

EBMH Notebook: What are the effects of treatments on cognitive symptoms of dementia?

This EBMH Notebook summarises key messages about the effects of treatments in dementia, sourced from: *Warner JP, Butler R, Prabhakaran P. Dementia. Clin Evid 2003; 9: 1010–33*. The authors searched for evidence to October 2002.

Definition

Dementia is characterised by chronic, global, non-reversible impairment of cerebral function. It usually results in loss of memory (initially of recent events), loss of executive function (such as the ability to make decisions or sequence complex tasks), and changes in personality. Alzheimer's disease is a type of dementia characterised by an insidious onset and slow deterioration, and involves speech, motor, personality, and executive function impairment. It should be diagnosed after other systemic, psychiatric, and neurological causes of dementia have been excluded clinically and by laboratory investigation. Vascular dementia is multi-infarct dementia involving a stepwise deterioration of executive function with or without language and motor dysfunction occurring as a result of cerebral arterial occlusion. It usually occurs in the presence of vascular risk factors (diabetes, hypertension, and smoking). Characteristically, it has a more sudden onset and stepwise progression than Alzheimer's disease. Lewy body dementia is a type of dementia involving insidious impairment of executive functions with (1) Parkinsonism, (2) visual hallucinations, and (3) fluctuating cognitive abilities and increased risk of falls or autonomic failure.[1][2] Careful clinical examination of people with mild to moderate dementia, and the use of established diagnostic criteria, has an antemortem positive predictive value of 70–90% compared with the gold standard of postmortem diagnosis.[3][4]

Incidence / prevalence

About 6% of people aged over 65 years and 30% of people aged over 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 35–50% of dementia, and Lewy body dementia is estimated to account for up to 20% of dementia in the elderly, varying with geographical, cultural, and racial factors.[1] [5][6][7][8][9][10]

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.[11] Most people with the relatively rare condition of early onset Alzheimer's disease (before age 60 years) show an autosomal dominant inheritance due to mutations on presenilin or amyloid precursor protein genes. Several genes (*APP*, *PS-1*, and *PS-2*) have been identified.

Later onset dementia is sometimes clustered in families, but specific gene mutations have not been identified. Head injury, Down's syndrome, and lower premorbid intellect may be risk factors for Alzheimer's disease. Vascular dementia is related to cardiovascular risk factors, such as smoking, hypertension, and diabetes.

Lewy body dementia

The aetiology of Lewy body dementia is unknown. Brain acetylcholine activity is reduced in many forms of dementia, and the level of reduction correlates with cognitive impairment. Many treatments for Alzheimer's disease enhance cholinergic activity.[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. Average life expectancy after diagnosis is 7–10 years.[10]

Lewy body dementia

People with Lewy body dementia have an average life expectancy of around 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

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

Cognitive symptoms and global assessment of function

Quality of life of the person with dementia and their carer (rarely used in clinical trials). 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, 30-point scale, higher scores indicate better function[15] Clinical Dementia Rating Scale [CDR], 3-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]).

ADAS-cog is more sensitive than Mini Mental State Examination, but neither scale directly reflects outcomes important to people with dementia or their carers. A 7 point

change in the ADAS-cog has been regarded as clinically important. Measures of global state (e.g. clinician interview based impression of change with caregiver input scale, Clinician's Interview Based Impression of Change-Plus, 7 points scale).

Behavioural and psychological symptoms

Measures of psychiatric symptoms (eg Neuropsychiatric Inventory, 12-item caregiver rated scale, maximum score 144, higher scores indicate greater difficulties; Dementia Mood Assessment Scale and Brief Psychiatric Rating Scale, which use lower scores to signify improved symptoms; Behave-AD scale, scores 0–75, lower scores indicate better function). Time to institutionalisation or death are rarely reported because of the short duration of most trials.[16] Functional measures include the Disability Assessment for Dementia, a 40-item scale assessing 10 domains of function[17] and the Instrumental Activities of Daily Living Scale, maximum score 14 (higher scores indicate better function).[18]

Methods

Clinical Evidence search and appraisal October 2002. 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. 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.

What are the effects of treatments on cognitive symptoms of dementia?

Donepezil

One systematic review and two subsequent RCT have found that donepezil compared with placebo improves cognitive function and global clinical state at up to 52 weeks in people with mild to moderate Alzheimer’s disease. The review found no significant difference in patient rated quality of life at 12 or 24 weeks between donepezil and placebo. One RCT in people with mild to moderate Alzheimer’s disease found no significant difference in cognitive function at 12 weeks between donepezil and rivastigmine, although significantly fewer people taking donepezil withdrew from the trial for any cause.

Benefits

Versus placebo: We found one systematic review[19] and three subsequent RCTs in people with Alzheimer’s disease (see comment below).[20][21][22] The systematic review (search date 2000) identified eight RCTs of 12, 24, and 52 weeks’ duration

(2664 people with mild to moderate Alzheimer's disease) comparing donepezil versus placebo.[19]

Five RCTs identified by the review reported results using the Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog) or the Clinician's Interview Based Impression of Change-Plus (CIBIC-Plus). The review found that donepezil (10 mg daily) significantly improved cognitive function (measured by ADAS-cog scores) at 12 and 24 weeks compared with placebo, and significantly improved global clinical state at 24 weeks (CIBIC-Plus score unchanged or worse: 5 RCTs, 799 people; 295/390 [76%] with donepezil v 356/409 [87%] with placebo; OR for improvement in CIBIC-Plus score 2.1, 95% 1.3 to 3.6), but found no significant difference in patient rated quality of life at 12 or 24 weeks (at 24 wks: WMD +2.79, 95% CI 2.56 to 8.14).[19] An unblinded extension of one of the RCTs identified by the review observed 133 people taking donepezil (3–10 mg daily) for up to 240 weeks.[23] It found that improved cognitive function compared with baseline was present for 38 weeks in people taking donepezil, and throughout the period of observation cognitive function remained above the level estimated had people not been treated.

