BMJ Open | Interventions to delay functional decline in people with dementia: a systematic review of systematic reviews

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ABSTRACT

Objective: To summarise existing systematic reviews that assess the effects of non-pharmacological, pharmacological and alternative therapies on activities of daily living (ADL) function in people with dementia.

Design: Overview of systematic reviews.

Methods: A systematic search in the Cochrane Database of Systematic Reviews, DARE, Medline, EMBASE and PsycInfo in April 2015. Systematic reviews of randomised controlled trials conducted in people with Alzheimer's disease or dementia measuring the impact on ADL function were included. Methodological quality of the systematic reviews was independently assessed by two authors using the AMSTAR tool. The quality of evidence of the primary studies for each intervention was assessed using GRADE.

Results: A total of 23 systematic reviews were included in the overview. The quality of the reviews varied; however most (65%) scored 8/11 or more on the AMSTAR tool, indicating high quality. Interventions that were reported to be effective in minimising decline in ADL function were: exercise (6 studies, 289 participants, standardised mean difference (SMD) 0.68, 95% CI 0.08 to 1.27; GRADE: low), dyadic interventions (8 studies, 988 participants, SMD 0.37, 95% CI 0.05 to 0.69; GRADE: low) acetylcholinesterase inhibitors and memantine (12 studies, 4661 participants, donepezil 10 mg SMD 0.18, 95% CI 0.03 to 0.32; GRADE: moderate), selegiline (7 studies, 810 participants, SMD 0.27, 95% CI 0.13 to 0.41; GRADE: low), huperzine A (2 studies, 70 participants, SMD 1.48, 95% CI 0.95 to 2.02; GRADE: very low) and Ginkgo biloba (7 studies, 2530 participants, SMD 0.36, 95% CI 0.28 to 0.44; GRADE: very low).

Conclusions: Healthcare professionals should ensure that people with dementia are encouraged to exercise and that primary carers are trained and supported to provide safe and effective care for the person with dementia. Acetylcholinesterase inhibitors or memantine should be trialled unless contraindicated.

Trial registration number: CRD42015020179.

INTRODUCTION

Dementia affects approximately 35.6 million people worldwide.[1] This figure is expected to nearly double every 20 years due to population ageing.[2] It is one of the leading causes of mortality and morbidity, particularly in people aged 60 years or over in which it affects approximately 5–7% of the population.[1]

The trajectory of dementia is associated with gradual functional decline whereby the person with dementia requires more assistance to manage activities over time due to cognitive and physical impairment. Functional decline is associated with reduced quality of life in people with dementia[3] and increased care costs.[4] It is also associated with increased need for informal care and can increase the carer burden, particularly when the rate of decline is rapid.[5]

While dementia is a terminal condition, the length of time between diagnosis and death can be many years.[6] Therefore, one of the goals of treatment, particularly in the earlier stages of the disease, is to promote independence and reduce functional decline.[7] Consumers have called for a greater focus on rehabilitation and restorative care in order to maximise the quality of life.[8]

There are a number of intervention approaches that have been trialled to manage the symptoms of dementia including pharmacological approaches (such as acetylcholinesterase

Strengths and limitations of this study

- This overview examines the efficacy for a number of different treatment approaches in delaying functional decline.
- The effect sizes of the different treatment approaches are compared providing clinicians and policymakers with information regarding treatments that should be prioritised.
- The quality of the included reviews is appraised using AMSTAR and the quality of evidence for each intervention is appraised using GRADE.
- There is a debate regarding the most appropriate methodology for conducting overviews including how authors should capture the most recent evidence and avoid including overlapping reviews.

inhibitors) and non-pharmacological approaches (such as exercise). The vast amount of research literature means that it can be difficult for health professionals to keep themselves up to date in understanding which interventions are thought to be effective overall and the relative efficacy of different intervention approaches. Systematic reviews of systematic reviews (overviews) are useful in that they examine the effectiveness of a number of different interventions for a particular health condition.[9] Systematic reviews do not traditionally attempt to do this due to time and resources involved in conducting such a review.

The aim of this review was to summarise systematic reviews that assess the effects of intervention for functional decline in people with dementia.

METHODS

An a priori review protocol was developed and registered on the PROSPERO International prospective register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO; registration number CRD42015020179). The protocol provides full details of the methods used. There were no changes made to the protocol during the review.

Inclusion and exclusion criteria
Types of studies

This overview included the most recent and comprehensive systematic reviews. Systematic reviews were defined as 'a review of the evidence on a clearly formulated question that uses systematic and explicit methods to identify, select and critically appraise relevant primary research, and to extract and analyse data from the studies that are included in the review'.[10] In order to be eligible, the systematic review must have included randomised controlled trials (RCTs). Cochrane Reviews and systematic reviews published in other peer-reviewed journals were eligible. Systematic reviews that overlapped with the most up to date and comprehensive review in terms of the intervention approach were excluded to avoid double counting of studies where possible. Reviews published in non-English languages were excluded.

Population

Reviews which included populations of people with a diagnosis of dementia (any cause) or Alzheimer's disease were included. Reviews were excluded if they included people with non-Alzheimer's dementia only (eg, people with vascular dementia). Studies conducted in any setting, whether community or residential, were included.

Intervention and comparison

All interventions intended to treat or manage the symptoms of dementia were eligible; this included non-pharmacological interventions (such as exercise, counselling or education), pharmacological interventions (such as acetylcholinesterase inhibitors) and alternative

therapies (such as *Ginkgo biloba*). Reviews including RCTs which compared the intervention to usual care, placebo or another form of intervention were included.

Outcome

The overview included reviews where performance of global activities of daily living (ADL) was reported as a primary or secondary outcome. ADL whether measured by observation, self-report or proxy report or tools such as the Functional Independence Measure, Barthel Index, Alzheimer's Disease Co-operative Study —ADL Inventory, Disability Assessment for Dementia or Cleveland Scale for ADL were eligible.

