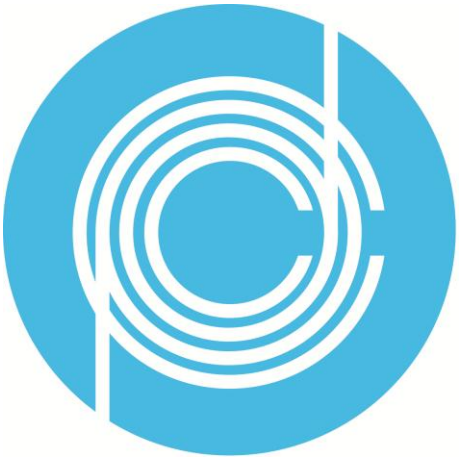

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CLINICAL PRACTICE GUIDELINES AND PRINCIPLES OF CARE FOR PEOPLE WITH DEMENTIA

Technical Report Volume 1

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Members of the Guideline Adaptation Committee generously contributed their time to assist in the development of this Guideline. Consumers have played a key role in the development of this Guideline and their input has been critical to ensuring the document remains relevant to the needs of people with dementia and their carers.

The main guideline is an adaptation of 'Dementia: Supporting people with dementia and their carers in health and social care', published by the NCC-MH in 2006. The original publication is available from www.nice.org.uk/guidance/cg42/evidence. The adaptation has been reproduced with permission of the NCC-MH. The NCC-MH, however, has not checked the adaptation to confirm that it accurately reflects the original NCC-MH publication and no guarantees are given by the NCC-MH in regard to the accuracy of the adaptation. The NCC-MH guideline that this adaptation is based upon was prepared for the National Institute for Health and Care Excellence (NICE) for use by the National Health Service in England and Wales. NICE guidance does not apply to Australia and NICE has not been involved in the development or adaptation of this guidance for use in Australia. Throughout this document the NCC-MH publication will be referred to as the NICE Guideline.

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Abbreviations

3MS	Modified Mini Mental Exam
6-CIT	6-item cognitive impairment test
ACE-R	Addenbrooke's Cognitive Examination – Revised
ACR	Annual Conversion Rate
AD	Alzheimer's Disease
ADAS-Cog	Alzheimer's Disease Assessment Scale - Cognition
ADL	Activities of Daily Living
AMTS	Abbreviated Mental Test Score
ATSI	Aboriginal and Torres Strait Islander peoples
AUC	Area Under the Curve
BMI	Body Mass Index
BPSD	Behavioural and psychological symptoms of dementia
BQ	Background question
CALD	Culturally and linguistically diverse
CBR	Consensus-based recommendation
CBT	Cognitive Behavioural Therapy
CI	Confidence Interval
CJD	Creutzfeldt-Jakob disease
CT	Computed tomography
DARE	Database of Abstracts of Reviews of Effects
DOMS	Dementia Outcomes Measurement Suite
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders - Text Revision
EBR	Evidence-based recommendation
EEG	Electroencephalography
FAB	Frontal Assessment Battery
FICA	Federal Insurance Contributions Act
FTD	Frontotemporal dementia
GDS	Geriatric Depression Scale
GPCOG	General Practitioner Assessment of Cognition
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HQO	Health Quality Ontario
HTA	Health technology assessment
IQ-CODE	Informant Questionnaire on Cognitive Decline in the Elderly

KGOWS	Koori Growing Old Well Study
KICA	Kimberley Indigenous Cognitive Assessment
LR-	Negative Likelihood Value
LR+	Positive Likelihood Value
MCI	Mild Cognitive Impairment
MD	mean difference
MMSE	Mini Mental State Examination
MoCA	Montreal Cognitive Assessment
MRI	Magnetic resonance imaging
NHMRC	National Health and Medical Research Council
NHSEED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence (UK)
NPV	Negative Predictive value
NSD	not statistically different
PAS	Psychogeriatric Assessment Scale
PP	Practice Point
PPV	Positive Predictive Value
QoL	Quality of Life
RCT	Randomised controlled trial
ref std	reference standard
rehab	rehabilitation
ROC	Receiver Operating Characteristic
RR	risk ratio
RUDAS	Rowland Universal Dementia Assessment Scale
SD	Standard deviation
sig	significant(ly)
SMD	Standardised Mean Difference
Sn	Sensitivity
Sp	Specificity
SPECT	Single photon emission computed tomography
SR	Systematic Review
SRQ	Systematic review question
SSRI	Selective serotonin re-uptake inhibitor
STARD	Standards for Reporting of Diagnostic Accuracy Studies
TCA	Tri-cyclic antidepressant
WMS	Wechsler memory scale

Background

Purpose of the guideline

The purpose of this Guideline is to provide recommendations for the optimal diagnosis, management and treatment of dementia in Australia. The Guideline provides clear guidance which is relevant to Australian settings.

The intended users of the Guideline are staff working with people with dementia in the health and aged care sectors in Australia. This includes medical specialists (general physicians, general practitioners, geriatricians, neurologists, psychiatrists, psychogeriatricians, rehabilitation physicians), nurses, aged care workers and allied health professionals. The Guideline is also relevant to health system planners and managers and administrators whose organisations provide services for people with dementia and their carers. People with dementia and their carer(s) and family will also find the guideline highly useful as it provides information on the standard of care that should be provided. The clinical questions addressed in the guideline are listed below (page 8).

NHMRC Cognitive Decline Partnership Centre and Funding

The Guideline was developed, published and disseminated by the National Health and Medical Research Council (NHMRC) Partnership Centre for Dealing with Cognitive and Related Functional Decline in Older People (the Cognitive Decline Partnership Centre or CDPC). The Partnership Centre receives support from the NHMRC and Funding Partners including HammondCare, Alzheimer's Australia, Brightwater Care Group and Helping Hand Aged Care.

The primary aim of the NHMRC CDPC is to deliver excellence in research and knowledge exchange for the purpose of improving public health and health care in regard to cognitive and related functional decline in older people.

The CDPC brings together clinicians, researchers, aged care practitioners, policy makers and consumers who have a wide range of expertise in working with older people with cognitive and related functional decline.

Over a five-year period, the CDPC is working on a number of activities to achieve four key objectives.

1. Support implementation of **research-informed changes** in health and health care systems
2. **Synthesise and disseminate existing research** relevant to improving health and health care system performance
3. Undertake **collaborative new research** to improve health and health care using methods that are cross-sectional, inter-disciplinary, and trans-national in scope
4. **Build capacity** within the research community to do applied research and within the system to use research as part of change management.

One of the activities of the CDPC is to review international dementia guidelines and develop an Australian Clinical Practice Guideline.

Scope

Population addressed in the guideline

The Guideline is intended to apply to people with dementia, of both genders and all ages. Throughout the guideline "people with dementia" is considered to include people with Alzheimer's disease, vascular dementia, Dementia with Lewy Bodies, subcortical dementia, frontotemporal dementias and mixed dementias. Dementia encountered in the course of Parkinson's Disease will also be addressed. Dementia in Huntington's chorea is considered out of scope. Where appropriate, the Guideline addresses the differences in treatment and care for people with mild, moderate and severe dementia.

Dementia usually affects the whole family or household and the Guideline recognises the role of carers and family in the care and support of people living with dementia. The review also aims to identify issues that relate specifically to dementia care for Aboriginal and Torres Strait Islander people and people from Culturally and Linguistically Diverse (CALD) backgrounds. A separate search was conducted to identify relevant literature specifically relating to people of Aboriginal or Torres Strait Island descent.

Setting

This Guideline applies to community, residential and hospital settings. Community care settings include care provided in the home. It covers care provided by staff employed within the health and aged care sectors.

Methodology

Overview of methodology

Development of these Australian Guidelines was based on the ADAPTE process [1]. The ADAPTE process attempts to reduce duplication of effort by utilising existing high quality and current guidelines as the foundation for developing a local guideline. The National Institute for Health and Care Excellence (NICE) Guideline [2] was identified as being the most appropriate guideline to adapt. A Chairperson was appointed and the Guideline Adaptation Committee formed to adapt the NICE Guideline for the Australian setting.

A protocol for the evidence update was developed *a priori* and the plan for the evidence review was presented to the Guideline Adaptation Committee. The protocol was reviewed by a methodologist (Associate Professor Tracy Merlin) with experience in clinical practice guideline development who provided feedback on the protocol. Systematic reviews to identify studies published since the NICE Guideline were conducted. Evidence summaries including GRADE (Grading of Recommendations Assessment, Development and Evaluation) Evidence Profiles summarising the quality and findings of the body of literature were circulated to Guideline Adaptation Committee members in advance of meetings. [3] The Guideline Adaptation Committee discussed each recommendation at whole day face-to-face meetings held in October 2014 and February 2015. Recommendations were accepted, rejected or modified by the committee and classed as evidence based recommendations, consensus based recommendations or practice points using the definitions provided in the NHMRC 2011 Standards [4] (Table 1). Consensus-based recommendations were formulated when a systematic review of the evidence failed to identify sufficient studies meeting the inclusion criteria for that clinical question to inform a recommendation. Practice points were those recommendations that address clinical practice that is outside the scope of the systematic evidence review, or for which a systematic review was not conducted, and is based on expert opinion

Modification was frequently required in order to ensure the recommendations fit the Australian context and current standard practice. In addition, there were occasions when recommendations were modified to reflect recent evidence or to increase the clarity of the recommendation. Recommendations were reviewed to ensure that they reflected the strength of the body of evidence and the balance between the desirable and undesirable consequences and were presented as strong ("should" or "should not") or weak ("should/could be considered" or "suggest not") recommendations. [3] The strength of the recommendation also reflects values, preferences and resource use. A strong recommendation indicates that there will generally not be variation in application of the recommendation between individuals and settings.[5] A weak recommendation indicates that there may be variation in application of the recommendation between individuals or settings, ie that the balance of benefits and harms may depend on patient preferences or values.[5] Thus, whilst high quality evidence is more likely to lead to a strong recommendation this is not necessarily the case, and vice-versa with low quality evidence. The draft Guideline was circulated to all Guideline Adaptation Committee members for further comment and refinement prior to release for public consultation in March 2015.

Table 1 Definitions of types of recommendations

Type of recommendation	Description
Evidence-based recommendation (EBR)	Recommendation formulated after a systematic review of the evidence, with a rating of the overall quality of the evidence and supporting references provided.
Consensus based recommendation (CBR)	Recommendation formulated in the absence of adequate evidence, when a systematic review of the evidence has failed to identify sufficient studies meeting the inclusion criteria for that clinical question to inform a recommendation.
Practice point (PP)	A recommendation that is outside the scope of the search strategy for the systematic evidence review, or for which a systematic review was not conducted, and is based on expert opinion.

The Guideline underwent public consultation from the 3rd of April until the 15th of May 2015. The Guideline was assessed by two reviewers who were not involved in the guideline development using the AGREE II Instrument [6].Further modifications were made to the text of the guideline and technical reports based on these reviews.

The ADAPTE process

The three phases of the ADAPTE process include set-up, adaptation and finalisation and the process is outlined in detail in the ADAPTE handbook [1]. The adaptation phase includes defining the health questions and searching for existing guidelines. Existing guidelines are then assessed using the AGREE II instrument, a checklist designed to assess the methodological rigour and transparency with which a guideline has been developed [6]. Guidelines are then selected for adaptation and customised for the local context. The application of the ADAPTE process in developing this Guideline is described in further detail below.

Phase 1: Set-up

An organising committee was formed at the commencement of the project. The organising committee comprised the two project lead investigators, the project coordinator and a consumer representative. The organising committee were aware of existing international guidelines for the management of dementia and were confident that guideline adaptation would be feasible. The organising committee was responsible for drafting the scope of the guidelines, identifying the skills and expertise required on the Guideline Adaptation Committee and determining the organisational and governance arrangements for developing the guidelines. The organising committee appointed a Chairperson to oversee the guideline adaptation process. The organising committee, in conjunction with the Chairperson, invited clinical experts in dementia care and representatives of consumer and other groups to join the Guideline Adaptation Committee (see membership page 367).

Phase 2: Adaptation

A rigorous search of guideline clearinghouses and Medline was conducted to identify existing guidelines based on pre-determined inclusion criteria (see Appendix 1, page 365). Three guidelines met the inclusion criteria and were appraised independently by three people using the AGREE II instrument (see Appendix 1, page 365). The guideline of highest quality was the NICE Guideline [7], which was selected for adaptation. Permission was obtained from NICE and the UK National Collaborating Centre for Mental Health (NCCMH) to adapt the guideline. Methodological details of the process undertaken to identify and appraise existing guidelines are provided in Appendix 1 (page 365).

The NICE Guideline was published in 2006 and lists 29 "key questions". Each of the questions was addressed in a different way in terms of the search for relevant evidence. Details of each of the questions linked to a systematic review, the methods used to answer the questions and the validity, applicability and acceptability of the related recommendations were rated by the project officer and systematic reviewer using the tools within the ADAPTE toolkit [1] (see Technical Report Volume 2). While the quality of the NICE Guideline was rated high and the guideline scored well in terms of its validity, applicability and acceptability, it was felt that some changes would be required for Australian users and that more recent evidence may impact on the recommendations made in 2006. Thus it was decided that the guideline could not be accepted in its current form and that recommendations would need to be reviewed individually and potentially modified based on the findings of systematic reviews of more recent evidence and the views of the Guideline Adaptation Committee.

The Guideline Adaptation Committee met for the first time in March 2014. At this meeting consensus was reached regarding the purpose, intended users, scope and target population. The key clinical questions to be included in the Guideline were decided following a vote by the Guideline Adaptation Committee members based on the key clinical questions addressed within the NICE Guideline. The Guideline Adaptation Committee identified 17 of the 29 questions included within the NICE Guideline that would be addressed via systematic review. A protocol was developed detailing the Population, Intervention, Comparator and Outcome (PICO) for each of the questions (based on the NICE PICO statements) and the methodology for the systematic review. ADAPTE proposes the use of the PIPOH framework, which also considers the professional specialties and the healthcare settings in framing the clinical question. These guidelines were aimed at all health and aged care professionals and all healthcare setting and therefore these items were not included in the structure of the individual clinical questions.

Guideline customisation was informed based on a systematic search for evidence published following the searches conducted in 2005/2006 as part of the NICE Guideline. Full details of the update search strategies and results are provided in the Guideline Technical Report Volume 1 and Volume 2. Multiple databases were searched between April 2014 and March 2015. An additional search was conducted for literature relating to CALD and Indigenous Australian populations to identify issues unique to these Australian populations. The search included a number of databases and was not restricted by date (see Box 2).

Evidence summaries for each of the clinical questions were sent to all Guideline Adaptation Committee members prior to the face-to-face meetings. The evidence summaries included the clinical question, background information, the current NICE recommendation, a narrative summary of the evidence, evidence tables with details of the literature considered within the systematic review and GRADE Evidence Profiles summarising the quality and findings of the body of literature for each outcome. Recommendations were accepted, rejected or modified by the committee and classed as evidence based recommendations, consensus based recommendations or practice points using the definitions provided in the NHMRC 2011 Standards [4]. Recommendations were reviewed to ensure that they reflected the strength of the body of evidence and the balance between the desirable and undesirable consequences and were presented as strong ("should" or "should not") or weak ("should/could be considered" or "suggest not") recommendations.[3]

The draft Guideline was circulated to all Guideline Adaptation Committee members for further comment and refinement prior to release for public consultation in April 2015.

Research questions

The Guideline Adaptation Committee prioritised clinical questions from the key questions listed in the NICE guideline. All members of the Guideline Adaptation Committee (and three additional consumer representatives) were asked to select five of the 29 questions within the NICE Guideline they felt to be of highest priority. The results were collated and a prioritised list was developed. Several of the questions within the NICE Guideline were not identified as being of high priority; these were considered as being out of scope and were not addressed by systematic review. For some other questions (for example, how to ensure that people with dementia have a choice regarding their care environment), it was determined that it would be more appropriate to provide a narrative summary of current literature rather than conduct a systematic review as there was perceived to be likely to be sparse high level evidence. These questions were referred to as background questions and were not used to inform evidence-based or consensus-based recommendations.

The following clinical questions were prioritised by the Guideline Adaptation Committee and the evidence was examined by conducting a systematic review. The detailed PICO criteria for each question are provided in the remainder of the Technical Report Volume 1, under the relevant section headings.

Box 1 Clinical questions addressed by systematic review

1. Which interventions can reduce barriers to accessing optimal healthcare?
2. Are there any advantages/disadvantages to early identification?
3. For people with symptoms of dementia, does assessment from a memory assessment specialist or service provide benefits in comparison to attendance at another service?
4. How frequently should memory assessment services review people with Mild Cognitive Impairment (MCI) for progression to dementia?
5. What is the evidence for the validity of the Kimberley Indigenous Cognitive Assessment (KICA) and Rowland Universal Dementia Assessment Scale (RUDAS) cognitive assessment tools in Indigenous and Culturally and Linguistically Diverse (CALD) populations?
6. Does every person with dementia need structural imaging (with CT or MRI) of the brain?
7. Does the routine use of functional imaging (with SPECT) improve the diagnostic differentiation of dementia from MCI over and above that of standard comprehensive assessment?
8. For people with dementia, what type of information and support is beneficial?
9. For people with dementia, what is the best way of organising services in terms of integration of care, consumer directed care, multidisciplinary assessment and case management?
10. What models of training for health and aged care staff have positive outcomes for people with dementia?
11. For people with dementia, are there strategies for promoting independence that produce benefits?
12. For people with dementia, do cognitive rehabilitation interventions produce benefits?
13. For people with dementia, do acetyl-cholinesterase inhibiting drugs/memantine produce benefits/harms?
14. For people with dementia, does Souvenaid produce benefits/harms?
15. For people with behavioural and psychological symptoms of dementia, do non-pharmacological interventions produce benefits?
16. For people with behavioural and psychological symptoms of dementia (BPSD), does appropriate drug treatment when compared to placebo/a comparator produce benefits/harm?
17. Does assessment or intervention for carers produce benefits?

The following clinical questions were defined as background questions (BQ) and were addressed by a non-systematic overview of relevant information.

Box 2 Clinical questions defined as background questions and addressed by non-systematic review

1. What are the characteristics of the process of assessment and diagnosis associated with a positive or negative experience of the assessment process?
2. For people with dementia, what are the issues concerning end of life that support the dignity and intrinsic worth of the individual?
3. How can it be ensured that people with dementia have a choice about their care environment?
4. Are there circumstances in which acting without/contrary to the consent of a person with dementia is appropriate?
5. What is the best practice design of care homes?

Review of literature

Hierarchical approach

For all questions, a hierarchical approach was used in the selection of the evidence – that is, only the highest level of evidence/best quality evidence was included to answer each question. The NHMRC evidence hierarchy was used. [8]

Whenever possible, the approach recommended by Whitlock and colleagues (2008) for using existing systematic reviews in complex systematic reviews was used.[9] This process involved

(1) Locating existing systematic reviews,

(2) Assessing the relevance of existing systematic reviews (considering study designs, date of search and databases searched, population, intervention, comparisons, outcomes, and language restrictions)

(3) Assessing the quality of existing systematic reviews (via the AMSTAR tool) to ensure they are comprehensive and likely to have found all relevant studies [10], and

(4) Determining how to incorporate existing systematic reviews

Recommendations on the use of existing systematic reviews from the Agency for Healthcare Research and Quality (AHRQ) were also incorporated into the approach [11]. In particular this review clearly distinguishes newly identified studies from those in any existing review, and strength of evidence ratings were based on the underlying primary evidence.

Literature sources and search strategies

The following electronic databases were searched for studies published between 2005 and 2014: PubMed, Medline (via Ovid), PsycINFO (via Ovid), Embase (via Ovid), Health Technology Assessment database (CRD, York, NHSEED) and the Cochrane Library (Cochrane Database of Systematic Reviews, DARE). The specific search strategies used for each question are provided in Volume 2 of the Technical Report.

Each search utilised applicable components of the following Medline search strings, in addition to intervention-specific terms (see **Error! Reference source not found.**). Search strings were adapted for other databases; full details are provided in Volume 2 of the Technical Report. Search limits for humans and English language articles were applied.

The search terms used are based on terms used by the Cochrane Dementia and Cognitive Improvement Group for participants [12], BMJ Clinical Evidence for study design [13] and by the source guideline for intervention [7]. The search terms were checked by a specialist medical librarian with expertise in developing search strategies for systematic reviews (Raechel Damarell). The search terms used for participants (based on the Cochrane Dementia and Cognitive Improvement Group) were broader than our inclusion criteria. For example, the Cochrane string includes the terms 'Huntington' whereas people with Huntington's were excluded from our reviews. Nevertheless, the Cochrane search strategies were not altered as these were considered the gold standard.

Box 3 Medline search strings utilised in multiple search strategies

Dementia search string for interventions:

1 exp Dementia/
2 Wernicke Encephalopathy/
3 Delirium, Dementia, Amnestic, Cognitive Disorders/
4 dement*.mp.
5 alzheimer*.mp.
6 (lewy* adj2 bod*).mp.
7 (chronic adj2 cerebrovascular).mp.
8 ("organic brain disease" or "organic brain syndrome").mp.
9 ("normal pressure hydrocephalus" and "shunt*").mp.
10 "benign senescent forgetfulness".mp.
11 (cerebr* adj2 deteriorat*).mp.
12 (cerebral* adj2 insufficient*).mp.
13 (pick* adj2 disease).mp.
14 (creutzfeldt or jcd or cjd).mp.
15 huntington*.mp.
16 binswanger*.mp.
17 korsako*.mp.
18 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17

Dementia search string for diagnostics:

1. dement*.ti.
2. alzheimer*.ti.
3. (AD or VaD or lewy or frontotemporal).ti.
4. exp Dementia/di [Diagnosis]
5. exp Dementia/ep [Epidemiology]
6. ("conversion to" adj6 (dement* or alzheimer* or AD or lewy or VaD)).ab.
7. ((endpoint* or "end point*" or outcome*) adj6 (dement* or alzheimer* or AD or VaD or lewy)).ab.
8. (predict* adj6 (dement* or alzheimer* or AD or VaD or lewy)).ab.
9. (progress* adj5 (dement* or alzheimer* or AD or VaD or lewy)).ab.
10. or/1-9

Systematic reviews and HTAs search string:

1. (review or review,tutorial or review, academic).pt.
2. (medline or medlars or embase or pubmed or cochrane).tw,sh.
3. (scisearch or psychinfo or psycinfo).tw,sh.
4. (psychlit or psyclit).tw,sh.
5. cinahl.tw,sh.
6. ((hand adj2 search$) or (manual$ adj2 search$)).tw,sh.
7. (electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw,sh.
8. (pooling or pooled or mantel haenszel).tw,sh.
9. (peto or dersimonian or der simonian or fixed effect).tw,sh.
10. (retraction of publication or retracted publication).pt.
11. or/2-10
12. 1 and 11
13. meta-analysis.pt.
14. meta-analysis.sh.
15. (meta-analys$ or meta analys$ or metaanalys$).tw,sh.
16. (systematic$ adj5 review$).tw,sh.
17. (systematic$ adj5 overview$).tw,sh.
18. (quantitativ$ adj5 review$).tw,sh.
19. (quantitativ$ adj5 overview$).tw,sh.
20. (quantitativ$ adj5 synthesis$).tw,sh.
21. (methodologic$ adj5 review$).tw,sh.
22. (methodologic$ adj5 overview$).tw,sh.
23. (integrative research review$ or research integration).tw.
24. or/13-23

12 or 24

Randomised controlled trials search string:

1 "randomized controlled trial".pt.
2 (random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.
3 (retraction of publication or retracted publication).pt.
4 1 or 2 or 3
5 (animals not humans).sh.
6 ((comment or editorial or meta-analysis or practice-guideline or review or letter or journal correspondence) not "randomized controlled trial").pt.
7 (random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not "randomized controlled trial".pt.
8 4 not (5 or 6 or 7)

The databases in Box 4 were searched for literature related to Aboriginal and Torres Strait Islander people and the main electronic databases listed above were searched for literature related to culturally and linguistically diverse (CALD) Australians. The search for evidence for a cognitive assessment tool specifically developed for Indigenous Australians (the Kimberley Indigenous Cognitive Assessment, KICA) also involved searching grey literature and contacting authors to access additional study information.

Box 4 Databases searched for publications specifically relevant to Indigenous Australians

Health Infonet:	http://www.healthinfonet.ecu.edu.au/
ATSI Health:	http://www.health.gov.au/internet/main/publishing.nsf/Content/health-publicat.htm
Informit: Indigenous Collection, RURAL (rural and remote health database), Family & Society collection	http://www.informit.com.au/indigenous.html
The Lowitja Institute	http://www.lowitja.org.au/publications

Study selection

Existing systematic reviews

Existing systematic reviews were integrated into the evidence update wherever possible. Systematic reviews were used that included the study designs relevant to each question. Where the systematic review included additional study designs, this information was not usually extracted or included in the Evidence Tables.

Where multiple systematic reviews were identified by the search, we chose the "best" review/s (based on date of search, quality (as assessed by AMSTAR) and fit in terms of population, intervention, comparison and outcome).[9] For a systematic review to be used as a source of primary research, it met the following criteria: described clear inclusion criteria, performed a comprehensive literature search in at least two databases, provided a list of included studies and described the characteristics of the included studies. Where the systematic review assessed the quality of the included studies, the studies were not reappraised. Where no quality appraisal was reported, the individual studies were retrieved and appraised. Where necessary, primary studies were accessed to clarify information reported in the systematic review.

For some clinical questions, multiple systematic reviews were included to address all elements of the PICO (for example, reviews of the interventions "occupational therapy" and "exercise" were both utilised to address the question of prevention of functional decline in people with dementia). Where necessary, searches for primary studies relevant to each question that may have been outside of the scope of the included systematic review/s were also conducted (for example, where the source systematic review addressed only people with Alzheimer's Disease, searches were conducted for studies that included people with dementia of other types.)

Included systematic reviews were updated with searches for additional primary studies published following the search dates of the included review/s. For questions focussing on established diagnostic technologies, where systematic reviews were identified that included a search to 2012 or later, no further update of these reviews was undertaken (in accord with the World Health Organisation handbook for guideline development recommendations)[14].

Inclusion/exclusion criteria

One reviewer independently reviewed the titles identified from the searches. The reviewer assessed the titles and abstracts based on the inclusion criteria and labelled the studies as included, unsure or excluded. Explicit inclusion and exclusion criteria for each systematic review question are provided separately, under the relevant sections in the Technical Report Volume 1, below. General inclusion/exclusion criteria were as follows.

- The most recent, comprehensive and high quality systematic review was included and updated.
- Studies providing the highest quality of evidence according to the NHMRC levels of evidence were included
- Studies of people with a diagnosis of dementia of any type were included. Studies conducted in people with Huntington's Disease or people with delirium were excluded.
- Articles published in languages other than English and conference proceedings were excluded.

Specific inclusion and exclusion criteria for each systematic review question were included in the protocol and were presented to the Guidelines Adaptation Committee and other experts (for example, a pharmacist) as necessary for comment (see Acknowledgements page 367). Feedback was used to refine the inclusion/exclusion criteria when appropriate.

All citations labelled as unsure or included were reviewed in full text. Where the reviewer was unsure about final inclusion, a decision was made based upon discussion and consensus with a second reviewer. Authors were not contacted for more study details to determine eligibility, except for an Australian cognitive assessment tool developed for Indigenous Australians (the Kimberley Indigenous Cognitive Assessment tool, KICA) due to the need for additional information to appraise this tool which is highly relevant to practice in Australia.

Studies reporting harms or health economic outcomes in the absence of any of the pre-specified effectiveness outcomes were not included.

As there are few economic evaluations in dementia care conducted for the Australian setting, health economic information was treated as secondary information. That is, information regarding the health economic impact of assessment and treatment options was provided when reported in the included studies, but specific searches for these types of studies were not conducted and studies only reporting these outcomes were not included.

Data extraction

One reviewer independently extracted study characteristics and results from the included studies directly into Evidence Summary tables for each clinical systematic review question. Where existing systematic reviews were included, data from primary studies as reported in the systematic review was extracted. Where necessary, primary studies were accessed to clarify information reported in the systematic review. Data extraction of results was checked by a second reviewer for approximately 25% of questions. Data calculations were checked by a statistician when appropriate. We did not contact trial authors to provide or clarify information on missing data, except for studies of an Australian cognitive assessment tool, the KICA.

Harms were extracted from the included studies where this outcome was specified, noting the limitations of the included study designs to capture evidence of adverse events.

Quality assessment of studies

One reviewer assessed the methodological quality of the studies meeting the inclusion criteria. The quality assessment is summarised in the Evidence Summary table for each included study.

- Systematic reviews were appraised using the AMSTAR tool (http://amstar.ca/).
- Randomised Controlled Trials were appraised using the Cochrane Risk of Bias Tool (sequence generation; allocation concealment; blinding of participants, personnel and outcome assessors; incomplete outcome data; selective reporting), with Review Manager 5.2 or 5.3
- Diagnostic accuracy studies were assessed using the Cochrane Risk of Bias Tool (patient selection; index tests; reference standard; flow and timing), with Review Manager 5.3
- Studies of other quantitative research designs (e.g.cohort studies) were assessed using the Downs and Black Scale.[15]

Where included systematic reviews had conducted a risk of bias assessment (for example within a Cochrane Review), the quality assessment conducted by the original authors was accepted. Where a systematic review was included, if no quality assessment had been conducted, or not all of the components of the quality assessment were performed, the primary studies were retrieved to complete the risk of bias assessment.