The first subsequent RCT (24 wks, 290 people with more severe Alzheimer's disease aged 48-92 years, Mini Mental State Examination [MMSE] score 5 to 17) compared donepezil (5–10 mg daily) versus placebo.[20] It found that donepezil significantly improved CIBIC-Plus scores at 24 weeks compared with placebo (mean difference 0.54, no 95% CI provided, results presented graphically; NNT 5, 95% CI 4 to 10 for improved or no change on CIBIC-Plus).[20] The second subsequent RCT (431 people with mild to moderate Alzheimer's disease aged 49–94 years, MMSE score 12–20) compared donepezil (10 mg daily) versus placebo for 1 year. It found that donepezil delayed the median time to “clinically evident functional decline” by 5 months compared with placebo (median 357 days with donepezil v 208 days with placebo; CI not provided). It found that a significantly higher proportion of people had no “clinically evident functional decline” at 1 year with donepezil compared with placebo (no functional decline: 123/207 [59%] with donepezil v 92/208 [44%] with placebo; NNT 7, 95% CI 5 to 17).

Versus rivastigmine: We found one open label RCT (111 people with mild to moderate Alzheimer's disease, MMSE score 10–26) comparing donepezil (5–10 mg daily) versus rivastigmine (1.5–6 mg twice daily). It found no significant difference in cognitive function at 12 weeks between donepezil and rivastigmine (assessed by clinicians blind to intervention; mean difference in ADAS-cog -0.15, 95% CI -1.47 to 1.71).[22]

Harms

Adverse effects common to all cholinesterase inhibitors include anorexia, nausea, vomiting, and diarrhoea.

Versus placebo: The RCTs identified by the review found that donepezil was associated with nausea, vomiting, and diarrhoea, which tended to be mild and transient.[19] The review found no difference between donepezil and placebo in the proportion of people who withdrew for any cause (27% with 10 mg donepezil v 20% with 5 mg v 21% with placebo).[19]

Long term follow up of people taking donepezil (10 mg; open label extension) found that 86% experienced at least one adverse effect, often occurring later in the study. Common adverse events included agitation (24%), pain (20%), insomnia (11%), and diarrhoea (9%).[23] The first subsequent RCT found no significant difference between donepezil and placebo in the proportion of people who experienced any adverse event over 24 weeks (120/144 [83%] v 117/146 [80%]; RR 1.04, 95% CI 0.93 to 1.16).[20]

Versus rivastigmine: The RCT found that fewer people had at least one adverse event with donepezil than with rivastigmine, but the difference was not significant (24/56 [43%] with donepezil v 32/55 [58%] with rivastigmine; RR 0.74, 95% CI 0.51 to 1.07). It found that, compared with rivastigmine, donepezil significantly reduced the proportion of people who withdrew from the trial for any cause (6/56 [11%] with donepezil v 17/55 [31%] with rivastigmine; RR of withdrawal 0.35, 95% CI 0.15 to 0.81; NNH 5, 95% CI 3 to 20).[22]

Comment

In the second subsequent RCT, “clinically evident functional decline” was defined as a decline of at least one point on the Alzheimer’s Disease Functional Assessment and Change Scale or an increase of at least one point on the Clinical Dementia Rating Scale. Donepezil is taken once daily; this is a potential advantage over other cholinesterase inhibitors for people with dementia. Improvement usually starts within 2–4 months of starting donepezil. Open label studies should be interpreted with caution but do suggest that the effect of continued treatment is sustained in the long term.[23] We found no RCTs of donepezil in people with Lewy body or vascular dementia.

Galantamine

RCTs identified by a systematic review, and one additional RCT, have found that galantamine improves cognitive function compared with placebo in people with Alzheimer’s disease or vascular dementia.

Benefits

We found one systematic review (search date 2002, 7 RCTs)[24] in people with mild to moderate Alzheimer’s disease and one additional RCT in people with vascular dementia (see comment below).[25] The review found that galantamine (12 mg or 16 mg twice daily) significantly improved cognitive function compared with placebo

(measured by Alzheimer's Disease Assessment Scale cognitive subscale [ADAS-cog] score) over 6 months and improved global status (Clinician's Interview Based Impression of Change [CIBIC] Plus score unchanged or improved: galantamine 12 mg twice daily, 3 RCTs 339/508 [67%] with galantamine v 286/567 [50%] with placebo OR for improvement in CIBIC-Plus score 2.0, 95% CI 1.5 to 2.5; galantamine 16 mg twice daily, 3 RCTs 233/459 [51%] with galantamine v 212/568 [37%] with placebo; OR for improvement in CIBIC-Plus score 1.9, 95% CI 1.4 to 2.5).