Search methods for identification of reviews

Searches were conducted in the Cochrane Database of Systematic Reviews Dementia and Cognitive Improvement Group domain, Cochrane DARE, Medline, EMBASE and PsycINFO in April 2015. The Medline search strategy is attached as an online supplementary file and was adapted for the other databases. The search strategy was formulated including the dementia search string used by the Cochrane Dementia and Cognitive Improvement Group for dementia.

Data collection and analysis
Selection of reviews

One author (KL) conducted the searches and assessed all retrieved citations meeting the inclusion criteria on the basis of title and abstract. A second author (SD) independently reviewed 10% of the excluded articles. Potentially eligible reviews were reviewed in full text. Two authors (KL and SD) independently assessed all articles obtained in full text. A third author was consulted in cases of disagreement. Eligible reviews were classified based on intervention approach (eg, exercise) and discussion occurred regarding the most appropriate review to include (based on recency and quality). We used methods consistent with the Cochrane Handbook; we did not repeat the searches, determine eligibility, assess risk of bias, conduct additional meta-analysis or aim to identify any additional studies.[9] Thus, we accepted included reviews as being 'complete' and did not check other reviews for missing studies.

Data extraction and management

One author (KL) extracted the data which was checked by a second researcher. Disagreements were resolved by a third author. A data collection form was developed and tested prior to starting the review. Fields extracted included review details (author, title, year), review aims, inclusion criteria, date of last search and data from included RCTs that provided a comparison to usual care, placebo or another form of treatment. If the review included data from RCTs and other study designs, we extracted the data for the RCTs only. Where RCTs and quasi-RCTs were included, we extracted only the RCT data when possible (ie, when individually

reported). We extracted details on the number of RCTs included in the review, population size and characteristics, intervention and comparator characteristics and outcomes (on an individual study basis or pooled values as reported in the included review). Authors of the included reviews were not contacted for further information.

Assessment of quality of included reviews

Two people (KL and a second researcher) independently assessed the methodological quality of the included reviews using the AMSTAR checklist.[11] The AMSTAR checklist includes a number of criteria which reflect whether the review was guided by a protocol, whether there was duplicate study selection and data extraction, the comprehensiveness of the search, inclusion of grey literature, use of quality assessment, appropriateness of data synthesis and documentation of conflict of interest. Disagreements regarding AMSTAR score were resolved by discussion or a decision made by a third author.

Assessment of quality of the body of evidence for each intervention

GRADE was used to rate the quality of the evidence for each intervention.[12] The GRADE level was determined based on information provided in the systematic review. The level considers the risk of bias of included studies, indirectness of evidence, inconsistency of results (heterogeneity), imprecision of results and possibility of publication bias.[12]

Data synthesis

Data was synthesised in tables and a narrative synthesis was used to provide a summary of results. Effect sizes were also expressed graphically using standardised mean difference. Where meta-analysis had already been conducted within the review, we used the meta-analysis performed by the authors. We did not conduct additional meta-analyses, however where the results were presented as mean difference, we calculated the standardised mean difference to enable comparison of effect sizes across reviews.

RESULTS

The study selection process is presented in figure 1 (PRISMA). There were 23 systematic reviews meeting all inclusion criteria and included in this overview.[13–35] An additional 10 reviews were identified that listed ADL as an outcome of interest; however the reviews failed to identify any applicable studies. These reviews were for socially assistive robots, animal-assisted therapy, transcutaneous electrical nerve stimulation, social support groups for the person with dementia, naftidrofuryl, respite care, smart home technologies, metal protein-attenuating compounds, ibuprofen and educational interventions for the person with dementia.[36–45] One review evaluated the

efficacy of metrifonate, however identified serious harms associated with use; metrifonate was since withdrawn from the market.[46] These reviews are not discussed further. In most cases, the most recent comprehensive review (ie, dementia or Alzheimer's disease) reporting ADL outcomes was deemed as being of acceptable quality for inclusion. There were two intervention categories where this was not the case. We excluded two reviews of cognitive rehabilitation which were published more recently than the included Cochrane Review but involved a search date that was not as recent as the included review.[47 48] We also excluded two systematic reviews of exercise that were published more recently than the included review. One of the excluded reviews was of lower quality than the Cochrane Review and included non-randomised trials, but involved a search date that was 6 months more recent.[49] A second review included studies where exercise was included as one component of a multifactorial programme.[50]

Characteristics of the included reviews

Characteristics of the included reviews are summarised in table 1. Fifteen (65%) of the reviews were Cochrane Reviews. Eleven reviews addressed non-pharmacological approaches. These were cognitive training, cognitive stimulation therapy, light therapy, exercise, aromatherapy, nutritional supplementation, validation therapy, psychological treatment, case management, music therapy and intervention for the person with dementia and carer dyad. Eight reviews addressed pharmacological approaches. These were acetylcholinesterase inhibitors and memantine, pharmacotherapies to improve sleep, latrepirdine, melatonin, statins, selegiline, lecithin and nimodipine. Four reviews addressed alternative therapies. These were vitamin B supplementation, *G. biloba*, huperzine A and acupuncture.

Most (65%) of the reviews included people with any form of dementia. The remaining reviews included only people with Alzheimer's disease. The mean age of participants in all reviews was people in their 70s or 80s with the exception of the *G. biloba* and huperzine A reviews which involved younger participants. Most participants had mild-to-moderate severity dementia, although some reviews of pharmacological interventions (eg, acetylcholinesterase inhibitors) included a large number of participants with severe dementia. The duration of different interventions varied from days to months and a large number of outcome assessment measures were used to assess ADL function.