The overall quality of the body of evidence for each outcome was explicitly assessed according to the GRADE criteria of risk of bias, directness, consistency of results, precision, publication bias and magnitude of the effect (http://www.gradeworkinggroup.org/).[16] The NHMRC 2011 Standards for clinical practice guidelines indicate that either the GRADE or NHMRC grades for recommendations should be used to determine the grade of each recommendation. [4] The GRADE system was used for this guideline as it has greater recognition internationally. The results of the assessment for each systematic review question are presented in the GRADE Evidence Profiles in the remainder of the Technical Report, Volume 1.

Data synthesis

Included studies were summarised narratively and results presented in the Evidence Tables. Effect sizes were calculated where possible, if not presented in the original paper. Meta-analysis of studies that were similar in terms of intervention, comparison, outcomes and timing of follow-up was conducted where possible. If more than one method was used to measure an outcome from the same study, we pooled the measure most frequently used across all of the included studies. Results were pooled to provide an overall estimate of the treatment effect using a fixed-effects model, where not precluded by heterogeneity. The meta-analyses were conducted using RevMan 5.2 or 5.3 [17] and 95% confidence intervals (CI) were calculated for each pooled estimate of effect. Heterogeneity was assessed by forest plots in addition to consideration of statistical heterogeneity using the Cochran Q test for heterogeneity and the I^2 statistic. [18]

Evidence of the effectiveness of diagnostic tests was interpreted within the context of the hierarchy of outcomes proposed by Fryback and Thornbury [19], considering the assumptions required to link the evidence for lower levels of evidence to patient-important outcomes (see Methodological Considerations, page 18). [20]

Grading of Recommendations Assessment, Development, and Evaluation (GRADE)

The GRADE system was used to provide an overall rating of the quality of evidence informing evidence-based recommendations. [3 16 21] The GRADE system involves assessment of the criteria of risk of bias, directness, consistency of results, precision, publication bias and magnitude of effect. Risk of bias is assessed based on the quality assessment of the individual studies as described above (see Quality assessment of studies, page 14), considering their weighting in the overall body of evidence. Assessment of directness considers the external validity of each of the PICO elements of the included studies. In particular, surrogate outcomes (i.e., where the outcome is not a direct measure of a patient-important outcome such as quality of life, patient function or behaviour) downgrade the overall quality of the body of evidence due to indirectness. Consistency of results considers the consistency of findings across the included trials, ie whether or not there is unexplained heterogeneity in the results. Precision addresses the amount of statistical variation in

the estimate of effect, based upon the total number of participants or events in the studies and is represented by the confidence intervals. The precision is concerned with the degree of uncertainty in the results. Other considerations, such as whether or not publication bias has been demonstrated, whether there is a large effect (a relative risk of greater than 2 or less than 0.5 from at least two studies) or whether there is a dose-response gradient are also assessed.

To summarise this assessment into one overall rating, the body of evidence is initially given a rating of quality based upon the study design (eg. randomised controlled trials for interventions are considered 'high', observational studies considered 'low'). Then each of the criteria are considered separately and rated as having no limitations, serious limitations (whereby the quality of evidence is downgraded by one point), or very serious limitations (whereby the quality is downgraded by two points). The overall quality can also be upgraded due to the magnitude of effect or the presence of a dose-response gradient. Thus the quality of the evidence was rated as high, moderate, low or very low (Table 3).

Table 2 Definitions of GRADE ratings of the quality of the evidence

GRADE of quality of the evidence	Description
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

The overall quality of the evidence for a recommendation is determined based upon the lowest quality of the critical outcomes, as listed in Table 3. GRADE Profiler 3.6 software was used.

Table 3 Critical and important outcomes for GRADE assessment of quality of the evidence

Critical	Important[§]
Quality of life	Cognition
ADL	Institutionalisation
BPSD	Carer impact
Adverse events - Mortality	Care plans
Serious adverse events	Pain
Trial withdrawals due to adverse events	Safety/Adverse consequences (eg social impact)
	Change in diagnosis/management
	Patient satisfaction with care
	Patient knowledge regarding their condition
	Level of distress
	Self esteem
	Total adverse events, individual adverse event rates
	Trial withdrawals for any reason
	Proportion of people with MCI converting to dementia

[§]Important outcomes were generally those surrogate to the critical outcomes

When considering diagnostic accuracy, true positive, false positive, true negative and false negative outcomes were considered on a case-by-case basis and rationale provided within the relevant sections of the technical report and the GRADE Evidence Profiles. Diagnostic accuracy studies that provide an independent comparison with a valid reference standard among consecutive subjects with a defined presentation were considered as high quality study design within the GRADE quality of evidence rating system.

The GRADE Working Group have provided a list of criteria that should be met when using the GRADE system.[22] The following describes how these criteria have been used in applying the GRADE system to this Guideline.

- The “quality of evidence” was defined consistently with the definitions for systematic reviews used by the GRADE working group.
- The quality of evidence was explicitly assessed according to the GRADE criteria of risk of bias, directness, consistency of results, precision, publication bias, magnitude of the effect and dose-response gradient.
- The overall quality of the evidence was assessed for each important outcome for each systematic review question and expressed as one of four categories: high, moderate, low or very low.
- Evidence summary documents for each systematic review question including background information, description of the systematic review methods, narrative of results, and GRADE Evidence Profiles were produced and circulated to the Guidelines Adaptation Committee as completed and in advance of each face-to-face meeting at which recommendations were discussed.
- For each systematic review question, explicit consideration was given to the balance of desirable and undesirable consequences by considering outcomes of both effectiveness and

harm and the overall quality of evidence according to the GRADE rating for each. Where relevant, public funding and out-of-pocket costs to consumers was considered and is documented in the technical report. Values and preferences of consumers were captured by considering input from all Guideline Adaptation Committee members, including those representing different consumer groups (see the Guideline Adaptation Committee Membership, page 367).

- The strength of recommendations was expressed as weak/conditional when the wording "could/should be considered" or "suggest not" was used; strong recommendations were expressed by using the wording "should" or "should not".

Methodological Considerations

Diagnostic and screening tests

When considering the evidence for the effectiveness of a diagnostic test; ideally, studies would report impact on patient outcomes, such as improved quality of life, in comparison to an alternative testing strategy (e.g. comprehensive clinical assessment) as for any intervention (8). However, randomised controlled trials of diagnostic test strategies rarely exist, and in certain circumstances they are unnecessary.[23] Other diagnostic test outcomes, such as test accuracy, are a surrogate for patient centred outcomes (Table 4). The consideration of evidence from studies reporting such outcomes must involve identifying assumptions made to link these outcomes to patient benefits and harms.[19 24] Technical efficacy (e.g. resolution) may not necessarily translate to an increased accuracy for diagnosis. If a test is accurate, it is still necessary for the test result to change diagnosis and management, and for the management implemented to be effective for there to be an improvement in patient outcomes. Consideration of all of these steps in the pathway is necessary when considering the evidence for the effectiveness of a diagnostic test.[24]

Table 4 Hierarchy of diagnostic test efficacy

Level	Efficacy measure	Example of efficacy measures
lowest ↓	Technical efficacy	Resolution, sharpness, reproducibility
	Diagnostic accuracy efficacy	Sensitivity, specificity, likelihood ratios, positive or negative predictive values
	Diagnostic thinking efficacy	Proportion of cases in which image assisted diagnosis
	Therapeutic thinking efficacy	Proportion of cases in which image contributed to planning patient management
	Patient outcome efficacy	Proportion of patients with improved health outcome (eg. quality of life)
highest	Societal efficacy	Cost-effectiveness

(adapted from Fryback and Thornbury, 1991) [19]

The interpretation of test results will vary in primary or specialist settings. In particular, the positive predictive value of a cognitive assessment tool or the chance that a positive test result reflects the presence of dementia, will vary according to dementia prevalence.[20] Hence the positive predictive value is likely to be lower in a primary care setting (i.e. less likely to be predictive of a dementia

diagnosis). Similarly, whilst the sensitivity and specificity of a tool are not directly affected by prevalence, they are likely to alter with severity of disease, and therefore may also be lower in a primary care than a memory clinic setting.[20]

Complex interventions

Care for people with dementia often involves complex interventions, such as carer education and training interventions or case coordination. These interventions can be difficult to describe and categorise as they may vary in terms of the theoretical approach, content, dose and person delivering the intervention. Wherever possible, we examined which specific intervention approaches had the strongest evidence of effectiveness or safety and considered the most appropriate population or subgroup with optimal effectiveness or safety. However, this was not always possible as there may not have been enough studies to enable such evaluations. For example, while exercise appears to be beneficial generally, there was not enough information to determine which type and dose was most effective and at which point in the course of dementia it is most effective.

Quality of body of evidence

As this evidence update used a hierarchical approach, for many systematic review questions, this frequently meant that only randomised controlled trials were included. This process meant that studies of a lower level of evidence, i.e. of a study design that is more prone to bias, were excluded from review. In some cases this meant that evidence from a small number of randomised controlled trials was considered, although a number of observational studies existed, regardless of their size or quality.

In some areas, such as staff training and carer interventions, there are a number of large high quality studies included for review. However, there is also a number of lower quality studies and therefore, when considered as a whole, the body of evidence is not as strong as may be expected.

As one of the main symptoms of dementia is cognitive impairment, research in the dementia field frequently assesses cognition as a primary outcome. Cognition is considered by GRADE to be a surrogate outcome for function as the relevance of a change on a cognitive assessment scale to patient important outcomes (e.g., function, quality of life) is not always clear.[16] Therefore, the quality of evidence from some well conducted trials in dementia (i.e., with a low risk of bias) was downgraded on this basis.

Formulation of recommendations

Stage One – Review of the evidence

Evidence summary documents for each systematic review question, including background information, description of the systematic review methods, narrative of key results, Evidence Summary Tables and GRADE Evidence Profiles were circulated to all members of the guideline committee prior to the face-to-face meetings in which the recommendations were discussed. Members of the committee were asked to email any initial thoughts or questions directly back to the guidelines coordinator and these comments were addressed at the face-to-face meeting. This process ensured that all committee members were allowed time to consider the evidence and gave all members the opportunity to raise questions or provide comments.

Stage Two - Discussion

At the face-to-face meeting the Chairperson guided the committee through the proposed recommendations and answered any questions regarding the body of evidence.

The Chairperson opened discussions and addressed questions or comments. The committee then made a decision for each proposed recommendation regarding whether they accepted the existing NICE recommendation, rejected it or wished to modify it.

Stage Three – Formulation of draft recommendations

The committee discussions were used to inform recommendations. Changes were prompted by updated evidence in the evidence review or where the committee felt that changes were needed to ensure the wording was specific, unambiguous, clearly described the actions taken by users, to ensure wording matched the strength of the body of evidence and when required to suit the Australian setting or current standards of practice. Recommendations supported by the body of evidence were classed as evidence based recommendations (Table 1). Where evidence was systematically reviewed but considered insufficient to inform a recommendation, expert opinion was sought from the committee and used to make consensus based recommendations. The committee also developed practice points to provide guidance in areas that were outside of the scope of the systematically reviewed literature. In one case (Souvenaid), where the intervention had not been previously considered by NICE, the GRADE evidence-to-decision framework (which incorporated considerations of values, cost and equity) and automated voting was used. This recommendation was later modified in response to feedback received in the public consultation phase.

Stage Four – Call for agreement

The Chair called for agreement and facilitated discussion where there was disagreement. Where consensus was gained the committee moved to the next section of the guideline. Where consensus was not gained, differences in opinion were discussed and in all cases resolved. Differing opinions were noted.

Stage Five – Draft recommendations circulated to committee

The guideline manuscript, containing the recommendations, was circulated to the committee for review prior to public consultation.

Stage Six –The Guidelines and the Technical report were released for public consultation on the 3rd of April 2015.

Stage Seven – Revision of recommendations and the Guideline after public consultation

Evidence updates

SRQ1: Barriers to care

Clinical question

The systematic research question as defined in the protocol and the associated PICO criteria are listed below in Table 5).

Table 5 PICO for SRQ1: Barriers to care

Clinical question: Which interventions can reduce barriers to accessing optimal healthcare?			
Population	**Intervention**	**Comparator**	**Outcome**
People with all forms of dementia	Interventions to reduce barriers, increase access or enhance equity	Usual care	Access to optimal care Quality of life of the person with dementia ADL function

Literature review search strategies:

Searches for existing HTAs and Systematic reviews

Searches to identify existing Health Technology Assessment reports (HTAs) and systematic reviews were conducted in the databases specified in Table 6, using the search terms listed in the Guideline Technical Report Volume 2.

Table 6 Searches for existing HTAs and systematic reviews SRQ1: Barriers to care

Database	Date searched	Period covered	Citations retrieved
HTA	4 June 2014	2005 to 2014	0
Cochrane (Cochrane reviews, Cochrane protocols, DARE)	4 June 2014	2005 to 2014	16
MEDLINE	4 June 2014	2005 to 2014	12
PsycInfo	4 June 2014	2005 to 2014	5
EMBASE	4 June 2014	2005 to 2014	4
PubMed	4 June 2014	2005 to 2014	15

No systematic reviews addressing the systematic research question addressing interventions to reduce barriers were identified.

Searches for primary studies

Searches were conducted in the databases listed in Table 7 to identify primary studies. The search terms used are listed in the Guideline Technical Report Volume 2.

Table 7 Searches for primary studies SRQ1: Barriers to care

Database	Dates searched	Period covered	Citations retrieved
MEDLINE	11 June 2014	2005 to 2014	475
PsycInfo	11 June 2014	2005 to 2014	156
EMBASE	11 June 2014	2005 to 2014	113
PubMed	11 June 2014	2005 to 2014	418

Criteria for selecting studies for review:

Table 8 Inclusion and exclusion criteria SRQ1: Barriers to care

Characteristic	Criteria
Study design	Inclusion: Quantitative studies
Population	Inclusion: People with a diagnosis of dementia
Intervention	Inclusion: Any intervention designed to increase equity or overcome barriers to care
Comparator	Inclusion: Usual care
Outcomes	Inclusion: Access to optimal care, quality of life of the person with dementia, ADL function
Publication type	English language Studies published in the last ten years (from 2005-2014). Studies published prior to 2005 were excluded as barriers to care may change over time and barriers identified in older studies may no longer be applicable

Search results:

Primary studies

A total of 1162 citations were retrieved in the electronic database searches. No studies evaluated the efficacy of interventions which were designed to overcome barriers to care (GRADE Evidence Profile Table 12).

Evidence summary:

SRQ1: Which interventions can reduce barriers to accessing optimal healthcare?

No studies were identified which met the inclusion criteria for *interventions designed to overcome* barriers to care.

Evidence statement	***GRADE Quality***	***Related recommendation***
No studies were identified that evaluated interventions designed to overcome barriers to accessing optimal health care in people with dementia. (Table 12)	NA	CBR 9

NA – not applicable

Non-systematic review of which barriers to care have been identified

In the absence of evidence regarding the effectiveness of *interventions* designed to overcome barriers to care, the Guidelines Adaptation committee decided to make a consensus based recommendation. The committee used a non-systematic review of information on *what barriers* to care for people living with dementia have been identified to inform their decision making. This review addressed the background question 'Are there barriers to people with dementia getting optimal physical healthcare?'. Due to the large amount of information identified, the studies were summarised in Table 9, Table 10 and Table 11 below.

We searched for empirical studies of all research design published in the last ten years (from 2005-2014) that identified barriers to accessing services and healthcare disparities for people with dementia. The studies identified were mixed in terms of study design, types of barriers examined and setting. The studies identified were categorised in terms of Australian and international studies, subpopulations and settings. Australian studies were examined in greater detail. The study characteristics and findings are summarised in Table 9 to Table 11.

Australian studies

We identified seven studies [25-32] which explored barriers to care or disparities in health care utilisation for people with dementia in Australia. Study methods used included interviews, focus groups or retrospective analysis of cohort data. All Australian studies identified are summarised below.

Access to services at national/state level

Analyses of large Australian datasets revealed that people with Alzheimer's disease were more likely to spend their last year of life living in residential care than those without dementia [28] and that certain groups (those living in rural and remote areas and those of lower socioeconomic status) were less likely to be prescribed cholinesterase inhibitors than other groups (those in metropolitan areas and of higher socioeconomic status) [31]. Surveys of public hospitals in New South Wales demonstrate the reduced availability of specialist services and appropriate hospital wards for people with dementia in rural areas [25].

Remote Aboriginal Communities

Two of the studies examined barriers to care for people living in remote Aboriginal communities [26 30]. These studies identified a number of barriers to delivering and accessing care including poor community awareness regarding dementia, lack of culturally appropriate services and poor links between service providers, in which there was often high turnover and heavy workload, and the community. Smith and colleagues (2011) conducted interviews and focus groups to determine ways to overcome factors affecting the successful delivery of services to Aboriginal people with dementia living in the community [30]. Key themes included: the role of the family carer, perspectives of dementia, community and culturally appropriate care, workforce education and training and issues affecting remote communities and service issues. The authors concluded that people with dementia and their families in remote Aboriginal communities are struggling to cope and that they are requesting better community care. Recommendations included: community representation in all services and initiatives; enhanced communication and cooperation among services and with the community; the availability of a community-based advocate accessible to community members and external service providers; community based and culturally appropriate care; employment and training of community based Aboriginal staff and training throughout the community for both service providers and community members and their families.

Focus groups conducted by Lindeman and colleagues (2012) with Indigenous aged care workers, community members and service users in the Northern Territory (n=26) evaluated the impact of a dementia awareness resource developed for use in remote Aboriginal communities [26]. The trainers and educators reported that implementation and impact of the resource was limited due to poor relationships with remote clinic staff. The trainers felt that relationships were strained due to staff turnover, a 'perceived lack of interest' in ageing-related issues and a lack of awareness about dementia. It was felt that clinics were not accurately identifying people with dementia in the community due to heavy workloads. The authors recommended that dementia awareness needed to be considered broadly and not just by aged care services. Furthermore, they felt that health professionals working in remote communities needed to develop skills in timely recognition of dementia.

Culturally and linguistically diverse (CALD) populations

One Australian study examined attitudes to care based on cultural background; people from different CALD backgrounds were presented with a vignette and asked to describe the main sources of support they would turn to. The results showed that members of the general population from Italian, Greek and Chinese backgrounds were more likely than 'third generation Australians' to provide family based care for family members with dementia and less likely than third generation Australians to use respite or residential care services [27].

International studies

Barriers to care for people with dementia

Two international studies were identified which reported quantitative measures of access to care in populations with and without dementia [33 34]. These studies provided evidence of reduced access to care for people living with dementia, both in residential care and in the community. Amongst patients with diabetes living in residential care in the Unites States, people with dementia received fewer diabetic treatments than those without dementia [34]. Similarly, another study in Canada found that people with dementia living in the community were more likely to report unmet needs in regards to community care than people without dementia [33].

Barriers at key points over the course of dementia

We identified one systematic review which reported on the barriers present when accessing primary care [35]. Barriers stemmed from patient factors (such as perceived stigma), GP factors (such as diagnostic uncertainty) and system characteristics (such as time constraints).

We identified one study which examined barriers in access to hospice care for people with dementia [36]. The study involved focus groups and interviews with health professionals working in palliative care. Staff reported a number of barriers including a traditional focus on cancer care in hospice, scarce resources and a lack of acknowledgement that people with dementia required specialist services provided in palliative, care such as complex pain management.

Disparities in care due to cultural background

A systematic review was identified that examined use of health and social services, treatments for dementia and dementia research in different cultural groups [37]. The review found that people from culturally diverse backgrounds in the United States presented to diagnostic dementia services later and with more advanced cognitive decline. However, use of community services following

diagnosis did not differ between groups. People with dementia from culturally diverse backgrounds were 40% less likely to enter residential care; reasons for this were not reported [37].

Disparities in care due to socio-economic characteristics

In England, a study of people with dementia living in the community suggested that prescriptions for acetylcholinesterase inhibitors were less likely to be provided to people from lower socioeconomic backgrounds [38]. This finding is in agreement with observations made in Australia [31].

Qualitative data regarding experiences with the health care system and unmet needs

A recent systematic review of qualitative studies in which people described their experiences in accessing the health care system and barriers to care was included for review [39]. The review found that people with dementia and their families and carers often reported delays in finding assistance. They felt that primary care providers gave limited information and support regarding available services. Delays in accessing memory clinics were common and participants spoke of how important it was that services addressed their specific needs and goals.

Table 9 Studies examining barriers to care for people with dementia in Australia (summary of studies identified in non-systematic review of barriers to care conducted following a systematic review of *interventions to reduce barriers* which failed to identify any included studies)

Reference Country	Study Description	Results
Rosenwax 2008 [28] Australia	*Type:* Retrospect. cohort (comparison with non-dementia group) *Participants:* Data from 992 people who died with a diagnosis of Alzheimer's disease 90% of people with AD were aged 75 or more at the time of death and 69% were female. Most (77%) lived in a major city *Methods:* Linkage of Western Australia data to report health service use for people in the last year of life with and without Alzheimer's disease	Most people with Alzheimer's disease (67%) died in a residential aged care facility whereas most people without Alzheimer's disease (53%) died in hospital. 46.3% of people with documented AD received hospital care in the last year of life compared to over 80% of people without AD. Fewer people in the Alzheimer's group received community care when compared to those without documented AD (10.8% vs. 28.5%). Conclusion: Most people with AD lived and died in an RACF in their final year of life and had their care provided in this setting
Zilkens 2014 [31] Australia	*Type:* Retrospect cohort (within dementia) *Participants:* Data from 99,016 Australians receiving a choline-esterase inhibitor for the first time. 61% female. Most common age groups were 65-74 (18%), 75-84 (53%) and 85-94 (24%) *Methods:* Data were analysed from the Australian Pharmaceutical Benefit Scheme records 2003-2010	Socioeconomic data revealed that the most disadvantaged population (decile 1) had the lowest rate of prescriptions. Rates increased in a steplike fashion with socioeconomic status. Index prescription rates decreased as distance from cities increased with lowest prescription rates in very remote areas (prescription rates were 1.4 to 1.7 times higher in metropolitan areas).
Bail 2013 [25] Draper 2013 [32] Australia	*Type:* Mixed methods (survey + qualitative data) *Participants:* 163 hospitals, Public hospitals in NSW*Methods:* Public hospitals in New South Wales were surveyed regarding the services available. Site visits were conducted to 20 of the hospitals and key informant interviews were conducted	Rural hospitals were significantly less likely than major city hospitals to have beds for aged care services or specialist mental health services for older people (80% vs 90%), memory clinics (10% vs 58%), rehabilitation beds (24% vs 67%) and secure beds (8% vs 41%). Geriatricians were on site or visited in 82% of major city hospitals vs 26% of outer regional, remote and very remote hospitals. Psychogeriatricians were on site or visited in 29% of major city hospitals and no outer regional, remote and very remote hospitals. Staff in rural areas used a range of strategies to manage BPSD. These were not always consistent with best practice; this was thought to be linked to limited staffing, expertise and resources. Committed clinical staff in rural areas attempted to overcome access issues by helping to negotiate patient pathways, flexibility and creativity.
Lindeman 2012 [40] Australia	*Type:* Qualitative: focus groups, interviews and observation *Participants:* Focus group participants (n=26), Interviews (n=5), Study took place in the Northern Territory *Methods:* Focus groups with Indigenous aged care workers, community members and aged care services users. Interviews with health care professionals and service coordinators. Qualitative evaluation designed to explore the outcomes of a dementia awareness resource in remote Aboriginal communities	The focus groups felt that there was poor dementia awareness in the general community. They agreed that dementia was 'everyone's business' and that dementia should not just be portrayed as an 'aged care issue'. There were poor relationships between the trainers and educators attempting to introduce the resource and remote clinic staff; these were thought to be due to high staff turnover, a perceived lack of interest in aged care issues and competing demands on staff.

Reference Country	Study Description	Results
Smith 2011 [30] Australia	*Type:* Qualitative (focus groups and interviews) *Participants:* Data from 42 service providers, 31 family carers and 3 focus groups. Service providers and communities in the Kimberley *Methods:* Interviews and focus groups were held to determine ways to overcome factors affecting the successful delivery of services to Aboriginal people with dementia living in remote communities, and to their families and communities	Main themes included: Culturally appropriate care: all participants felt that dementia initiatives must be driven by the community and the community must be engaged in order to ensure success. Community based care was prioritised. The need for culturally appropriate activities was discussed. Workforce: Carers and providers felt that employing more Aboriginal community based staff was the best way to improve the quality of care for Aboriginal people with dementia. Families and carers needed time to gain trust in professional caregivers before leaving their loved one in their care. There was a shortage of staff and high turnover in community health settings. Positions in community care were seen as underpaid and undervalued. Workers needed pathways or guidelines to direct care. It was noted that service providers, families and carers and community workers would benefit from dementia training and education regarding the availability of services to support a person with dementia and their family. Training in how to recognise and manage elder abuse was requested. Overcrowded housing meant that family carers had to discontinue caring in some cases. High living costs and lack of transport caused additional carer strain. Communication and coordination between service providers was perceived to be poor. Intolerant attitudes were evident amongst service providers and the general community. Barriers to service access: It was felt that services needed to be more flexible and not see aged care as a specialist field. Interpreters were often not available in health and community care settings. There were a lack of specialist, community care and family carers support services available.
Low 2011 [41] Australia	*Type:* Survey *Participants:* 1701 participants. People selected from the White Pages with Italian, Greek or Chinese surnames using a method found to be effective in previous studies. Third generation Australians were selected by randomly sampling phone numbers and excluding Italian, Greek and Chinese surnames. Mean age 58 (Italian sample), 61 (Greek sample), 46 (Chinese sample), 56 (third generation Australian sample). Gender: ranged from 57-61% women across groups *Methods:* Cross sectional telephone survey. Participants were asked how they would seek help for a character in a vignette with dementia and what aged care services they would use	Common supports identified as being of use were General Practitioners (55%), community organisations (27%) and family (26%). More participants from CALD backgrounds than third generation Australians reported that they would seek help from families (32% vs 13%). CALD groups were equally or more likely to use community services as third generation Australians but less likely to use respite services. Participants of Italian descent were less likely to use permanent residential care.

Reference Country	Study Description	Results
Singh 2014 [29] Australia	*Type:* Qualitative (interviews) *Participants:* 17 family carers. Gender 88% female *Methods:* Interviews conducted to determine use and access to formal services amongst family carers of people with dementia	Themes included: Delays in initial diagnosis. Several family carers felt that the GP was not objective in their assessment in making a diagnosis. There were delays in accessing specialist services. There was a lack of information available regarding non-medical support services. There was a lack of understanding in health care services regarding the needs of families and carers. Family carers reported unhappiness with having to take on the role of case manager and were frustrated by the inflexibility of services. Quality of in-home and day care services: staff turnover, lack of punctuality, lack of compassion and poor communication skills were reported. Family carers wanted appropriate and accessible opportunities for participation in formal services.

Abbreviations: AD: Alzheimer's disease; BPSD: behavioural and psychological symptoms of dementia; NA: not applicable; CALD: culturally and linguistically diverse; RACF: Residential Aged Care Facility; Y=yes; N=no; NA=not applicable

Downs and Black Scale: (1) clear study aim, (2) main outcomes described in methods, (3) participant inclusion criteria defined, (4) interventions of interest clearly described, (5) principal confounders described, (6) clear summary of main findings, (7) estimates of random variability, (8) adverse events reported, (9) characteristics of patients lost to follow up reported, (10) actual probability values reported, (11) representative population invited, (12) representatives included, (13) setting representative, (14) blinding of participants, (15) blinding of outcome assessor, (16) data dredging apparent, (17) consistent length of follow up or differences accounted for, (18) statistical tests used appropriate, (19) intervention compliance, (20) outcome measures valid and reliable, (21) same target population, (22) time period, (23) randomisation, (24) allocation concealment, (25) adjustment for confounders, (26) loss to follow up accounted for, (27) powered to detect difference.

Table 10 Systematic reviews examining barriers to care (summary of studies identified in non-systematic review of barriers to care conducted following a systematic review of *interventions to reduce barriers* which failed to identify any included studies)

Reference	Study Description	Results
Systematic review examining barriers to care in primary care		
Koch 2010 [35]	Systematic Review All study designs People with dementia	The review included 11 studies There were three types of barriers: patient factors, GP factors and system characteristics. Main themes were found to be lack of support, time constraints, financial constraints, stigma, diagnostic uncertainty and disclosing the diagnosis.
Systematic review examining differences in care due to cultural background		
Cooper 2010 [38]	Systematic Review Primary research comparing access to services, treatment or research between two or more cultural groups People with dementia	The review included 33 studies, most of which took place in the United States and two of which were Australian [42 43]. The authors found that there were not differences between groups in terms of use of community services. There was low level evidence that people from CALD backgrounds presented at a later stage than those from non-CALD backgrounds. There was low level evidence that: (1) people from different cultural backgrounds with dementia in the United States use more inpatient and emergency services (2) CALD Americans with dementia were less likely to be institutionalised
Systematic review reporting on the qualitative experience of people with dementia and their families and carers in accessing services		
Prorok 2013 [39]	Systematic review Qualitative studies People with dementia and their families and carers in primary care settings Experience of health care services	The authors included 46 studies in the review. The main themes were: seeking a diagnosis; accessing supports and services; addressing information needs; disease management; and communication and attitudes of providers. Authors conclusions: "The health care experience of people with dementia and their caregivers is a complex and dynamic process, which could be improved for many people"

Abbreviations: Y=yes; N=no; CA=can't answer

1.Appraisal criteria: (1) 'a priori' design provided, (2) duplicate study selection and data extraction, (3) comprehensive literature search, (4) grey literature search, (5) list of included and excluded studies provided, (6) characteristics of included studies provided, (7) scientific quality of the included studies assessed and documented, (8) scientific quality of included studies used to formulate conclusions, (9) methods to combine findings appropriate, (10) publication bias assessed, (11) conflict of interest included for review and each of the included studies.