The additional RCT (592 people with vascular dementia or Alzheimer's disease plus cerebrovascular disease) compared galantamine 24 mg daily (396 people) versus placebo (196 people) for 6 months.[25] It found that galantamine significantly improved cognitive function from baseline at 6 months compared with placebo (4 point improvement in ADAS-cog: 35% with galantamine v 22% with placebo; NNT 8, 95% CI 5 to 17). It also found that galantamine significantly improved global clinical state at 6 months compared with placebo (CIBIC score "improved" or "no change": 74% with galantamine v 59% with placebo; NNT for "no deterioration" 7, 95% CI 5 to 15).[25]

Harms

Adverse effects common to all cholinesterase inhibitors include anorexia, nausea, vomiting, and diarrhoea. The review in people with Alzheimer's disease found that adverse effects over 6 months were more frequent with larger doses of galantamine, including nausea (42% with galantamine 16 mg twice daily v 25% with placebo) and vomiting (21% with galantamine 16 mg twice daily v 7% with placebo). It also found that higher doses of galantamine increased the proportion of people who discontinued treatment because of adverse effects over 6 months (27% with galantamine 16 mg twice daily v 15% with galantamine 12 mg twice daily v 8% with placebo).[24]

The additional RCT comparing galantamine versus placebo in people with vascular dementia found that more people taking galantamine withdrew because of adverse effects (20% with galantamine v 8% with placebo).[25]

Comment

We found no RCTs of galantamine in people with Lewy body dementia.

Rivastigmine

One systematic review and one additional RCT have found that rivastigmine improves cognitive function in people with Alzheimer's disease or Lewy body dementia compared with placebo, but adverse effects such as nausea, vomiting, and anorexia are common. Subgroup analysis from one RCT in people with Alzheimer's disease suggests that people with vascular risk factors may respond better to rivastigmine than those without. One RCT in people with mild to moderate Alzheimer's disease found no significant difference in cognitive function at 12 weeks between donepezil and

rivastigmine, although rivastigmine significantly increased the proportion of people who withdrew from the trial for any cause.

Benefits

Versus placebo: We found one systematic review (search date 2000, 4 RCTs, 12 or 26 weeks' duration, 3370 people with mild to moderate Alzheimer's disease)[26] and one additional RCT[27] in people with Lewy body dementia (see comment below). The review found that, over 26 weeks, rivastigmine (6–12 mg twice daily) produced small but significant improvements in cognitive function compared with placebo in people with Alzheimer's disease (Alzheimer's Disease Assessment Scale cognitive subscale [ADAS-cog]: 4 RCTs; 1917 people WMD -2.1, 95% CI -2.7 to -1.5; Mini Mental State Examination: WMD 0.8, 95% CI 0.5 to 1.1) and global clinical state (Clinician's Interview Based Impression of Change [CIBIC] score unchanged or worse: 4 RCTs, 715/973 [73%] v 675/839 [80%] with placebo; OR for improvement in CIBIC score 1.5, 95% CI 1.2 to 1.8). Quality of life results were not provided. A subgroup analysis of an RCT identified by the review[26] (699 people with Alzheimer's disease) comparing rivastigmine 1–4 mg daily or 6–12 mg daily versus placebo over 26 weeks found that people with vascular risk factors responded better than those without (mean ADAS-cog difference -2.3).[28] The additional RCT (120 people with Lewy body dementia) found that rivastigmine (dose titrated to 6 mg twice daily) significantly improved a computerised psychometric measure of cognitive function at 20 weeks compared with placebo (intention to treat analysis; P=0.05; no further data provided) and improved a global measure of behavioural function (NNT for at least 30% improvement on Neuropsychiatric Inventory score 3, 95% CI 2 to 6).[27]

Versus donepezil: We found one RCT comparing rivastigmine versus donepezil (see donepezil section).[22]

Harms

Adverse effects common to all cholinesterase inhibitors include anorexia, nausea, vomiting, and diarrhoea. The systematic review in people with Alzheimer's disease found that rivastigmine increased the proportion of people who discontinued treatment compared with placebo (35% with 6–12 mg rivastigmine v 18% with 1–4 mg rivastigmine v 17% with placebo).[26] The RCT in people with Lewy body dementia found that rivastigmine increased the proportion of people who had nausea compared with placebo (37% v 22%), vomiting (25% v 15%), anorexia (19% v 10%), and somnolence (9% v 5%; no further data provided).[27]

Comment

We found no RCTs of rivastigmine in people with vascular dementia.

Physostigmine

One systematic review in people with Alzheimer's disease found limited evidence that slow release physostigmine improved cognitive function compared with placebo but adverse effects, including nausea, vomiting, diarrhoea, dizziness, and stomach pain, were common.

Benefits

We found one systematic review (search date 2000, 15 RCTs) comparing physostigmine versus placebo in people mild to severe Alzheimer's disease (see comment below).[26] The RCTs differed widely in the preparations of physostigmine used, and most had weak reporting methods so the review could not perform a meta-analysis. Four were small trials of intravenous physostigmine, which did not report quantitative results. Seven were small trials (131 people, 6 crossover design) of standard oral preparation. The crossover trials did not provide precrossover results. One RCT (16 people) found no significant difference in cognition between oral physostigmine and placebo but it is likely to have been too small to exclude a clinically important difference. Four RCTs (1456 people) used controlled release preparations, but three of these reported results only for people who responded to physostigmine in a prestudy titration phase (see comment below). One RCT (170 people) found that physostigmine (27 mg daily) improved cognition after 12 weeks compared with placebo (Alzheimer's Disease Assessment Scale cognitive subscale: -2.0, 95% CI -3.6 to -0.5) but did not significantly improve activities of daily living or Clinician Based Impression of Change.

Harms

Common adverse effects of physostigmine include nausea, vomiting, diarrhoea, dizziness, and stomach pain. In RCTs that randomised all people with Alzheimer's disease rather than selecting those who tolerated and responded to physostigmine, withdrawals were more common with physostigmine (234/358 [65%] with physostigmine v 31/117 [26%] with placebo; OR 4.80, 95% CI 3.17 to 7.33).[29]

Comment

We found no RCTs of physostigmine in people with Lewy body or vascular dementia. Physostigmine is a sympathomimetic drug and has a very short half life. Screening out non-responders to a drug before the trial is likely to overestimate its effectiveness.