Methodological quality of included reviews

The quality of the included review reflects the rigour and transparency of the review team rather than the quality of evidence for the intervention approach. Most of the reviews (65%) were of high quality (scores ≥8/11) as assessed using the AMSTAR tool (table 1). High-quality reviews were for latrepirdine, light therapy, exercise, aromatherapy, pharmacotherapies for sleep,
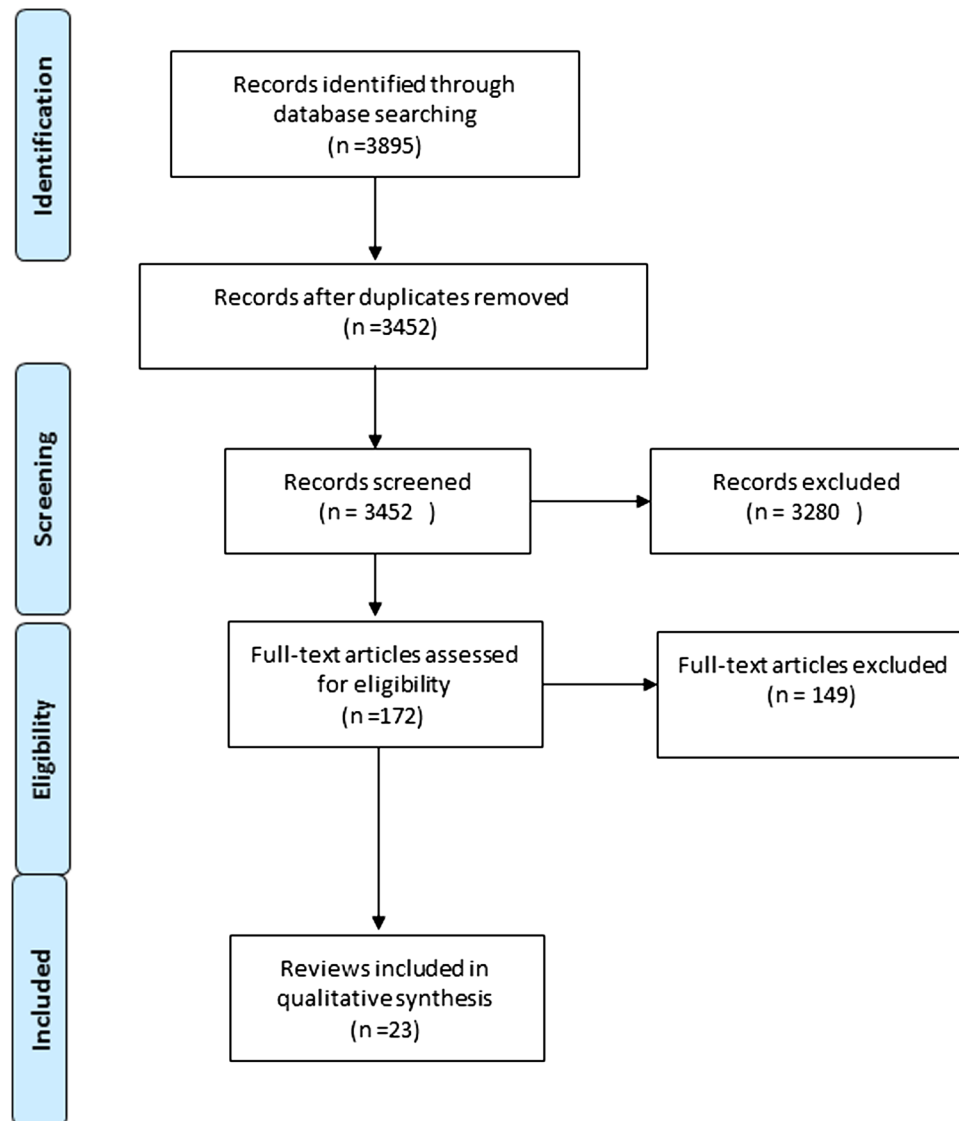
Figure 1 PRISMA 2009 flow diagram.

case management, cognitive stimulation therapy, huperzine A, lecithin, selegiline and nimodipine. However, there were also two lower quality reviews (scoring 5 or less on AMSTAR). Low-quality reviews were for *G. biloba* and dyadic interventions.

Quality of evidence in included reviews

While the authors of this overview did not reassess the risk of bias of primary studies included in the reviews, it was necessary to examine the quality of these studies as determined by the original review authors to determine the overall quality of the evidence using GRADE. It can be seen from figure 2 that studies in most of the reviews had a risk of bias resulting in downgrading of the quality overall.

The quality of evidence for all non-pharmacological interventions was low with the exception of nutritional supplementation for which the evidence base was of moderate quality. The quality of evidence for pharmacological interventions ranged from low (latrepirdine) to high (statins). In contrast, alternative therapies had very low (huperzine A, *G. biloba*, acupuncture)-to-moderate (vitamins B) evidence.

