer's disease or vascular dementia, but not in reducing agitation. We don't know whether olanzapine is more effective at reducing neuropsychiatric symptoms (measured by NPI or BEHAVE-AD) at 6 to 12 weeks in people with Alzheimer's disease, vascular dementia, or mixed dementia. We don't know whether quetiapine is more effective at reducing aggressive behaviour (measured by Cohen-Mansfield Agitation Inventory [CMAI] scores) at 26 weeks in people with Alzheimer's disease or vascular dementia. Olanzapine, risperidone, and quetiapine may be no more effective at reducing time to discontinuation of treatment for any reason in people with Alzheimer's disease and psychosis, aggression, or agitation, but olanzapine and risperidone may be more effective at reducing time to discontinuation of treatment due to lack of efficacy (not further defined) (very low-quality evidence).

Note

CAUTION: In people with dementia, antipsychotics have been associated with severe adverse events including cerebrovascular adverse events and death. Regulatory bodies have issued warnings that both conventional and atypical antipsychotics are associated with an increased risk of death in older people treated for dementia-related psychosis.

For GRADE evaluation of interventions for dementia, see table, p 26 .

Benefits:

Antipsychotics versus placebo:

We found one systematic review of antipsychotics versus placebo for the treatment of people with behavioural and psychological symptoms of dementia, [28] and one narrative review of antipsychotics (see comment). [54] We have reported one RCT [55] included in the second review [54] from the original report as the review did not perform a meta-analysis. We found one further RCT reporting on harms of antipsychotics. [56]

The first systematic review (search date 2006) did not pool data for antipsychotics as a group, but pooled data for each individual agent. The review identified 5 RCTs (1862 people with Alzheimer's disease, vascular dementia, or mixed dementia; treatment duration 6–10 weeks) of olanzapine versus placebo. [28] The review found no significant difference between olanzapine and placebo in reduction of neuropsychiatric symptoms at 6 to 12 weeks (measured by Neuropsychiatric Inventory [NPI] or Behavioral Pathology in Alzheimer's Disease Rating [BEHAVE-AD] scale: 4 RCTs, 841 people; SMD –0.09, 95% CI –0.23 to +0.05). The review identified one RCT (62 people with Alzheimer's disease or vascular dementia; treatment duration 26 weeks), which found no significant difference between quetiapine and placebo in a reduction in aggressive behaviour at 26 weeks (measured by Cohen-Mansfield Agitation Inventory [CMAI]: 1 RCT, 57 people; SMD +0.06, 95% CI –0.45 to +0.57). The review found 5 RCTs (1905 people with Alzheimer's disease; 10–13 weeks' duration) of risperidone. It found that risperidone significantly reduced neuropsychiatric symptoms compared with placebo at 6 to 12 weeks (measured by NPI or BEHAVE-AD: 3 RCTs, 839 people; SMD –0.3, 95% CI –0.5 to –0.2). It identified one earlier review that found 5 RCTs (555 people; Alzheimer's disease or vascular dementia; treatment duration 3–16 weeks) comparing haloperidol versus placebo. The review found that haloperidol significantly reduced aggression compared with placebo (3 RCTs, 489 people; SMD –0.3, 95% CI –0.5 to –0.1). It found no significant difference between groups in agitation (4 RCTs, 369 people; SMD –0.12, 95% CI –0.33 to +0.08). [28]

The RCT included in the second review (421 people with Alzheimer's disease and psychosis, aggression, or agitation; symptoms severe enough to justify antipsychotics in the opinion of study physicians) compared olanzapine (100 people), quetiapine (94 people), risperidone (85 people), and placebo (142 people). [55] People with a primary psychotic disorder (e.g., schizophrenia) were excluded. The primary outcome was time to discontinuation of treatment, which was to reflect the judgements of participants, carers, and clinicians with regard to efficacy, safety, and tolerability into a global measure. The RCT found no significant difference between groups in time to discontinuation of treatment for any reason (range 5–8 weeks; P = 0.52; between-group analysis). It found that olanzapine and risperidone significantly increased time to discontinuation of treatment due to lack of efficacy (outcome not further defined) compared with placebo (22 weeks with olanzapine *v* 9 weeks with placebo; P <0.001; 27 weeks with risperidone *v* 9 weeks with placebo; P = 0.01). It found no significant difference between quetiapine and placebo (9 weeks with quetiapine *v* 9 weeks with placebo; P = 0.24). [55]