Table 11 International studies examining barriers to care (summary of studies identified in non-systematic review of barriers to care conducted following a systematic review of *interventions to reduce barriers* which failed to identify any included studies)

Reference Country	Study Description	Results
Studies comparing care for people with dementia and people without dementia		
Quinn 2009 [34] United States	*Type:* Retrospect. cohort study (comparison of people with dementia and people without dementia) *Participants:* N = 399. Participants were living in a nursing home and had a diagnosis of diabetes mellitus. Mean age 79 (SD 7), Gender 71% female ***Methods**:* Medicare claims data were matched to nursing home record data. Data was examined to study the role of nursing home admission and dementia status on the provision of five procedures related to diabetes	Residents without dementia received more procedures than those with dementia (glycosylated haemoglobin (P=0.001) & eye examination (P<0.001)). Adjusted data (for demographics, dependence, comorbidities) showed that some differences remained (glycosylated haemoglobin, P=0.007)
Forbes 2006 [33] Canada	*Type:* Retrospect. cohort (comparison of people with dementia and people without dementia) *Participants:* N = 49,999 older Canadians (313 people reported a diagnosis of dementia) *Methods:* Analysis of data to examine the characteristics of older Canadians with dementia (compared to those without dementia), their use of health care services and the impact of place (rural/urban) on use of services	Older persons with dementia were more likely to receive home care than their counterparts without dementia. "Although persons with dementia tended to receive more health care services, the younger sub-groups with dementia were more likely to report that their health care needs were not met than were similar sub-groups without dementia. Among those with dementia, the reasons for not receiving needed health care services were (in order of frequency): the service was considered inadequate, the waiting time was too long, the service was not available in the area, and the service was not available when required" (p324).
Studies examining barriers to hospice care		
Ryan 2012 [36] United Kingdom	*Type:* Qualitative (focus groups and interviews) *Participants:* N = 58. Palliative care practitioners (medical, nursing and allied health professionals) *Methods:* The study aimed to explore the experiences of health care practitioners working in palliative care and sought to establish the issues relating to end-of-life care for people with dementia	Some participants questioned whether dementia constituted a condition that might on its own be a cause of death. Failure to acknowledge this provided a barrier to services of a palliative nature. Data suggested that some professionals fail to recognise the legitimacy of non-malignant diseases when it comes to the provision of palliative care, particularly when resources are scarce. Health professionals felt that people with dementia did not have the same needs in terms of pain management and that palliative care should focus on basic nursing skills which did not need to be provided by palliative care specialists. Participants felt that there was limited competence, skills and capability in working with people with dementia, particularly in the advanced stages. Participants advocated for greater emphasis on 'planning ahead' to facilitate decision making around palliative care.
Studies examining differences in care associated with socio-economic status amongst people with dementia		
Cooper 2010 [38] England	*Type:* Retrospect. cohort (comparison amongst people with dementia) *Participants:* N = 215. People with dementia living independently, 73% female, Mean age 82 (SD 8)	22% of people with dementia were prescribed cholinesterase inhibitors. 32% of home owners were prescribed vs 11% of people that were living in rental accommodation suggesting inequities based on sociodemographics (OR 4.2, 1.8 to 9.8; p=0.001).

Reference Country	Study Description	Results
	Methods: Case note audit of people living in the community with dementia	People receiving cholinesterase inhibitors were younger, had fewer ADL impairments, physical illnesses and neuropsychiatric symptoms.

Abbreviations: AD: Alzheimer's disease; NA: not applicable; CALD: culturally and linguistically diverse; RACF: Residential Aged Care Facility; Y=yes; N=no; NA=not applicable; SD=Standard deviation

1. Downs and Black Scale: (1) clear study aim, (2) main outcomes described in methods, (3) participant inclusion criteria defined, (4) interventions of interest clearly described, (5) principal confounders described, (6) clear summary of main findings, (7) estimates of random variability, (8) adverse events reported, (9) characteristics of patients lost to follow up reported, (10) actual probability values reported, (11) representative population invited, (12) representatives included, (13) setting representative, (14) blinding of participants, (15) blinding of outcome assessor, (16) data dredging apparent, (17) consistent length of follow up or differences accounted for, (18) statistical tests used appropriate, (19) intervention compliance, (20) outcome measures valid and reliable, (21) same target population, (22) time period, (23) randomisation, (24) allocation concealment, (25) adjustment for confounders, (26) loss to follow up accounted for, (27) powered to detect difference

Table 12 GRADE Evidence Profile: *Interventions* to reduce barriers to optimal healthcare (from systematic review of interventions to reduce barriers)

Quality Assessment							Effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**		
Quality of life (person with dementia)								
0	No evidence available for interventions to reduce barriers[1]							
ADL function								
0	No evidence available for interventions to reduce barriers							
Access to optimal healthcare								
0	No evidence available for interventions to reduce barriers[1]							

[1] Studies presented are from a non-systematic review describing which barriers existing addressing the background question, in the absence of evidence of interventions to reduce barriers.

SRQ 2: Early identification

Clinical question

The research question as defined in the protocol and the associated PICO criteria are listed below in Table 13.

Table 13 PICO for SRQ2: Early identification

Clinical question: Are there any advantages or disadvantages to early identification?			
Population	**Intervention**	**Comparator**	**Outcome**
Asymptomatic population, people with Mild Cognitive Impairment	Screening Early diagnosis	Not screening Later diagnosis (based on severity of symptoms)	Quality of life, care plans, disadvantages

Literature review search strategies:

Searches for existing HTAs and Systematic reviews

Searches to identify existing Health Technology Assessment reports (HTAs) and systematic reviews were conducted in the databases specified in Table 14, using the search terms listed in the Guideline Technical Report Volume 2.

Table 14 Searches for existing HTAs and systematic reviews SRQ2: Early identification

Database	Date searched	Period covered	Citations retrieved
HTA	11 April 2014	2005-April 2014	0
Cochrane (Cochrane reviews, Cochrane protocols, DARE)	11 April 2014	2005-April 2014	1
MEDLINE	11 April 2014	2005-April 2014	52
PsycInfo	11 April 2014	2005-April 2014	52
EMBASE	11 April 2014	2005-April 2014	10
PubMed	11 April 2014	2005-April 2014	10

The most recent, comprehensive and highest quality systematic review/HTA identified was conducted by Lin and colleagues [44] and involved a search of studies in December 2012.

Searches for additional primary studies

Searches were conducted in the databases listed in Table 15 to identify any primary studies published since the search period of the included review. The search terms used are listed in the Guideline Technical Report Volume 2.

Table 15 Searches for primary studies SRQ2: systematic review update: Early identification

Database	Dates searched	Period covered	Citations retrieved
MEDLINE	1 May 2015	2005-May 2015	17
PsycInfo	1 May 2015	2005-May 2015	11
EMBASE	1 May 2015	2005-May 2015	8
PubMed	1 May 2015	2005-May 2015	10

As we were unable to identify any studies examining the potential benefits and harms associated with screening we conducted a search for studies of all designs (published between 2006 and 2014) that compared outcomes between people who had received a diagnosis earlier in the course of illness and those that had received a diagnosis later in the course of the illness. The search failed to identify any studies making this comparison.

Table 16 Searches for primary studies SRQ2: Early identification: search for studies of early vs late diagnosis

Database	Dates searched	Period covered	Citations retrieved
MEDLINE	1 May 2015	2005-May 2015	1120
PsycInfo	1 May 2015	2005-May 2015	422
EMBASE	1 May 2015	2005-May 2015	349
PubMed	1 May 2015	2005-May 2015	187

Criteria for selecting studies for review:

Table 17 Inclusion and exclusion criteria SRQ2: Early identification

Characteristic	Criteria
Study design	Inclusion: Randomised controlled trials, controlled trials, cohort studies
Population	Inclusion: Asymptomatic population, people with Mild Cognitive Impairment
Intervention	Inclusion: screening, early diagnosis (relative to onset of symptoms)
Comparator	Inclusion: not screening, later diagnosis (relative to onset of symptoms)
Outcomes	Inclusion: Quality of life, care plans, disadvantages
Publication type	English language

Search results:

Existing HTAs and systematic reviews

The most recent, comprehensive and highest quality systematic reviews/HTA identified was conducted by Lin and colleagues [45].

Primary studies

A total of 2124 citations were retrieved in the electronic database searches. 45 studies were viewed in full text. None met the inclusion criteria and therefore none were included in the evidence update.

Evidence summary

The search identified a high quality systematic review published in 2013 [45] (see Table 18. The review addressed the questions: (1) Does screening for cognitive impairment in community-dwelling

older adults improve decision-making, patient, family/caregiver, or societal outcomes? and (2) What are the harms of screening for cognitive impairment? The authors of the review were unable to identify any studies that examined the direct effect or harms of screening for cognitive impairment. No new studies were identified although the Committee are aware of a large randomised controlled trial underway in the United States which is due to be completed in 2017 [46]. Results of this study will provide important information regarding the benefits and harms of early diagnosis.

In addition, the evidence update included a search for studies of all designs published between 2006 and 2014 that compared outcomes between people that had received a diagnosis earlier rather than later in the course of the illness relative to first noticing symptoms. There were no studies that addressed this issue.

Evidence statement	*GRADE Quality*	*Related recommendation*
No studies were identified that evaluated screening for cognitive impairment in the general population. (Table 19)	NA	CBR 22, 24

NA – not applicable

Table 18 Evidence Table for included systematic review for early identification

Reference	Study Design/Level of Evidence	Types of studies included	Participants	Intervention	Comparison	Results	Quality appraisal[1]
Lin 2013 [45]	Systematic Review	Systematic reviews, randomised controlled trials or controlled clinical trials	Adults who live at home or in senior living communities, assisted living or residential care facilities	Screening: Methodically administering an instrument to patients in order to detect an illness /condition in "apparently" healthy individuals	No screening	No trials were identified that examined the direct effect of screening on patient or societal outcomes or harms	1. Y 2. Y 3. Y 4. Y 5. Y 6. Y 7. Y 8. Y 9. Y 10. Y 11. N

Abbreviations: Y – yes; N – no; NA – not applicable.

1. Appraisal criteria: (1) 'a priori' design provided, (2) Duplicate study selection and data extraction, (3) Comprehensive literature search, (4) Grey literature search, (5) List of included and excluded studies provided, (6) Characteristics of included studies provided, (7) Scientific quality of the included studies assessed and documented, (8) Scientific quality of included studies used to formulate conclusions, (9) Methods to combine findings appropriate, (10) Publication bias assessed, (11) Conflict of interest included for review and each of the included studies.

Table 19 GRADE Evidence Profile: Early diagnosis compared to later diagnosis

Quality Assessment							Effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**		
Quality of life (person with dementia)								
0	No evidence available[1]							
Care plans (treatment options, support for carers)								
0	No evidence available[1]							
Disadvantages (eg. loss of license, social impact)								
0	No evidence available[1]							

[1] Included systematic review did not identify any trials of screening.

SRQ 3: Memory assessment services/specialists

Clinical question

The research question as defined in the protocol and the associated PICO criteria are listed below.

Table 20 PICO for SRQ3: Specialist assessment services

Clinical question: For people with symptoms of dementia, does assessment from a memory assessment specialist or service provide benefits in comparison to attendance at another service?			
Population	**Intervention**	**Comparator**	**Outcome**
Symptomatic people – people with a suspected diagnosis of dementia	Memory clinic or memory assessment service	Other service design	Quality of life (person with dementia) BPSD Cognition ADL function Quality of life (carer)

Literature review search strategies:

Searches for existing HTAs and Systematic reviews

Searches to identify existing Health Technology Assessment reports (HTAs) and systematic reviews were conducted in the databases specified in Table 21, using the search terms listed in the Guideline Technical Report Volume 2.

Table 21 Searches for existing HTAs and systematic reviews SRQ3: Specialist assessment services

Database	Date searched	Period covered	Citations retrieved
HTA	22 April 2014	to 2014	1
Cochrane (Cochrane reviews, Cochrane protocols, DARE)	22 April 2014	to 2014	0
MEDLINE	22 April 2014	1946 to April 2014	3
PsycInfo	22 April 2014	1806 to April 2014	8
EMBASE	22 April 2014	1947 to April 2014	5
PubMed	22 April 2014	2005 to April 2014	0

No systematic reviews meeting the inclusion criteria were identified.

Searches for primary studies

Searches were conducted in the databases listed in Table 22 to identify primary studies. No date restrictions were applied as the NICE Guideline did not provide a detailed summary of studies investigating the efficacy of memory assessment services. The search terms used are listed in the Guideline Technical Report Volume 2.

Table 22 Searches for primary studies/randomised controlled trials SRQ3: Specialist assessment services

Database	Dates searched	Period covered	Citations retrieved
MEDLINE	22 April 2014	1946 to April 2014	31
PsycInfo	22 April 2014	1806 to April 2014	23
EMBASE	22 April 2014	1947 to April 2014	5
PubMed	22 April 2014	2005 to April 2014	0

Criteria for selecting studies for review:

Table 23 Inclusion and exclusion criteria SRQ3: Specialist assessment services

Characteristic	Criteria
Study design	Inclusion: Randomised controlled trial Exclusion: Other study designs
Population	Inclusion: People with symptoms of dementia Exclusion: Other
Intervention	Inclusion: Memory assessment service, eg memory clinic
Comparator	Inclusion: Other service design
Outcomes	Inclusion: Quality of life (person with dementia), BPSD, Cognition ADL function, Quality of life (carer)
Publication type	English language

Search results:

Primary studies

A total of 59 citations were retrieved in the electronic database searches. Two studies were viewed in full text and 2 were included evidence update.

Evidence summary

Our search revealed two RCTs [47] [48] (see Table 24). The first study was conducted in the Netherlands and involved 175 patient-caregiver pairs. A pragmatic design was used to compare the effects of the two complex interventions (memory clinic attendance versus general practitioner care) in real life conditions [47] The memory clinic evaluated involved specialist consultation, consideration of acetylcholinesterase inhibiting drug prescription and tailored non-pharmacological intervention (eg occupational therapy, referral to a nurse specialist, day care or home care). The study found no significant differences in patient outcomes at 12 months and thus there were no clear advantages in attending a memory clinic. The trialists examined the costs associated with both models of care and found no evidence that there were no significant differences in costs of care between memory clinics and general practitioner care [49]. The second RCT was conducted in Australia by Logiudice and colleagues [48]. The intervention included specialist consultation, carer advice and counselling from a nurse specialist, neuropsychology assessment and family conference. The study focussed on outcomes for the family carer and found that those that had attended a memory clinic had significantly improved psychosocial status at six months relative to the control group.

Evidence statements	*GRADE Quality*	*Related recommendation*
One RCT conducted in Australia found that carers who attended a memory clinic with someone with dementia reported improved quality of life (psychosocial status) at six months compared to those visiting the GP.[48](Table 25)	Low	EBR 25
One RCT conducted in the Netherlands did not find a significant difference between memory assessment service and GP visits (in which care was delivered based on local guidelines for GPs) for quality of life of the person with dementia, ADL function or BPSD.[47](Table 25)	Moderate	EBR 25

Table 24 Evidence summary of randomised controlled trials for SRQ3: Specialist assessment services

Reference Country	Study Design/Level of Evidence	N	Participants	Intervention	Comparison	Main Outcomes	Measure/s	Length of follow up	Results/ Effect size	Risk of bias[1]
Meeuwsen 2012 [47] Netherlands	RCT	175 patient-caregiver pairs (153 pairs were assessed at 12 months) Note that initial power calculation was for 220 couples	Age mean 78.1 61% of patients female 60% of participants had Alzheimer's disease Most patients had very mild to mild dementia (Mean MMSE 22.7)	Usual care provided by a Memory Clinic (Treatment was tailored and may have included prescription of cholinesterase inhibitors/memantine and non-pharmacological interventions (eg OT, nurse specialist)) Nine different memory clinics were involved in the study	Usual care provided by the General Practitioner (noting that existing Dutch GP guidelines stated that use of cholinesterase inhibitors was not recommended at the time the study was conducted)	Quality of life of the person with dementia Caregiver impact	For the person with dementia: Quality of life in Alzheimer's disease; Geriatric Depression Scale; Neuropsychiatric Inventory questionnaire; Interview for deterioration in daily living activities in dementia scale; Inventory for measuring social involvement	Assessments at 6 and 12 months	No significant difference between groups in quality of life or any of the other patient outcomes at 12 months.	1. Low 2. Low 3. High 4. Low 5. Low 6. High (not all outcomes reported)

Reference Country	Study Design/Level of Evidence	N	Participants	Intervention	Comparison	Main Outcomes	Measure/s	Length of follow up	Results/ Effect size	Risk of bias[1]
Logiudice 1999 [48] Australia	RCT	50	Age mean 73 in intervention group, mean 78 in the control group Gender 52% female in the intervention group and 61% female in the control group	Attendance at a Memory Clinic on two occasions. The initial attendance included a complete medical assessment including cognitive assessment. Family carers were interviewed by the research nurse who provided advice and counselling. Participants were invited back for a neuropsychological assessment by a neuropsychologist or speech pathologist. Following this, a family conference was undertaken with carers, patient and family members to discuss details of the outcomes of this assessment. Participants were free to ask questions and a plan of assistance was formed which included referral to appropriate services. GPs were provided with information regarding the assessment.	All tools were administered to control group participants. Any questions raised by carers were addressed and referral back to the GP was encouraged.	Caregiver outcomes	General Health Questionnaire; Zarit burden interview; Memory and Behaviour Problems Checklist; knowledge of dementia; Psychosocial health status	Assessments at 6 and 12 months	No significant differences in institutionalisation or service utilisation between groups. No significant differences between groups in GHQ scores, burden, cross-product of behaviour frequency and carer tolerance and dementia knowledge. At 6 months, there was a significant improvement in psychosocial health status overall in the intervention group ((+1.63 points) in the intervention group versus the control group (-6.02 points)($p<0.01$).	1. Unclear 2. Low 3. High 4.High 5. Unclear 6.Unclear

Abbreviations: OT: occupational therapy; GP: general practitioner

1. Risk of bias: (1) Random sequence generation, (2) Allocation concealment, (3) Blinding of participants and personnel, (4) Blinding of outcome assessment, (5) Incomplete outcome data, (6) Selective reporting

Table 25 GRADE Evidence Profile: Memory assessment service versus alternative service model

Quality assessment							Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Quality of life of the person with dementia								
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	None	One RCT (Meeuwsen[47]) found no significant differences between groups	⊕⊕⊕O MODERATE
Behavioural and psychological symptoms of dementia								
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	None	One RCT (Meeuwsen[47]) found no significant differences between groups	⊕⊕⊕O MODERATE
Cognition								
0	No evidence available					None		
ADL function								
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	None	One RCT (Meeuwsen[47]) found no significant differences between groups	⊕⊕⊕O MODERATE
Quality of life (carer)								
1	randomised trial	serious risk of bias[1]	no serious inconsistency	no serious indirectness	serious[2]	None	One RCT (Logiudice[48]) found significant increase in family carer psychosocial status at 6 months (+1.63 points) in the intervention group versus the control group (-6.02 points)(p<0.01)	⊕⊕OO LOW
Institutionalisation								
1	randomised trial	serious risk of bias[1]	no serious inconsistency	no serious indirectness	serious[2]	None	One RCT (Logiudice[48]) found no significant differences between groups	⊕⊕OO LOW

[1] Methodology unclear due to reporting of trial
[2] Sample size

SRQ 4: Follow-up for people with Mild Cognitive Impairment

Clinical question

The research question as defined in the protocol and the associated PICO criteria are listed below. There is currently no consensus on how frequently people with MCI should be assessed by memory clinic services.

Table 26 PICO for SRQ4: Follow-up for people with MCI

Clinical question: How frequently should memory assessment services review people with mild cognitive impairment (MCI) for progression to dementia?			
Population	**Intervention**	**Comparator**	**Outcomes**
People with a diagnosis of Mild Cognitive Impairment (MCI)	Monitoring in memory clinics comprising: •Comprehensive clinical assessment •Cognitive assessment	Alternative monitoring frequency No monitoring	*Primary outcomes:* Health-related quality of life Anxiety/depression *Secondary outcomes:* ADL function Safety Proportion of patients converting to dementia

Literature review search strategies:

Searches for existing HTAs and Systematic reviews

Searches to identify existing Health Technology Assessment reports (HTAs) and systematic reviews were conducted in the databases specified in Table 27, using the search terms listed in the Guideline Technical Report Volume 2.

Table 27 Searches for existing HTAs and systematic review for SRQ4: Follow-up for people with MCI

Database	Date searched	Period covered	Citations retrieved
HTA & NHSEED	4 Nov 2014	2005 to 2014	99
Cochrane (Cochrane reviews, Cochrane protocols, DARE)	4 Nov 2014	2005 to 2014	30
MEDLINE	4 Nov 2014	2005 to week 4 Oct 2014	143
PsycInfo	4 Nov 2014	2005 to 2014	62
EMBASE	6 Nov 2014	2005 to 2014	10
PubMed	6 Nov 2014	2005 to 2014	12
Total			356

Searches for primary studies

Searches were conducted in the databases listed in Table 28 to identify primary studies comparing alternative frequencies of follow-up of people with MCI in memory clinics. The search terms used are listed in the Guideline Technical Report Volume 2.

Table 28 Searches for SRQ4: randomised controlled trials or comparative studies of alternative frequencies of follow-up for people with MCI

Database	Dates searched	Period covered	Citations retrieved
MEDLINE	4 Nov 2014	2005 to week 4 Oct 2014	31
PsycInfo	4 Nov 2014	2005 to 2014	18
EMBASE	4 Nov 2014	2005-2014	29
PubMed	1 Dec 2014	Various, by class	34
Total			112

Criteria for selecting studies for review:

Table 29 Inclusion and exclusion criteria for SSRQ4: Follow-up for people with MCI

Characteristic	Criteria
Study design	Inclusion: Systematic reviews, randomised controlled trials, comparative studies
Population	Inclusion: People with a diagnosis of Mild Cognitive Impairment (MCI) Exclusion: People with subjective memory loss
Intervention	Inclusion: Monitoring in memory clinics comprising: •Comprehensive clinical assessment •Cognitive assessment
Comparator	Inclusion: Alternative monitoring frequency; no monitoring
Outcomes	Inclusion: Health-related quality of life, Anxiety/depression, ADL function, Safety, Proportion of patients converting to dementia
Publication type	English language

Search results:

Existing HTAs and systematic reviews

No systematic reviews or HTAs that addressed the frequency of monitoring of people with MCI were identified.

Primary studies

A total of 112 citations were retrieved in the electronic database searches. After exclusion of duplicate citations, 96 were excluded on review of abstract and title. The search did not identify any studies that compared alternative assessment frequencies, or compared follow-up assessment to no review, for patients with mild cognitive impairment (MCI) attending memory clinics (GRADE Evidence Profile Table 30).

Evidence summary

The NICE Guideline Committee recommended that people with MCI should be followed up in order to monitor cognitive decline. However, they did not provide guidance on how frequently reviews should occur. The recommendation was not linked to a source of evidence.

In the absence of evidence regarding the optimal frequency of review, the Guidelines Adaptation committee decided to make a consensus based recommendation. The committee used conversion rates of MCI to dementia to inform their decision making.

A recent systematic review by Ward et al [50] identified cohort studies providing rates of conversion from MCI to Alzheimer's disease published since 2006. In a clinic (or specialist) setting the annual conversion rate (ACR) of MCI to Alzheimer's Disease (AD) across 13 studies was a median of 10.2% (range 5.9% - 18.8%). The conversion rates were similar, whether studies enrolled patients with MCI broadly (e.g. according to a Clinical Dementia Rating of 0 or 0.5, or a Global Deterioration Score of 2 or 3) or with amnestic MCI (MCI median ACR = 9.7%, range 7.5% - 11% across 5 studies; a-MCI ACR = 10.6%, range 5.9% - 18.8% across 8 studies). Annual conversion rates in studies that recruited subjects from the community were lower (median 6.0%, range 4.3% - 11.5% across 11 studies).

Other studies found similar annual conversion rates from MCI to Alzheimer's disease or vascular dementia (ACR = 10.3%, n=65 [51]); or from MCI in Parkinson's disease to dementia (in a community-based sample ACR = 15.5%, n=29 [52]).

Evidence statements	*GRADE Quality*	*Related recommendation*
No studies were identified that compared outcomes for people with MCI attending memory clinics for review at alternative frequencies. (Table 30)	NA	CBR 27

NA – not applicable

Table 30 GRADE Evidence Profile: Frequency of memory clinic review of people with MCI for progression to dementia

Quality Assessment							Effect	Quality	Link to patient centred outcomes
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Health-related quality of life									
0	No evidence available[1]								
Anxiety-depression									
0	No evidence available[1]								
ADL function									
0	No evidence available[1]								
Safety									
0	No evidence available[1]								
Proportion of patients converting to dementia									
0	No evidence available[1]								

1. No evidence available comparing alternate review frequencies

SRQ 5: KICA and RUDAS cognitive assessment tools

Clinical question

The research question as defined in the protocol and the associated PPICO criteria are listed below in Table 31. These tools are expected to identify people with dementia with the same spectrum of disease as existing cognitive assessment tools. Thus evidence from comparative diagnostic accuracy studies of existing cognitive assessment tools and the Kimberley Indigenous Cognitive Assessment (KICA) or Rowland Universal Dementia Assessment Scale (RUDAS) is considered to suffice for evidence of impact on patient outcomes [53]. Although a comparison of the accuracy of alternate tests is important in diagnostic test accuracy reviews [54], the developers of the KICA have indicated that, as the KICA is the first cognitive assessment tool developed for use in remote Indigenous Australian populations, there is no appropriate alternative cognitive assessment tool for this population [55]. Subpopulations of remote and non-remote Indigenous Australians were considered separately in this review for the evidence update.

Table 31 PPICO for SRQ5: cognitive assessment tools KICA and RUDAS

Clinical question: What is the evidence for the validity of the Kimberley Indigenous Cognitive Assessment (KICA) in Indigenous Australian populations and the Rowland Universal Dementia Assessment Scale (RUDAS) in Culturally and Linguistically Diverse (CALD) populations?				
Population	**Prior tests**	**Intervention**	**Comparator**	**Outcomes**
Symptomatic people – people with suspected dementia *Subgroups:* Remote living Indigenous Australians Non-remote living Indigenous Australians	Nil prior tests	Kimberley Indigenous Cognitive Assessment (KICA) Rowland Universal Dementia Assessment Scale (RUDAS)	*RUDAS:* Cognitive testing not specifically targeted at CALD populations *KICA non-remote population:* Cognitive testing not specifically targeted at Indigenous populations *KICA remote population:* None	Diagnostic accuracy for diagnosis of dementia
Reference standard: pathology or comprehensive clinical assessment with follow-up (both imperfect reference standards as MCI may progress, no perfect reference standard available)				

Abbreviations: CALD – culturally and linguistically diverse; MCI – mild cognitive impairment; PPICO– population, prior tests, intervention, comparator, outcomes

Literature review search strategies:

Searches for existing HTAs and Systematic reviews

Searches were conducted in the DARE, NHSEED, HTA and Cochrane reviews databases to identify existing Health Technology Assessment reports (HTAs) and systematic reviews of the KICA or RUDAS retrieved no citations (dates: 2000 to 2014). Searches in databases for studies of the KICA and

RUDAS were not limited by study design or publication type (see Table 32); no high quality, relevant systematic reviews were identified.

Searches for primary studies

Searches were conducted in the databases listed in Table 32 to identify primary studies of the accuracy of the KICA or RUDAS to diagnose dementia. Searches used intervention terms only and were not limited by study design or publication type. Searches for grey literature were also conducted through the sites listed. The search terms used are listed in the Guideline Technical Report Volume 2.