EFFECT OF INTERVENTIONS

Effects are presented in table 2. Non-pharmacological interventions: two non-pharmacological interventions demonstrated a significant effect in reducing to functional decline in people with dementia. Exercise had a large magnitude of effect (six studies, 289 participants, SMD 0.69, 95% CI 0.08 to 1.27) however the quality of evidence was low due to a risk of bias in some studies and the limited number of participants in the analysis. Dyadic interventions, in which the therapeutic intervention aims to engage the person with dementia and their carer in maximising quality of life (utilising interventions, defined broadly as psychosocial but which also included meaningful activities, daily living activities and

Table 1 Characteristics of included reviews

Review	Date of search	Population included in the review	Intervention addressed in the review	Comparison intervention	Measures of ADL	Quality of the review (AMSTAR)
Non-pharmacological interventions						
Forbes	Oct 2013	Older people (over 65 years of age) and diagnosed as having dementia using accepted criteria Mean age ranged from 73 to 89 Baseline MMSE ranged from 8 to 23	Exercise programmes	Usual care or social contact/activities	Barthel ADL index, Katz Index of ADLs, Changes in Advanced Dementia Scale	10/11
Van't Leven	Jan 2012	Older people (aged 65 years or more) with a diagnosis of dementia. Participants were included if they were living in informal carers in the community and excluded if they were living in residential care settings. Mean age not reported though inclusion criteria states >65. Participants had mild-to-moderate severity dementia.	Dyadic interventions	Not specified	Barthel Index AMPS IDDD Functional Dependence Scale	5/11
Neal	Aug 2005	Older people (aged over 65 years) diagnosed with Alzheimer's disease, dementia or other forms of cognitive impairment Nursing home residents with BPSD. Mean age 88.	Validation therapy (affirming the person's beliefs and experiences)	Usual care or alternative intervention (eg, social contact group)	Not specified	7/11
Orgeta	Jan 2013	Older people (aged over 65 years) diagnosed with Alzheimer's disease or other forms of dementia Mean age range 75–76 Mean MMSE range 22–24	Psychological treatments for depression and anxiety	Usual care or non-specific psychosocial therapy	Bristol Activities of Daily Living ADSC-ADL	8/11
Reilly	March 2014	Diagnosis of dementia of any subtype and of any severity Mean age range 78–80 Most participants had mild-to-moderate severity dementia	Case management	Usual care or alternative intervention	Everyday Abilities Scale for India ADCS-ADL Barthel Index	9/11
Ueda	Feb 2011	Diagnosis of dementia of any type according to accepted criteria. Mean age 83 Severity not reported	Music therapy	Not specified	Barthel Index	7/11
Woods	Dec 2011	Diagnosis of dementia or any subtype and of any severity. Mean age range 74–85 Mean MMSE range 20–22	Cognitive stimulation intervention targeting cognitive and social functioning	No treatment, usual care or placebo	Barthel Index IADL Stewart ADL Scale	10/11

Continued

Table 1 Continued

Review	Date of search	Population included in the review	Intervention addressed in the review	Comparison intervention	Measures of ADL	Quality of the review (AMSTAR)
Bahar Fuchs	Nov 2012	Diagnosis of dementia. Targeting people with minimal, mild or moderate dementia (MMSE>12) Mean age was 78 in the studies reporting this info. Baseline MMSE range 23–25/30	Cognitive training or cognitive rehabilitation	No treatment, usual care, wait list control or active control	Basic and Instrumental Activities of Daily Living scales Physical Self Maintenance Scale Bayer Activities of Daily Living Scale	8/11
Forbes	Jan 2014	Diagnosis of dementia (all types considered) according to accepted criteria Mean age 85, all participants were nursing home residents	Light therapy	Not specified	Nurse-Informant Activities of Daily Living Measure	10/11
Forrester	Jan 2014	Diagnosis of dementia of any subtype and of any severity Mean age 85 Nursing home residents with agitation for >4 weeks	Aromatherapy	Placebo aromatherapy	Barthel ADL Scale	9/11
Liu	Sept 2012	Older people (over 65 years of age) and diagnosed as having dementia using accepted criteria Mean age range 73–79 MMSE not reported in two of the three studies in the review. The third study involved people with mild Alzheimer's disease	Mealtime interventions (incl. nutritional supplementation)	Not specified	ADCS-ADL	8/11
Pharmacological interventions						
Tan	Nov 2013	Diagnosis of probable or possible Alzheimer's disease consistent with accepted criteria Mean age participants 76 Five of the trials included people with mild-to-moderate dementia. Seven trials included people with severe dementia	Acetylcholinesterase inhibitors and memantine	Placebo	ADCS-ADL	7/11
Chau	June 2014	Clinical diagnosis of mild, moderate or severe AD Population age and severity not described	Latrepirdine	Placebo	ADCS-ADL	10/11
Jansen	June 2009	Diagnosis of dementia of any subtype and of any severity Mean age 85–86 Moderate severity dementia	Melatonin	Placebo or no treatment	Nurse-Informant Activities of Daily Living Measure	8/11

Continued

Table 1 Continued

Review	Date of search	Population included in the review	Intervention addressed in the review	Comparison intervention	Measures of ADL	Quality of the review (AMSTAR)
McCleery	March 2013	People who had both: A. Alzheimer's disease diagnosed using any well-validated criteria, such as DSM, at the time of the study, and B. a sleep problem diagnosed on the basis of subjective or objective measures Mean age ranged 77–81 Mean MMSE range 11–14	Pharmacotherapies for sleep	Placebo	Katz Index	10/11
McGuinness	Jan 2014	Patients with a diagnosis of probable or possible AD according to accepted criteria. Mean age 74–79 Mild-to-moderate severity dementia	Statins	Placebo	ADCS-ADL ADFACS	7/11
Birks	July 2002	Diagnosis of probable Alzheimer's disease Mean age ranged from 70 to 83 in the studies reporting ADL outcomes Studies included people with mild-to-moderate dementia	Selegeline	Placebo	Unclear	9/11
Birks	March 2010	People with unclassified dementia, Alzheimer's disease, vascular dementia or mixed dementia Mean age ranged from 74 to 80 in the studies reporting ADL outcomes Studies included people with mild-to-moderate dementia	Nimodipine	Placebo	Unclear	9/11
Higgins	May 2004	Diagnosis of dementia of any type Mean age 74 years Mild-to-moderate severity	Lecithin	Placebo	PADL Scale	9/11
Alternative therapies						
Yang	June 2013	Diagnosis of Alzheimer's disease. People with other forms of dementia were excluded. All studies but one conducted in China Age range 50–85 Details regarding severity of dementia not reported	Huperzine A	No treatment, usual care or placebo.	Activities of Daily Living Scale ADCS-ADL	9/11
Tan	March 2014	Diagnosis of dementia of any type or people with mild cognitive impairment	*Gingko biloba*	Placebo	ADL-IS GBS-ADL	3/11