Harms:

Antipsychotics versus placebo:

Antipsychotics have been associated with cerebrovascular adverse events and death in people with dementia. [57] [58] [59] [56]

The first review reported that olanzapine, risperidone, and haloperidol significantly increased the risk of leaving the study early because of adverse effects (olanzapine: NNH 17, 95% CI 11 to 33; risperidone: NNH 20, 95% CI 12 to 100; haloperidol: NNH 10, 95% CI 5 to 50). [28] The review highlighted advice from the UK Committee on Safety of Medicines (CSM) from 2004 that risperidone or olanzapine should not be used for the treatment of behavioural symptoms of dementia, and that prescribers should carefully consider the risks of cerebrovascular events. [28] The FDA and the CSM issued initial warnings that olanzapine and risperidone should not be used for the treatment of behavioural symptoms of dementia. In 2008, the FDA issued a further alert that both conventional and atypical antipsychotics were associated with an increased risk of mortality in older people treated for dementia-related psychosis (www.fda.gov).

An alert was issued by the FDA in 2007 on the association of haloperidol with QT prolongation and torsades de pointes and sudden death (www.fda.gov).

One earlier systematic review (search date 2005) [60] included in the first review [28] found that haloperidol significantly increased the proportion of people who had a least one extrapyramidal symptom (34/101 [34%] with haloperidol *v* 18/103 [18%] with placebo; OR 2.3, 95% CI 1.2 to 4.4). [60]

The RCT included in the second review found a significant difference among groups in parkinsonism or extrapyramidal signs, gait disturbance, cognitive disturbance, psychotic symptoms, and confusion or mental state change (parkinsonism or extrapyramidal signs: 12% with olanzapine *v* 2% with quetiapine *v* 12% with risperidone *v* 1% with placebo; P <0.001 between groups; gait disturbance:

4% with olanzapine *v* 3% with quetiapine *v* 1% with risperidone *v* 2% with placebo; P <0.001 between groups; cognitive disturbance: 5% with olanzapine *v* 0% with quetiapine *v* 1% with risperidone *v* 1% with placebo; P = 0.03 between groups; psychotic symptoms: 7% with olanzapine *v* 0% with quetiapine *v* 0% with risperidone *v* 2% with placebo; P = 0.004 between groups; confusion or mental state change: 18% with olanzapine *v* 6% with quetiapine *v* 11% with risperidone *v* 5% with placebo; P = 0.03 between groups). [55] It found a significant difference among groups with regard to reasons for discontinuation due to intolerability of treatment, with higher rates in the active treatment groups (intolerability, adverse effects, or death: 24% with olanzapine *v* 16% with quetiapine *v* 18% with risperidone *v* 5% with placebo; P <0.001 between groups). [55]

We found one RCT whose primary outcome was mortality in people with Alzheimer's disease taking antipsychotics (thioridazine, chlorpromazine, haloperidol, trifluoperazine, or risperidone) over 12 months. [56] In the RCT, 165 people were randomised to either continued antipsychotic treatment or to replacing antipsychotic treatment with placebo. The RCT found that, in the 128 people who took at least one dose of study medication, antipsychotics significantly increased the risk of mortality compared with placebo (HR 0.58, 95% CI 0.35 to 0.95; P = 0.03). The 24-month survival rate was 46% in people taking antipsychotics compared with 71% in people taking placebo (absolute numbers not reported). [56]

Comment: People with dementia and their carers should be made aware of the significant dangers of these medications before their prescription. They should not be used as first-line treatment. The narrative systematic review (search date 2010, 30 RCTs of second-generation antipsychotics versus placebo), which did not perform a meta-analysis, concluded that there is insufficient evidence to recommend this group of medications for treatment of dementia complicated with behavioural symptoms. [54]

OPTION BENZODIAZEPINES (DIAZEPAM, LORAZEPAM) VERSUS PLACEBO IN PEOPLE WITH BEHAVIOURAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

We found no direct information from RCTs about benzodiazepines (diazepam, lorazepam) in the treatment of people with behavioural and psychological symptoms of dementia.

For GRADE evaluation of interventions for dementia, **see table, p 26 .**

Benefits: **Benzodiazepines versus placebo:**
We found one systematic review (search date 2006), which compared benzodiazepines versus placebo for the treatment of people with behavioural and psychological symptoms of dementia, which found no RCTs of sufficient quality (see comment). [28] We found no subsequent RCTs.