Tacrine

Two systematic reviews found limited evidence that tacrine improved cognitive function and global state in Alzheimer's disease compared with placebo, but adverse effects, including nausea and vomiting, diarrhoea, anorexia, and abdominal pain, were common.

Benefits

We found two systematic reviews comparing tacrine versus placebo in people with Alzheimer's disease (search date not stated, 12 RCTs, 1984 people;[30] search date 1997, 21 RCTs, including 12 RCTs identified by the first review, 3555 people;[31] see comment below). Various doses of tacrine were used in the RCTs, and the duration of treatment varied from 3–36 weeks. The first review found that tacrine significantly increased the proportion of people with overall clinical improvement compared with placebo (OR 1.58, 95% CI 1.18 to 2.11) and improved cognition (Mini Mental State Examination at 12 wks: SMD 0.77, 95% CI 0.35 to 1.20; Alzheimer's Disease Assessment Scale cognitive subscale at 12 wks: SMD -2.7, 95% CI -1.36 to -2.78).[30]

A subsequent subgroup analysis indicated that the five non-industry sponsored studies found no significant effect between tacrine and placebo, but most (6/7) manufacturer supported studies found clinical benefit (1 RCT could not be located for inclusion in the subgroup analysis).[32]

Harms

One RCT identified by the review found that withdrawals because of adverse events were common (OR for withdrawal 3.6, 95% CI 2.8 to 4.7)[30] and were more likely with higher doses (265/479 [55%] with high dose tacrine v 20/184 [11%] with placebo; RR 5.1, 95% CI 3.3 to 7.7; NNH 3, 95% CI 2 to 3), and reversible elevation of liver enzymes was found in 133/265 (50%) of people taking tacrine.[33] Common adverse events included nausea and vomiting (35% with 160 mg daily), diarrhoea (18%), anorexia (12%), and abdominal pain (9%).

Comment

The quality of tacrine trials was generally poor.[30] [31] We found no RCTs of tacrine in people with Lewy body or vascular dementia.

Lecithin

Small, poor RCTs identified by a systematic review provided insufficient evidence to assess lecithin in people with Alzheimer's disease.

Benefits

We found one systematic review (search date 2000, 10 RCTs, 256 people with Alzheimer's disease) comparing lecithin versus placebo (see comment below).[34] It found no significant improvement in cognition, functional performance, quality of life, or global impression between lecithin and placebo (see comment below).[34] One RCT identified by the review (90 people with "Parkinsonian dementia"), which may have included people with Lewy body dementia, found no benefit from lecithin compared with placebo.

Harms

The review found that adverse effects were more common with lecithin (41% with lecithin v 10% with placebo; OR 6.0, 95% CI 1.5 to 24).[34] The specific nature of the adverse effects was not stated.

Comment

One RCT (included in the systematic review)[34] comparing lecithin versus placebo in people with minimal cognitive impairment found that some components of cognition were significantly better in the placebo group. Most studies of lecithin were small and weak. Meta-analysis in the systematic review was hampered by diverse outcome criteria. We found no RCTs of lecithin in people with Lewy body or vascular dementia.

Nicotine

We found one systematic review, which found no RCTs of adequate quality in people with dementia.

Benefits

One systematic review (search date 2001) found no RCTs of adequate quality.[35]

Harms

We found no RCTs.

Non-steroidal anti-inflammatory drugs

One RCT in people with Alzheimer's disease found no significant difference in cognitive function after 25 weeks' treatment with diclofenac plus misoprostol compared with placebo. Another RCT in people with Alzheimer's disease found that indometacin improved cognitive function after 6 months' treatment compared with placebo.

Benefits

We found two RCTs in people with Alzheimer's disease (see comment below).[36] [37] The first RCT (41 people with Alzheimer's disease) found no significant difference in cognitive function after 25 weeks' treatment with diclofenac plus misoprostol compared with placebo (Alzheimer's Disease Assessment Scale cognitive subscale [ADAS-cog] score: mean difference +1.14, 95% CI -2.9 to +5.2) or global status (Clinician's Interview Based Impression of Change score: +0.24, 95% CI -0.26 to +0.74).[36] The second RCT (44 people with mild to moderate Alzheimer's disease) found that indometacin (indomethacin) (150 mg daily) for 6 months significantly improved cognitive function compared with placebo (Mini Mental State Examination and ADAS-cog score; inadequately described results for only 28/44 completers).[37]

Harms

In one RCT,[36] more people withdrew by week 25 with diclofenac plus misoprostol than with placebo (12 [50%] v 2 [12%]). No serious drug related adverse events were reported.[36] In the RCT of indometacin, 21% of people on indometacin withdrew because of gastrointestinal symptoms.[37]

Comment

We found one systematic review of aspirin for vascular dementia (search date 2000), which identified no RCTs.[38] Earlier versions of a systematic review of aspirin in vascular dementia included one RCT (70 people), which was subsequently removed because of inadequate quality, including a lack of placebo control.[38] We found no RCTs of lecithin in people with Lewy body dementia.

Oestrogen

One systematic review has found that, in women with mild to moderate Alzheimer's disease, oestrogen improves cognition over 7 weeks to 12 months' treatment compared with no oestrogen.

Benefits

We found one systematic review (search date 2000, 8 RCTs, 313 women with mild to moderate Alzheimer's disease aged over 56 years) comparing oestrogen (0.625-1.25 mg daily) versus no oestrogen for 7 weeks to 12 months (see comment below).[39] The review found that oestrogen improved cognitive function compared with no oestrogen (5 RCTs, Mini Mental State Examination: WMD 2.3, 95% CI 1.7 to 3.4).