Continued

Table 1 Continued

Review	Date of search	Population included in the review	Intervention addressed in the review	Comparison intervention	Measures of ADL	Quality of the review (AMSTAR)
Lee	Aug 2008	Mean age 65–82 Most participants had mild-to-moderate severity dementia Diagnosis of Alzheimer's disease Population details not reported except to state that one of the two trials included people with mild-to-moderate severity AD	Acupuncture	Usual care or alternative intervention	Not specified	6/11
Li	April 2014	Diagnosis of probable or possible Alzheimer's disease consistent with the DSM-IV Mean age ranged from 75 to 78 Mean MMSE range 19–24/30	Vitamins B supplementation	Not specified	ADL Scale IADL Scale ADCS-ADL	7/11

NR, not reported.
ADL, activities of daily living; ADFAC, Alzheimer's disease functional assessment and change Scale; ADSC, Alzheimer's disease co-operative study; AMPS, Assessment of Motor and Process Skills; BPSD, behavioral and psychological symptoms of dementia; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders; GBS, Guillain-Barré syndrome; IADL, instrumental activities of daily living Scale; IDDD, Interview for deterioration in daily living activities; MMSE, mini-mental state examination; PADL, physical ADL.

environmental adaptations) were also associated with a significant positive effect on ADL (eight studies, 988 participants, SMD 0.37, 95% CI 0.05 to 0.69). Again, a number of studies were at risk of bias and there were mixed findings among studies. There was insufficient evidence to conclude whether or not the other intervention approaches were effective due to the small number of studies and the low quality of evidence.

Pharmacological interventions: two pharmacological interventions demonstrated a significant effect on ADL function. The use of acetylcholinesterase inhibitors or memantine was associated with a small but statistically significant effect on function (12 studies, 4661 participants, donepezil 5 mg SMD 0.18, 95% CI 0.10 to 0.46; donepezil 10 mg SMD 0.18, 95% CI 0.03 to 0.32; galantamine 24 mg SMD 0.15, 95% CI 0.04 to 0.25; rivastigmine 12 mg SMD 0.19, 95% CI 0.02 to 0.36). Overall, the evidence for acetylcholinesterase inhibitors and memantine was of moderate quality. Effect sizes varied slightly according to the specific agent and dose used, although the effect size was consistently small. Selegiline was also found to have a small statistically significant effect on ADL function at 8–17-week follow-up (seven studies, 810 participants, SMD 0.27, 95% CI 0.13 to 0.41). Studies were at risk of bias and there were mixed findings between studies hence the quality of evidence was low.

Alternative therapies: two of the alternative therapies were reported to significantly improve ADL function. Huperzine A was reported to be effective although this was based on only two studies (two studies, 70 participants, SMD 1.48, 95% CI 0.95 to 2.02). Furthermore, the studies included in the review were at a high risk of bias due to unclear allocation concealment, possible selective reporting and risk of incomplete outcome data in both of the studies, and possible non-blinded outcome assessor in one of the studies. In addition, the outcome measure used in the pooled analysis in the review is not clearly reported. Overall, the quality of evidence for huperzine A was considered very low. *G. biloba* was also reported to be effective in the included systematic review, however it was also associated with very low-level evidence; the quality of the systematic review (AMSTAR=3/11) and the included studies was low (seven studies, 2530 participants, SMD 0.36, 95% CI 0.28 to 0.44). Furthermore, although there were seven included studies in the review, the findings were inconsistent between the studies.