Harms: **Benzodiazepines versus placebo:**
We found no RCTs. The potential harms of benzodiazepines are well described. Benzodiazepines may be associated with confusion and falls in older people, and there is a risk of tolerance and dependence (see *Clinical Evidence* review on generalised anxiety disorder).

Comment: The review identified one RCT (135 people with Alzheimer's disease or vascular dementia) comparing intramuscular lorazepam versus placebo with a follow-up of 24 hours, which is below the minimum period of follow-up for this *Clinical Evidence* review. [28] The review found that intramuscular lorazepam significantly reduced aggressive behaviour or agitation as measured by the Cohen-Mansfield Agitation Inventory (CMAI) at 2 hours (CMAI 2 hours after first dose; SMD –0.40, 95% CI –0.74 to –0.06). The review found no significant difference between groups in the proportion of people leaving the RCT early for any reason (RR 0.86, 95% CI 0.33 to 2.24). [28]

OPTION MEMANTINE VERSUS PLACEBO IN PEOPLE WITH BEHAVIOURAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

Behavioural and psychological symptoms
Compared with placebo Memantine may be marginally more effective at reducing neuropsychiatric symptoms (measured by Neuropsychiatric Inventory [NPI] scores) in people with Alzheimer's disease (very low-quality evidence).

For GRADE evaluation of interventions for dementia, **see table, p 26 .**

Benefits: **Memantine versus placebo:**
We found two systematic reviews (search dates 2007) [61] [62] comparing memantine versus placebo for the treatment of people with behavioural and psychological symptoms of dementia, and one subsequent RCT in people with Lewy body dementia. [36] The reviews identified the same

6 RCTs and found similar results. As the second review [62] mainly reported results graphically with no detailed data, we report only the first review here. [61]

The first review identified 6 RCTs of memantine versus placebo of 24 to 28 weeks' duration, all of which were in people with Alzheimer's disease who were at least 50 years old. Three RCTs had a Jadad score of 5 and three RCTs had a score of 2, and losses to follow-up ranged from 11% to 27% between studies. [61] The review found that memantine significantly reduced neuropsychiatric symptoms as measured by the Neuropsychiatric Inventory (NPI) scale compared with placebo (1730 people; total difference in mean NPI value: –1.99, 95% CI –3.91 to –0.08; P = 0.04; intention-to-treat analysis by last observation carried forward). [61] The review noted that studies were clinically heterogeneous, particularly with respect to disease severity and the use of concomitant treatment with acetylcholinesterase inhibitor. The review also noted that three RCTs had not been published in full, scored 2 on the Jadad scale, and lacked adequate information on blinding, randomisation, and description of withdrawals. [61]

The subsequent RCT assessed memantine in people with Parkinson's disease dementia or Lewy body dementia. We report results from the subgroup of 75 people with Lewy body dementia. [36] The RCT found that, at 24 weeks, people with Lewy body dementia taking memantine had significantly improved NPI scores compared with those taking placebo (change from baseline in NPI scores: –4.3 with memantine *v* +1.7 with placebo; mean difference –5.9, CI not reported; P = 0.041).

Harms:

Memantine versus placebo:
The reviews did not report on adverse effects (see memantine versus placebo in people with cognitive symptoms of dementia, p 10). [61] [62]

Comment:

Studies were designed to measure cognition, so they included people without clinically significant behavioural or psychological symptoms of dementia. Memantine seems well tolerated, but at best confers only minimal benefit for the treatment of behavioural or psychological symptoms of dementia.

OPTION NON-PHARMACOLOGICAL INTERVENTIONS (AROMATHERAPY, CBT, EXERCISE) VERSUS PLACEBO IN PEOPLE WITH BEHAVIOURAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

Behavioural and psychological symptoms
Aromatherapy compared with placebo Aromatherapy may be more effective at reducing agitation and neuropsychiatric symptoms (measured by Cohen-Mansfield Agitation Inventory [CMAI] and Neuropsychiatric Inventory [NPI]) in people with severe dementia (type unspecified). However, evidence was weak (very low-quality evidence).

Cognitive behavioural therapy compared with placebo We don't know whether CBT is more effective at improving neuropsychiatric symptoms (very low-quality evidence).