Harms

There is concern that oestrogen treatment may increase the risk of developing breast cancer and cardiovascular events.

Comment

Most RCTs in the review were small and heterogeneity may have distorted the results of the meta-analysis. We found no RCTs of oestrogen in people with Lewy body or vascular dementia. A meta-analysis of 14 observational studies (5990 people, length of follow up not stated) found that hormone replacement therapy is associated with a lower risk of developing dementia (dementia in 13% with HRT v 21% with controls; RR 0.56, 95% CI 0.46 to 0.68).[39] Observational studies provide only indirect evidence; the observed association may be explained by confounders (eg educational level, lifestyle factors).

Selegiline

One systematic review has found that, in people with mild to moderate Alzheimer's disease, selegiline improves cognitive function, behavioural disturbance, and mood compared with placebo, but has found no significant difference in global clinical state.

Benefits

We found one systematic review (search date not stated, 15 RCTs) comparing selegiline versus placebo in people with mild to moderate Alzheimer's disease (average number of people 50, typical duration of treatment 3 months; see comment below).[40] Analysis of pooled results found that selegiline improved several outcome measures: cognitive function scores (measured by several parameters: 4 RCTs, 160 people; SMD -0.56, 95% CI -0.88 to -0.24), mood score (Dementia Mood Assessment Scale: 1 RCT, 20 people; SMD -1.14, 95% CI -2.11 to -0.18), and behavioural symptom score (Brief Psychiatric Rating Scale: 3 RCTs, 98 people; SMD -0.53, 95% CI -0.94 to -0.12). The review found no significant difference in global clinical state between selegiline and placebo (4 RCTs, 94 people; SMD -0.11, 95% CI -0.49 to +0.27).

Harms

The RCTs identified by the review found no difference in adverse effects (anxiety, agitation, dizziness, nausea, dyspepsia) between selegiline and placebo.[40]

Comment

The trials used a variety of outcomes, making comparison with other treatments difficult. We found no RCTs of selegiline in people with Lewy body or vascular dementia.

Ginkgo biloba

RCTs found limited evidence that ginkgo biloba may improve cognitive function compared with placebo in people with Alzheimer's disease or vascular dementia.

Benefits

We found one systematic review (search date 2002, 33 RCTs) comparing ginkgo biloba versus placebo in people with cognitive impairment, Alzheimer's disease, or vascular dementia (see comment below).[41] Trial duration ranged from 3-53 weeks, doses and preparations of ginkgo biloba varied widely, and diverse outcomes were assessed, making results difficult to synthesise.[41] The review stated that it was unable to provide intention to treat analyses as most RCTs provided only completer analyses. It found that ginkgo biloba at any dose significantly improved cognition over 24 weeks (cognition assessed by a variety of validated scales: 5 RCTs, 3 of which were in people with Alzheimer's disease or vascular dementia [757 people]; results presented as SMD; P=0.008).

The review included two large RCTs in people with Alzheimer's disease or vascular dementia. The first large RCT (216 people with mild to moderate Alzheimer's disease or vascular dementia) found that ginkgo biloba (200 mg daily) significantly increased the proportion of people who were rated as improved at 24 weeks (completer analysis: improvement in Clinician's Interview Based Impression of Change [criteria for improvement not defined] 57/79 [72%] v 42/77 [55%] with placebo; RR 1.32, 95% CI 1.03 to 1.69).

The second large RCT (327 people, 236 people with Alzheimer's disease) provided an intention to treat analysis.[42] It found that, in people with Alzheimer's disease, ginkgo biloba significantly improved cognition (intention to treat analysis for people with Alzheimer's disease, change in Alzheimer's Disease Assessment Scale cognitive subscale score: -1.7, 95% CI -3.1 to -0.20; NNT for 4 point change in ADAS-cog: 8, 95% CI 5 to 50) and care giver assessed improvement over 26 weeks compared with placebo (change in Geriatric Evaluation by Relative's Rating Instrument score: -0.16, 95% CI -0.25 to -0.06), but did not significantly improve the mean Clinician's Global Impression of Change score (change in score: +0.1, 95% CI -0.1 to +0.2).[42] The RCT had a high withdrawal rate; 137/309 (44%) people withdrew from the trial.

Harms

The review found no significant difference between ginkgo biloba and placebo in the proportion of people who had at least one adverse effect (adverse effects not specified: 117/591 [19.7%] with ginkgo v 59/471 [12.5%] with placebo; RR 0.95, 95% CI 0.72 to 1.26).

Comment

Many of the RCTs in the review included people with memory and cognitive impairment other than dementia so the results of the meta-analysis may not be fully generalisable to people with Alzheimer's disease or vascular dementia. We found no RCTs of ginkgo biloba in people with Lewy body dementia. Preparations of ginkgo biloba available over the counter differ in terms of purity and concentration of active ingredients compared with high purity extract (EGb 761) used in most RCTs.

Vitamin E

One RCT in people with moderate to severe Alzheimer's disease found no significant difference in cognitive function between vitamin E and placebo after 2 years' treatment, but found that vitamin E reduced mortality, institutionalisation, loss of ability to perform activities of daily living, and the proportion of people who developed severe dementia.