DISCUSSION

This overview identified 23 systematic reviews (including 84 studies reporting on ADL performance outcomes). These reviews addressed a range of different interventions that may be considered for use in people with dementia. Of the 23 interventions reviewed, only six were reported to be successful in reducing functional decline. Acetylcholinesterase inhibitors and memantine,
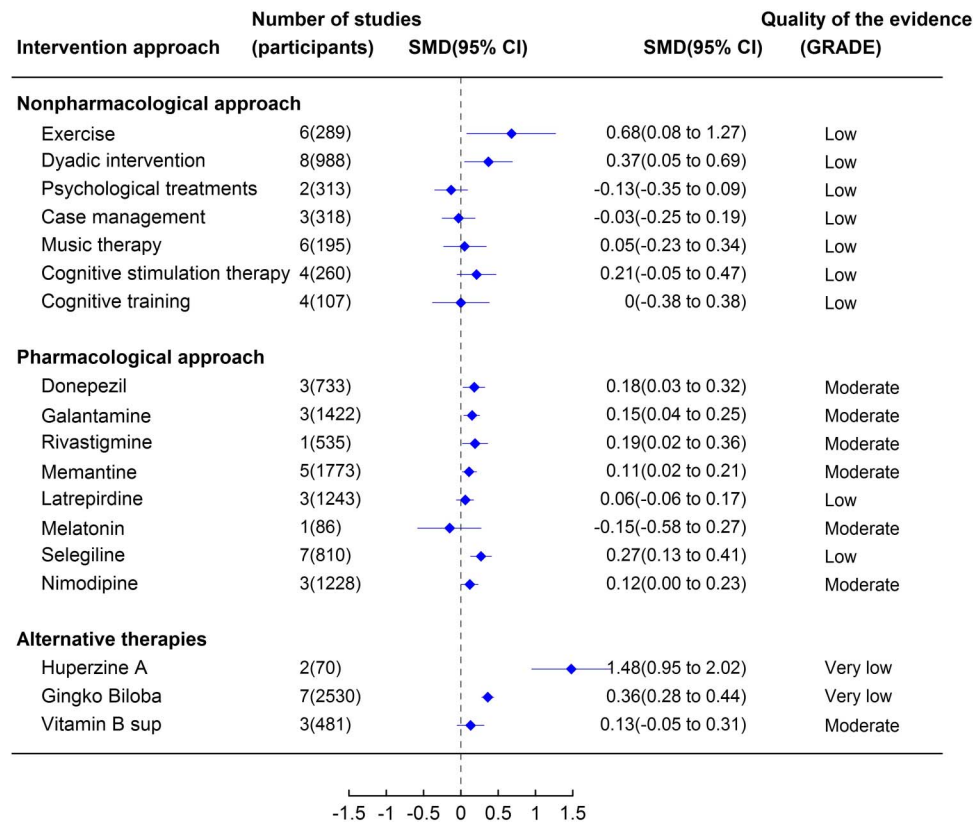
Intervention approach	Number of studies (participants)	SMD(95% CI)	SMD(95% CI)	Quality of the evidence (GRADE)
Nonpharmacological approach				
Exercise	6(289)		0.68(0.08 to 1.27)	Low
Dyadic intervention	8(988)		0.37(0.05 to 0.69)	Low
Psychological treatments	2(313)		-0.13(-0.35 to 0.09)	Low
Case management	3(318)		-0.03(-0.25 to 0.19)	Low
Music therapy	6(195)		0.05(-0.23 to 0.34)	Low
Cognitive stimulation therapy	4(260)		0.21(-0.05 to 0.47)	Low
Cognitive training	4(107)		0(-0.38 to 0.38)	Low
Pharmacological approach				
Donepezil	3(733)		0.18(0.03 to 0.32)	Moderate
Galantamine	3(1422)		0.15(0.04 to 0.25)	Moderate
Rivastigmine	1(535)		0.19(0.02 to 0.36)	Moderate
Memantine	5(1773)		0.11(0.02 to 0.21)	Moderate
Latrepirdine	3(1243)		0.06(-0.06 to 0.17)	Low
Melatonin	1(86)		-0.15(-0.58 to 0.27)	Moderate
Selegiline	7(810)		0.27(0.13 to 0.41)	Low
Nimodipine	3(1228)		0.12(0.00 to 0.23)	Moderate
Alternative therapies				
Huperzine A	2(70)		1.48(0.95 to 2.02)	Very low
Gingko Biloba	7(2530)		0.36(0.28 to 0.44)	Very low
Vitamin B sup	3(481)		0.13(-0.05 to 0.31)	Moderate

-1.5 -1 -0.5 0 0.5 1 1.5

Figure 2 The effect of different treatment approaches on activities of daily living function in people with dementia.

pharmacological agents that are widely used in treating dementia, were convincingly demonstrated to improve the ADL (based on moderate quality evidence), although the effect sizes were small. The quality of the evidence was considered low for two non-pharmacological approaches (exercise and dyadic psychosocial interventions), however the effect sizes were small-to-moderate, suggesting that more research is required to confirm effect on ADL. Evidence was very low for the two alternative therapies (huperzine A and *G. biloba*) indicating that the findings of improving ADL should be interpreted with extreme caution for these therapies. In addition, we found insufficient evidence to conclude that the remaining intervention approaches are ineffective due to the lack of studies examining each approach and poor methodological quality of existing studies. While caution is required, due to the absence of effective treatment options and trajectory of functional decline associated with dementia, it is recommended that after consideration of potential benefits, harms and costs, health professionals consider prescription of acetylcholinesterase inhibitors/memantine as a method of reducing functional decline. Furthermore, the effects of exercise and dyadic interventions are thought to be greater and they are not associated with side effects, therefore these interventions should be routinely recommended for people with dementia.

The magnitude of the effect sizes of the interventions demonstrated to be effective were considered small to moderate.[51] Thus, while the intervention may significantly improve performance of the ADL, the effect may not be strong enough to impact on outcomes of institutionalisation, carer impact or quality of life. Two recent systematic reviews revealed that only a small number of studies have been shown to improve quality of life for people with dementia.[52 53] The reviews found that carer interventions and dyadic interventions for people living in private dwellings and cognitive stimulation therapy for people in group homes had the best evidence for positively impacting on quality of life.[52]

The number of studies, particularly of pharmacological agents, that measured the impact on ADL was generally small. Interventional studies in dementia research frequently focus on outcomes of cognitive function as the key symptoms of dementia, particularly in the earlier phases of the condition, are cognitive. However, studies should also examine impact on ADL function as improvements in cognitive function may not translate to gains in ADL performance or other patient-important outcomes such as quality of life. For example, the included review of acetylcholinesterase inhibitors and memantine included 23 studies of which only 12 looked at the effect of the interventions on ADL function.[27] Similarly, the included review of exercise comprised 16 RCTs; nine of the studies reported cognitive outcomes, whereas only six reported ADL function outcomes despite the expectation that this would be a key expected outcome of any exercise programme.[16]