Exercise therapy compared with placebo or usual care We don't know whether exercise therapy is more effective at improving neuropsychiatric symptoms in people with dementia (low-quality evidence).

For GRADE evaluation of interventions for dementia, see table, p 26 .

Benefits:

We found one systematic review (search date 2006) of non-pharmacological interventions versus placebo for the treatment of behavioural and psychological symptoms of dementia, [28] two systematic reviews of exercise versus placebo, [63] [64] and one subsequent RCT of aromatherapy. [65]

Aromatherapy versus placebo:
The first systematic review identified two RCTs (71 people and 21 people; all with severe dementia) of aromatherapy versus placebo. [28] One RCT (71 people) was cluster randomised, and treatment length was 2 to 4 weeks. The review found that aromatherapy significantly reduced agitation and improved neuropsychiatric symptoms compared with placebo (agitation as measured by the Cohen-Mansfield Agitation Inventory [CMAI]: WMD –11.1, 95% CI –20.0 to –2.2; neuropsychiatric symptoms as measured by the Neuropsychiatric Inventory [NPI]: WMD –15.8, 95% CI –24.4 to –7.2). The type of dementia was unspecified in both RCTs, the level of blinding was not reported in one RCT, and the time of outcome assessment was not reported. [28]

The subsequent RCT was a three-armed trial assessing donepezil, aromatherapy with *Melissa officinalis* oil, and placebo in 114 people with Alzheimer's disease. [65] The RCT found no significant difference in NPI scores (per-protocol analysis) at 4 or 12 weeks between aromatherapy and placebo (change from baseline in NPI, 12 weeks: –7.2 with aromatherapy *v* –10.0 with placebo; P = 0.52), although aromatherapy improved quality-of-life scores compared with placebo (–2 with placebo *v* +17 with aromatherapy [Blau Quality of Life scale]; P = 0.033). Only 55/77 (71%) of

people randomised completed 12 weeks' treatment, although the figure of 77 includes 7 people who withdrew after randomisation but before treatment began. [65]

CBT versus placebo:
The review included 6 RCTs and several case studies of behavioural management versus placebo. [28] A meta-analysis of RCTs was not possible and the review reported each RCT narratively (absolute numbers, statistical analysis between groups, and time of outcome assessment were not reported). Three of the RCTs focused on training carers in behavioural techniques. In the first RCT (62 carers), training consisted of 4 individual sessions on behavioural management of aggression or discussion sessions; in the second RCT (95 couples), this consisted of "community consultants" who trained family carers in a behavioural treatment protocol; in the third RCT (148 couples), training consisted of 11 sessions of behaviour management over 3 months including videotapes. In the first two RCTs, the review reported that the intervention was associated with a reduction in carer-rated aggression, although there were no significant effects on agitation in the third RCT. [28] Two RCTs focused on behavioural interventions in care homes. In one RCT, which reported a comparison of two adjacent units, one of which received "behavioural treatment" (including pleasant event scheduling), the other receiving "usual care", the review reported that the intervention was associated with a reduction in staff-reported troubling behaviour, and that both groups showed lower frequency of difficult behaviour over time. [28] In the other RCT (179 people), people were allocated to receive either an activities of daily living intervention, a psychosocial activities intervention, both interventions combined, placebo, or no intervention. The review reported that no changes in disruptive behaviour were observed. [28] The remaining RCT (36 carers and people with dementia) focused on using behavioural approaches to improve sleep. The intervention included sleep hygiene education, daily waking, and increased light exposure. The review reported that the intervention was associated with a reduction in waking at night and less time awake in total. [28]

Exercise versus placebo or usual care:
The first systematic review (search date 2007) [63] identified 4 RCTs. However, only two trials were included in the analyses because the required data from the other two trials were not made available. The review found no significant difference between exercise and placebo in NPI scores at 12 months (1 RCT, [66] 110 people; 8.3 with exercise *v* 8.9 with placebo; mean difference –0.40, 95% CI –4.22 to +3.02; P = 0.75). [63]

The second systematic review (search date 2009) [64] identified 4 RCTs (that reported measures of depression). The review reported primarily on physical function and did not perform a meta-analysis for our outcome of interest. The three RCTs that had acceptable follow-up found no significant difference in depression scores between exercise and placebo at between 3 and 12 months. [64]

Harms:

Aromatherapy versus placebo:
The review did not report on harms. [28]

CBT versus placebo:
The review did not report on harms data from the RCTs. [28] Qualitative evidence in the systematic review suggested that it is important to avoid compounding feelings of failure and humiliation where people with dementia have difficulty with interventions, activities, and games. [28]

Exercise versus placebo or usual care:
One RCT reported in both systematic reviews [63] [64] found no significant difference between groups in total number of falls, fractures, or deaths (reported as not significant; P value not reported). [66] The mean number of hospital admissions per person was significantly higher in the exercise group at 6 and 12 months (6 months: 0.3 with exercise *v* 0.2 with routine care; P = 0.04; 12 months: 0.6 with exercise *v* 0.2 with routine care; P = 0.04). [66]

Comment:

CBT versus placebo:
The review also identified a series of single case studies. [28] These involved tailored behavioural interventions. Several were associated with a reduction in symptoms.

Exercise versus placebo or usual care:
The results from this review [63] suggest that there is insufficient evidence of the effectiveness of physical activity programmes in managing or improving behaviour and depression in people with dementia.

OPTION ANTIDEPRESSANTS (CLOMIPRAMINE, FLUOXETINE, IMIPRAMINE, SERTRALINE) VERSUS PLACEBO IN PEOPLE WITH DEPRESSION AND DEMENTIA

Behavioural and psychological symptoms

Compared with placebo We don't know whether antidepressants (clomipramine, fluoxetine, imipramine, sertraline) are more effective at improving depression in people with depression and Alzheimer's disease as we found insufficient evidence (low-quality evidence).

Note
Most of the RCTs we found were of less than 12 weeks' duration, which may not have been long enough to show an effect of treatment. We found few trials of longer duration.

For GRADE evaluation of interventions for dementia, see table, p 26 .

Benefits:

Antidepressants (clomipramine, fluoxetine, imipramine, sertraline) versus placebo:
We found one systematic review of antidepressants in people with depression and dementia. [67] We found one additional RCT of sertraline in people with Alzheimer's disease [68] and one subsequent RCT of sertraline or mirtazapine for depression in dementia. [69]

The systematic review [67] identified 7 RCTs. However, most of the included RCTs were of only 6 or 8 weeks' duration. Response was defined as 50% improvement on the Hamilton Depression Rating Scale (HDRS), Montgomery Asberg Depression Rating Scale (MADRS), or Cornell Scale for Depression in Dementia (CSDD), or was defined as much or very much improved on a global assessment scale such as the Clinical Global Impression scale.The meta-analysis found no significant difference in the proportion of responders between antidepressants (clomipramine, fluoxetine, imipramine, sertraline, and venlafaxine) and placebo (6 RCTs, responders: 80/150 [53%] with antidepressants *v* 58/149 [39%] with placebo; OR 2.12, 95% CI 0.95 to 4.70; P = 0.07). [67]

The additional RCT (131 people with Alzheimer's disease) compared sertraline 100 mg daily versus placebo for 24 weeks. [68] However, as non-responders were given the option of withdrawing from randomised treatment at 12 weeks in favour of any open-label treatment, we report only 12-week data here. The RCT found no significant difference at 12 weeks between groups in the CSDD (difference +1.20, 95% CI –1.65 to +4.05). [68]

The subsequent RCT was a three-armed trial that randomised 326 people to either sertraline 150 mg daily, mirtazapine, or placebo. The RCT found no significant difference between sertraline and placebo in CSDD scores at 13 weeks (218 people; mean difference +1.17, 95% CI –0.23 to +2.58; P = 0.1). [69]

Harms:

Antidepressants (clomipramine, fluoxetine, imipramine, sertraline) versus placebo:
The additional RCT [68] found that sertraline significantly increased the proportion of people with diarrhoea, dizziness, and dry mouth compared with placebo (diarrhoea: 36/63 [57%] with sertraline *v* 22/66 [33%] with placebo; P = 0.03; dizziness: 44/63 [70%] with sertraline *v* 26/66 [39%] with placebo; P = 0.005; dry mouth: 37/63 [59%] with sertraline *v* 23/66 [35%] with placebo; P = 0.03). There was a significantly greater proportion of pulmonary serious adverse events with sertraline compared with placebo (8/67 [12%] with sertraline *v* 0/64 [0%] with placebo; P = 0.006). [68]

The second subsequent RCT found a significantly greater proportion of people with adverse events with sertraline at 39 weeks compared with placebo (46/107 [43%] with sertraline *v* 29/111 [26%] with placebo; P = 0.01). [69]

Comment:

The trials included in the review [67] were small and short term, so clinicians should be alert for adverse effects. More large-scale RCTs are needed to clarify the benefits, and particularly the risks, of antidepressant treatment in people with Alzheimer's disease.