Table 32 Searches for studies for SRQ5: cognitive assessment tools KICA and RUDAS

Database	Dates searched	Period covered	Citations retrieved
MEDLINE	3 July 2014	1946 to June week 3 2014	25
PsycInfo	3 July 2014	1806 to June week 4 2014	25
EMBASE	3 July 2014	1947 to Aug 25 2014	41
Cochrane Central Register of Controlled Trials	3 July 2014	No date restrictions applied	3
PubMed	13 August 2014	2004 to 3 July 2014	10
Grey literature: Alzheimer's Australia Informit Health InfoNet Author contact	 6 August 2014 7 August 2014 6 August 2014	No date restrictions applied	6
Total			110

Criteria for selecting studies for review:

Table 33 Inclusion and exclusion criteria for SRQ5: cognitive assessment tools KICA and RUDAS

Characteristic	Criteria
Study design	Inclusion: Systematic reviews, randomised controlled trials, non-randomised controlled trials, or cross sectional diagnostic accuracy studies with consistently applied reference standard Exclusion: diagnostic case control studies; nested case control studies (ie those excluding people enrolled in the study that are subsequently diagnosed with MCI or cognitive impairment, no dementia)
Population	Inclusion: People with a suspected diagnosis of dementia (ie, symptomatic people, includes those with MCI) Exclusion: People with subjective memory loss
Intervention	Inclusion: Kimberley Indigenous Cognitive Assessment (KICA); Rowland Universal Dementia Assessment Scale (RUDAS) Exclusion: Non-English versions of the RUDAS
Comparator	Inclusion: Comprehensive cognitive testing not specifically targeted at Indigenous or CALD populations (for RUDAS or KICA in non-remote populations), eg. MMSE, GPCOG etc Inclusion: No comparator (KICA in remote populations)

Characteristic	Criteria
	Exclusion: No comparison to an alternative cognitive assessment tool (for RUDAS or KICA in non-remote populations)
Outcomes	Inclusion: Diagnostic accuracy to differentiate dementia from non-dementia patients, as determined by application of an appropriate reference standard Exclusion: diagnostic yield without a reference standard; correlation to alternative cognitive assessment tools; reliability; reproducibility (and other technical efficacy outcomes)
Publication type	Inclusion: English language, peer reviewed or grey literature

Studies or outcomes of technical efficacy (e.g. reliability)were not included for review (according to the protocol defined *a priori*; see Table 4, page 18). Only outcomes considering the use of the complete tool (not selected questions or shortened versions) were reviewed. Studies that included subjects with mild cognitive impairment (MCI) in the analysis of accuracy data were included for review. Studies that excluded patients with mild cognitive impairment (or cognitive impairment, no dementia) from the accuracy analyses (eg. nested case-control studies) were excluded.

Search results:

Primary studies

A total of 110 citations were retrieved in the electronic database searches. After exclusion of duplicate citations, 61 citations remained; 30 articles were excluded on review of abstract and title, 31 were reviewed in full text. The complete study following on from a pilot study identified in the literature review was provided by contact with the authors as an in-press publication and was included for review [56].

Eight publications of the KICA tool were identified. Two studies were excluded as they did not report diagnostic accuracy data [57 58]; three studies were excluded as the reported accuracy data was for a nested case control population [55 59 60]. No studies conducted in subjects with suspected dementia were identified. Therefore, studies conducted in the general population were included for review. Four studies were included in this evidence update (Evidence Summary Table 34). These included two studies conducted in a remote living Indigenous Australian population; one of the KICA-Cog [61] (GRADE Evidence Profile Table 36) and another of the KICA-Screen (GRADE Evidence Profile Table 37), a shortened version of the KICA-Cog [62]. Also included was a pilot study and an in-press publication of the modified KICA (mKICA) conducted in a non-remote living Indigenous Australian population (GRADE Evidence Profile Table 38) [56 63]. One of these studies [61] met the inclusion criteria when supplemented with additional data provided by personal communication [64].

Seventeen publications of the validity of the RUDAS tool were identified. Thirteen studies were excluded as they were of translated versions of the RUDAS or provided a lower level of evidence (e.g. did not report accuracy outcomes, did not compare the RUDAS to alternative cognitive assessment tools or excluded patients with mild cognitive impairment from the accuracy calculations [nested case-control studies]) [65-81]. Three studies of the comparative accuracy of the RUDAS tool, that directly addressed the research question, were included for review (Evidence Summary Table 35) [82-84]. One additional study that was performed in a population-based sample was also included due to the paucity of evidence available (Evidence Summary Table 35).[85] The GRADE Evidence Profile is shown in Table 39.

Evidence summary:

Kimberley Indigenous Cognitive Assessment (KICA-Cog)

Subpopulations of remote and non-remote Indigenous Australians were considered separately. Two studies met the inclusion criteria for non-remote populations [56 63]; two publications met the criteria for remote populations [61 62] and additional data were provided by personal communication [64] (see Evidence Summary Table 34).

Remote Indigenous populations

Although a comparison of the accuracy of alternate tests is important in diagnostic test accuracy reviews [54], the developers of the KICA have indicated that, as the KICA is the first cognitive assessment tool developed for use in remote Indigenous Australian populations, there is no appropriate alternative cognitive assessment tool for this population. [55]. Two publications involving the KICA-Cog and KICA-Screen (a shortened version of the KICA-Cog) conducted in a remote population were included [61 62]. Additional data were provided by personal communication [64]. The Evidence Summary is presented in Table 34 and the GRADE Evidence Profiles in Table 36 and Table 37.

Smith (2008) conducted a study to determine the prevalence of dementia and cognitive impairment in remote Indigenous populations in the Kimberley. The accuracy of the KICA-Cog for the diagnosis of dementia in this population, at the optimal cut-off of 33/34, was high, with a sensitivity of 93% and a specificity of 98% (see Table 34, Table 36) [64]. For the diagnosis of dementia, the KICA-Cog had a PPV of 36% at a cut-off of 36/37 in this population-based study (Table 34). The sample in this study was not a consecutive series of patients presenting to a clinician and so the applicability of these data to clinical practice is limited. Also, not all subjects were reviewed by a specialist (there was incomplete verification).

In the same population, the KICA Screen (a shortened, 10-item version of the KICA-Cog) was developed [62]. In this population in whom the tool was developed, the KICA-Screen had high accuracy (Table 34, Table 37). The screening tool was tested in 55 Indigenous Australians (including Torres Strait Islanders) from North Queensland at the cut-off of 21/22 which was defined as optimal in the Kimberley study. The KICA Screen had a moderately high sensitivity of 76% and a specificity of 89% in the North Queensland population. However the subjects included some healthy controls and the spectrum of cognition is likely to differ to that seen in clinical practice.

Non-remote Indigenous populations

In non-remote (rural or urban) populations, included studies of diagnostic accuracy (as determined by an appropriate reference standard) were those that provided a comparison to an alternative cognitive assessment tool. A modified version of the KICA for urban dwelling Aboriginal populations (the mKICA) was developed as part of the Koori Growing Old Well Study (KGOWS) project [63]. Two studies which compared the accuracy of the modified KICA (mKICA) to alternative cognitive assessment tools were included for review.[56 63] The Evidence Summary is presented in Table 34 and the GRADE Evidence Profile in Table 38.

One high quality study was conducted in 235 Aboriginal Australians from 5 urban and regional areas in NSW. Diagnostic accuracy for the differentiation of dementia from non-dementia was reported for the standard and optimal cut-offs for the MMSE, mKICA and the RUDAS. There was no significant difference in AUC values between the three tests; however the AUC was slightly higher for the mKICA and MMSE than the RUDAS (see Table 34). At standard published cut-offs, the sensitivity of the tests were not significantly different, but were slightly higher for the MMSE (68%) than for the mKICA (57%) or the RUDAS (61%). However, the specificities of the mKICA and MMSE were higher

than that of the RUDAS (Table 34) and accuracy was good for both the MMSE and mKICA at 94.0%, compared to 88.5% for the RUDAS. At optimal cut-offs, the MMSE and mKICA both had good sensitivity, but the MMSE was more specific than the mKICA. The RUDAS had lower sensitivity and specificity at both standard and optimal cut-offs.

A small pilot study of 19 subjects also compared the mKICA with the MMSE and the RUDAS [63]. All of the cognitive assessment tools correctly classified the nine subjects with cognitive impairment (those with MCI or an abnormal cognitive finding without a cognitive or functional decline) or dementia. The mKICA and MMSE had one false positive result of the ten subjects that did not have any cognitive impairment; the RUDAS had none.

In 2007, the Dementia Outcomes Measurement Suite Project made an interim recommendation to use the Kimberley Indigenous Cognitive Assessment tool for the cognitive assessment of rural and remote Indigenous people [86]. It was recommended that further research be undertaken on the KICA-Cog tool to ensure its validity and reliability. Since that time, additional research has been conducted on the KICA-Cog in a remote population indicating a high accuracy of the tool in a population-based study. Further studies conducted in a consecutive series of presenting patients would assess the applicability of these findings to a clinical setting, however large studies of this type may not be feasible.

Rowland Universal Dementia Assessment Scale (RUDAS)

Four studies of the comparative accuracy of the RUDAS tool were included for review [82-85] (see Evidence Summary Table 35 and GRADE Evidence Profile Table 39). All four studies compared the accuracy of the RUDAS to the Folstein Mini-mental State Examination (MMSE), one also compared the RUDAS to the Informant Questionnaire on Cognitive Decline in the Elderly (IQ-CODE) and another to the General Practitioners Assessment of Cognition (GPCOG). In one study the main analysis of accuracy was based on case control data; hence only the results from the sensitivity analyses which includes all patients are considered here [85].

In all four studies the area-under the ROC curve (AUC) did not significantly differ between the RUDAS and the MMSE (Table 35). Neither did it significantly differ between the RUDAS and the IQ-CODE in one study or the RUDAS and the GPCOG in another.

In one study of 137 consecutive memory clinic patients the RUDAS and the MMSE did not significantly differ in their sensitivity, specificity or likelihood ratios, however the MMSE accuracy was reported for a cut-off score of <25, which differs to that recommended in practice (Table 35).[77] Dementia was questionable or mild in 71 percent of subjects diagnosed with dementia. In this study having an immigrant background significantly affected the MMSE score but not the RUDAS. In another study of 204 memory clinic patients the MMSE (at the recommended cut-off <24) had a significantly higher sensitivity than the RUDAS (sensitivity MMSE 83% versus RUDAS 66% at the optimal cut-off score of <21, as determined by the Youden index which takes into account both the sensitivity and specificity) (Table 31).[82] Accuracy measures for the RUDAS and the IQ-CODE did not significantly differ (Table 31). In both of these studies the accuracy estimates contain a risk of bias as the cognitive assessment results were considered as a component of the consultant diagnosis (the reference standard).

One population-based study of the RUDAS provided area under the curve (AUC) values for all subjects in a community dwelling sample including those with mild cognitive impairment (MCI) [85]. Subjects were selected from a database of referrals to an aged care team and did not necessarily have suspected cognitive impairment. The AUC did not differ between the RUDAS and the MMSE. In another study of the RUDAS conducted in subjects recruited from both memory and other clinics,

the AUC did not significantly differ between the RUDAS, MMSE and GPCOG. [84] For the diagnosis of dementia, the accuracy of the RUDAS was slightly higher than that of the MMSE at the recommended cut-off scores (sensitivity 88% vs 79%, specificity 77% vs 79% for RUDAS and MMSE, respectively.[84] The GPCOG demonstrated a higher sensitivity (98%), but lower specificity (62%) in comparison to the RUDAS. For the accuracy to diagnose MCI or dementia compared to normal cognition, the sensitivity of the MMSE and the RUDAS at the recommended cut-off scores did not significantly differ, but were significantly lower than that of the GPCOG.[84] The specificity of the GPCOG was slightly but not significantly lower than that of the RUDAS and MMSE, which did not differ from each other. In this study the relationship between the RUDAS and cognitive status was not affected by CALD status, whereas the MMSE was affected.

In 2007, the Dementia Outcomes Measurement Suite Project made an interim recommendation to use the RUDAS tool in those from Culturally and Linguistically Diverse (CALD) backgrounds [86]. It was recommended that further research be undertaken on the RUDAS tool to ensure its validity and reliability in different culturally and linguistically diverse (CALD) populations. Since that time, there have been few additional studies conducted reporting the accuracy of the English version in consecutive patients using the recommended cut-off scores.

Evidence statements	*GRADE Quality*	*Related recommendation*
One diagnostic accuracy study of the KICA-Cog has demonstrated high accuracy for the diagnosis of dementia in a remote Indigenous Australian population.[61 64] (Table 36)	Low	EBR 39
The KICA-Screen had a high accuracy for dementia in one study in a remote Indigenous Australian population, in which the tool was developed.[62] Accuracy of the KICA-Screen was moderately high in a small study in a North Queensland remote Indigenous Australian population.[62] (Table 37)	Very low	EBR 39
A large accuracy study and a small pilot study of the mKICA have demonstrated comparable accuracy of the mKICA and the MMSE in urban and regional living Indigenous Australian populations.[56 63] The accuracy of the RUDAS was slightly lower than that of the mKICA and MMSE in this population.[56] (Table 38)	Low	EBR 40
The accuracy (as determined by the AUC) of the RUDAS and the MMSE did not significantly differ in four diagnostic accuracy studies.[82-85] Three diagnostic accuracy studies compared the sensitivity and specificity of the MMSE and the RUDAS, with inconsistent results.[82-84] There is a high degree of uncertainty due to biases inherent in the studies. The RUDAS was less influenced by cultural background than the MMSE in two studies.[83 84] (Table 39)	Very low	EBR 41

Resource requirements

The KICA tool is freely available on-line at www.perkins.org.au/wacha/.

The RUDAS tool and training is freely available on-line at https://fightdementia.org.au/about-dementia-and-memory-loss/cultural-diversity/culturally-appropriate-dementia-assessment-tools/RUDAS.

Methodological issues

In several studies of the RUDAS, the MMSE was incorporated into the reference standard of clinical diagnosis, which is likely to inflate the accuracy of the MMSE.

Studies also applied varied cut-off scores. In practice, a clinician is unlikely to apply a strict cut-off value from cognitive testing in isolation, but rather will consider the test score in combination with other factors such as patient function.

Several of the included studies for the Kimberley Indigenous Cognitive Assessment (KICA) and Rowland Universal Dementia Assessment Scale (RUDAS) cognitive assessment tools involve reporting accuracy measures according to the optimal cut-off as determined by receiver operating characteristic (ROC) analysis. Selective reporting of thresholds in a data driven manner can introduce bias [54].

In the included studies of the KICA and RUDAS cognitive assessment tools, the choice of reference standard as comprehensive clinical assessment often involving a presentation to a multidisciplinary team and multiple tests is appropriate.

The interpretation of test results for cognitive assessment tools will vary in primary or specialist settings. In particular, the positive predictive value of a tool or the chance that a positive test result reflects the presence of dementia, will vary according to dementia prevalence.[20] Hence the positive predictive value is likely to be lower in a primary care setting (i.e. less likely to be predictive of a dementia diagnosis). Similarly, whilst the sensitivity and specificity of a tool are not directly affected by prevalence, they are likely to alter with severity of disease, and therefore may also be lower in a primary care than a memory clinic setting. [20]

Table 34 Evidence Summary of primary studies of KICA

Reference Country Recruitment period	Study Design	N(n)	Participants	Test	Comparison	Reference standard	Main Outcomes	Results [2]	Risk of bias[1]
Remote Indigenous Australian populations – KICA-Cog									
Smith 2014 (pers comm) [64] Smith 2008 [61] Australia, Kimberley region Recruitment period NR	Cross-sectional diagnostic accuracy study	363 (45 dem, 29 MCI, 289 norm)	Semi-purposeful sampling of all Indigenous Australians >45 years living in six remote communities and random sample of 1 in 3 Indigenous people in a town. Population based, will include some healthy controls. Age: (mean ±SD): 60.7 ± 11.9 Gender: 55% F Severity of dementia: NR Education: 40% no formal education Interpreter: as required (% NR)	KICA-Cog	None	Geriatrician or geriatric psychiatrist, independently reviewed by 2 specialists to DSM-IV and ICD-10, blind to KICA, performed within 3 months. Verification: 165 met criteria for verification (100% of those with KICA <37, random 50% of those KICA = 37, random 5% those scoring >37), 147 (89.1%) verified, 18 not verified (10.9%). Unverified with KICA >37 assumed to be true.	Smith 2014 (pers comm): AUC, Sn, Sp Smith 2008 [61], raw data enabling calculation of PPV	*Normal/MCI vs dementia:* Cut-off 33/34 [64]: AUC 0.963 (0.943-0.984), Sn 93.3%, Sp 89.9%, LR+ 9.3, LR- 0.1 Cut-off <37 [3] [61]: PPV 0.36 *Normal vs MCI/dementia:* Cut-off 35/36 [64]: AUC 0.945, Sn 87.8%, Sp 85.5%, LR+ 6.1, LR- 0.1 Cut-off <37 [3][61]: PPV 0.57	1. Low 2. Unclear 3. Low 4. High
Remote Indigenous Australian populations – KICA-Screen									
Lo Guidice 2011 [62] Australia, Kimberley region & Far North Queensland Recruitment period NR	Cross-sectional diagnostic accuracy study	363 Kimberley (45 dem, 29 MCI, 289 norm) 55 Nth Qld (26 dem, 17 MCI, 12 norm)	<u>Kimberley</u>: semi-purposeful sampling of all residents >45 years living in 6 remote communities and random sample of 1/3 Indigenous people in a town. Population based, will include some healthy controls. Age: (mean ± SD): 60.6 ±11.9 Gender: 55% F Severity dem: NR	KICA-Screen (short 10-item version of the KICA), developed retrospect-ively in Kimberley pop.	None	<u>Kimberley:</u> Geriatrician or geriatric psychiatrist, independently reviewed by 2 specialists to DSM-IV and ICD-10, blind to KICA, performed within 3 months. Partial verification. Unverified test results of KICA-Cog >37assumed to be true.	Accuracy: Sn, Sp, AUC	<u>Kimberley:</u> AUC 0.95 (95%CI 0.91-0.98); Optimal cut-point 21/22 *Normal vs MCI/dementia:* Sn 87.8%, Sp 88.6% *Normal/MCI vs dementia:* Sn 95.6%, Sp 82.7% No difference in mean total KICA-Screen score between those with no education and some education, after adjusting for age and dementia diagnosis.	<u>Kimberley:</u> 1. Low 2. High 3. Low 4. High

			Nth Qld: >45 years, Convenience sampling, same as above, includes Torres Strait. Age: mean 69.6, range (45-95) Gender: 64% F Severity dem: NR			Nth Qld: Comprehensive geriatric assessment, including domains of CIBIS/CIBIC Plus, MMSE when possible and CT when available, independently reviewed by 2 specialists using DSM-IV and ICD-10.		Nth Qld: AUC 0.87 (95%CI 0.77-0.97); cut-point 21/22 *Normal vs MCI/dementia:* Sn 75.9%, Sp 88.5% *Normal/MCI vs dementia:* Sn 82.4%, Sp 71.1%	Nth Qld: 1. High 2. Low 3. Low 4. Unclear
Non-remote Indigenous Australian populations									
Pulver 2012 [63] Australia Recruitment period NR	Pilot accuracy study	19 (2 dem, 7 cog imp, 10 normal)	Aboriginal Australian volunteers from communities in Sydney (La Perouse) and the mid-north coast of NSW (Kempsey) Characteristics (n=30) Age: mean 58yrs Gender: 73% F Education: mean 10yrs Interpreter: NR Informant: NR	mKICA cut-off <34	MMSE (cut-off <24), RUDAS (cut-off <23) Unclear if incorpora-tion bias	Diagnosis by panel of two geriatricians & one clinical neuro-psychologist on clinical history, physical exam, cognitive testing, speaking to informant, using DMS-III-R. Applied in 19/30 subjects. Time lag from screening mean 4.9 months (range 3.3 – 7.2)	Sn, Sp, correlation	*Cog imp/dem vs normal:* mKICA Sn 100% (9/9), Sp 90% (9/10)[5] MMSE Sn 100% (9/9), Sp 90% (9/10)[5] RUDAS Sn 100% (9/9), Sp 100% (10/10)	1. High 2. Low 3. Low 4. High

Radford 2015 [87] Australia Recruitment period NR	Diagnostic accuracy study	235 (28 dem, 26 cog imp, 181 normal)	336 Aboriginal Australians from 5 urban and regional areas in NSW. 101 excluded if didn't complete all 3 tests, or diagnosed with cognitive disorder other than dementia or MCI, or no reference standard within 6 months. Age mean (SD): 65.8yrs (5.8) Gender: 60% F Education mean (SD): 9.6yrs (2.9) Interpreter: NR Informant: NR Remoteness: 42.6% urban	mKICA cut-off <34, <37	MMSE (cut-off <24, <26), RUDAS (cut-off <23, <24)	Diagnosis by physicians trained in geriatrics on history, neurological exam, cognitive testing & informant interview, and consensus diagnosis by panel of ≥3 clinicians (geriatricians & neuro-psychologists) by NIA-AA, or Winblad MCI criteria, blind to initial screening results. Applied in 20% of those scoring MMSE ≤ 26, mKICA ≤ 35 and RUDAS ≤ 25 & all subjects scoring over these cut-offs. Time lag from screening mean 2.1 months (range 0-6 months; SD 1.90)	AUC, Sn, Sp, LRs, correlations to demographic variables	<u>mKICA</u> AUC 0.93 (95%CI 0.88 – 0.99) *Normal/MCI vs dementia:* Standard cut-off (<34) Sn 57.1% (95%CI 37.2 – 75.5) Sp 99.0% (95%CI 96.6 – 99.9) Accuracy 94.0% Optimal cut-off (<37)[4]: Sn 85.7% (95%CI 67.3 – 96.0) Sp 89.9% (95%CI 84.9 – 93.6) LR+ 8.5 (95%CI 5.5 – 13.0) LR- 0.2 (0.1 – 0.4) <u>MMSE</u> AUC 0.94 (95%CI 0.89 – 0.99) *Normal/MCI vs dementia:* Standard cut-off (<24) Sn 67.9% (95%CI 47.6 – 84.1) Sp 97.6% (95%CI 94.5 – 99.2) Accuracy 94.0% Optimal cut-off (<26)[4]: Sn 85.7% (95%CI 67.3% - 96.0%) Sp 94.7% (90.7% - 97.3%) LR+ 16.1 (8.9 – 29.2) LR- 0.2 (95%CI 0.1 – 0.4) <u>RUDAS</u> AUC 0.89 (0.83 – 0.95) *Normal/MCI vs dementia:* Standard cut-off (<23): Sn 60.7% (95%CI 40.6 – 78.5) Sp 92.3% (95%CI 87.8 – 95.5) Accuracy 88.5% Optimal cut-off (<24)[4]: Sn 71.4% (95%CI 51.3 – 86.8) Sp 90.3% (95%CI 85.5 – 94.0) LR+ 7.4 (95%CI 4.6 – 11.9) LR – 0.3 (95%CI 0.2 – 0.6)	1. Low 2. Low 3. Low 4. Low

Abbreviations: cog imp – cognitive impairment; dem – dementia; DMS-III-R – Diagnostic and Statistical Manual of Mental Disorders - Revision; mKICA – modified Kimberley Indigenous Cognitive Assessment; NR – not reported; NSW – New South Wales; RUDAS – Rowland Universal Dementia Assessment Scale
Sn – sensitivity; Sp –specificity;

1. Risk of bias according to Cochrane Revman 5 items: (1) whether patient sampling is random, consecutive and avoiding inappropriate exclusions (2) whether conduct and interpretation of index test(s) were blinded and according to a pre-specified threshold (3) whether conduct and interpretation of reference standard was blind and met pre-specified criteria in review protocol, (4) flow and timing: whether all patients received same reference standard within an appropriate time period from index test and were included in the analysis.
2. The Area Under the ROC Curve (AUC) summarises the accuracy across a range of thresholds; a value of 1.0 indicates a perfect test, a value of 0.5 a completely uninformative test [54]. The likelihood ratio represents a combination of the sensitivity and specificity and measures the probability of the test result in patients with the disease compared to those without the disease. A likelihood ratio of 1 indicates that the test does not provide any useful diagnostic information. Positive likelihood ratios > 10 and negative likelihood ratios < 0.1 can provide convincing diagnostic evidence. Positive likelihood ratios > 5 and negative likelihood ratios < 0.2 can provide strong diagnostic evidence. However, the interpretation depends on the context in which the test is used and the pre-test probability [20].
3. This cut-off differs to that recommended and the prevalence in a population-based sample is likely to be lower than that in a series of presenting patients.
4. Determined according to Youden's index
5. Authors report 1 false positive result in 10 normal subjects, describing this as specificity 94%

Table 35 Evidence Summary of primary comparative studies of Rowland Universal Dementia Assessment Scale (RUDAS)

Reference Country Recruitment period	Study Design	N(n)	Participants	Test	Comparison [4]	Reference standard	Main Outcomes	Results/Effect size [1]	Risk of bias[3]
Goncalves 2011 [82] Australia June 2007 – June 2010	Cross-sectional diagnostic accuracy study	204 (152 dem, 27 cog imp, 25 other)	Consecutive memory clinic attendees. Excluded if no informant (14%), missing data (1.6%). All non-institutionalised Age mean(SD): 76.9 yrs (8.85) Gender: 56% F Severity dem: NR Bkgd: 10% English not first language Education: 61% not graduated high school Interpreter: NR No informant: 100%	RUDAS, blinded Cut-offs not pre-defined	SMMSE IQ-CODE [5] Not blinded Incorporated into ref std	Diagnosis by consultant using DM-IV-TR, including SMMSE, IQCODE-SF cognitive assessments	Accuracy : AUC, Sn, Sp, PPV, NPV, LR+, LR-	RUDAS: *Normal/MCI vs dementia:* AUC = 0.83 (95%CI = 0.77 – 0.88) Optimal cut-off [7] <21 Sn = 0.66 (95% CI: 0.58 - 0.74) Sp = 0.90 (95% CI: 0.78 - 0.96) LR+ = 6.91 (95%CI 2.98 - 16.02) LR- = 0.37 (95%CI 0.30 - 0.47) Correct classification: 73% Youden's index = 0.56 SMMSE: *Normal/MCI vs dementia:* AUC = 0.82 (95% CI = 0.76 - 0.87) Optimal cut-off <24[7] (same as recommended) Sn = 0.83 (95% CI: 0.76 - 0.88) Sp = 0.73 (95% CI: 0.59 - 0.84) LR+ = 3.08 (95% CI: 1.96, NR) LR- = 0.23 (95%CI 0.16, 0.34) Correct classification: 80% Youden's index = 0.61 IQCODE: *Normal/MCI vs dementia:* AUC = 0.77 (95% CI = 0.71 - 0.83) Optimal cut-off [7] >4.1 Sn = 0.72 (95% CI: 0.64 - 0.79) Sp = 0.67 (95% CI: 0.53 - 0.79) LR+ = 2.21 (95%CI 1.48, 3.31) LR- = 0.41 (95%CI 0.31 – 0.54) Correct classification: 71% Youden's index = 0.64	1. High 2. High 3. High 4. Unclear

Reference **Country** **Recruitment period**	**Study Design**	**N(n)**	**Participants**	**Test**	**Comparison** [4]	**Reference standard**	**Main Outcomes**	**Results/Effect size** [1]	**Risk of bias**[3]
Nielsen 2013 [77] Denmark Sept 2011-March 2012	Cross-sectional diagnostic accuracy study	137 (dem 72, other 65)	Consecutive patients referred to 3 memory clinics. Excluded: moderate or severe psychiatric disorders (n=5) Age: (median) 77 yrs (dem) (Q1-Q3 71.5 – 81), 61 yrs (Q1-Q3 50.5 – 70) (other) Gender: 47.4% F Severity dem: 27.8% questionable, 43.1% mild, 27.8% moderate, 2.8% severe Bkdg: 24.8% Immigrants Education: 9.3yrs ± SD 3.6 (dem), 10.4yrs ± SD 3.7 (other) Interpreter: 16.1% Informant: 66% (dem), 46% (other)	RUDAS Threshold not pre-specified	MMSE Not performed in n=6 Incorporated into ref std	Consensus diagnosis by multidisciplinary team by DSM-IV-TR, including clinical assessment, MMSE and Danish ACE, laboratory screening, structural imaging and further investigations as necessary. Referral for neuro-psychological exam or psychiatric evaluation as necessary. Blind to RUDAS	Accuracy: AUC, Sn, Sp, PPV, NPV, LR+, LR- Determined for dementia vs non-dementia Effects of patient characteristics on RUDAS & MMSE score	<u>RUDAS:</u> *Normal/MCI vs dementia:* AUC = 0.838 Optimal cut-off score <24/30: Accuracy (correct classification) = 74%, Sn = 0.69 (95%CI 0.57–0.79) Sp = 0.80 (95%CI 0.68–0.89) LR+ = 3.47 (95%CI 2.09–5.78) LR - = 0.38 (95%CI 0.27–0.55) Published cut-off score < 23/30 [85]: Accuracy = 73% Sn = 0.64 (95%CI 0.52–0.75) Sp = 0.83 (95%CI 0.71–0.91) LR+ = 3.78 (95%CI 2.14–6.65) LR - = 0.43 (95%CI 0.32–0.59) <u>MMSE:</u> *Normal/MCI vs dementia:* AUC = 0.840 Optimal cut-off score <25/30: Accuracy (correct classification) = 79% Sn = 0.76 (95%CI 0.64–0.85) Sp = 0.83 (95%CI 0.71–0.91) LR+ = 4.56 (95%CI 2.55–8.16) LR - = 0.29 (95%CI 0.19–0.44) Logistic regression indicated age sig affected RUDAS score, whereas age and having an immigrant background sig affected MMSE score. Years of education and having an informant present did not affect either.	1. Low 2. Unclear 3. High 4. Unclear