Benefits

We found one systematic review (search date 2000, 1 multicentre RCT, 169 people with moderate to severe Alzheimer's disease; see comment below).[43] The RCT

compared four treatments: vitamin E (2000 IU daily); selegiline; vitamin E plus selegiline; or placebo.[44] It found that no significant difference in cognitive function with high dose vitamin E alone for 2 years compared with placebo (measured by the cognitive portion of the Alzheimer's Disease Assessment Scale: mean change in score 8.3 with vitamin E v 6.7 with placebo; reported as non-significant; no further details reported; see comment below). It found that vitamin E significantly increased event free survival compared with placebo (defined as death, or survival until institutionalisation, loss of ability to perform activities of daily living, or severe dementia [clinical dementia rating of 3]; OR 0.49, 95% CI 0.25 to 0.96).[44]

Harms

The RCT found no significant difference in adverse effects between placebo and vitamin E.[44] Other studies have found weak evidence of associations between high dose vitamin E and bowel irritation, headache, muscular weakness, visual complaints, vaginal bleeding, bruising, thrombophlebitis, deterioration of angina pectoris, worsening of diabetes, syncope, and dizziness.[45] A few case reports have created concern that vitamin E may increase the risk of haemorrhagic stroke.

Comment

The groups in the RCT identified by the review were not matched evenly at baseline: the placebo group had a higher mean Mini Mental State Examination score, and these baseline scores were a significant predictor of outcome.[44] Attempts to correct for this imbalance suggested that vitamin E might increase mean survival, but the need for statistical adjustments weakens the strength of this conclusion. We found no RCTs of vitamin E in people with Lewy body or vascular dementia.

Music therapy

Poor studies identified by a systematic review provided insufficient evidence to assess music therapy.

Benefits

We found one systematic review of music therapy (search date 1998, 21 studies, 336 people with various types of dementia).[46] It included studies with weak methods and found that music therapy significantly improved cognitive and behavioural outcomes compared with control interventions (mean effect size 0.79, 95% CI 0.62 to 0.95; see comment below). Significant effects were noted with different types of music therapy (active v passive, taped v live).

Harms

The systematic review gave no information on harms.[46]

Comment

The primary studies lacked adequate controls, had potential for bias, used diverse interventions, and used inadequate outcome measures. Although one meta-analysis found significant benefits for music therapy on pooling the results of many studies, further high quality studies are needed to clarify whether the results are explained by a true effect or by bias. A previous Cochrane systematic review has been withdrawn.[47]

Reality orientation

One systematic review of small RCTs found that reality orientation improved cognitive function compared with no treatment in people with various types of dementia.

Benefits

We found one systematic review (search date 2000, 6 RCTs, 125 people with various types of dementia).[48] The RCTs compared reality orientation versus no treatment and used different measures of cognition. The review found that reality orientation significantly improved cognitive function score compared with no treatment (SMD - 0.59, 95% CI -0.95 to -0.22). No separate analysis was done for specific types of dementia.

Harms

The RCTs gave no information on adverse effects.[48]

Comment

The RCTs did not use standardised interventions or outcomes.[48]

Reminiscence therapy

Reminiscence therapy involves encouraging 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. RCTs provided insufficient evidence to assess reminiscence therapy.

Benefits

We found one systematic review of reminiscence therapy; search date 2000, 2 RCTs, 42 people).[49] Analysis of pooled data was hindered by poor trial methods, diverse outcomes, and no separation of data for different types of dementia.

Harms

We found no RCTs.

What are the effects of treatments on behavioural and psychological symptoms of dementia?

Antipsychotics

One systematic review in people with various types of dementia found no significant difference in agitation between haloperidol and placebo, but found that haloperidol may reduce aggression. One RCT in people with moderate to severe dementia, including Alzheimer's disease and vascular dementia, found that risperidone significantly improved behavioural and psychological symptoms over 12 weeks compared with placebo, but another RCT in people with severe dementia and agitation found no significant difference in symptoms over 13 weeks. One RCT in people with Alzheimer's disease found that olanzapine reduced agitation, hallucinations, and delusions compared with placebo. RCTs have found no significant difference in efficacy between different antipsychotics. Two RCTs in people with dementia found no significant difference in agitation between trazodone and haloperidol, but may have been too small to exclude a clinically important difference.

Benefits

Antipsychotics (various) versus placebo: We found one systematic review comparing antipsychotics versus placebo (search date 1995, 7 RCTs, 4–12 wks' duration, 294 people with various types of dementia and behavioural problems).[50] It assessed a variety of antipsychotics, including haloperidol (2 RCTs). The other antipsychotics assessed (acetophenazine, loxapine, trifluoperazine, thiothixene) are no longer commonly used. It found that antipsychotics significantly increased the proportion of people who improved compared with placebo (61% with antipsychotics v 34% with placebo; $P < 0.001$).[50]

Haloperidol versus placebo: We found one systematic review of haloperidol for agitation in various types of dementia, including Alzheimer's disease and vascular dementia (search date 2000, 5 RCTs, none of which were included in the older review).[51] It found no significant difference in agitation at 6–16 weeks between haloperidol and placebo (change in symptoms from baseline measured by the Cohen-Mansfield Agitation Inventory or the psychomotor score of the Behavioural Symptoms Scale for Dementia; WMD -0.48, 95% CI -1.43 to +0.53). However, it found that haloperidol significantly reduced aggression from baseline at 3–6 weeks compared with placebo (2 RCTs, 240 people: WMD -1.11, 95% CI -2.02 to -0.11).[51]

Risperidone versus placebo: We found two RCTs.[52] [53] The first RCT (double blind, 625 people with moderate to severe dementia plus behavioural and psychological symptoms, 73% with Alzheimer's disease, mean age 83 years, 68% women) compared risperidone versus placebo over 12 weeks.[52] A response was defined as a reduction of at least 50% in the Behave-AD scale. It found that risperidone (1 and 2 mg daily) significantly improved the chance of responding over