Table 2 Effects of interventions as reported in the included systematic reviews

Intervention and comparison intervention	Number of participants included in the meta-analysis (studies)	Measure of ADL	Effect measure (expressed as SMD or MD)	Statistically significant	Quality of the evidence (GRADE)
Non-pharmacological interventions					
Exercise programmes vs usual care (postintervention)[16]	6 studies (289 participants)	Multiple	SMD 0.68 (0.08 to 1.27)	Yes	⊕⊕○○ Low[1a,3]
Dyadic interventions vs control[30]	8 studies (988 participants)	Multiple	SMD 0.37 (0.05 to 0.69)	Yes	⊕⊕○○ Low[1b,2]
Validation therapy vs usual care (1 year)[24]	1 study (88 participants)	Unclear	Review stated effect on ADL was not significant (data not reported)	No	⊕⊕○○ Low[1c,3]
Psychological treatments for depression and anxiety vs usual care (postintervention (6 weeks/8–12 months))[25]	2 studies (313 participants)	Multiple	SMD −0.13 (−0.35 to 0.09)	No	⊕⊕○○ Low[1b,3]
Case management vs usual care (6 months)[26]	3 studies (318 participants)	Multiple	SMD −0.03 (−0.25 to 0.19)	No	⊕⊕○○ Low[1d,3]
Music therapy vs control (postintervention) B[29]	6 studies (195 participants)	Multiple	SMD 0.05 (−0.23 to 0.34)	No	⊕⊕○○ Low[1e,3]
Cognitive stimulation vs no cognitive stimulation (postintervention)[31]	4 studies (260 participants)	Multiple	SMD 0.21 (−0.05 to 0.47)	No	⊕⊕○○ Low[1f,3]
Cognitive training vs control (postintervention)[13]	4 studies (107 participants)	Multiple	SMD 0.00 (−0.38 to 0.38)	No	⊕⊕○○ Low[1g,3]
Light therapy vs control (at 1 year)[15]	1 study (94 participants)	NI-ADLs	MD −5.0 (−11.16 to 1.16) Data not available for conversion to SMD	No	⊕⊕○○ Low[1h,3]
Aromatherapy vs placebo (postintervention)[17]	1 study (63 participants)	Barthel Scale	MD −0.50 (−1.79 to 0.79) Data not available for conversion to SMD	No	⊕⊕○○ Low[1i,3]
Nutritional intervention vs control[A] (postintervention (3 months))[21]	3 studies (1262 participants)	Multiple	Not pooled The individual trials reported no significant differences between the groups	No	⊕⊕⊕○ Moderate[1j]
Pharmacological interventions					
Acetylcholinesterase inhibitors and memantine vs placebo at end point[27]	12 studies (4661 participants)	ADCS/ADL subscale	Donepezil 5 mg MD 1.0 (−0.53 to 2.53) SMD 0.18 (−0.10 to 0.46) Donepezil 10 mg MD 1.03 (0.21 to 1.85) SMD 0.18 (0.03 to 0.32) Galantamine 24 mg MD 0.68 (0.04 to 1.32) SMD 0.15 (0.04 to 0.25) Rivastigmine 12 mg MD 1.8 (0.20 to 3.40) SMD 0.19 (0.02 to 0.36) Memantine 20 mg MD 1.02 (0.27 to 1.78) SMD 0.11 (0.02 to 0.21)	Yes	⊕⊕⊕○ Moderate[1k]
Latrepirdine vs placebo (postintervention)[14]	3 studies (1243 participants)	ADCS-ADL Scale	MD 1.00 (−1.15 to 3.15) SMD 0.06 (−0.06 to 0.17)	No	⊕⊕○○ Low[1l,2]
Melatonin vs placebo (6 weeks)[18]	1 study (86 participants)	NI-ADLs	MD −2.0 (−7.50 to 3.50) SMD −0.15 (−0.58 to 0.27)	No	⊕⊕⊕○ Moderate[3]
Pharmacotherapies for sleep vs placebo (melatonin, trazodone) (postintervention (2–8 weeks))[22]	2 studies (193 participants)	Multiple	Not pooled The individual trials reported no significant differences between the groups	No	⊕⊕⊕○ Moderate[3]

Continued

Table 2 Continued

Intervention and comparison intervention	Number of participants included in the meta-analysis (studies)	Measure of ADL	Effect measure (expressed as SMD or MD)	Statistically significant	Quality of the evidence (GRADE)
Statins vs placebo (3 months)[23]	3 studies (1109 participants)	Multiple	Not pooled. The individual trials reported no significant differences between the groups	No	⊕⊕⊕⊕ High
Selegiline vs placebo (8–17 weeks)[33]	7 studies (810 participants)	Multiple	SMD 0.27 (95% CI 0.13 to 0.41)	Yes	⊕⊕○○ Low[1m,2]
Nimodipine vs placebo (6 months)[34]	3 studies (1228 participants)	Multiple	SMD −0.12 (95% CI −0.23 to 0.00)	No	⊕⊕⊕○ Moderate[1m]
Lecithin vs placebo (6 months)[35]	1 study (63 participants)	PADL Scale	The trial reported no significant differences between the groups	No	⊕⊕⊕○ Moderate[3]
Alternative therapies					
Huperzine A vs placebo (12 weeks)[32]	2 studies (70 participants)	ADL Scale	MD −8.82 (−11.47 to −6.16)[C] SMD −1.48 (−2.02 to −0.95)	Yes	⊕⊕○○ Very low[3,4]
Gingko biloba vs placebo (endpoint)[28]	7 studies (2530 participants)	Multiple	SMD −0.36 (−0.44 to −0.28)[D]	Yes	⊕⊕○○ Very low[2,4]
Acupuncture vs herbal mixture (8 weeks)[19]	1 study (104 participants)	Not reported	ES=0.29, not significant	No	⊕⊕○○ Very low[3,4]
Vitamins B supplementation vs control (postintervention (6–18 months))[20]	3 studies (481 participants)	Multiple	SMD 0.13 (−0.05 to 0.31)	No	⊕⊕⊕○ Moderate[1n]

A. Note the nutritional interventions included daily oral nutritional supplementation, medical food (Souvenaid) and a health and nutrition promotion programme for physicians, caregivers and people with dementia.

B. Note that the meta-analysis conducted in the systematic review by Ueda and colleagues included randomised and non-randomised trials.