Reference **Country** **Recruitment period**	**Study Design**	**N(n)**	**Participants**	**Test**	**Comparison** [4]	**Reference standard**	**Main Outcomes**	**Results/Effect size** [1]	**Risk of bias**[3]
Rowland 2006 [85] Australia (South Western Sydney Area Health Service) 1997-1999	Cross-sectional diagnostic accuracy study	129 (63 dem, 28 normal 18 MCI)	Community people selected randomly from database. Stratified into 6 language groups matched for age and gender. Random selection and matching process unclear. Invited by telephone. Age: normal 77.7yrs ± 8.6, dem 81.5yrs ± 7.5 Gender (% female): normal 72.9%, dem 71.4% Severity dem: 23.8% questionable, 20.6% mild, 23.8% moderate, 31.8% severe Bkgd: 65% born in non-English speaking countries Education: normal 6.5yrs median, dem 6.0yrs median Interpreter: normal 55.3%, dem 61.9% Informant: normal 58.3%, dem 92.1%	RUDAS (blinded) Cut-point not pre-defined RUDAS & MMSE in random order	MMSE Cut-point not pre-defined	Blind diagnosis (to all assessments) by geriatrician using DSM-IV. Performed within several days of RUDAS & MMSE.	Accuracy: AUC, Sn, Sp, LR+, LR- Analysis reporting Sn,Sp, LRs excluded as based only on normal & dementia subjects (case control data, n = 111) [2]	<u>RUDAS</u>: *Normal vs MCI/dementia:* AUC = 0.88 (NSD to MMSE) *Normal/MCI vs dementia:* AUC = 0.89 (NSD to MMSE) <u>MMSE</u>: *Normal vs MCI/dementia:* AUC = 0.87 *Normal/MCI vs dementia:* AUC = 0.89	1. Unclear 2. Low 3. Unclear 4. Low

Reference Country Recruitment period	Study Design	N(n)	Participants	Test	Comparison [4]	Reference standard	Main Outcomes	Results/Effect size [1]	Risk of bias[3]
Rowland 2007 [84] Australia (Melbourne & Adelaide) Recruitment period: NR	Cross-sectional diagnostic accuracy study	151 (dem 58, 33 MCI, 60 norm)	Recruited from dementia & memory clinics plus "control" clinics (one falls & balance, one day rehab. centre) and day respite programs. Excluded severe visual, hearing or physical impairment, or acute decline in brain function in preceding week. Age mean (SD): 77yrs (8.9), range 46-97 yrs Gender: 70% F Severity dem: 8% MCI, 49% questionable, 41% mild, 2% severe Bkgd: 42% CALD Education mean (SD): 8 yrs (4.2) Interpreter: 32% Informant: 72%	RUDAS by research officer, blinded Cut-point <23/30	MMSE (cut point <24), GPCOG [6] (cut-point < 25) by geriatrician Unclear if incorporation bias	DSMIV-TR (cognitive assessment tools used unclear). Blinded to RUDAS	Accuracy: Sn, Sp, LR+, LR- Effects of covariates on scores	RUDAS (<23/30): *Normal vs MCI/dementia:* AUC = 0.88 (95%CI 0.82-0.94), Sn = 0.73 (95%CI 0.65 – 0.80), Sp = 0.90 (95%CI 0.85 – 0.95), LR+ = 7.25, LR- = 0.31 *Normal/MCI vs dementia:* Sn = 0.88, Sp = 0.77, LR+ = 3.89, LR- = 0.16 RUDAS (optimal cut-point): *Normal vs MCI/dementia:* (<25): Sn = 0.86 (95%CI 0.80 – 0.91), Sp = 0.85 (95%CI 0.79 – 0.91) (<26): LR+ = 5.71, LR- = 0.17 *Normal/MCI vs dementia:* (<23): Sn = 0.88, Sp = 0.77, (<26): LR+ = 2.90, LR- = 0.05 MMSE (<24): *Normal vs MCI/dementia:* AUC = 0.86 (95%CI 0.80 – 0.93), Sn = 0.65 (95%CI 0.57 – 0.72), Sp = 0.88 (95%CI 0.83 – 0.93), LR+ = 5.54, LR- = 0.40 *Normal/MCI vs dementia:* Sn = 0.79, Sp = 0.79, LR+ = 3.69, LR- = 0.26 GPCOG (2 stage score, <9, n = 140): *Normal vs MCI/dementia:* AUC = 0.90 (95%CI 0.85 – 0.96), Sn = 0.89 (95%CI 0.84 – 0.94), Sp = 0.80 (0.73 – 0.87), LR+ = 4.56, LR- = 0.13 *Normal/MCI vs dementia:* Sn = 0.98, Sp = 0.62, LR+ = 2.55, LR- = 0.26	1. High 2. Low 3.Unclear 4.Unclear

Reference Country Recruitment period	Study Design	N(n)	Participants	Test	Comparison[4]	Reference standard	Main Outcomes	Results/ Effect size [1]	Risk of bias[3]
Rowland 2007 (cont)								No sig diff in AUC z-score for any analysis In multifactorial regression analysis, no covariates confounded the relationship between the RUDAS and cognitive status, whereas the MMSE was confounded by CALD status and the GPCOG by Geriatric Depression Scale score.	

Abbreviations: ACE – Addenbrooke's Cognitive Examination; AD – Alzheimer's disease; AUC – area under the receiver operating characteristic curve; Bkgd – background; CALD – culturally and linguistically diverse; CI – confidence interval; cog imp – cognitive impairment; dem – dementia; DSM-IV-TR – Diagnostic and Statistical Manual of Mental Disorders - Text Revision; dx – diagnosis(es); GPCOG – General Practitioner Assessment of Cognition; IQ-CODE – Informant Questionnaire on Cognitive Decline in the Elderly; LR+(-) – positive (negative) likelihood ratio; MCI – mild cognitive impairment; (S)MMSE - (Standardized) mini mental state examination; norm – normal; NPV – negative predictive value; NR – not reported; NSD – not statistically significantly different; pop – population PPV – positive predictive value; pts – patients; rehab – rehabilitation; RUDAS – Rowland Universal Dementia Assessment Scale; ROC – receiver operating characteristic; SD – standard deviation; sig – significant(ly); Sn – sensitivity; Sp – specificity; yrs – years.

1. The likelihood ratio represents a combination of the sensitivity and specificity and measures the probability of the test result in patients with the disease compared to those without the disease. A likelihood ratio of 1 indicates that the test does not provide any useful diagnostic information. Positive likelihood ratios > 10 and negative likelihood ratios < 0.1 can provide convincing diagnostic evidence. Positive likelihood ratios > 5 and negative likelihood ratios < 0.2 can provide strong diagnostic evidence. However, the interpretation depends on the context in which the test is used and the pretest probability [20] . The Area Under the ROC Curve (AUC) summarises the accuracy across a range of thresholds; a value of 1.0 indicates a perfect test, a value of 0.5 a completely uninformative test [54].
2. Case control studies are excluded according to the protocol determined a priori.
3. Risk of bias according to Cochrane Revman 5 items: (1) whether patient sampling is random, consecutive and avoiding inappropriate exclusions (2) whether conduct and interpretation of index test(s) were blinded and according to a pre-specified threshold (3) whether conduct and interpretation of reference standard was blind and met pre-specified criteria in review protocol, (4) flow and timing: whether all patients received same reference standard within an appropriate time period from index test and were included in the analysis.
4. The Mini Mental State Examination (MMSE) is a well-established and widely applied cognitive assessment screening tool (5). The maximum possible score is 30, with a recommended cut-off score of ≤23 for cognitive impairment (20-23 mild, 16-19 moderate, 0-15 severe) (6). Limitations of the tool have been reported including lack of sensitivity and specificity when used with people with milder forms of impairment, false positive responses due to low education level and floor and ceiling effects [86]. The Modified Mini Mental Exam (3MS) is a preferred variation of the MMSE.
5. The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) aims to assess change in cognitive function over the previous ten years (5). The maximum possible score is 5 and a cut-off score of 3.3 to 3.6 is recommended for community-living adults, with a higher score indicating greater cognitive decline. The IQCODE requires an informant for completion.
6. The General Practitioners Assessment of Cognition (GPCOG) was developed for use by primary health care providers and consists of two stages (5). The initial patient section has a maximum possible score of 9, with a score of less than 5 indicating cognitive impairment. If a patients scores between 5 and 8 then the score from an informant section is considered and a score of less than 3 on this section indicates cognitive impairment.
7. Optimal cut-off score determined by the Youden index, which is the vertical point on the ROC curve that is most distant from chance, and is a function of both sensitivity and specificity. Values close to 1 indicate high accuracy, a value of zero indicates no diagnostic value [54].

Table 36 GRADE Evidence Profile: Accuracy of the KICA Cognitive assessment tool in remote Indigenous Australian populations

Quality Assessment							Effect	Quality[4]	Link to patient centred outcomes
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Diagnostic accuracy of the Kimberley Indigenous Cognitive Assessment tool – True Positives (TPs)									
1	Cross-sectional diagnostic accuracy study	Serious limitations[1]	No serious limitations	Serious limitations[2]	No serious limitations	No publication bias detected[3]	For the diagnosis of dementia, at recommended optimal cut-off 33/34: Sn 93.3%. [61 64]	⊕⊕OO LOW	These patients receive uncertain benefit of early diagnosis and treatment.
Diagnostic accuracy of the Kimberley Indigenous Cognitive Assessment tool – False Positives (FPs)									
1	Cross-sectional diagnostic accuracy study	Serious limitations[1]	No serious limitations	Serious limitations[2]	No serious limitations	No publication bias detected[3]	For the diagnosis of dementia, at recommended optimal cut-off 33/34: Sp 98.4% [61 64]	⊕⊕OO LOW	These patients would experience likely psychological harms and possible detriment from unnecessary testing and treatment.
Diagnostic accuracy of the Kimberley Indigenous Cognitive Assessment tool – False Negatives (FNs)									
1	Cross-sectional diagnostic accuracy study	Serious limitations[1]	No serious limitations	Serious limitations[2]	No serious limitations	No publication bias detected[3]	For the diagnosis of dementia, at recommended optimal cut-off 33/34: Sn 93.3% [61 64]	⊕⊕OO LOW	These patients may have a possible negative effect from delayed diagnosis.
Diagnostic accuracy of the Kimberley Indigenous Cognitive Assessment tool – True Negatives (TNs)									
1	Cross-sectional diagnostic accuracy study	Serious limitations[1]	No serious limitations	Serious limitations[2]	No serious limitations	No publication bias detected[3]	For the diagnosis of dementia, at recommended optimal cut-off 33/34: Sp 98.4% [61 64]	⊕⊕OO LOW	These patients would experience benefit from reassurance.

Abbreviations: Sn – sensitivity; Sp – specificity

1. Risk of bias: use of a pre-defined test threshold is unclear, partial verification (11% of those randomly selected for verification not verified).
2. The setting is population based rather than a consecutive series of presenting patients. Accuracy is a surrogate for patient-centered outcomes.
3. Publication bias cannot be ruled out however the study was funded by the (Australian) National Health and Medical Research Council (NHMRC).
4. Study quality commenced as high quality due to design feature of these studies (considering unpublished data provided by personal communication).
5. N = 363, 95%CI for AUC narrow (not provided for Sn, Sp)

Table 37 GRADE Evidence Profile: Accuracy of the KICA-Screen in remote Indigenous Australian populations

Quality Assessment							Effect	Quality[4]	Link to patient centred outcomes
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Diagnostic accuracy of the KICA-Screen – True Positives (TPs)									
2	Cross-sectional comparative accuracy studies	Serious limitations[1]	No serious limitations[5]	Serious limitations[2]	Serious limitations[6]	No publication bias detected[3]	For the diagnosis of dementia, at optimal cut-off 21/22: Sn 87.8% (Kimberley), 75.9% (Nth Qld). [62]	⊕OOO VERY LOW	These patients receive uncertain benefit of early diagnosis and treatment.
Diagnostic accuracy of the KICA-Screen – False Positives (FPs)									
2	Cross-sectional comparative accuracy studies	Serious limitations[1]	No serious limitations	Serious limitations[2]	Serious limitations[6]	No publication bias detected[3]	For the diagnosis of dementia, at optimal cut-off 21/22: Sp 88.6% (Kimberley), 88.5% (Nth Qld).[62]	⊕OOO VERY LOW	These patients would experience likely psychological harms and possible detriment from unnecessary testing and treatment.
Diagnostic accuracy of the KICA-Screen – False Negatives (FNs)									
2	Cross-sectional comparative accuracy studies	Serious limitations[1]	No serious limitations[5]	Serious limitations[2]	Serious limitations[6]	No publication bias detected[3]	For the diagnosis of dementia, at optimal cut-off 21/22: Sn 87.8% (Kimberley), 75.9% (Nth Qld). [62]	⊕OOO VERY LOW	These patients may have a possible negative effect from delayed diagnosis.
Diagnostic accuracy of the KICA-Screen – True Negatives (TNs)									
2	Cross-sectional comparative accuracy studies	Serious limitations[1]	No serious limitations	Serious limitations[2]	Serious limitations[6]	No publication bias detected[3]	For the diagnosis of dementia, at optimal cut-off 21/22: Sp 88.6% (Kimberley), 88.5% (Nth Qld).[62]	⊕OOO VERY LOW	These patients would experience benefit from reassurance.

Abbreviations: Nth Qld – north Queensland; Sn – sensitivity; Sp – specificity

1. Risk of bias: not a consecutive series of patients in Nth Qld study, interval between index test and reference standard unclear in Nth Qld study, threshold not pre-specified in Kimberley study, partial verification (11% of those randomly selected for verification not verified) in Kimberley study.
2. The settings are population based rather than a consecutive series of presenting patients. Accuracy is a surrogate for patient-centered outcomes.
3. Publication bias cannot be ruled out however the study was funded by the (Australian) National Health and Medical Research Council (NHMRC).
4. Study quality commenced as high quality due to design feature of these studies.
5. Sensitivity lower in Nth Qld population, but not considered serious.
6. Total N = 418, however 95%CIs around AUC in Nth Qld sample wide; 95%CIs for sensitivity & specificity not reported.

Table 38 GRADE Evidence Profile: Accuracy of the modified KICA (mKICA) tool compared to MMSE in non-remote Indigenous Australian populations

Quality Assessment							Effect	Quality[3]	Link to patient centred outcomes
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Diagnostic accuracy of the modified Kimberley Indigenous Cognitive Assessment tool compared to the MMSE– True Positives (TPs)									
2	Cross-sectional comparative accuracy studies	No serious limitations	No serious limitations	Serious limitations[4]	Serious limitations[6]	No publication bias detected[2]	mKICA and MMSE had comparable sensitivity At optimal cut-off: mKICA Sn 85.7% (95%CI 67.3 – 96.0); MMSE Sn 85.7% (95%CI 67.3% - 96.0%) [56] Pilot: mKICA and MMSE both detected all cases of dementia (9/9) [63]	⊕⊕OO LOW	These patients receive uncertain benefit of early diagnosis and treatment.
Diagnostic accuracy of the modified Kimberley Indigenous Cognitive Assessment tool compared to the MMSE – False Positives (FPs)									
2	Cross-sectional comparative accuracy studies	No serious limitations	No serious limitations	Serious limitations[4]	No serious limitations[5]	No publication bias detected[2]	mKICA and MMSE both had high specificity. At optimal cut-off mKICA Sp 89.9% (95%CI 84.9 – 96.3); MMSE Sp 94.7% (90.7% - 97.3%) [56] Pilot: 1/10 detected by mKICA and MMSE [63]	⊕⊕⊕O MODERATE	These patients would experience likely psychological harms and possible detriment from unnecessary testing and treatment.
Diagnostic accuracy of the modified Kimberley Indigenous Cognitive Assessment tool compared to the MMSE – False Negatives (FNs)									
2	Cross-sectional comparative accuracy studies	No serious limitations	No serious limitations	Serious limitations[4]	Serious limitations[6]	No publication bias detected[2]	mKICA and MMSE had comparable sensitivity At optimal cut-off: mKICA Sn 85.7% (95%CI 67.3 – 96.0); MMSE Sn 85.7% (95%CI 67.3% - 96.0%) [56] Pilot: None detected by mKICA or MMSE [63]	⊕⊕OO LOW	These patients may have a possible negative effect from delayed diagnosis.

Diagnostic accuracy of the modified Kimberley Indigenous Cognitive Assessment tool compared to the MMSE – True Negatives (TNs)									
2	Cross-sectional comparative accuracy studies	No serious limitations	No serious limitations	Serious limitations[4]	No serious limitations[5]	No publication bias detected[2]	mKICA and MMSE both had high specificity. At optimal cut-off mKICA Sp 89.9% (95%CI 84.9 – 96.3); MMSE Sp 94.7% (90.7% - 97.3%) [56] Pilot: Same number detected on mKICA and MMSE (9/10) [63]	⊕⊕⊕O MODERATE	These patients would experience benefit from reassurance.

Abbreviations: mKICA – modified Kimberley Indigenous Cognitive Assessment; MMSE – mini mental state examination; Sn – sensitivity; Sp – specificity

1. Evidence for a comparison to the MMSE is presented as this is the most commonly used tool. The study also compared the mKICA to the RUDAS. The MMSE and mKICA performed slightly better than the RUDAS.
2. Publication bias cannot be ruled out however the main study was funded by the NHMRC and the pilot by the Dementia Collaborative Research Centre – Assessment and Better Care, University of New South Wales as part of an Australian Government Initiative and Alzheimer's Australia Research
3. Study quality commenced as high quality due to design feature of these studies
4. The setting is population based rather than a consecutive series of presenting patients. Outcome as defined in the question is comparative accuracy between alternative tools as a replacement test, so there are no serious limitation of the directness of outcomes.
5. The sample size was 235, confidence intervals are narrow.
6. The confidence intervals around the sensitivity are wide.

Table 39 GRADE Evidence Profile: Accuracy of the RUDAS Cognitive assessment tool

Quality Assessment							Effect[9]	Quality[8]	Link to patient centered outcomes
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
Diagnostic accuracy of the Rowland Universal Dementia Assessment Scale (RUDAS) compared to the MMSE – True Positives (TPs)									
3[1]	Cross-sectional comparative accuracy studies	Very serious limitations[2]	Serious limitations[3]	Serious limitations[4]	No serious limitations[5]	No publication bias detected[6]	For the diagnosis of dementia, Sn not sig diff in 1 study [77], Sn sig lower in 1 study (with incorporation bias of MMSE) [82], Sn slightly higher (no 95%CIs reported) in 1 study [84].	⊕OOO VERY LOW	These patients receive uncertain benefit of early diagnosis and treatment.
Diagnostic accuracy of the Rowland Universal Dementia Assessment Scale (RUDAS) compared to the MMSE – False Positives (FPs)									
3[1]	Cross-sectional comparative accuracy studies	Very serious limitations[2]	No serious limitations[7]	Serious limitations[4]	No serious limitations[5]	No publication bias detected[6]	For the diagnosis of dementia, Sp not sig diff in any of 3 studies [82-84]	⊕OOO VERY LOW	These patients would experience likely psychological harms and possible detriment from unnecessary testing and treatment.
Diagnostic accuracy of the Rowland Universal Dementia Assessment Scale (RUDAS) compared to the MMSE – False Negatives (FNs)									
3[1]	Cross-sectional comparative accuracy studies	Very serious limitations[2]	Serious limitations[3]	Serious limitations[4]	No serious limitations[5]	No publication bias detected[6]	For the diagnosis of dementia, Sn not sig diff in 1 study [77], Sn sig lower in 1 study (with incorporation bias of MMSE), Sn slightly higher (no 95%CIs reported) in 1 study [84].	⊕OOO VERY LOW	These patients may have a possible negative effect from delayed diagnosis.
Diagnostic accuracy of the Rowland Universal Dementia Assessment Scale (RUDAS) compared to the MMSE – True Negatives (TNs)									
3[1]	Cross-sectional comparative accuracy studies	Very serious limitations[2]	No serious limitations[7]	Serious limitations[4]	No serious limitations[5]	No publication bias detected[6]	For the diagnosis of dementia, Sp not sig diff in any of 3 studies [82-84]	⊕OOO VERY LOW	These patients would experience benefit from reassurance.

Abbreviations: CI – confidence interval; IQ-CODE – Informant Questionnaire on Cognitive Decline in the Elderly; MMSE – Mini Mental State Examination; sig diff – significantly different; Sn – sensitivity; Sp – specificity; yrs – years.

1. One additional population-based study provided only AUC data, this does not inform true and false positive and negative rates [85].
2. Studies were considered to have a high risk of bias due to factors including incorporation of MMSE into the reference standard in two studies (which may falsely inflate the accuracy of MMSE), and using cut-off scores different to that recommended.
3. One study showed a significant difference (RUDAS cut-off score different to recommended) [82], the other did not (MMSE cut-off score different to recommended) [83].

4. One study excluded patients not attending with an informant, hence the prevalence of dementia in the study population was inflated [82]. Another study included control patients from clinics other than memory clinics [84]. Accuracy is a surrogate for patient-centered outcomes.
5. Study size was 137 & 204.
6. The possibility of publication bias cannot be ruled out, however the two studies were supported by research grants.
7. One study shows a trend to a higher specificity for the RUDAS and the other shows very similar specificities between the tests. However both studies show no statistically significant difference.
8. Study quality commenced as high quality due to design feature of these studies
9. Evidence for a comparison to the MMSE is presented as this is the most commonly used tool. 1 study also compared the RUDAS to the GPCOG and 1 to the IQ-CODE.

SRQ 6: Structural imaging

Following an extensive systematic evaluation of the evidence for indications for structural imaging in dementia, the Guideline Adaptation Committee agreed that structural imaging was necessary to exclude cerebral pathologies in most patients and therefore this was stated in a Practice Point. Evidence based recommendations regarding its use to assist in making a diagnosis of dementia subtype became obsolete in the absence of evidence for harms associated with structural imaging. Therefore, the following review did not inform any evidence-based recommendations, but the findings are nevertheless presented for the information of readers.

Background

A recent systematic review by the Cochrane Dementia and Cognitive Improvement Group examined the quantity and quality of evidence available from diagnostic test accuracy studies to assess the effectiveness of diagnostic tools for dementia [88]. These authors considered the evidence base for biomarkers for Alzheimer's disease (including markers for β-amyloid, or markers of neuronal injury including tau, positron emission tomography [PET] using ^{18}F-fluorodeoxy-glucose [FDG] or atrophy on magnetic resonance imaging [MRI]). The greatest number of studies identified that would be useful for a meta-analysis of accuracy outcomes were of structural MRI. Whilst there was a large body of literature reporting diagnostic accuracy studies of biomarkers for Alzheimer's disease, there was also wide variation in the methodology and reporting, with many limitations relating to the quality of the studies. The authors concluded that the body of evidence for biomarkers for dementia diagnosis is not large. In addition, although recent United States National Institute on Aging-Alzheimer's Association (NIAA) criteria for the diagnosis of Alzheimer's disease provide a "semantic and conceptual distinction" between Alzheimer's disease clinical syndromes and pathophysiological processes, the NIAA does not recommend the routine use of biomarkers for the diagnosis of Alzheimer's disease at this time. [89 90]

A review of studies comparing the performance of MRI and CT is considered beyond the scope of this review question. A recent health technology assessment (HTA) report reviewed the evidence for this to 2013 [91] and didn't find any RCTs, systematic reviews, meta-analyses, observational studies, or diagnostic accuracy studies that directly answered a question of which modality should be used when structural imaging is indicated. They identified one systematic review of more than 19,000 citations published to 2011 that compared these modalities for the detection of a vascular component to dementia. This included 38 studies, of which four assessed both CT and MRI. Direct and indirect comparisons of accuracy had similar results, with no statistically significant differences found. The included studies were limited in terms of quality and size, with variability in study results. The HTA concluded that there was a lack of evidence that MRI was superior to CT for the detection of a vascular component to dementia (GRADE: very low).

Clinical prediction rules are sets of clinical and/or demographic characteristics (e.g. age, condition severity, symptoms) which can be used to select patients for imaging or other procedures. When used to select patients for neuroimaging (in comparison to the alternative of all patients undergoing imaging), clinical prediction rules are applied as a triage test.[23] The key test accuracy characteristic required for an effective triage test is high sensitivity, rather than overall accuracy, in order to minimise the number of patients with disease that are missed (false negatives).[92] In the alternative scenario (not applying a clinical prediction rule), all patients would undergo imaging and no patients would be "missed".[92]

Clinical question

The research question as defined in the protocol and the associated PICO criteria are listed below in Table 41. A review of studies comparing the performance of MRI and CT is considered beyond the scope of this review question.

Table 40 PPICO for SRQ6: Structural imaging

Clinical question: Does every person with dementia need structural imaging (with CT or MRI) of the brain?				
Population	**Prior tests**	**Intervention**	**Comparator**	**Outcomes**
People with a diagnosis of dementia *Subgroups:* Different dementia subtypes (indications, by criteria identifiable *prior* to imaging)	Clinical assessment, tests for diagnosis of dementia	CT Structural MRI	No structural imaging	Diagnostic accuracy Health outcomes (health related quality of life, rate of decline, BPSD) Change in patient management/diagnosis
Reference standard: pathology or clinical assessment with follow-up				

Abbreviations: BPSD – behavioural and psychological symptoms of dementia; CT – computed tomography; MRI – magnetic resonance imaging; PPICO – population, prior tests, intervention, comparator, outcomes

Literature review search strategies:

Searches for existing HTAs and Systematic reviews

Searches to identify existing Health Technology Assessment reports (HTAs) and systematic reviews were conducted in the databases specified in Table 41, using the search terms listed in the Guideline Technical Report Volume 2. The search strategies were broad, covering a number of diagnostic techniques. Reviews of the accuracy of CT or MRI in a broad dementia patient population that did not report findings according to patient presentation subgroups were excluded.

Table 41 Searches for existing HTAs and systematic review for structural imaging

Database	Date searched	Period covered	Citations retrieved
HTA	28 May 2014	2005 to 2014	16
NHSEED	29 May 2014	2005 to 2014	18
Cochrane (Cochrane reviews, Cochrane protocols, DARE)	28 May 2014	2005 to 2014	40
MEDLINE	28 May 2014	2005 to week 4 Oct 2014	57
PsycInfo	29 May 2014	2005 to 2014	33
EMBASE	27 May 2014	2005 to 2014	7
PubMed	16 Sept 2014	2005 to 29 May 2014	6
Total			177

Searches for primary studies

The included HTA report included a search to 2013, therefore no search for primary studies published since this date addressing this question was undertaken (in accord with WHO handbook for guideline development recommendations).[14]

Search results

Existing HTAs and systematic reviews

The most recent, comprehensive and highest quality HTA report identified and included in the current update was that conducted by Health Quality Ontario (HQO) which involved a systematic search for studies to February 2013 (Evidence Summary Table 42).[91] The HTA report addressed a number of questions relating to neuroimaging. This review includes the evidence from three key questions of the HQO review: "What are the indications for a structural imaging investigation for dementia diagnosis?", "What is the clinical utility or adjunctive value of neuroimaging for dementia diagnosis?" and "What is the diagnostic accuracy of neuroimaging for discriminating dementia types?" Results of the included studies as reported in the HQO HTA report are presented and discussed below.

Evidence summary

The NICE guideline committee did not present the findings of a systematic search in relation to assessment for the diagnosis of dementia.

Clinical prediction rules

The Health Quality Ontario HTA included three studies addressing the indications for structural imaging. The three studies (one systematic review, one diagnostic accuracy study and one accuracy study with therapeutic impact data) examined the use of clinical and/or demographic characteristics (separately or in groups) to identify patients who are more likely to benefit from neuroimaging (clinical prediction rules) (Evidence Summary Table 43 and Table 44). The clinical prediction rules are applied as a triage test to select patients for imaging [93]. The ideal test characteristics of a triage test are a high sensitivity or negative predictive value, in order to minimise false negatives, whilst overall accuracy may be lower than that for structural imaging in all patients.

The accuracy of these groups of indications (clinical prediction rules) to predict abnormal scans showing potentially reversible causes of dementia varied highly between the prediction rules, and between different studies of the same sets of prediction rules (Table 43 and Table 44).[94 95] The rules that would miss the fewest cases of potentially reversible causes of dementia (the Dietch and Canadian Consensus Conference [CCC] prediction rules) would also scan the largest proportion of patients relative to the other rules (Table 44).

In one retrospective study of memory clinic patients, no single indications from clinical prediction rules significantly predicted the impact of the CT result on diagnosis or management and the detection of vascular or structural lesions on CT did not necessarily alter the clinical decisions [96] (Table 44).

The relationship between the accuracy of clinical prediction rules to detect potentially reversible causes of dementia and patient centred outcomes such as quality of life is uncertain. Although the definition of a potentially reversible cause of dementia indicates that a clear management path following detection on neuroimaging exists, it has been estimated that while 9% of dementia cases may be identified as potentially reversible, only 0.6% are partially or fully reversed.[97] In addition,

these accuracy data do not consider the accuracy of the clinical prediction rules to predict the contribution of MRI to other diagnostic outcomes (e.g. differentiating subtypes of dementia).

An associated economic analysis on the use of the Canadian Consensus Conference decision rule to select patients with mild to moderate dementia for structural imaging was conducted for the Canadian setting [98]. This analysis found that the most effective and cost-effective strategy was to image patients who meet CCC criteria with CT and to follow-up with MRI for suspected cases of space-occupying lesions. However, the author indicated that limitations in the evidence base and its interpretation meant results from the model should not be considered to provide definitive answers.

The conclusion of the Health Quality Ontario (2014) review was that clinical indications or prediction rules do not reliably predict the presence of abnormalities on structural imaging, nor influence diagnosis or treatment (very low level of confidence based on their GRADE evidence recommendation; Table 42). The GRADE Evidence Profile is presented in Table 45.

Accuracy of neuroimaging for discriminating dementia types

The Health Quality Ontario HTA also presented studies providing evidence on the accuracy of MRI or CT to distinguish types of dementia.