OPTION MOOD STABILISERS (CARBAMAZEPINE, SODIUM VALPROATE/VALPROIC ACID) VERSUS PLACEBO IN PEOPLE WITH BEHAVIOURAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

Behavioural and psychological symptoms
Compared with placebo Carbamazepine may be more effective at improving symptoms (measured by Brief Psychiatric Rating Scale [BPRS]) in people with dementia. We don't know whether sodium valproate/valproic acid is more effective at improving neuropsychiatric symptoms in people with dementia (very low-quality evidence).

For GRADE evaluation of interventions for dementia, see table, p 26 .

Benefits:

Mood stabilisers versus placebo:
We found one systematic review (search date 2007), which compared anticonvulsants versus placebo for the treatment of behavioural and psychological symptoms of dementia, and no subsequent RCTs. [70] The review did not pool data, but reported each RCT separately. The review identified one RCT (51 people; 6 weeks' treatment duration) of carbamazepine of sufficient quality.

It found that carbamazepine significantly improved symptoms measured by the Brief Psychiatric Rating Scale (BPRS) compared with placebo (7.7-point decrease with carbamazepine *v* 0.9 with placebo; absolute numbers not reported; reported as significant; P value not reported). [70] The time of assessment was not reported. [70] The review reported that the physician and pharmacist were not blinded, but did not report whether the assessment was blinded. The review found three RCTs of valproate/valproic acid of sufficient quality. The review reported that none of the three RCTs found a significant difference between groups in outcomes measured by the BPRS or the Bech-Rafaelsen Mania Scale (first RCT [56 people]; % improved measured by BPRS: 68% with valproate *v* 33% with placebo; P = 0.07; second RCT [172 people] and third RCT [153 people]: absolute numbers not reported; reported as no significant difference between groups; P values not reported). [70] The time of outcome assessment was not reported. [70]

Harms:

Mood stabilisers versus placebo:
The review found that carbamazepine was associated with significantly more adverse effects than placebo (59% with carbamazepine *v* 29% with placebo; P = 0.03). [70] The most common adverse effects with carbamazepine were: falls, ataxia, drowsiness, and fever (falls: 44% with carbamazepine *v* 46% with placebo; ataxia: 33% with carbamazepine *v* not reported for placebo; drowsiness: 30% with carbamazepine *v* 33% with placebo; fever: 30% with carbamazepine *v* not reported for placebo; statistical analysis between groups not reported). One included RCT (56 people) found significantly more adverse effects with valproate than placebo (68% with valproate *v* 33% with placebo; P = 0.03). Another included RCT (153 people) found that, compared with placebo, valproate significantly increased diarrhoea and drop in platelet count (diarrhoea: P = 0.01; drop in platelet count: P = 0.002). The remaining RCT (172 people) was discontinued early because of significantly more adverse effects in the valproate group (most often somnolence). [70] For further harms data on anticonvulsants, see *Clinical Evidence* review on Epilepsy.

Comment: None.

GLOSSARY

Music therapy A process where a therapist uses active or passive musical experiences, and the relationships that develop through them, to promote health, either in an individual or group setting.

Reminiscence therapy The encouragement of people to talk about the past in order to enable past experiences to be brought into consciousness. It relies on remote memory, which is relatively well preserved in mild to moderate dementia.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine) versus placebo in people with behavioural and psychological symptoms of dementia New evidence added. [21] [26] Categorisation unchanged (Likely to be beneficial).

Acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine) versus placebo in people with cognitive symptoms of dementia New evidence added [21] [23] [25] [26] [27] [29] including one updated Cochrane systematic review. [22] Categorisation unchanged (Likely to be beneficial).

Antipsychotic medications (haloperidol, olanzapine, quetiapine, risperidone) versus placebo in people with behavioural and psychological symptoms of dementia New evidence added. [54] [56] Categorisation unchanged (Trade-off between benefits and harms).