12 weeks compared with placebo (45% with risperidone 1 mg v 33% with placebo v 50% with risperidone 2 mg; for risperidone 1 mg v placebo NNT 9, 95% CI 5 to 100; for risperidone 2 mg v placebo NNT 6, 95% CI 4 to 17). Gender and the type of dementia did not significantly affect the results. The second RCT (344 people with agitation and severe dementia, 67% with Alzheimer's, 26% with vascular dementia, mean age 81 years, 56% women) compared adjusted doses of risperidone (mean dose 1.1 mg) versus placebo or haloperidol (mean dose 1.2 mg) over 13 weeks for the treatment of behavioural symptoms.[53] A response was defined as a reduction of at least 30% in the Behave-AD scale. It found no significant difference in the proportion of people who responded over 13 weeks between risperidone and placebo (37/68 [54%] with risperidone v 35/74 [47%] with placebo; ARI +7%, 95% CI, -9% to +23%; see below for risperidone v haloperidol).

Olanzapine versus placebo: We found one RCT (double blind, 6 wks' duration, 206 elderly US nursing home residents with Alzheimer's disease [177 people] or Lewy body dementia [29 people] plus psychotic or behavioural symptoms).[53] The RCT compared olanzapine (given as a fixed dose of 5, 10, or 15 mg daily) versus placebo. Agitation, hallucinations, and delusions were improved by the two lower doses but not by the highest dose of olanzapine compared with placebo (subscale of the Neuropsychiatric Inventory [nursing home version]: -7.6 with olanzapine 5 mg v -6.1 with olanzapine 10 mg v -4.9 with olanzapine 15 mg v -3.7 with placebo).

Comparisons between antipsychotics: The review (search date 1995) identified eleven RCTs comparing different antipsychotics.[50] It found no significant difference in efficacy among haloperidol, diazepam, thioridazine, loxapine, or oxazepam.[50] One subsequent RCT comparing adjusted doses of risperidone versus haloperidol or placebo found no significant difference in the proportion of people who responded over 13 weeks between risperidone and haloperidol.[53] A response was defined as a reduction of at least 30% in the Behave-AD scale.

Harms

Antipsychotics (various) versus placebo: One systematic review (search date 1995) found that antipsychotics significantly increased adverse effects, including sedation (21%), movement disorders (13%), and orthostatic hypotension (8%) compared with placebo ($P < 0.01$).[50] However, it found no significant difference between antipsychotics and placebo in the proportion of people who withdrew from the trial ($P=0.50$).[50] One study (2 year prospective, longitudinal, 71 people with dementia) found that the mean decline in cognitive scores in 16 people who took antipsychotics was twice that of people who did not (expanded Mini Mental State Examination 21 v 9; $P=0.002$).[54]

Risperidone versus placebo: The first RCT found that discontinuation because of adverse events was more common with high dose risperidone than with low dose risperidone or placebo (16% with 1 mg risperidone v 24% with 2 mg v 12% with

placebo v 8% with 0.5 mg).[52] Olanzapine versus placebo: The RCT found that olanzapine increased sedation (25% with 5 mg olanzapine v 26% with 10 mg v 36% with 15 mg v 6% with placebo) and gait disturbance compared with placebo (20% with 5 mg olanzapine v 14% with 10 mg v 17% with 15 mg v 2% with placebo).[55] Comparisons between antipsychotics: In the RCT comparing risperidone versus placebo or haloperidol, about 18% of people withdrew because of adverse effects from each of the three arms.[53] Extrapyramidal adverse effects were more common in people receiving haloperidol than placebo (22% with haloperidol v 15% with risperidone v 11% with placebo).

Comment

High response rates with placebo indicate that many behavioural problems resolve spontaneously in the short term. Most people with dementia are sensitive to adverse effects from antipsychotics, especially sedation and extrapyramidal symptoms. People with Lewy body dementia are particularly sensitive to these adverse effects,[56] suggesting that antipsychotics have a poor balance of benefits and harms in people with Lewy body dementia. More studies are needed to determine whether newer atypical antipsychotics have a better ratio of benefits to harms than older antipsychotics.

Antiepileptics

One RCT found that carbamazepine significantly reduced agitation and aggression compared with placebo in people with agitation and dementia. One RCT found that sodium valproate reduced agitation over 6 weeks in people with dementia, but another RCT found no significant difference in aggressive behaviour over 8 weeks between sodium valproate and placebo. We found no RCTs about other antiepileptic drugs.

Benefits

We found no systematic review.

Carbamazepine: We found one RCT (single blind, 51 nursing home patients with agitation and Alzheimer's disease, vascular dementia or mixed Alzheimer's disease and vascular dementia, 6 wks' duration) comparing carbamazepine (individualised doses; modal dose 300 mg; mean serum level 5.3 µg/mL) versus placebo.[57] It found that carbamazepine significantly improved a measure of agitation and aggression (mean total Brief Psychiatric Rating Scale score: 7.7 with carbamazepine v 0.9 with placebo) and a measure of global status compared with placebo (Clinical Global Impressions rating: 77% with carbamazepine v 21% with placebo).