Alzheimer's disease

Three systematic reviews were identified which provided accuracy estimates of MRI or CT for the diagnosis of Alzheimer's disease (Table 43).[99-101] Many studies included in the reviews were diagnostic case control studies (NHMRC level III-3 evidence for diagnostic accuracy) and two of the reviews did not conduct meta-analyses due to the high degree of heterogeneity in the study designs and outcomes. One study reported pooled sensitivity and specificity measures despite a high degree of heterogeneity. The results of these studies can be found in the evidence summary table below (Table 43) and the GRADE Evidence Profile is presented in Table 46.

The Health Quality Ontario (2014) authors concluded that CT has moderate to high sensitivity and specificity for differentiating AD from MCI, other types of dementias, and healthy aging (compared to a reference standard of clinical or autopsy diagnosis). They also concluded that MRI has good sensitivity and specificity, although there is a wide range in both accuracy estimates due to variability in cortical structures assessed, comparison groups, and methods of assessment (GRADE: Very low; Table 46).

Creutzfeldt-Jakob disease

Two studies examined the accuracy of MRI by high signal intensity in the basal ganglia to diagnose Creutzfeldt-Jakob disease (CJD) in patients referred to the German CJD Surveillance Unit.[102 103] The HQO authors pooled the accuracy outcomes from these studies, reporting a sensitivity of 64% (95%CI 58%–69%) and specificity of 90% (95%CI 82%–95%), with no statistically significant heterogeneity. The review concluded that MRI has high specificity and moderate sensitivity for the diagnosis of CJD. Also, that "there is some potential influence of the specific MRI sequence on accuracy, and some authors recommend diffusion-weighted and FLAIR MRI sequences to visualize the pathological changes" [91]. (GRADE: Low; GRADE Evidence Profile Table 46)

Clinically ambiguous dementia

One recent study examined the role of MRI in 69 patients referred to a memory centre with clinically ambiguous dementia (Table 44).[104] The patients had an MMSE score of greater than or equal to 18. After two years' follow-up, 80% of patients had received a clinical diagnosis. In this study the accuracy of MRI at baseline to predict the clinical diagnosis after 2 years' follow-up was determined, using receiver operating characteristic (ROC) curve analysis (which takes into account both the sensitivity and the specificity of the test, and depicts the trade-off). MRI was found to contribute significantly to the diagnosis of vascular dementia (sensitivity 88%, specificity 85%), and in a

statistically significant but limited way to the diagnosis of Alzheimer's disease (sensitivity 56%, specificity 86%, area under the ROC curve 0.68 [95% CI 0.51-0.85, P=0.04]). The HQO HTA conclusions were that MRI had a high sensitivity for differentiating clinically ambiguous dementias, a moderate specificity for discriminating vascular dementia, and a moderate sensitivity but high specificity for discriminating Alzheimer's disease. (GRADE: very low; GRADE Evidence Profile Table 46)

Accuracy of neuroimaging in addition to comprehensive clinical assessment

In practice, structural imaging would be performed in addition to comprehensive clinical assessment. Only the studies by Boutoleau- Bretonniere et al [105] and Massoud et al [106] provide information on the accuracy of structural imaging in comparison to, or as an addition to comprehensive clinical assessment. None of these studies provide information on whether or not a diagnosis results in a change in management from that planned based on clinical assessment alone.

Clinical utility of structural neuroimaging (diagnostic or therapeutic impact)

Four additional studies provided information on the contribution of MRI to the diagnosis or management of dementia patients (Table 44, GRADE Evidence Profile Table 47).[106-109] A prospective study reported that MRI had a significant impact on initial memory clinic diagnosis, however results according to initial diagnosis were not reported separately for MRI and neuropsychological testing [108]. In a retrospective study of 146 dementia patients, CT changed diagnosis in 12% (±2%) and management in 11% (±2%) of patients overall [107]. The most common changes in diagnosis were the exclusion or inclusion of a vascular component; less frequent changes in diagnosis were the confirmation of atypical Alzheimer's disease, or identification of a structural lesion (the latter in an average of 1% of patients).

In a study conducted in patients with mixed dementia of cerebrovascular and Alzheimer's type, cerebral infarcts were detected on neuroimaging in 21% (13/61) of patients where they were not suspected clinically (Table 44) [106]. The use of CT or MRI in combination with clinical diagnosis increased the sensitivity for detection of cerebrovascular disease by clinical diagnosis alone by 53% with a decrease in specificity of 17% [106]. Thus, the addition of CT or MRI increased both true positive and false positive diagnoses of cerebrovascular disease.

One good quality retrospective study found that MRI altered the clinical diagnosis in most of 104 patients referred to a psychiatric hospital for evaluation of cognitive impairment [109]. Diagnoses were altered following MRI in patients clinically diagnosed as having unspecified dementia, Alzheimer's disease or vascular dementia in 100%, 63% and 11% of patients, respectively.

Impact of structural imaging on patient outcomes

Where the accuracy of a diagnostic test is proven, it is still necessary for the test result to change diagnosis and management, and for the management implemented to be effective for there to be an improvement in patient outcomes. Consideration of all of these steps in the pathway is necessary when considering the evidence for the effectiveness of a diagnostic test [24] (see Methodological Considerations, Diagnostic and screening tests, page 18).

Acetylcholinesterase inhibitors are recommended for the management of mild to moderate Alzheimer's disease. On the basis of existing evidence of effectiveness, these guidelines also include a weak recommendation for the use of acetylcholinesterase inhibitors for Dementia with Lewy Bodies, Parkinson's Disease dementia, vascular dementia or mixed dementia (see SRQ13: Acetylcholinesterase inhibitors and memantine, page 183). Management of risk factors for vascular dementia (such as hypertension or hyperlipidaemia) is likely to be part of management for many patients regardless of the subtype diagnosis. However, there is no treatment that can reverse or

modify existing dementia. A subtype diagnosis may benefit patients and carers in terms of psychological benefits and for planning for the future. Overall, the relationship between the accuracy of neuroimaging for dementia subtype diagnosis and patient centred outcomes such as quality of life is uncertain.

Structural imaging may be performed to detect potentially reversible causes of dementia. If a reversible cause is identified, the impact on outcomes for the person with dementia could be critical. Based on a systematic review of available data, the HQO HTA concluded that "With the exception of dementia related to vascular disease, prevalence of potentially treatable dementias is low (< 10%), and improvement after treatment of the underlying condition is less than 1% (GRADE: Very low)."

Direct evidence for the relative benefits and harms of a dementia subtype diagnosis by structural imaging for patients and carers is lacking (GRADE Evidence Profile Table 47).

Resource requirements

MRI and CT are listed on the Medical Benefits Scheme (MBS) in Australia. Relevant listings are:

- MBS 63001 MRI for tumour of the brain or meninges Fee: $403.20 (MBS 63013 Fee$201.60 NK)
- MBS 56001 brain CT without contrast Fee: $195.05 (NK $98.75); MBS brain CT with contrast Fee: $250.00 (NK $126.10)

Summary

The Health Quality Ontario (2014) authors concluded that the impact of information from CT or MRI varied according to the type and severity of dementia (GRADE: Low; Table 47).

The HQO HTA also concluded that the clinical utility of structural neuroimaging is:

- high for patients with potentially mixed dementia
- high for patients where there is uncertainty for 2 years or more about the type of dementia
- low for patients with Alzheimer's disease clinically diagnosed by follow-up over time (e.g., 1 year)
- low for patients where vascular dementia has been clinically excluded (GRADE: Low)

The Guideline Adaptation Committee agreed that structural imaging was necessary to exclude cerebral pathologies and therefore this was stated in a Practice Point. In the absence of evidence for harms associated with structural imaging, evidence based recommendations regarding its use to assist in making a diagnosis of dementia subtype became obsolete.

Evidence statements	*GRADE Quality*	*Related recommendation*
Evidence from nine accuracy studies indicated that clinical indications or prediction rules did not reliably predict the presence of abnormalities on structural imaging.[94 95] One accuracy study indicated that single indications from clinical prediction rules did not influence diagnosis or treatment.[96] (Table 45)	Very low	NA[1]

Evidence statements	*GRADE Quality*	*Related recommendation*
Six accuracy studies indicated that CT has moderate to high sensitivity and specificity for the diagnosis of Alzheimer's disease.[99] (Table 46)	Very low	NA[1]
Twenty-eight studies indicated that MRI has good sensitivity and specificity for the diagnosis of Alzheimer's disease, with a wide range in the accuracy estimates. [99-101] (Table 46)	Very low	NA[1]
Two accuracy studies indicated that MRI has a high specificity and moderate sensitivity for the diagnosis of Creutzfeldt-Jakob disease. [102 103] (Table 46)	Low	NA[1]
One study indicated that when the subtype was unclear on comprehensive clinical assessment, MRI had a high sensitivity for differentiating subtypes, a moderate specificity for vascular dementia and a moderate sensitivity and high specificity for Alzheimer's disease. [104] (Table 46)	Very low	NA[1]
Four studies indicated that structural imaging can change the diagnosis in people with dementia; the magnitude of this effect varied depending on dementia subtypes (Quality: Very low). [106-109] One of these studies indicated that structural imaging increased the number of diagnoses of cerebrovascular disease over and above that of clinical diagnosis, with an increase in sensitivity of 53 per cent and a decrease in specificity of 17 per cent.[106] One study indicated that CT changed treatment plans in approximately 10 per cent of dementia patients (Quality: Low).[107] (Table 47)	Very low - Low	NA[1]
No studies reported on the impact of structural imaging on patient outcomes. (Table 47)	N/A	NA[1]

[1] As a practice point was formulated that all patients should usually undergo structural imaging to exclude potentially reversible causes of dementia, EBRs for the use of structural imaging in patient subgroups became unnecessary.

Table 42 Evidence Summary of Included Health Technology Assessment report

Reference	Study Design	Types of studies included Search period	Types of participants included Relevant research question	Test	Comparison	Reference standard	Results Conclusions	Quality appraisal[1]
Health Quality Ontario 2014 [91]	Systematic Review &Health Technology Assessment	RCTs, systematic reviews, meta-analyses, observational studies, diagnostic accuracy studies, studies reporting impact on clinical decision making Jan 2000-Feb 2013	Symptomatic patients with suspected or established dementia (including Alzheimer's disease, vascular dementia, Lewy body dementia, frontotemporal dementia, Creutzfeld-Jakob disease, mixed dementia) Research questions: 1. "What are the indications for a structural imaging investigation for dementia diagnosis?" 2. "What is the clinical utility or adjunctive value of neuroimaging for dementia diagnosis?" 3. "What is the diagnostic accuracy of neuroimaging for discriminating dementia types?"	Neuroimaging during diagnosis with structural CT or MRI	Not specified in inclusion/ exclusion criteria	Not specified in inclusion/ exclusion criteria	Addressing current clinical question: 1. Included 1 systematic review of 7 accuracy studies, plus 1 retrospective accuracy study and 1 study of therapeutic impact (quality assessed by HQO as accuracy studies). 2. Included four studies 3. Included 3 systematic reviews on the diagnosis of AD, 2 accuracy studies on the diagnosis of CJD and 1 accuracy study on MRI accuracy in clinically ambiguous dementia Evidence summaries of the individual included studies are provided in Tables 2 & 3.	Score: 9/11 1. Y 2. N 3. Y 4. Y 5. N 6. Y 7. Y 8. Y 9. Y 10. Y 11. Y

Author Conclusions:

1. "Prediction rules and individual clinical indications do not appear to significantly predict abnormalities on a CT or MRI scan. Groups of indications (in prediction rules) have variable accuracy in predicting abnormalities, and prediction rules that are most accurate also scan the highest proportions of patients. Clinical indications (individually and together) also do not significantly predict [the] influence on clinical decision making (i.e., diagnosis, treatment/management), nor does the detection of abnormalities always influence these decisions." (GRADE: Very low)

2. "…the clinical utility of neuroimaging in these studies is variable. Information from CT or MRI scans may result in revision of clinical diagnosis in as few as 10% to nearly two-thirds of patients, depending on the type and severity of dementia" (GRADE: Low).

3. a. "Compared to clinical or autopsy diagnosis, CT has moderate to high sensitivity and specificity for differentiating AD from MCI, other types of dementias, and healthy aging. MRI also has good accuracy, although there appears to be a wide range in both accuracy estimates due to variability in cortical structures assessed, comparison groups, and methods of assessment (quantitative, visual assessment, volumetric) (GRADE: Very low).
b. "MRI has high specificity and moderate sensitivity for the diagnosis of Creutzfeld-Jakob disease. There is some potential influence of the specific MRI sequence on accuracy, and some authors recommend diffusion-weighted and FLAIR MRI sequences to visualize the pathological changes." (GRADE: Low)
c. "MRI has high sensitivity for differentiating clinically ambiguous dementias, moderate specificity for discriminating VaD, and moderate sensitivity but high specificity for discriminating AD (GRADE: Very low)."

Health Quality Ontario 2014 [91] Conclusions Cont[d]

"The clinical utility of structural neuroimaging is [3]:

- o high for patients with potentially mixed dementia
- o high for patients where there is uncertainty for 2 years or more about the type of dementia [3]
- o low for patients with Alzheimer's disease clinically diagnosed by follow-up over time (e.g., 1 year)
- o low for patients where vascular dementia has been clinically excluded" (GRADE: Low)

Abbreviations: CJD = Creutzfeld-Jakob disease, CT = computed tomography, HTA = Health Technology Assessment, MRI = magnetic resonance imaging, AD = Alzheimer's disease, FLAIR = Fluid attenuated inversion recovery, RCT = randomised controlled trial, VaD = vascular dementia

1. Appraisal criteria: (1) 'a priori' design provided, (2) Duplicate study selection and data extraction, (3) Comprehensive literature search, (4) Grey literature search (considered screening reference lists of included studies as grey literature search), (5) List of included and excluded studies provided (6) Characteristics of included studies provided, (7) Scientific quality of the included studies assessed and documented, (8) Scientific quality of included studies used to formulate conclusions, (9) Methods to combine findings appropriate, (10) Publication bias assessed, (11) Conflict of interest included for review and each of the included studies.
2. The likelihood ratio represents a combination of the sensitivity and specificity and measures the probability of the test result in patients with the disease compared to those without the disease. A likelihood ratio of 1 indicates that the test does not provide any useful diagnostic information. Positive likelihood ratios > 10 and negative likelihood ratios < 0.1 can provide convincing diagnostic evidence. Positive likelihood ratios > 5 and negative likelihood ratios < 0.2 can provide strong diagnostic evidence. However, the interpretation depends on the context in which the test is used and the pretest probability [20] .
3. The link between the evidence base and the conclusions is not clearly presented in the HQO report. The conclusion regarding patients with uncertainty of the type of dementia for 2 years or appears to be based on the Boutoleau- Bretonniere (2012) study, which included clinically ambiguous dementia cases and 2-year follow-up, in which 80% of patients had a clinical diagnosis after 2 years. The MRI accuracy data is for patients unclassifiable at the commencement of the study, rather than those remaining unclassified after 2 years.

Table 43 Evidence Summary of Systematic Reviews included in Health Quality Ontario HTA

Reference	Study Design	Types of studies included Search period	Types of participants included	Test	Comparison	Reference standard	Results	Quality appraisal
Accuracy of clinical prediction rule selection of patients for neuroimaging to detect potentially reversible causes of dementia								
Gifford 2000 [94]	Systematic Review	All studies reporting the use of a clinical prediction rule and applying neuroimaging in all patients and reporting sufficient data to calculate sensitivity and specificity. Jan 1993 - Dec 1998	Dementia patients	Clinical prediction rules with explicit clinical variables	Any	Potentially reversible cause (PRC) of dementia on imaging	Included 7 articles on 6 sets of clinical prediction rules. All rules considered duration or acuity of dementia symptoms. All studies were of CT. Prevalence of PRCs in included studies 0 – 10.4%. Meta-analysis precluded by heterogeneity Accuracy of prediction rules for PRC: Dietch (2 studies): Sn 87.5-100%, Sp 37.2-52.9; Larson High-Risk (3 studies): Sn 25.0-100%, Sp 64.2-85.7% Larson Low-Risk (2 studies): Sn 50.0-100%, Sp 68.6-76.0% Bradshaw (2 studies): Sn 12.5-67.3%, Sp 69.2-79.1% AAN (1 study): Sn 66.7%, Sp 42.1% CCC (1 study): Sn 83.3%, Sp 63.2% Accuracy of prediction rules for PRC used to identify patients who need a scan [1 2]: Dietch (2 studies): LR+ 1.39,2.12; LR- 0.0,0.58 Larson High-Risk (2 studies): LR+ 0.70,7.0; LR- 0.0,1.17 Bradshaw (2 studies): LR+ 0.60,2.19; LR- 0.47,1.10, CCC (1 study): LR+ 1.0, LR- 1.0 Accuracy of prediction rules for PRC used to identify patients who *do not* need a scan [1]: Larson Low-Risk (2 studies): LR+ 2.08,3.19; LR- 0.0,0.66 AAN (1 study): LR+ 1.15, LR- 0.79 Dietch[2] and CCC[3] prediction rules miss the fewest cases of PRCs in a hypothetical cohort of dementia patients (ie have the lowest false negative rate), but also scan the largest proportion of patients. In 1000 patients with a PRC prevalence of 1%, Dietch and CCC rules would miss 1 and 2 patients with a PRC, respectively. If prevalence = 10%, the estimated missed cases would be 13, and 17 respectively. The Dietch and CCC rules would send 63% and 58% of patients to imaging, respectively.	Used as source of studies in HQO report, individual study data reanalysed in HTA Quality assessment of SR not reported, individual included studies appraised for risk of bias.

Reference	Study Design	Types of studies included Search period	Types of participants included	Test	Comparison	Reference standard	Results	Quality appraisal
Accuracy of MRI or CT for the diagnosis of Alzheimer's disease								
Bloudek 2011 [99]	Systematic Review	Accuracy studies reporting Sn and Sp for AD diagnosis. Probably includes many case control studies (unclear). Jan 1990 - March 2010	Alzheimer's disease	MRI, CT, SPECT, FDG-PET, CSF analysis Excludes MRI imaging sequences that are experiment-al or investiga-tional and not routinely used	AD vs MCI, other dementias, or controls without dementia	Clinical or histopatholog-ical diagnosis	Included 26 studies of MRI and 6 studies of CT to synthesise accuracy estimates. Found significant unexplained heterogeneity for Sn and Sp for CT and MRI. Includes comparisons to normal controls (case control studies), MCI and other dementias. <u>Accuracy for diagnosis of AD (combined for all comparisons, significant heterogeneity):</u> MRI: Sn 83% (79% - 87%), Sp 85% (80%-89%) CT: Sn 80% (68%-88%), Sp 87% (78%-93%) Sensitivity analyses were also conducted on subgroups including comparison group, reference standard and severity (with assumptions made on study design and descriptors), however significant heterogeneity was observed in the subgroup analyses. Accuracy was non-significantly lower for mild compared to moderate dementia cases, however significant heterogeneity was observed in the subgroup analyses.	Quality assessment of SR not reported, individual included studies appraised for risk of bias.
Wahlund 2005 [100]	Systematic Review	Studies reporting data allowing calculation of Sn, Sp, and LRs compared to normal and other disease controls, case-control studies ≥ 20 cases and controls each, or ≥ 30 cases	Alzheimer's disease	MRI	Normal and other diseased controls	Clinical or neuropatholo-gical criteria	36 studies of MRI. Results presented separately by comparison group (including case control studies), method of estimation of brain volume and brain region assessed. Meta-analyses excluded and authors did not make conclusions due to large variations in study methods used.	Quality assessment of SR not reported, individual included studies appraised for risk of bias.
Wollman 2003 [101]	Systematic Review	Accuracy studies. Sn and Sp for diagnosis or differentiation from normal or other diseases	Alzheimer's disease	CT (MTL width), MRI (hippocam pal or MTL volume), PET, SPECT.	Current clinical diagnosis. Normal controls or other diseases	Clinical criteria	4 studies of MRI, 2 studies of CT. Sn and Sp reported individually for each study. Accuracy for AD diagnosis (3 case control studies):[4] MRI, vs normal controls (3 studies): Sn 88%-95%, Sp 92%-96% MRI vs other disease (1 study): Sn 90%, Sp 94% CT, vs normal controls (1 study): Sn 80%-85%, Sp 78%-93% CT, vs other diseases (VaD, depression, paraphrenia): Sn 75%, Sp 90%	Quality of SR not reported, individual included studies appraised.

Abbreviations: AAN = American Academy of Neurology, AD = Alzheimer's disease, CCC = Canadian Consensus Conference, HQO = Health Quality Ontario, HTA = Health Technology Assessment, LRs = likelihood ratios, LR+ = positive likelihood ratio, LR- = negative likelihood ratio, MCI = mild cognitive impairment, MTL = medial temporal lobe, PRC = potentially reversible cause of dementia, Sn = sensitivity, Sp = specificity, VaD = vascular dementia.

1. As calculated by Health Quality Ontario (2014) authors [91]. The likelihood ratio represents a combination of the sensitivity and specificity and measures the probability of the test result in patients with the disease compared to those without the disease. A likelihood ratio of 1 indicates that the test does not provide any useful diagnostic information. Positive likelihood ratios > 10 and negative likelihood ratios < 0.1 can provide convincing diagnostic evidence. Positive likelihood ratios > 5 and negative likelihood ratios < 0.2 can provide strong diagnostic evidence. However, the interpretation depends on the context in which the test is used and the pretest probability [20] .
2. Components of Dietch prediction rule according to Health Quality Ontario (2014): Symptom duration <1 month, Change in cognitive function <48 hours, Focal signs or symptoms, Papilledema or visual field defects, Headache, Trauma, History of malignant tumor, Seizures, History of stroke, Urinary incontinence, Apraxia or ataxia
3. Components of Canadian Consensus Conference predication rule according to Health Quality Ontario (2014): Age <60years, Symptom duration less than 2 years, Change in cognitive function in <1-2 months, Focal signs or symptoms, Headache, Trauma, History of malignant tumor, Seizures, Urinary incontinence, Gait disturbance
4. Accuracy data as reported in Wollman systematic review [101], differs slightly to that reported in HQO HTA [91].

Table 44 Evidence summary of primary studies included in Health Quality Ontario review

Reference Country	Study Design	N(n)	Participants Age Gender Other	Test	Comparison	Reference standard	Main Outcomes	Results	Risk of bias[1]
Accuracy of clinical prediction rule selection for neuroimaging to detect potentially reversible causes of dementia									
Sitoh 2006 [95] Singapore	Retrospective accuracy study	210	Memory clinic outpatients Age (years): mean (SD) males 72.5 (9.8) females 74.7 (7.9) Gender: Females 62.4%	5 sets of clinical prediction rules selecting patients for CT	Nil	Neuroimaging of stroke, hydrocephalus, meningiomas, subdural hematomas, subdural hygromas, or any other space-occupying lesions that may be amenable to surgical intervention	Likelihood ratios[2] for detection on neuroimaging of stroke, hydrocephalus, meningiomas, subdural hematomas, subdural hygromas, or any other space-occupying lesions that may be amenable to surgical intervention	Accuracy of prediction rules for PRC used to identify patients who need a scan: Dietch: LR+ 2.02, LR- 0.58 Larson High-Risk: LR+ 2.13, LR- 0.91 Bradshaw: LR+ 1.56, LR- 0.87 CCC: LR+ 1.0, LR- 1.0 NB. These likelihood ratios indicate the test is not highly discriminatory[2] Accuracy of prediction rules for PRC used to identify patients who *do not* need a scan: Larson Low-Risk: LR+ 0.80, LR- 1.39	1. low 2. low 3. high 4. low 5. low 6. low
Accuracy of clinical prediction rule selection for CT to predict change in diagnosis or management									
Condefer 2003 [96] UK	Retrospective accuracy and therapeu-tic impact study	146	Memory clinic patients Age: NR Gender: NR	Indications from clinical prediction rules selecting patients for CT[3]	Nil	Nil	Accuracy for change in diagnosis or management (Clinical utility)	Accuracy *to predict change in diagnosis or management*: Sn 5%-59%, Sp 43% - 89% No individual indications from clinical prediction rules significantly predicted clinical utility of CT (ie change in diagnosis or management). Detection of vascular or structural lesions by CT did not necessarily affect clinical decisions	1. low 2. low 3. high 4. high 5. low 6. low

Reference Country	Study Design	N(n)	Participants Age Gender Other	Test	Comparison	Reference standard	Main Outcomes	Results	Risk of bias[1]
Accuracy of MRI or CT for the diagnosis of CJD									
Schroter 2000 [103] Germany	Diagnostic accuracy study	245 (162)	Suspected cases of CJD reported to the German CJD Surveillance Unit, 1993 - 1998	T2-weighted MRI	Nil	Autopsy or clinical diagnosis	Accuracy for diagnosis of Creutzfeldt-Jakob disease	MRI accuracy for CJD diagnosis: Sn 67.3% (59.5–74.4) Sp 93.1% (83.3–98.1)	1. low 2. high 3. high 4. low 5. high 6. high
Tschampa 2005 [102] Germany	Diagnostic accuracy study	193 (144)	Consecutive cases referred to the German CJD Surveillance Unit, 2001 to 2003	T2-weighted, diffusion-weighted, FLAIR, proton-density-weighted MRI	Nil	Autopsy or clinical diagnosis (including probable according to WHO criteria)	Accuracy for diagnosis of Creutzfeldt-Jakob disease	MRI accuracy for CJD diagnosis (3 observers): Sn 59.7% (51.6–67.4), 58.3% (50.2–66.1), 70.8% (62.9–77.6) Sp 84.2% (69.6–92.6), 89.5% (75.9–95.8), 81.6% (66.6–90.8)	1. high 2. high 3. high 4. high 5. high 6. high
					Pooled estimate from HQO for Schroter and Tschampa:			MRI accuracy for CJD diagnosis: Sn: 64% (58%–69%), I^2 46.9% (1.89, 0.1698) Sp: 90% (82%–95%), I^2 47.3% (1.90, 0.1685)	

Reference Country	Study Design	N(n)	Participants Age Gender Other	Test	Comparison	Reference standard	Main Outcomes	Results	Risk of bias[1]
Accuracy of MRI or CT in dementia patient subgroups									
Boutoleau-Bretonniere 2012 [104] France	Prospect-ive diagnostic accuracy study	60	"Unclassifi-able"memory centre patients. Fulfilled DSM-IV criteria ≥18 MMSE Don't fulfil criteria for FTD, VaD, Parkinson disease, LBD, or progressive supranuclear palsy/ corticobasal degeneration spectrum ≥ NINCDS-ADRDA "atypical" features of AD Age: 63.9 years ±9.4 Gender: Female 38%	MRI analysed after 2 years follow-up	Nil	Clinical diagnosis at follow-up (AD: NINCDS-ADRDA clinical criteria and MTA rated with Scheltens visual rating scale with threshold ≥ 2; VaD: NINCDS-AIREN clinical criteria and WMH rated with Fazekas scale with threshold of Fazekas grade 3)	Accuracy (ROC curve analysis)	After 2 years follow-up 20% (12/60) remained unclassifiable. In clinically ambiguous cases, MRI at baseline compared to a reference standard of clinical diagnosis after 2 years follow-up contributed: - significantly to diagnosis of VaD (Accuracy for vascular changes and VaD Sn 88%, Sp 85%) - significantly, but limited in diagnosis of AD (Sn 56%, Sp 86%, AUC 0.68 (95%CI 0.51-0.85; P = 0.04); authors suggest may be due to poor specificity of MTLA) - reliably (by MTLA) in discriminating organic dementia from psychiatric controls (AUC = 0.87, P<0.01)	1. low 2. low 3. high 4. low 5. high 6. low

Reference **Country**	**Study Design**	**N(n)**	**Participants** **Age** **Gender** **Other**	**Test**	**Comparison**	**Reference standard**	**Main** **Outcomes**	**Results**	**Risk of bias**[1]
Massoud 2000 [106] USA	Diagnostic accuracy and impact study	61	Mixed dementia (concomitant CVD and AD) at AD research and tertiary care centre Age mean (SD): 69yrs (11) Gender: Female 41%	Clinical diagnosis plus CT or MRI	Clinical diagnosis alone	Pathology	*Accuracy:* for CVD for cerebral infarcts *Diagnostic impact:* Number of cerebral infarcts detected	*Comparative accuracy* clinical diagnosis (CD) vs CD&CT/MRI To detect CVD: Sensitivity: 6% vs 59% (↑ 53%) Specificity: 98% vs 81% (↓ 17%) To detect cerebral infarcts: Sensitivity: 8% vs 54% (↑ 46%) Specificity: 98% vs 83% (↓ 15%) *Diagnostic impact:* 13 infarcts detected on neuroimaging not suspected clinically (13/61 = 21%; plus 2 suspected clinically) (NB specificity decreased with MRI so some findings weren't accurate, see accuracy outcome above)	1. low 2. low 3. low 4. high 5. low 6. high
Impact of CT and /or MRI on clinical diagnosis and/or management									
Condefer 2004 [107] UK	Retrospective diagnostic & therapeu-tic impact study	146	Patients meeting DSM-IV criteria for dementia Age: ≥65 years	Non-contrast CT with complete assessment with clinical evaluation (on history, physical & neurological exam, functional assessment, full neuropsychological exam, routine blood chemistry)	Clinical evaluation (2 geriatricians)	None	Change in diagnosis or treatment plan	CT led to change in diagnosis and treatment in approx. 10% cases. CT changed diagnosis in 12% (±2%), most commonly: exclusion or inclusion of vascular component less frequently: confirmation of atypical AD, identification of structural lesion in average of 1.1% of cases [4] Changes in treatment plans in 11% (±2%) Most common: addition of low-dose aspirin or Acetylcholineserase inhibitors, or referral to further neuroimaging or neurosurgery in average of 1.1% of cases [4]	1. low 2. low 3. high 4. high 5. low 6. low

Reference Country	Study Design	N(n)	Participants Age Gender Other	Test	Comparison	Reference standard	Main Outcomes	Results	Risk of bias[1]
Hentschel 2005 [108] Germany	Prospect-ive before-after diagnostic impact study	106	Memory clinic patients with primary care diagnosis of dementia Age mean (SD): 68.6 yrs (SD 8.6) Gender: NR	MRI Neuropsycholo-gical testing (NP)	Initial clinical diagnosis in memory clinic	Comprehensive diagnosis including all tests by group clinician consensus	Change in diagnosis Influence of tests on final comprehensive diagnosis	MRI and NP combined changed initial clinical diagnosis in 26% of patients (95% CI, 17–35). Altered diagnosis by MRI and NP combined: - 11.1% (3/27) of neurodegenerative diagnoses (including Alzheimer's, Lewy body and frontotemporal dementias) - 28.6% (8/28) of vascular dementia diagnoses - 11.1% (5/45) of non-dementia diagnoses The main effects of MRI and of NP diagnosis on the final diagnosis were statistically significant (P < 0.01).	1. low 2. low 3. low 4. low 5. low 6. high
Jani 2000 [109] UK	Retrospect ive diagnostic impact study	104	Elderly inpatients and outpatients of psychiatric hospital with cognitive impairment referred for MRI Age: ≥65 years Gender: Female 66.3%	MRI	Clinical evaluation (all given dementia diagnosis)	None	Concordance between clinical and MRI diagnosis	Overall, correlations between MRI and clinical evaluation weak, agreement in only 10.6% (11/104). Altered diagnoses on MRI: - 2% (2/104) prompted "other diagnosis" - 28% (29/104) diagnosed normal age-related changes - 61% (63/104) specific diagnosis determined in all (100%, 63/63) of those clinically diagnosed with unspecified dementia - 11.1% (3/27) clinical diagnosis of vascular dementia revised - 62.5% (5/8) clinical diagnosis of Alzheimer's disease revised	1. low 2. low 3. low 4. low 5. low 6. low

Abbreviations: AAN = American Academy of Neurology, AD = Alzheimer's disease, AUC = Area under the Receiver-operating characteristic curve), CCC = Canadian Consensus Conference, CJD = Creutzfeldt-Jakob disease, CVD = cardiovascular disease, HQO = Health Quality Ontario, LR+ = positive likelihood ratio, LR- = negative likelihood ratio, MTLA = medial temporal lobe atrophy, PRC = potentially reversible cause of dementia, Sn = sensitivity, Sp = specificity, VaD = vascular dementia, WMH = white matter hyperintensity.