Memantine versus placebo in people with behavioural and psychological symptoms of dementia New evidence added. [36] [62] Categorisation unchanged (Likely to be beneficial).

Non-pharmacological interventions (aromatherapy, CBT, exercise) versus placebo in people with behavioural and psychological symptoms of dementia New evidence added. [63] [64] [65] Categorisation unchanged (Unknown effectiveness), as there remains insufficient evidence to judge the effectiveness of this intervention.

Non-pharmacological interventions (cognitive stimulation, music therapy, reminiscence therapy) versus placebo in people with cognitive symptoms of dementia New evidence added. [40] Categorisation unchanged (Unknown effectiveness), as there remains insufficient evidence to judge the effectiveness of this intervention.

Non-steroidal anti-inflammatory drugs (NSAIDs) versus placebo in people with cognitive symptoms of dementia New data added. [49] Categorisation unchanged (Unknown effectiveness), as there remains insufficient evidence to judge the effectiveness of this intervention.

Omega 3 (fish oil) versus placebo in people with cognitive symptoms of dementia New evidence added. [41] Categorisation unchanged (Unknown effectiveness), as there remains insufficient evidence to judge the effectiveness of this intervention.

Statins versus placebo in people with cognitive symptoms of dementia New evidence added. [43] Categorisation unchanged (Unknown effectiveness), as there remains insufficient evidence to judge the effectiveness of this intervention.

Antidepressants (clomipramine, fluoxetine, imipramine, sertraline) versus placebo in people with depression and dementia New evidence added. [67] [68] [69] Categorisation changed from Likely to be beneficial to Unknown effectiveness.

Ginkgo biloba versus placebo in people with cognitive symptoms of dementia New evidence added, [31] [32] including one Cochrane systematic review amended. [30] Categorisation changed from Unlikely to be beneficial to Unknown effectiveness.

Memantine versus placebo in people with cognitive symptoms of dementia New evidence added. [35] [36] [37] Categorisation changed from Unknown Effectiveness to Likely to be beneficial.

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Disclaimer

TABLE **GRADE evaluation of interventions for dementia**

Important outcomes	Cognitive symptoms and function (cognitive scores, global scores, activities of daily living scores); behavioural and psychological symptoms; adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of treatments on cognitive symptoms of dementia (Alzheimer's, Lewy body, or vascular)?									
At least 14 (at least 4643) [21] [22] [23]	Cognitive symptoms and function (cognitive scores, global scores, activities of daily living scores)	Acetylcholinesterase inhibitors *v* placebo in people with Alzheimer's disease	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for statistical heterogeneity among RCTs
At least 8 (at least 4066) [24] [25] [26] [27]	Cognitive symptoms and function (cognitive scores, global scores, activities of daily living scores)	Acetylcholinesterase inhibitors *v* placebo in people with vascular dementia	4	–2	–1	0	0	Very low	Quality points deducted for weak methods (randomisation, allocation concealment) and subgroup analysis. Consistency point deducted for inconsistent effects depending on outcome measure used
1 (83) [28]	Cognitive symptoms and function (cognitive scores, global scores, activities of daily living scores)	Acetylcholinesterase inhibitors *v* placebo in people with Lewy body dementia	4	–3	0	0	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and no intention-to-treat analysis
At least 7 (at least 1752) [30] [31]	Cognitive symptoms and function (cognitive scores, global scores, activities of daily living scores)	Ginkgo biloba *v* placebo	4	–1	–1	–1	0	Very low	Quality point deducted for weak methods. Consistency point deducted for statistical heterogeneity among RCTs and dose variations. Directness point deducted for inclusion of people without dementia
At least 12 (at least 3066) [33] [34] [35]	Cognitive symptoms and function (cognitive scores, global scores, activities of daily living scores)	Memantine *v* placebo in people with Alzheimer's disease	4	–3	–1	0	0	Very low	Quality points deducted for incomplete reporting of results and for inclusion of large amount of unpublished data (4 out of 6 RCTs in 1 analysis), and for post-hoc and subgroup analyses. Consistency point deducted for statistical heterogeneity among RCTs
At least 2 (at least 815) [33]	Cognitive symptoms and function (cognitive scores, global scores, activities of daily living scores)	Memantine *v* placebo in people with vascular dementia	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for significance of result dependent on analysis performed
1 (75) [36]	Cognitive symptoms and function (cognitive scores, global scores, activities of daily living scores)	Memantine *v* placebo in people with Lewy body dementia	4	–3	0	0	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and subgroup analysis
4 (93) [38]	Cognitive symptoms and function (cognitive scores, global scores, activities of daily living scores)	Reminiscence therapy *v* placebo or no treatment	4	–3	–1	0	0	Very low	Quality points deducted for sparse data, unclear inclusion criteria (type and severity of dementia), and weak methods. Consistency point deducted for short follow-up and unclear outcome measurement
7 (270) [40]	Cognitive symptoms and function (cognitive scores, global scores, activities of daily living scores)	Cognitive stimulation *v* placebo	4	–1	0	–2	0	Very low	Quality point deducted for weak methods. Directness points deducted for unclear outcome measurement and widely differing treatment duration between RCTs
2 (476) [41] [42]	Cognitive symptoms and function (cognitive scores, global scores, activities of daily living scores)	Omega 3 (fish oil) *v* placebo	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for heterogeneity between trials
3 (704) [43]	Cognitive symptoms and function (cognitive scores, global scores, activities of daily living scores)	Statins *v* placebo	4	–1	–1	0	0	Low	Quality point deducted for sparse data. Consistency point deducted for heterogeneity between trials