C. The authors report this outcome as an ADL Scale but do not specify the particular scale. A lower score in the meta-analysis was interpreted by the authors as an improvement in ADL function.

D. The authors reported this reduction in score as an improvement in function. Examination of the meta-analysis suggests that outcome measures were combined. Where outcome measures used higher scores to represent better function, the scores were multiplied by −1 so that all outcome measures were reporting in the same direction in the meta-analysis.

Note: Where MD was reported, the authors of the review calculated the SMD in RevMan.

GRADE footnotes.

[1a]Unclear randomisation procedures in three studies. Unclear whether outcome assessor blinded in one study. Participants not blinded. Downgraded for risk of bias.

[1b]Unclear whether outcome assessor blinded in one study. Participants not blinded. Downgraded for risk of bias.

[1c]Unclear allocation concealment. Participants not blinded. Downgraded for risk of bias.

[1d]Unclear allocation concealment in one study. Participants not blinded. Outcome assessors not blinded or status unclear in two studies. Selective reporting in one study. Downgraded for risk of bias.

[1e]Unclear allocation concealment and blinding in two studies. Incomplete outcome data in two studies. Participants not blinded. Downgraded for risk of bias.

[1f]Unclear allocation concealment, randomisation sequence generation, incomplete outcome data and details of blinding in two studies. Downgraded for risk of bias.

[1g]Randomisation details unclear in all four studies. Details of incomplete outcome data and blinded outcome assessor unclear in single studies (×2). Participants not blinded. Downgraded for risk of bias.

[1h]Cluster randomisation by care home. Downgraded for risk of bias.

[1i]Unclear allocation concealment and unclear risk due to incomplete outcome data. Downgraded for risk of bias.

[1j]Two of the three studies were rated as being of moderate quality while the remaining study was rated as strong. Downgraded for risk of bias.

[1k]Mixed quality of studies and variability in transparency of reporting. Downgraded for risk of bias.

[1l]High risk of bias for incomplete outcome data and selective reporting in two studies. Unclear allocation concealment in one study. Downgraded for risk of bias.

[1m]Unclear details of randomisation in all studies. Downgraded for risk of bias.

[1n]Unclear selective reporting and unclear risk of bias in other areas reported for one study. Downgraded for risk of bias.

[2]Mixed findings among studies, CIs do not overlap. Downgraded for inconsistency.

[3]Total number of participants <400 in the analyses. Downgraded for imprecision.

[4]Very serious risk of bias: unclear or high in majority of studies for most aspects of quality assessment. Downgraded (−2) for risk of bias.

ADCS, Alzheimer's disease co-operative study; ADL, activities of daily living; ES, effect size; NI-ADL, nurse informant activities of daily living; PADL, physical ADL; SMD, standardised mean difference; MD, mean difference.

The interventions that were found to have a significant effect on ADL function should not be difficult to implement routinely for people with dementia as they are accessible in most Western countries. However, health professionals should note that the non-pharmacological interventions that were effective (exercise and dyadic interventions) involved regular participation. Exercise programmes ranged in frequency from 2 to 5 times per week and were programmed over a minimum of 7 weeks. Dyadic interventions were scheduled over a number of treatment sessions. It should be noted that the interventions reduced functional decline relative to the control group rather than leading to improvements in functional performance compared with the baseline, indicating a slowing of functional decline rather than prevention.

The number of research trials evaluating the efficacy of acetylcholinesterase inhibitors is large relative to research conducted in other aspects of dementia treatment. Published studies consistently demonstrate a positive effect on cognition and ADL function. Clinicians need to consider the potential bias of the research in this field given that many of the studies were funded by pharmaceutical companies. Killin et al[54] conducted a meta-analysis examining the differences in findings between industry-funded and independent RCTs of donepezil and found that studies sponsored by pharmaceutical companies reported a larger effect on standardised cognitive tests than independent research groups.

Policymakers should consider the results of this review and implications for practice. For example, in Australia, while the government spends a large amount of money subsidising acetylcholinesterase inhibitors and memantine (over $60 million per year[55]), there is less money invested in ensuring people with dementia can access appropriate exercise programmes or dyadic interventions, which may be associated with other benefits such as improved cardiovascular health, reduced carer burden and increased community participation.

The benefit of conducting an overview is that it provides a wide-ranging perspective on the intervention approaches available and their relative efficacy. One of the limitations of this approach is that the most recently published primary studies are not captured. However, the search dates of the included reviews were relatively recent in most cases. Furthermore, while the body of research for interventions in dementia care is slowly accumulating, there have not been any significant advances in the past couple of years that would alter routine care. Another limitation is that systematic reviews tend to examine single-intervention approaches and therefore more complex multifactorial interventions (eg, physical exercise plus cognitive stimulation) have not been captured. In addition, the detail of participants, intervention and results are less prominent at the level of overview and there is a little scope to delve into the details of the individual interventions. The findings of this review suggest that clinicians should familiarise themselves with the details of the type of exercise and dyadic interventions thought to be most effective.[16 30]

This particular overview did not seek to identify additional trials that may have been missed in the 'included' systematic review and excluded reviews in languages published other than English. Furthermore, we only included RCTs which restricted the number of studies included and information that can be drawn upon. The results of this overview highlight effective approaches but do not provide much needed information around cost-effectiveness as economic evaluations in dementia care are scarce.[56]

There is clearly more work to be performed in both developing interventions to delay functional decline and testing interventions to provide more evidence around the type of approaches that are most effective and for whom. For example, the review on exercise failed to provide recommendations about the type of exercise or population most likely to benefit due to the heterogeneity of studies.

In conclusion, at the current time in the absence of disease-modifying treatments for dementia, health professionals should attempt to minimise functional decline in people with dementia by considering prescription of acetylcholinesterase inhibitors and memantine, and recommending exercise and dyadic interventions.

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