1. Risk of bias according to Health Quality Ontario assessment: (1) Representative patients/diagnostic uncertainty, (2) Direct comparison to reference standard, (3) Consecutive patients, (4) Selection/Referral Process Clearly Described, (5) Tests on all patients, (6) Blind outcome evaluation
2. The likelihood ratio represents a combination of the sensitivity and specificity and measures the probability of the test result in patients with the disease compared to those without the disease. A likelihood ratio of 1 indicates that the test does not provide any useful diagnostic information. Positive likelihood ratios > 10 and negative likelihood ratios < 0.1 can provide convincing diagnostic evidence. Positive likelihood ratios > 5 and negative likelihood ratios < 0.2 can provide strong diagnostic evidence. However, the interpretation depends on the context in which the test is used and the pretest probability [20] .
3. Indications were: focal neurological signs, age less than 70 years, abrupt onset, noninsidious course, history of head injury, memory loss onset less than 2 years prior to the scan, history of hypertension/bleeding disorder, or physician prediction of an influential scan
4. As per study data, is an average of 2 reviewers , Reviewer A: 2 cases (1.4%), Reviewer B: 1 case (0.7%)

Table 45 GRADE Evidence Profile: Clinical prediction rules

Quality assessment[1]							Effect[89]	Quality	Link to patient centred outcomes
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Diagnostic accuracy of clinical prediction rules – False Negative (patients not selected for imaging but with a potentially reversible cause of dementia on scanning)									
1 2	Systematic review (7 accuracy studies) [94] Accuracy studies[2] [95 96]	Serious limitations[3]	Serious limitations[4]	Serious limitations[5]	Serious limitations[6]	None. No publication bias detected.[7]	Overall: Sn 25.0% - 100%; LR- 0.0-1.17 Dietch: Sn 87.5%-100.0%; LR-: 0.0-0.58 CCC: Sn 83.3% LR- 0.26-1.0	⊕OOO VERY LOW	These patients would have a missed scan detection of a PRC by not being selected for neuroimaging. However, in many patients with image detected PRC diagnoses are not reversed. In the minority (estimated 7%) that could have been reversed the impact on patient outcomes and quality of life is potentially large should the PRC remain undetected.
Diagnostic accuracy of clinical prediction rules – True Negative (patients not selected for imaging with no a potentially reversible cause of dementia detected on scanning)									
1 2	Systematic Review (7 accuracy studies) [94] Accuracy studies[2] [95 96]	Serious limitations[3]	Serious limitations[4]	Serious limitations[5]	Serious limitations[6]	None. No publication bias detected.[7]	Overall: Sp 37.2% to 85.7% LR- 0.0-1.17 Dietch: Sp 37.2% - 52.9% LR-: 0.0-0.58 CCC: Sp 63.2%; LR- 0.26-1.0	⊕OOO VERY LOW	With application of clinical prediction rules these patients would experience less inconvenience and cost than the alternative of undergoing neuroimaging. As testing is avoided, they may miss out on the value of reassurance from a negative test result.

Quality assessment[1]							Effect[89]	Quality	Link to patient centred outcomes
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Diagnostic accuracy of clinical prediction rules – False Positive (patients selected for imaging with no a potentially reversible cause of dementia detected on scanning)									
1	SR (7 accuracy studies) 93]	Serious limitations (-1)[3]	Serious limitations (-1)[4]	Serious limitations (-1)[5]	Serious limitations (-1)[6]	None. No publication bias detected.[7]	Overall: Sp 37.2% to 85.7% LR+ 0.6-3.19 Dietch: Sp 37.2% - 52.9% LR+ 1.39 – 2.12 CCC: Sp 63.2%; LR+ 1.0 - 2.26 No individual indications significantly predicted clinical utility of CT.	⊕OOO VERY LOW	Whether or not clinical prediction rules are applied, these patients would proceed to neuroimaging (although they do not have a potentially reversible cause of dementia), thus there is no impact on the clinical pathway followed for these patients.
2	Accuracy studies[2] [95 96]								
Diagnostic accuracy of clinical prediction rules – True Positive (patients selected for imaging with a potentially reversible cause of dementia on scanning)									
1	SR (7 accuracy studies) 93]	Serious limitations (-1)[3]	Serious limitations (-1)[4]	Serious limitations (-1)[5]	Serious limitations (-1)[6]	None. No publication bias detected.[7]	Overall: Sp 37.2% to 85.7% LR+ 0.6-3.19 Dietch: Sp 37.2% - 52.9% LR+ 1.39 – 2.12 CCC: Sp 63.2%; LR+ 1.0 - 2.26 No individual indications signif predicted clinical utility of CT.	⊕OOO VERY LOW	Whether or not clinical prediction rules are applied, these patients would proceed to neuroimaging, thus there is no impact on the clinical pathway followed for these patients.
2	Accuracy studies[2] [95 96]								

Abbreviations: AD = Alzheimer's disease, CCC = Canadian Consensus Conference, dx = diagnosis(es) LR+ = positive likelihood ratio, LR- = negative likelihood ratio, PRC = potentially reversible cause of dementia, pts = patients, Sn = sensitivity, Sp = specificity.

1. Quality assessment as per Health Quality Ontario (2014).
2. HQO report indicates 3 accuracy studies which includes Condefer et al (2004), which is not presented in the findings for this outcome, thus this evidence update indicates 2 accuracy studies (it excludes this study from this outcome, although it is considered to contribute to the evidence for the diagnostic and therapeutic impact (Table 47).
3. Evidence for this outcome started as high quality due to study design features. Three studies did not enrol consecutive patients. One study enrolled patients with diagnostic uncertainty (patients were investigated for general cognitive complaints or suspected dementia; or had not yet received a clinical assessment to determine type of dementia; and/or had not yet been diagnosed as having a particular dementia type). In one study the referral process was not clearly described (Condefer 2003). Six studies had limitations in blind outcome assessment.
4. There was inconsistency between accuracy estimates which prohibited meta-analysis. There were large difference in point estimates of sensitivity, specificity, and false negative rates between studies even for the same prediction rule.
5. Diagnostic accuracy is a surrogate for patient centered outcomes; the samples studied are similar to those presenting to tertiary care centres, however there was no data from primary care; all studies were of CT.
6. Confidence intervals for sensitivity and specificity were very wide in all studies and spanned the entire range of possible values depending on the prediction rule and population it was applied to, which may influence the conclusions and recommendations pertaining to the use of the prediction rules.
7. The possibility of publication bias cannot be ruled out, however, sample sizes were generally moderate in size (i.e., n >100 patients) with the exception of one study, and of the 6 studies reporting funding sources, all were reported to be supported by research grants.
8. The likelihood ratio represents a combination of the sensitivity and specificity and measures the probability of the test result in patients with the disease compared to those without the disease. A likelihood ratio of 1 indicates that the test does not provide any useful diagnostic information. Positive likelihood ratios > 10 and negative likelihood ratios < 0.1 can provide convincing diagnostic evidence. Positive likelihood ratios > 5 and negative likelihood ratios < 0.2 can provide strong diagnostic evidence. However, the interpretation depends on the context in which the test is used and the pretest probability [20] .
9. Results from [94-96], see Table 43 and Table 44

Table 46 GRADE Evidence Profile: Accuracy of structural imaging for distinguishing types of dementia

Quality assessment [1]							Effect	Quality	Link to patient outcomes
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Accuracy of CT for differential diagnosis of Alzheimer's disease									
6	Accuracy studies	Serious limitations[2]	Serious limitations[3]	Serious limitations[4]	Serious limitations[5]	None. No publication bias detected[6]	CT has moderate to high sensitivity and specificity for differentiating AD from MCI, other types of dementias, and healthy aging (compared to a reference standard of clinical or autopsy diagnosis). (See HTA report [91], studies from [99 101])	⊕OOO VERY LOW	Diagnostic accuracy is a surrogate for patient centred outcomes. The impact on patient management and outcomes is uncertain.[4]
Accuracy of MRI for differential diagnosis of Alzheimer's disease									
28	Accuracy studies (from systematic reviews)	Serious limitations[2]	Serious limitations[7]	Serious limitations[8]	Serious limitations[9]	None. No publication bias detected[10]	MRI has good sensitivity and specificity, but there is a wide range in these accuracy estimates. (See HTA report [91], studies from [99-101])	⊕OOO VERY LOW	Diagnostic accuracy is a surrogate for patient centred outcomes. The impact on patient management and outcomes is uncertain.[4]
Accuracy of MRI for differential diagnosis of Creutzfeldt-Jakob disease									
2	Accuracy studies	Serious limitations[11]	No serious limitations[12]	Serious limitations[13]	No serious limitations[14]	None. No publication bias detected[15]	MRI has high specificity and moderate sensitivity for the diagnosis of CJD. [102 103]	⊕⊕OO LOW	Diagnostic accuracy is a surrogate for patient centred outcomes. The impact on patient management and outcomes is uncertain.[4]
Accuracy of MRI for differential diagnosis of Clinically Ambiguous Dementias									
1	Accuracy study	Serious limitations[16]	No serious limitations	Serious limitations[17]	Serious limitations[18]	None. No publication bias detected[19]	*Additional to clinical assessment:* In clinically ambiguous dementias MRI has high sensitivity for differentiating subtypes: moderate specificity for discriminating VaD, and moderate sensitivity but high specificity for discriminating AD. [104]	⊕OOO VERY LOW	Diagnostic accuracy is a surrogate for patient centred outcomes. The impact on patient management and outcomes is uncertain.[4]

1. Quality assessment as per Health Quality Ontario (2014)
2. Evidence for this outcome started at low quality due to study design limitations.

3. A mixed-effects binary regression model was used to account for the correlation between sensitivity and specificity, yet significant unexplained heterogeneity remained in sensitivity (I^2 = 89.2%) and specificity (I^2 = 58.5%). Cochran's Q statistic for homogeneity was statistically significant for both estimates (P < 0.01, P = 0.03, respectively); subgroup analysis to explore heterogeneity also had significant heterogeneity (I^2 ≈ 87%–90%).
4. Diagnostic accuracy is a surrogate for patient-important outcomes. True positive or negative diagnoses inform patient planning and subtype specific treatment. False positive or negative diagnoses result in planning and treatment according to misleading subtype diagnosis. No treatments can reverse or modify existing dementia, however some subtype specific treatments may slow cognitive decline.
5. The rate of false positives and false negatives varied from as many as 1 in 4 to approximately 1 in 20 (modified by current authors from HQO statement of 1 in 5 to 1 in 10 considering the range in false negative rates reported in Wollman systematic review [101]), which may influence the conclusions and recommendations pertaining to the use of the prediction rules.
6. The possibility of publication bias cannot be ruled out. Although all studies received some or all funding from research organizations, foundations, or grants, 2 studies had co-funding support from industry.
7. A mixed-effects binary regression model was used to account for the correlation between sensitivity and specificity, yet significant unexplained heterogeneity in sensitivity (I^2 = 64.3%) and specificity (I^2 = 84.2%). Cochran's Q statistic for homogeneity was statistically significant for both estimates (P < 0.01 for all); subgroup analysis to explore heterogeneity also had statistically significant heterogeneity (I^2 ≈ 87%–90%).
8. Only 2 studies excluded patients with evidence of vascular changes which may not reflect the reality of patients to whom the diagnostic test will be applied; however, most studies included tertiary and some community-dwelling patients and employed widely available MRI sequences and interpretation methods (e.g., radiologist or neuroradiologist reports).
9. The confidence intervals around the summary estimates were within 10%, though confidence intervals for individual sensitivity estimates spanned 20%–50%, and for specificity most intervals varied across a span of approximately 30%.
10. The possibility of publication bias cannot be ruled out; however, there was no indication of industry sponsorship, sample sizes included both small and large studies, and most studies received some or all funding from independent grants or research organizations, although source of support was not stated for 4 studies (66-70).
11. Evidence for this outcome started at high quality due to study design features.
12. Meta-analysis revealed heterogeneity in estimates of sensitivity (I2 = 46.9%, p = 0.1698) and specificity (I2 = 47.3%, p = 0.1685) that was not statistically significant.
13. Diagnostic accuracy is a surrogate for patient-important outcomes. Demographics of patients were only reported in one study.
14. Confidence intervals for point estimates of sensitivity and specificity were relatively narrow, and varied across approximately 10% to 15%.
15. Both studies were funded by national grants and had relatively large sample sizes (i.e., ~200 participants).
16. Evidence for this outcome started at high quality as due to study design features.
17. Diagnostic accuracy is a surrogate for patient-important outcomes.
18. The 95% CI around the AUC for differentiating AD from non-AD dementias was wide and ranged from almost random chance to very useful (0.51–0.85).
19. Support for the research was provided by a local grant and no authors declared anything in the statement of disclosure.

Table 47 GRADE Evidence Profile: Diagnostic and therapeutic impact of CT or MRI for dementia diagnoses

Quality assessment[1]							Effect	Quality	Link to patient outcomes
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Change in diagnosis									
4	Accuracy studies	Serious limitations[2]	Serious limitations[3]	Serious limitations[4]	No serious limitations[5]	None No publication bias detected.[6]	Diagnostic impact in separate studies: - MRI&NP combined in 11% neurodegenerative, 11% non-dementia, 29% VaD diagnoses. [108] - MRI in 11% VaD, 63% AD, 100% pts with unspecified dementia, 28% pts altered to normal age-related changes. [109] - CT changed diagnosis in 12% (±2%) dementia pts, most commonly inclusion or exclusion of vascular component. [106] - identification of structural lesion in average of 1.1% of cases [107] *Comparison to clinical diagnosis:* - in mixed dementia pts addition CT/MRI to clinical diagnosis ↑ detection of cerebrovascular disease (with ↑ Sn 53% & ↓Sp 17%) [106]	⊕OOO VERY LOW	An alteration in diagnostic thinking is a necessary but not sufficient prerequisite for a change in patient outcomes. Changes across different clinical diagnostic subgroups indicate MRI may have an impact on patient outcomes in these subgroups.
Change in management									
1	Retrospective diagnostic & therapeutic impact study	Serious limitations[7]	No serious limitations	Serious limitations[8]	No serious limitations[9]	None No publication bias detected.[10]	CT Changed treatment plans in 11% (±2%) dementia patients. Most commonly addition of low-dose aspirin or Acetylcholineserase inhibitors, or referral to further neuroimaging or neurosurgery in 1.1% of cases [107]	⊕⊕OO LOW	An alteration in patient management is a necessary but not sufficient prerequisite for a change in patient outcomes.

Quality assessment[1]							Effect	Quality	Link to patient outcomes
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Change in patient outcomes									
0	No evidence available								

Abbreviations: AD = Alzheimer's disease, CCC = Canadian Consensus Conference, dx = diagnosis(es) LR+ = positive likelihood ratio, LR- = negative likelihood ratio, PRC = potentially reversible cause of dementia, pts = patients, Sn = sensitivity, Sp = specificity.

1. Quality assessment as per Health Quality Ontario (2014)[91]
2. Evidence for this outcome started as high quality due to study design features. Limitations were related to: blind outcome assessment [106 108], the study cohort was selected from the patient population rather than formed by consecutive patients [107], the referral process was not clearly described [106].
3. Estimated proportions of cases with change in diagnosis ranged from as few as 1 in 10 patients to nearly half of cases. MRI changed diagnosis in up to nearly half of cases (26–44%), combined CT or MRI changed 26%, while CT influenced 10% to 14% of diagnoses.
4. Change in diagnosis is a surrogate for patient-important outcomes as it remains unknown if or how change in diagnosis influenced treatment, patient experience, or quality of life in a meaningful way. The studies are conducted in tertiary settings but there are limitations in applicability to primary care.
5. The proportion of cases for which neuroimaging resulted in revision of clinical diagnosis was presented in 3 studies as a point estimate only; except for one study, (44) the standard deviation was narrow (e.g., 2%).
6. The possibility of publication bias cannot be ruled out, however research was funded by grants for 2 of 4 studies (45;46) and sample sizes ranged from 60 to 150 which is large for diagnostic studies.
7. Evidence for this outcome started as high quality due to study design features. Limitations were the study cohort was selected from the patient population rather than formed by consecutive patients [107]
8. Change in treatment is a surrogate for patient-important outcomes as it remains unknown if or how change in treatment influences patient experience or quality of life in a meaningful way. The studies are conducted in tertiary settings but there are limitations in applicability to primary care.
9. The standard deviation of the proportion of cases in which management was changed due to radiological information was very narrow (e.g., 2%).
10. The possibility of publication bias cannot be ruled out; however, no conflicts of interest or funding source were disclosed.

SRQ 7: Functional imaging with SPECT

Clinical question

The research questions as defined in the protocol and the associated PICO criteria are listed below in Table 48 and Table 49.

Table 48 PPICO for SRQ7: SPECT clinical question 1

Clinical question: Does the routine use of functional imaging (with SPECT) improve the diagnostic differentiation of dementia from MCI over and above that of standard comprehensive assessment?				
Population	**Prior tests**	**Intervention**	**Comparator**	**Outcomes**
People with a suspected diagnosis of dementia	Standard comprehensive assessment	Functional imaging with SPECT	No SPECT	Diagnostic accuracy for differentiating MCI from dementia Change in patient management/diagnosis
Reference standard: pathology or clinical assessment with follow-up (both imperfect reference standards as MCI may progress, no perfect reference standard available)				

Abbreviations: MCI – mild cognitive impairment; SPECT - single-photon emission computed tomography; PPICO– population, prior tests, intervention, comparator, outcomes

Table 49 PPICO for SRQ7: SPECT secondary clinical question 2

Secondary clinical question: What is the accuracy of SPECT to predict progression of MCI to dementia?				
Population	**Prior tests**	**Intervention**	**Comparator**	**Outcomes**
People with a suspected diagnosis of dementia	Standard comprehensive assessment	Functional imaging with SPECT (in combination with standard comprehensive assessment)	No SPECT (ie standard comprehensive assessment alone)	Diagnostic accuracy for predicting progression of MCI to dementia Change in patient management/diagnosis
Reference standard: pathology or clinical assessment with follow-up				

Abbreviations: MCI – mild cognitive impairment; SPECT - single-photon emission computed tomography; PPICO– population, prior tests, intervention, comparator, outcomes

Literature review search strategies:

Searches for existing HTAs and Systematic reviews

Searches to identify existing Health Technology Assessment reports (HTAs) and systematic reviews were conducted in the databases specified in Table 50, using the search terms listed in the Guideline Technical Report Volume 2. The search strategies were broad, covering a number of diagnostic techniques.

Table 50 Searches for existing HTAs and systematic review for SRQ7: SPECT

Database	Date searched	Period covered	Citations retrieved
HTA	28 May 2014	2005 to 2014	16
NHSEED	29 May 2014	2005 to 2014	18
Cochrane (Cochrane reviews, Cochrane protocols, DARE)	28 May 2014	2005 to 2014	40
MEDLINE	28 May 2014	2005 to week 4 Oct 2014	57
PsycInfo	29 May 2014	2005 to 2014	33
EMBASE	27 May 2014	2005 to 2014	7
PubMed	16 Sept 2014	2005 to 29 May 2014	6
Total			177

Searches for primary studies

Searches were conducted in the databases listed in Table 51 to identify primary studies of the accuracy of SPECT over and above that of standard comprehensive assessment. The search terms used are listed in the Guideline Technical Report Volume 2.

Table 51 Searches for primary studies of SRQ7: SPECT

Database	Dates searched	Period covered	Citations retrieved
MEDLINE	26 Aug 2014	2004 to 2014	248
PsycInfo	26 Aug 2014	2004 to Aug week 3 2014	55
EMBASE	26 Aug 2014	2004 to Aug 25 2014	151
PubMed	26 Aug 2014	2004 to 2014	28
Total			482

The included systematic review that addressed the secondary clinical question (of the predictive accuracy of SPECT) included a search to 2012, therefore no search for primary studies published since this date addressing this question was undertaken (in accord with WHO handbook for guideline development recommendations). [110]

Criteria for selecting studies for review

Table 52 Inclusion and exclusion criteria for review of SRQ7: SPECT

Characteristic	Criteria
Study design	Inclusion: Systematic reviews, randomised controlled trials, non-randomised controlled trials, or cross sectional studies with consistently applied reference standard OR longitudinal accuracy studies (secondary question) Exclusion: diagnostic case control studies
Population	Inclusion: People with a suspected diagnosis of dementia (ie, symptomatic people, includes those with MCI) Exclusion: People with subjective memory loss

Characteristic	Criteria
Intervention	Inclusion: HMPAO SPECT in combination with standard comprehensive assessment
Comparator	Inclusion: Standard comprehensive clinical assessment alone Exclusion: 123I-FP-CIT (DaTSCAN) SPECT[a]
Outcomes	Inclusion: Diagnostic accuracy to differentiation dementia from non-dementia patients Change in patient management/diagnosis Exclusion: Accuracy for differentiation of dementia subtypes; diagnostic yield without a reference standard
Publication type	English language

[a] DaTSCAN tracer not widely available in Australia

Search results:

Existing HTAs and systematic reviews

The most recent, comprehensive and highest quality systematic reviews/HTA reports identified and included in the current update are shown in Table 53.

Table 53 Systematic reviews/HTA reports included in the review of SPECT

Intervention	Included systematic reviews/HTAs
Question 1: differentiation of MCI vs dementia	
SPECT	Swedish Council on Technology Assessment in Health Care (SBU), 2006 [111] (Evidence Summary Table 54)
Question 2: predictive accuracy for progression of MCI to dementia	
SPECT	Frisoni 2013 [112] (Evidence Summary Table 54)

Primary studies

A total of 482 citations were retrieved in the electronic database searches. After exclusion of duplicate citations, 416 citations remained; 381 articles were excluded on review of abstract and title, 35 were reviewed in full text. Three studies were included in this evidence update, two provided data on the diagnostic accuracy of SPECT [113 114] and one on change in management/diagnosis following SPECT [115], over and above that of clinical assessment (Evidence Summary Table 55).

Evidence summary:

The NICE guideline committee considered evidence from a published systematic review by Dougall and colleagues of HMPAO SPECT to 2002 [116]. The evidence considered was of the diagnosis of dementia subtypes. Recent systematic reviews have reported similar accuracy values [99 117]. However, none of these reviews specifically consider the accuracy of SPECT over and above that of standard comprehensive assessment including structural imaging, nor do they exclude case control studies. NICE recommendations were made on the basis of these data. Based on clinical expert opinion, the guidelines adaptation committee considered that the additional value of SPECT in the differentiation of dementia subtypes did not support a recommendation for its use in this context.

The NICE Guideline recommended the use of dopaminergic iodine-123-radiolabelled 2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl) nortropane (FP-CIT) SPECT to help establish the diagnosis in those with suspected Dementia with Lewy bodies (DLB) if the diagnosis is in doubt. As 123I-FP-CIT SPECT is not generally available in Australia, no recommendation regarding the use of SPECT with this tracer was made in these guidelines.

Evidence addressing the use of SPECT specifically for the differentiation of dementia (or AD) from MCI or for the prediction of MCI conversion to dementia were not presented by the NICE guideline committee.

A recommendation was also made in the NICE Guideline for the use of ^{123}I-FP-CIT for the diagnosis of suspected dementia with Lewy Bodies (DLB). However ^{123}I-FP-CIT SPECT is not generally available in Australia, hence this recommendation was not included in these guidelines.

Differentiation of mild cognitive impairment (MCI) from dementia

This evidence update conducted a search for systematic reviews of SPECT published between 2005 and 2014. The Swedish Council on Technology Assessment in Health Care (SBU) conducted a systematic review of SPECT studies for the detection and differentiation of dementia disorders (including the differentiation of MCI from dementia), published from 1980 to July 2004 [111]. This HTA report was included and a search for primary studies of SPECT published from 2004 to 2014 was conducted.

In the SBU 2006 HTA, no included studies reported the accuracy of SPECT over that of clinical assessment in differentiating dementia from MCI [111] (Evidence Summary Table 54).

The search for primary studies identified three relevant studies providing data on the accuracy of HMPAO SPECT over and above that of clinical assessment (Evidence Summary Table 55, GRADE Evidence Profile Table 56).

One study provided individual patient data from 24 memory clinic patients in Germany, 12 with MCI and 12 with early dementia (Table 55).[113] A comparison was possible between the initial clinical diagnosis at their first visit, diagnosis on SPECT and a final comprehensive clinical diagnosis after a period of follow-up. Within the group of patients diagnosed with MCI at the initial clinical assessment, SPECT changed the diagnosis from MCI to dementia in eight subjects, correctly in four of these cases (against a reference standard of final clinical diagnosis at follow-up), giving positive and negative likelihood ratios of 1.0. Thus in this small study, SPECT was of no additional value for these patients. Six of 12 patients assessed as having MCI at the initial clinical diagnosis progressed to dementia during the period of follow-up, thus these data represent in part the use of SPECT at predicting conversion to dementia, rather than simply accuracy of diagnosis at the time of testing. This issue in addition to the incorporation of clinical assessment into the reference standard means that there is high risk of bias in these results.

The accuracy of 99mTc-HMPAO SPECT was also studied in a group of young, cognitively impaired patients with diagnostic uncertainty following standard comprehensive assessment including structural imaging [114]. No clinical diagnosis before testing with SPECT was reported for these patients. The authors concluded that SPECT was of little value in establishing a diagnosis in this group of patients attending a memory clinic (positive likelihood ratio = 1.14) (Table 55).

Logan-Sinclair and Davison conducted a medical audit of SPECT referrals in rural NSW [115]. Little information regarding the patient characteristics at referral were presented. In this study, 31% of referrals were from general practitioners and 98% were referred for suspected dementia. In a small subset of these patients, comparisons to computed tomography (CT) and neuropsychological

assessments were available. In 76% of cases SPECT was either in agreement with the other test results or further studies were recommended, thus there is unlikely to have been any major impact on diagnosis or management in these cases, although there may have been increased confidence in diagnosis and treatment choice where results concurred. The proportion of cases in which SPECT was performed for the differentiation of MCI from dementia is unclear. Data on patient management plans or the final clinical diagnosis were not reported.

An examination of the true accuracy of either SPECT or clinical assessment for differentiation of MCI from dementia is hampered by the lack of an appropriate reference standard. An accurate clinical diagnosis of MCI will not necessarily be confirmed by clinical assessment with follow-up as some conversion to dementia will occur during the intervening time period. Conversion to dementia will also occur for many MCI patients before pathology at autopsy can be performed, and pathology cannot differentiate MCI from normal. It is therefore not possible to get a true measure of the accuracy of clinical diagnosis (or SPECT) for differentiating MCI from dementia at one point in time.