Important outcomes	Cognitive symptoms and function (cognitive scores, global scores, activities of daily living scores); behavioural and psychological symptoms; adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
3 (786) [47] [48] [49]	Cognitive symptoms and function (cognitive scores, global scores, activities of daily living scores)	NSAIDs *v* placebo	4	–1	0	–1	0	Low	Quality point deducted for sparse data in some comparisons. Directness point deducted for poor follow-up
What are the effects of treatments on behavioural and psychological symptoms of dementia (Alzheimer's disease, Lewy body, or vascular)?									
14 (3397) [20] [21] [26] [28] [51] [52] [53]	Behavioural and psychological symptoms	Acetylcholinesterase inhibitors *v* placebo	4	–1	–1	–1	0	Very low	Quality point deducted for incomplete reporting of results. Consistency point deducted for statistical heterogeneity among RCTs and conflicting results. Directness point deducted as some studies primarily designed to measure cognition (included people without clinically significant behavioural or psychological symptoms)
15 (2647) [28] [55]	Behavioural and psychological symptoms	Antipsychotics *v* placebo	4	0	–1	–2	0	Very low	Consistency point deducted for conflicting results. Directness points deducted for subjective unclear outcome in 1 RCT and for short follow-up in most RCTs
7 (1815) [36] [61] [62]	Behavioural and psychological symptoms	Memantine *v* placebo	4	–3	0	–1	0	Very low	Quality points deducted for weak methods (blinding, randomisation), use of unpublished data (3 of 6 RCTs), and high rate of withdrawals. Directness point deducted for clinical heterogeneity (disease severity, co-interventions)
2 (148) [28] [65]	Behavioural and psychological symptoms	Aromatherapy *v* placebo	4	–3	0	–1	0	Very low	Quality points deducted for sparse data, unclear population (type of dementia), unclear blinding, and unclear time of outcome assessment. Directness point deducted for poor follow-up
6 (unclear) [28]	Behavioural and psychological symptoms	Cognitive behavioural therapy *v* placebo	4	–1	–1	–1	0	Very low	Quality point deducted for incomplete reporting of results. Consistency point deducted for inconsistent results between RCTs. Directness point deducted for subjective outcomes
5 (647) [63] [64]	Behavioural and psychological symptoms	Exercise *v* placebo	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for studies designed with physical outcomes as primary outcome
8 (648) [67] [68] [69]	Behavioural and psychological symptoms	Antidepressants (clomipramine, fluoxetine, imipramine, sertraline) *v* placebo	4	–1	0	–1	0	Low	Quality point deducted for weak methods. Directness point deducted for short follow-up (6–12 weeks)
4 (432) [70]	Behavioural and psychological symptoms	Mood stabilisers (carbamazepine, sodium valproate/valproic acid) *v* placebo	4	–3	0	0	0	Very low	Quality points deducted for incomplete reporting of results, early termination of 1 RCT, and unclear blinding

Type of evidence: 4 = RCT Consistency: similarity of results across studies.
Directness: generalisability of population or outcomes.
Effect size: based on relative risk or odds ratio.