Sodium valproate: We found two RCTs.[58] [59] The first RCT (single blind, 56 people with Alzheimer's disease or vascular dementia in nursing homes, 6 wks' duration) compared sodium valproate versus placebo.[58] It found that when several covariates were taken into account, sodium valproate significantly improved agitation

and aggression compared with placebo (measured by Brief Psychiatric Rating Scale score; $P=0.05$ only after adjustment) and a measure of global status (Clinical Global Impressions rating: 68% with sodium valproate ν 52% with placebo; $P=0.06$). The second RCT (43 people with various types of dementia plus behavioural problems, crossover design) comparing sodium valproate (480 mg daily) versus placebo for 3 weeks found no significant difference in aggressive behaviour over 8 weeks after crossover (mean change in Social Dysfunction and Aggression Scale-9 score -0.72 with valproate ν -0.72 with placebo; $P=0.99$).[59]

Harms

Carbamazepine: The RCT found that adverse effects were significantly more common with carbamazepine than with placebo (16/27 [59%] with carbamazepine ν 7/24 [29%] with placebo; $P=0.003$). These were considered clinically significant in two cases: 1 person with tics, 1 with ataxia. Carbamazepine in the elderly may cause cardiac toxicity. *Sodium valproate:* The first RCT found that adverse effects, generally rated as mild, were significantly more common with sodium valproate than with placebo (68% with sodium valproate ν 33% with placebo; $P=0.003$).[58]

Comment

The need to perform adjustments for covariates in the second RCT weakens the strength of the findings.

Antidepressants

One RCT in people with dementia found no significant difference in agitation between trazodone and haloperidol. Another RCT in people with Alzheimer's disease and agitated behaviour found no significant difference in outcomes among trazodone, haloperidol, behaviour management techniques, and placebo. The RCTs may have been too small to exclude a clinically important difference.

Benefits

We found no systematic review but found two RCTs.[60] [61] The first RCT (double blind, 28 elderly people with agitated behaviour associated with Alzheimer's disease, vascular dementia or mixed Alzheimer's disease and vascular dementia, 9 wks' duration) compared trazodone (50–250 mg daily) versus haloperidol (1–5 mg daily).[60] It found no significant difference in agitation between the groups, but the trial was too small to exclude a clinically important difference. The second RCT (double blind, 149 people with Alzheimer's disease and agitated behaviours, 16 wks' duration) compared four treatments: haloperidol (mean dose 1.1 mg daily); trazodone (mean dose 200 mg daily); behaviour management techniques; or placebo.[61] It found no significant difference in outcome (Alzheimer's Disease Co-operative Study Clinical Global Impression of Change) between the four interventions, but it may have been too small to exclude a clinically important difference.

Harms

In the first RCT, adverse effects were more common in the group treated with haloperidol than trazodone.[60] In the second RCT no significant differences in adverse events were seen between the trazodone group and the placebo group.[61] Priapism has been reported with trazodone, occurring in about 1/10 000 people.

Comment

The RCTs were too small to exclude clinically important differences between the interventions.[60] [61]

Cholinesterase inhibitors

RCTs provided inconclusive evidence about the effects of donepezil or galantamine compared with placebo on behavioural and psychiatric symptoms in people with mild to moderate Alzheimer's disease.

Benefits

Donepezil: We found no systematic review but found two RCTs.[20] [62] The first RCT (290 people with moderate to severe Alzheimer's disease aged 48–92 years, Mini Mental State Examination [MMSE] score 5–17) compared donepezil (5–10 mg daily) versus placebo.[20] It found that donepezil significantly improved functional and behavioural symptoms at 24 weeks compared with placebo (Disability Assessment for Dementia score; mean difference 8.23, no CI provided; $P < 0.001$; Neuropsychiatric Inventory score; mean difference 5.64, no 95% CI provided; $P < 0.0001$). The second RCT (208 people with mild to moderate Alzheimer's disease, at least 1 symptom on the Neuropsychiatric Inventory Nursing Home version and living in a nursing home) found no significant difference in psychiatric symptoms after 24 weeks of treatment between donepezil and placebo (change in mean Neuropsychiatric Inventory Nursing Home version scores -4.9 with donepezil v -2.3 with placebo; reported as non-significant; no further data provided).[62]

Galantamine: We found one systematic review (search date 2002), which identified two RCTs that assessed the effects of galantamine on behavioural and psychological symptoms.[24] A meta-analysis was not performed because of differences in length of follow up between the trials. Both trials used the Neuropsychiatric Inventory (NPI); scores range from 0-120, reduction indicates improvement. The first RCT (386 people with mild to moderate Alzheimer's disease; MMSE score 10–22) found no significant difference in psychiatric symptoms at 3 months between galantamine (12–16 mg twice daily) and placebo (mean reduction in NPI score: -0.30 with galantamine v $+0.50$ with placebo; WMD -0.80 , 95% CI -2.67 to $+1.07$). The second RCT (978 people with mild to moderate Alzheimer's disease; MMSE score 12–24) found that galantamine (16 mg daily) significantly reduced psychiatric symptoms at 6 months compared with placebo (mean reduction in NPI score -0.10 with galantamine v $+2.00$ with placebo; WMD -2.10 , 95% CI -4.04 to -0.16), but found no significant difference with galantamine (8 mg daily or 24 mg daily).[24]

Harms

See harms of donepezil and galantamine described above.

Comment

Cholinesterase inhibitors improve cognitive function and are well tolerated in older people.

Reality orientation

Reality orientation involves presenting information that is designed to reorient a person in time, place, or person. It may range in intensity from a board giving details of the day, date, and season, to staff reorienting a patient at each contact. One systematic review found that reality orientation improved behaviour compared with no treatment in people with various types of dementia.

Benefits

We found one systematic review (search date 2000, 6 RCTs, 125 people with various types of dementia).[48] It found that reality orientation significantly improved behavioural symptom score compared with no treatment (SMD -0.66, 95% CI -1.27 to -0.05). No separate analysis was done for specific types of dementia.

Harms

The RCTs gave no information on adverse effects.[48]

Comment

The RCTs did not use standardised interventions or outcomes.[48]

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Competing interests

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