Prediction of progression of MCI to dementia

A search for systematic reviews of SPECT published between 2005 and 2014 was conducted. A systematic review conducted by the Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment (ISTAART) reviewed studies of the accuracy of SPECT to differentiate progressive MCI from non-progressive MCI published to April 2012 [112] (Evidence Summary Table 54). Only studies of MCI progression to Alzheimer’s disease reporting sensitivity and/or specificity for this outcome were included, thus Doebert et al [113] was excluded. A review of primary studies of SPECT did not identify any additional studies on progression of MCI to non-AD dementias published during the same period.

The summary accuracy measures in the meta-analysis of Frisoni et al [112] indicated that SPECT had only a moderate sensitivity and specificity (Table 54). The summary positive likelihood ratio (LR+ 2.2, 95%CI 1.2 to 3.1) indicated that a positive SPECT result does not provide good discrimination of patients who will progress to dementia from those who will not (Table 54). The consequences of a positive SPECT result for MCI that will progress to dementia in terms of both patient management and outcomes are unclear.

The GRADE Evidence Profile for SPECT prediction of progression of MCI to dementia is shown in Table 57).

Resource requirements

SPECT is listed on the Medical Benefits Scheme (MBS) in Australia. Relevant listings are:

- MBS 61402 cerebral perfusion SPECT study fee $605.05
- MBS 61685 cerebral perfusion SPECT study fee (NK) $302.55

Evidence statements	*GRADE Quality*	*Related recommendation*
Two accuracy studies indicated that SPECT has little additional value of over that of standard comprehensive clinical assessment for differentiating dementia from MCI.[113 114] (Table 56)	Very low	EBR 44
Six studies indicated that SPECT does not provide good discrimination of patients who will progress to dementia from those who will not. [112] (Table 57)	Very low	EBR 44

Table 54 Evidence Summary of included Systematic Reviews for SRQ 7: SPECT

Reference	Study Design	Types of studies included Search period	Types of participants included Relevant research question	Relevant Test	Comparison	Reference standard	Relevant Results [3] Authors Conclusions	Quality appraisal[1]
SBU 2008 [111]	Systematic review	Diagnostic accuracy studies with ≥30 cases or 20 cases & 20 controls 1980 - July 2004	Patients who have undergone clinical examination, diagnosed according to standardised clinical or neuropathological criteria. To assess the role and validity of [SPECT] for the detection and differentiation of dementia disorders.	SPECT (HMPAO), Xenon SPECT	Not specified	Clinical or neuro-patho-logical criteria	No studies reported the value of SPECT over that of clinical assessment in differentiating MCI from dementia or AD. Conclusions: There is moderately strong evidence that [SPECT] helps the diagnostic workup differentiate AD (Alzheimer's disease) patients from controls and AD from non-AD dementia (Evidence Grade[2] 2). (Note: the authors conclusion is based upon data that does not directly address the clinical question for this evidence update)	1. CA 2. CA 3. N 4. CA 5. N 6. Y 7. Y 8. Y 9. N 10. N 11. N
Frisoni 2013 [112]	Systematic review	Diagnostic accuracy studies reporting sensitivity and specificity (with n/N) for MCI progression to AD or AD vs healthy controls 1989 – April 2012	Patients with MCI To estimate the diagnostic and prognostic accuracy of different AD imaging biomarkers and their operating procedures, and to investigate the amount and source of variance among them.	Temporoparietal hypoperfusion SPECT or SPET, all included studies used quantatiative/ semiquantititve assessment	Not specified	Clinical diagnosis	Differentiation of progressive vs non-progressive MCI: Any SPECT: Sn 78% (95%CI 72-85%; 6 studies), Sp 64% (95%CI 55-72%; 5 studies), LR+ 2.2 (95%CI 1.2 to 3.1), LR- 0.28 (0.25 to 0.32) [3] ^{99m}Tc-ECD and ^{123}I-IMP: Sn 79% (95%CI 71-91%; 4 studies), Sp 58% (95%CI 46-70%; 3 studies) ^{99}Tc-HMPAO: Sn 78% (95%CI 65-88%; 2 studies), Sp 64% (95%CI 51-75%; 2 studies)	1. CA 2. CA 3. N 4. Y 5. N 6. Y 7. N 8. N 9. Y 10. N 11. N

Abbreviations: AD = Alzheimer's disease, CA = can't answer, dem = dementia, LR+ = positive likelihood ratio, LR- = negative likelihood ratio, MCI = mild cognitive impairment, N = No, Sn = sensitivity; Sp = specificity; SPECT = single-photon emission computed tomography, Y = Yes.

1. Appraisal criteria: (1) 'a priori' design provided, (2) Duplicate study selection and data extraction, (3) Comprehensive literature search, (4) Grey literature search (considered screening reference lists of included studies as grey literature search), (5) List of included and excluded studies provided, (6) Characteristics of included studies provided, (7) Scientific quality of the included studies assessed and documented, (8) Scientific quality of included studies used to formulate conclusions, (9) Methods to combine findings appropriate, (10) Publication bias assessed, (11) Conflict of interest included for review and each of the included studies.
2. Evidence Grade 2 does not relate to the GRADE quality of evidence, but refers to moderately strong evidence, where the majority of studies indicate a sensitivity of >80%, a specificity of >80% and a LR+ ≥5.
3. The likelihood ratio represents a combination of the sensitivity and specificity and measures the probability of the test result in patients with the disease compared to those without the disease. A likelihood ratio of 1 indicates that the test does not provide any useful diagnostic information. Positive likelihood ratios > 10 and negative likelihood ratios < 0.1 can provide convincing diagnostic evidence. Positive likelihood ratios > 5 and negative likelihood ratios < 0.2 can provide strong diagnostic evidence. However, the interpretation depends on the context in which the test is used and the pretest probability [20]

Table 55 Evidence Summary of primary studies for SRQ 7: SPECT

Reference Country	Study Design Recruitment period	N(n)	Participants	Test	Comparison of interest	Reference standard	Relevant Outcomes	Relevant Results[2]	Risk of bias[1]
Accuracy studies reporting the additional value of SPECT									
Doebert 2005 [113] Germany	Diagnostic accuracy study[3] Jan 2001 – July 2002	24 (12 MCI, 12 mild dem on initial clinical assess-ment)	Memory clinic patients with clinical suspicion of early dementia Age (mean ± SD): 69 ± 6.8 years Gender: 54% female	^{99}mTc-HMPAO SPECT	Initial diagnosis. MCI: informant confirmed cognitive complaints, impaired cognitive function, intact activities of daily living, CDR score 0.5, MMSE ≥23 stable general health Mild dementia: CDR = 1, MMSE <23.	Clinical judgement by multi-professional team after clinical follow-up (16±12 months) and memory clinic assessment including structural MRI, neuropsychiatric tests, GDS, CDR, NINCDS-ADRDA and NINDS-AIREN (blind to SPECT)	Comparison of diagnoses by modalities (IPD) Non-comparative accuracy (excluded)	Accuracy in all patients: *SPECT:*[6] diagnostic yield 83%, Sn 89%, Sp 33%, PPV 80%, NPV 50%, LR+ 1.33, LR- 0.33 *Initial clinical assessment:*[5,6] diagnostic yield 50%, Sn 67%, Sp 100%, PPV 100%, NPV 50%, LR+ >100, LR- 0.33 SPECT accuracy in patients considered MCI at initial clinical assessment: Sn 67%, Sp 33%, PPV 50%, NPV 50%, LR+ 1.0, LR- 1.0 SPECT accuracy in dementia patients at initial clinical assessment: SPECT and clinical assessment positive in 100%, 100% confirmed as dementia on final clinical assessment. No additional value of SPECT. Agreement of SPECT and initial clinical diagnosis: SPECT diagnosed dementia in contrast to an initial diagnosis of MCI in 8 (33%) (correctly in 4 (17%), incorrectly in 4 (17%)). SPECT agreed with the initial diagnosis of dementia in all patients.	1. Unclear 2. Low 3. High 4. High

Reference Country	Study Design Recruitment period	N(n)	Participants	Test	Comparison of interest	Reference standard	Relevant Outcomes	Relevant Results[2]	Risk of bias[1]
Doran 2005 [114] UK	Retrospective diagnostic accuracy study Aug 1995 – end 1999	57 (18 AD, 16 FTD/ focal syndromes, 5 VaD, 5 normal, 3 psuedo-dementia, 4 others)	Young cognitively impaired patients with diagnostic uncertainty following standard comprehensive clinical assessment including structural imaging referred to 2 nuclear medicine centres Age (mean ± SEM): 59.1 ± 10.7 years Gender: 32% F	^{99}mTc-HMPAO SPET, rated by 2 neurologists and 3 nuclear medicine specialists, 2 x, 6 months apart, blinded but unblinded to brief clinical info	Additional to standard clinical and neuro-psychological assessment and structural brain imaging	Diagnosis by 2 neurologists reviewing all clinical, neuropsycholog-ical and neuroimaging data, blinded to SPECT	Accuracy (normal vs abnormal)	<u>SPECT Informed by brief pertinent clinical info (normal vs abnormal) – reflects practice:</u> Accuracy 32% to 58% Sn 71%, Sp 38%, PPV 87%, NPV 18% LR+ 1.14 (95%CI 0.65 – 2.01) LR- 0.77 (95%CI 0.44 – 1.36) Pre-test probability dementia 0.81, post-test probability = 0.83 Accuracy of clinical assessment NR <u>SPECT Blinded to clinical info (normal vs abnormal):</u> Accuracy 37% to 47% Sn 77%, Sp 44%, PPV 88%, NPV 27%, LR+ 1.38 (95%CI 0.75 – 2.53) LR – 0.52 (95%CI 0.28-0.95) Pre-test probability dementia 0.81, post-test probability = 0.85 Accuracy of clinical assessment NR	1. Unclear 2. Low 3. Unclear 4. Low
Change in diagnosis									
Logan-Sinclair & Davison 2007 [115] Australia	Retrospective medical audit NR	17 (NR)[4]	Selected records from rural NSW patients referred for SPECT, CT & neuropsychological assessment for dementia Of 88 SPECTs, 31% referred by GPs, 69% regional specialists; 98% referred for suspected dementia. Age: NR[4] Gender: NR[4]	SPECT (tracer details NR)	CT, neuro-psychological assessment (in 17/88)	None	Agreement	<u>Agreement in diagnosis between SPECT, CT and neuropsychological testing:</u> 35% (6/17) no consensus reached, follow-up study recommended 41% (7/17) agreement between assessments 24% (4/17) partial agreement	1. High 2. Unclear 3. N/A 4. Unclear

Abbreviations: AD = Alzheimer's disease, CI = confidence interval; CT = computed tomography; dem = dementia, F = female; FTD = frontotemporal dementia; IPD = individual patient data, LR+ = positive likelihood ratio, LR- = negative likelihood ratio, MCI = mild cognitive impairment, NR = not reported, NPV = negative predictive value; PPV = positive predictive value; SD = standard deviation; SEM = standard error of the mean; Sn = sensitivity, Sp = specificity, SPECT = single-photon emission computed tomography, VaD = vascular dementia.

1. Risk of bias Cochrane Revman 5 items: (1) patient selection, (2) conduct and interpretation of index test, (3) conduct and interpretation of reference standard, (4) flow and timing
2. The likelihood ratio represents a combination of the sensitivity and specificity and measures the probability of the test result in patients with the disease compared to those without the disease. A likelihood ratio of 1 indicates that the test does not provide any useful diagnostic information. Positive likelihood ratios > 10 and negative likelihood ratios < 0.1 can provide convincing diagnostic evidence. Positive likelihood ratios > 5 and negative likelihood ratios < 0.2 can provide strong diagnostic evidence. However, the interpretation depends on the context in which the test is used and the pretest probability [20]
3. Accuracy data reported in study not extracted as it does not provide a comparison to the accuracy of clinical assessment, however individual patient data reported enables calculation of change in diagnosis outcome.
4. Characteristics of 17 patients for whom all tests were available not reported. Of 88 patients referred to SPECT, 86 were referred for suspected dementia, 40% were diagnosed with Alzheimer's disease, 27% vascular causes, 6% mixed disease patterns. Average age was 70 years (range 21-88), 50% female.
5. Incorporation bias with the reference standard is likely to result in overestimation of true positive and underestimation of false positive results for clinical assessment.
6. Possible conversion of MCI to dementia during the period of follow-up may result in underestimation of true negative and overestimation of false positive results for both the initial clinical assessment and SPECT.

Table 56 GRADE Evidence Profile : Additional value of SPECT for the diagnostic differentiation of dementia from MCI in addition to standard comprehensive assessment

Quality Assessment							Effect	Quality	Link to patient centered outcomes
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Diagnostic accuracy – True Positives									
2	Diagnostic accuracy studies [1]	Serious limitations [2]	No serious limitations	No serious limitations[9]	Serious limitations[3]	None[10]	Doebert: 333 TP diagnoses per 1000 MCI patients, LR+ 1.0, Sn 67% [113] Doran: 575-624 TP diagnoses per 1000 memory clinic patients with diagnostic uncertainty LR+1.14-1.38, Sn 71-89% [114]	⊕OOO VERY LOW	These patients receive the uncertain benefit of early diagnosis and treatment. Any management implemented cannot reverse or modify existing dementia but may slow progression in some patients. There may be benefits for patient planning and there may be positive or negative psychological consequences.
Diagnostic accuracy – False Positives									
2	Diagnostic accuracy studies [1]	Serious limitations [2]	No serious limitations	No serious limitations[9]	Serious limitations [3]	None[10]	Doebert: 333 FP diagnoses per 1000 MCI patients, LR+ 1.0, Sp 33% [113] Doran: 118-106 FP diagnoses per 1000 memory clinic patients with diagnostic uncertainty, LR+1.14-1.38, Sp 38-44% [114]	⊕OOO VERY LOW	These patients would experience possible psychological harms and possible detriment from unnecessary testing and treatment.
Diagnostic accuracy – False Negatives									
2	Diagnostic accuracy studies [1]	Serious limitations[2]	No serious limitations	No serious limitations[9]	Serious limitations[3]	None[10]	Doebert: 167 FN diagnoses per 1000 MCI patients, LR- 1.0, Sn 67% [113] Doran: 235-186 FN diagnoses per 1000 memory clinic patients with diagnostic uncertainty, LR- 0.52 to 0.77, Sn 71-77% [114]	⊕OOO VERY LOW	These patients have a possible negative effect from delayed diagnosis.

Quality Assessment							Effect	Quality	Link to patient centered outcomes
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Diagnostic accuracy – True Negatives									
2	Diagnostic accuracy studies [1]	Serious limitations[2]	No serious limitations	No serious limitations[9]	Serious limitations [3]	None[10]	Doebert: 167 TN diagnoses per 1000 MCI patients, LR- 1.0, Sp 33% [113] Doran: 72-84 TN diagnoses per 1000 memory clinic patients with diagnostic uncertainty LR- 0.52 to 0.77, Sp 38-44% [114]	⊕OOO VERY LOW	These patients may experience benefit from reassurance, however where the alternative diagnosis is MCI this reassurance may be negligible.
Change in diagnosis[8]									
1	Retrospective medical audit	Serious limitations[4]	No serious limitations	Serious limitations[5]	Very Serious limitations[6]	None[11]	In rural referrals, 35% no consensus (follow-up study recommended), 41% agreement, 24% partial agreement with CT & neuropsychological assessment. [115]	⊕OOO VERY LOW	Impact on management and outcomes uncertain.

Abbreviations: LR+ = positive likelihood ratio, LR- = negative likelihood ratio, pts = patients, Sn = sensitivity, Sp = specificity.

1. Study quality commenced as moderate quality due to design features of this study. Studies were retrospective (or not clearly prospective) and not representative of a consecutive group of patients with a defined clinical presentation.
2. One study is retrospective, studies are based on referrals to nuclear medicine clinics, it is unclear whether or not it was a consecutive group of patients presenting with a defined clinical presentation. In one study the outcome was not predetermined and was calculated by the reviewers. The reference standard has inherent limitations and there is likely to be misclassification bias.
3. Doebert: 12 MCI patients, Doran: the 95%CIs of both the LR+ and LR- overlap 1.0
4. Patients do not represent a consecutive series of presenting patients, and the timing between tests is unknown.
5. It is unclear whether or not the change in diagnosis leads to a change in management. The medical audit does not report change in diagnosis but agreement between tests, it is unclear to what degree the clinician's final diagnosis would be influenced by the SPECT result.
6. These data are based upon 17 patients.
7. Study reported individual patient data enabling calculation of estimated change in diagnosis outcome
8. Study quality for this outcome commenced as low due to design features of the studies. The study was a medical audit in which the clinician's diagnostic decision was not reported.
9. Question is specifically addressing the outcome of "diagnostic differentiation", not impact on patient outcomes. Study applicable to memory clinic setting but not primary care.
10. The source of funding for the studies is not reported.
11. No funding was provided for this study

Table 57 GRADE Evidence Profile: Predictive accuracy of SPECT for the differentiation of progressive from non-progressive MCI

Quality Assessment							Effect [6]	Quality[1]	Link to patient centered outcomes
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Diagnostic accuracy – True Positives (TPs)									
1	Systematic review (5 accuracy studies) [1]	No serious limitations[2]	No serious limitations	Serious limitations [4]	No serious limitations	None[5]	TPs over 3 years per 1000 MCI patients: [112] Low risk[6]: 148 High risk[6]: 491 Sn 78% (95%CI 72-85), LR+ 2.2 (95%CI 1.2 to 3.1)	⊕⊕OO LOW	These patients would be correctly identified as those that will develop dementia in the future. The balance of patient benefits and harms is uncertain.
Diagnostic accuracy – False Positives (FPs)									
1	Systematic review (6 accuracy studies)[1]	Serious limitations [3]	No serious limitations	Serious limitations [4]	No serious limitations	None[5]	FPs over 3 years per 1000 MCI patients: ADDIN EN.CITE [**Error! Bookmark not defined.** Low risk[6]: 292 High risk[6]: 133 Sp 64% (95%CI 55-72), LR- 0.28 (0.25 to 0.32)	⊕OOO VERY LOW	These patients would experience likely psychological harms from receiving an incorrect diagnosis of MCI that will progress to dementia.
Diagnostic accuracy – False Negatives (FNs)									
1	Systematic review (5 accuracy studies)[1]	No serious limitations[2]	No serious limitations	Serious limitations [4]	No serious limitations	None[5]	FNs over 3 years per 1000 MCI patients: [112] Low risk[6]: 42 High risk[6]: 139 Sn 78% (95%CI 72-85), LR- 0.28 (0.25 to 0.32)	⊕⊕OO LOW	These patients would be incorrectly identified as those that will not progress to dementia. The balance of patient benefits and harms is uncertain.
Diagnostic accuracy – True Negatives (TNs)									
1	Systematic review (6 accuracy studies)[1]	Serious limitations [3]	No serious limitations	Serious limitations [4]	No serious limitations	None[5]	TNs over 3 years per 1000 MCI patients: [112] Low risk[6]: 518 High risk[6]: 237 Sp 64% (95%CI 55-72), LR+ 2.2 (95%CI 1.2 to 3.1)	⊕OOO VERY LOW	These patients would be correctly identified as those that would not progress to dementia. They would have psychological benefits of reassurance.

Abbreviations: CI = confidence interval; LR+ = positive likelihood ratio, LR- = negative likelihood ratio, MCI = mild cognitive impairment, pts = patients, Sn = sensitivity, Sp = specificity.

1. Study quality commenced as moderate as one study was retrospective and in another it is unclear whether the study was prospective or not.
2. Whilst the reference standard of follow-up with clinical assessment is imperfect and may misclassify some patients, the limitations are less for patients that are considered to progress to dementia. The majority of patients (77%) are from studies without serious other concerns. The sensitivity estimate includes one study of 200 patients with no serious concerns other than the reference standard, however this study does not provide an estimate of specificity.
3. 39% of patients enrolled in studies in which it is unclear whether a consecutive series of patients was enrolled. 14% of patients enrolled in a study in which the threshold was not prespecified and the reference standard included follow-up of only 1 year.
4. Accuracy is a surrogate for patient centered outcomes, the impact on patient centered outcomes is uncertain.
5. The possibility of publication bias cannot be ruled out, however all studies were supported by non-industry funding.
6. Low risk estimates from MCI cohort with general population recruitment, 19% progression over 3 years [118]. High risk estimate from MCI memory clinic cohort, 63% progression over 3 years [119].

SRQ 8: Information and support for the person with dementia

Clinical question

The research question as defined in the protocol and the associated PICO criteria are listed below in Table 58.

Table 58 PICO for SRQ8: Information and support

Clinical question: For people with dementia, what type of information and support is beneficial?			
Population	**Intervention**	**Comparator**	**Outcome**
People with all forms of dementia	Educational intervention Social support group	"standard care"	Quality of life (person with dementia) Self esteem Depression Patient satisfaction with care Level of distress Knowledge regarding the condition

Literature review search strategies:

Searches for existing HTAs and Systematic reviews

Searches to identify existing Health Technology Assessment reports (HTAs) and systematic reviews were conducted in the databases specified in Table 59, using the search terms listed in the Guideline Technical Report Volume 2.

Table 59 Searches for existing HTAs and systematic reviews SRQ8: Information and support

Database	Date searched	Date search re-run	Period covered	Citations retrieved
HTA	2 May 2014	7 August 2014	2005 to 2014	169
Cochrane (Cochrane reviews, Cochrane protocols, DARE)	2 May 2014	7 August 2014	2005 to 2014	50
MEDLINE	2 May 2014	7 August 2014	2005 to 2014	86
PsycInfo	2 May 2014	7 August 2014	2005 to 2014	72
EMBASE	2 May 2014	7 August 2014	2005 to 2014	30
PubMed	2 May 2014	7 August 2014	2005 to 2014	73

Educational interventions

A systematic review [120] conducted by Corbett and colleagues searched for randomised controlled trials which focussed predominantly on the provision of information and/or advice for the person with dementia. However, the authors of the review were unable to identify any studies that met their criteria and thus provided a summary of studies in which information provision for the person with dementia was one component of the intervention (see Table 62).

Support groups

The most recent, comprehensive and highest quality systematic review identified was conducted by Leung and colleagues [121]. This review was considered to be sufficiently up-to-date and no searches were conducted to identify additional primary studies published since this time (see Table 62).

Searches for additional primary studies

Educational interventions

As the review by Corbett and colleagues involved a search only for RCTs (and failed to identify any) searches were conducted in the databases listed in Table 60 to identify any primary studies evaluating educational interventions evaluated in controlled trials or cohort studies since the NICE Guideline (2006).

Table 60 Searches for primary studies SRQ8: Information and support

Database	Dates searched	Period covered	Citations retrieved
MEDLINE	6 June 2014	2005 to 2014	524
PsycInfo	6 June 2014	2005 to 2014	327
EMBASE	6 June 2014	2005 to 2014	60
PubMed	6 June 2014	2005 to 2014	1

Criteria for selecting studies for review:

Table 61 Inclusion and exclusion criteria SRQ8: Information and support

Characteristic	Criteria
Study design	Inclusion: Social support groups: Randomised controlled trials. Educational interventions: Randomised controlled trials, controlled trials, cohort studies
Population	Inclusion: People with a diagnosis of dementia
Intervention	Inclusion: A program designed to provide more comprehensive information and/or education for the person with dementia than is usually provided or an intervention including one type of information/ education compared to another type of information/education (considering all forms, eg written, video, verbal, online provided by any health professional). Social support group
Comparator	Inclusion: 'standard care'
Outcomes	Inclusion: Quality of life, self esteem, depression, patient satisfaction with care, level of distress, knowledge regarding the condition
Publication type	English language

Search results

The most recent, comprehensive and highest quality systematic reviews identified and included in the current update were conducted by Corbett and colleagues [120] for educational interventions. No additional controlled trials or cohort studies were identified in the search for primary studies.

Evidence summary

Educational interventions

No studies meeting the eligibility criteria were identified. Consideration should be given to studies of interventions which were multicomponent and involved education for carer(s), families and the person with dementia (see section on interventions for carers). When considered as a body of evidence, these studies have been shown to reduce behavioural and psychological symptoms, improve quality of life for both the person with dementia and their family carer, reduce institutionalisation and reduce carer impact.

Qualitative studies provide some relevant background information. Two systematic reviews of qualitative studies have synthesised the views of people living with dementia and their perceptions of their experiences with the health care system [39 122]. Prorok and colleagues [39] found that the need for additional information was a recurrent theme for people with dementia and they reported that they had to "push" to obtain information. People with dementia reported feeling appreciative when information was provided in a "clear fashion" and receiving written information that was written in layman's language. However, being provided with too much information was described as overwhelming. Topics frequently identified as important were: cognitive testing, medications, disease progression, financial matters and behaviour change and management. Bunn (2012) found that information needs of the person with dementia changed over time and that education and information provision needed to be ongoing and flexible in timing and format [123].

A qualitative study conducted by Edelman et al [124] investigated the information needs of people with dementia living in rural areas in the United States. Interviews with 100 people with mild to moderate Alzheimer's disease found that the topics of most interest (in order) were: (1) stages and symptoms of Alzheimer's disease, (2) approved drug treatments for memory loss, (3) experimental drugs for memory loss, (4) meaningful activities, (5) participation in research studies for memory loss, (6) improving communication, (7) support groups for people with memory loss and (8) coping with frustration.

Abley et al [125] interviewed 27 people with cognitive impairment to determine their views on high quality communication and information provision in a memory clinic setting in the UK. People reported that they wanted tailored information to be staggered over time. Respondents valued face to face information supplemented with written information. Most people wanted more information, particularly those with less common forms of dementia. Practical advice (such as finances and Power of Attorney) was preferred once the person had time to come to terms with the diagnosis. Memory retraining groups were valued; the information was considered beneficial as was the opportunity to meet other people 'in the same boat'.

Qualitative research conducted with CALD communities in Australia (Arabic, Chinese, Italian and Spanish-speaking) sought to determine where information regarding dementia was obtained, access issues and how access could be improved. It was acknowledged that CALD resources were scarce and that dementia-related information was hard to find but that people received information about dementia from a wide range of sources. These included: mass media, Alzheimer's Australia, the Internet, ethno-specific services, hospitals, general practitioners, social networks and community-based education sessions. There were several factors impacting on information provision. The medical concept of dementia is not necessarily recognised by all cultures and some cultures do not have a comparable term. The symptoms of dementia may be interpreted as a normal part of ageing. Furthermore, support services may be viewed as charities and not accepted by some families. The authors recommended that information sessions for CALD communities regarding dementia needed to occur regularly and locally and that services needed be widely promoted. It was recommended

that information regarding dementia should be provided in-person by someone credible (preferably a doctor). Information needed to be tailored to the situation of the person with dementia and their families and carers. Other recommendations included: the need for more information in CALD languages; information beyond the basics of dementia and greater education of the general public [126].

Support groups

A systematic review by Leung and colleagues examined the effect of social support group interventions for people with dementia and mild cognitive impairment [121] (see Table 62). The review identified two randomised controlled trials; one of the studies (n=43) evaluated a 20 week multifaceted program involving exercise, cognitive behavioural therapy and social support groups[127]. The other study (n=142) evaluated a 9 week structured social support group incorporating educational seminars, supportive discussion and strategies for enhancing communication[128]. Both studies were at risk of bias due to unclear reporting of methodology. Both studies measured levels of depression at follow-up; one of the studies found a positive effect, with lower levels of depression in the intervention group (effect size d=0.36; p<0.01) whereas the other study found no effect. One of the studies examined quality of life in the person with dementia; the study found that participants in the intervention group had significantly higher scores on a quality of life measurement tool than those in the control group (effect size d=0.44; p<0.001).Finally, the study involving multi-component intervention (exercise plus CBT plus social support groups) measured self-esteem and found that people in the intervention group reported higher scores (p<0.01). The authors of the systematic review concluded that support groups may be of benefit in reducing depression and improving quality of life and self-esteem however, only two studies were identified and both had methodological limitations.

Evidence statements	*GRADE Quality*	*Rec*
No RCTs or cohort studies were identified that evaluated the effects of an education program alone for people with dementia (Table 63).	NA	CBR 51
A systematic review [121] identified one RCT that found participation in a social support program led to increased quality of life (low). One of two RCTs included in the systematic review found that participation in a social support group led to reduced levels of depression (very low).[121](Table 64)	Very low-low	EBR 52

Table 62 Evidence summary of included systematic reviews for SRQ8: Information and support for the person with dementia

Reference	Study Design/Level of Evidence	Types of studies included	Types of participants included	Intervention	Comparison	Results	Quality appraisal[1]
Corbett 2012 [120]	Systematic Review	RCTs	People with dementia or their families and carers	Intervention with information provision as a key service component	No restrictions based on comparison intervention	Thirteen RCTs were included in the review. All of the studies involved the person with dementia/carer dyad or the primary family carer only. Most interventions included other elements included other elements such as skills training, telephone support and help to navigate the health and aged care system. Positive effects were found for quality of life in two of three studies measuring this outcome. There were also significant reductions in behavioural and psychological symptoms but no effect on carer burden.	1. CA 2. Y 3. Y 4. N 5.Y 6. Y 7. Y 8. Y 9. Y 10. N 11. N
Leung 2015 [121]	Systematic Review	RCTs	Older adults diagnosed with dementia or MCI living in any setting	A treatment program that provided any of the following: (i) education about dementia or MCI; (ii) mutual/peer support; (iii) education/mutual support; and (iv) opportunities to express feelings and concerns. Multicomponent programs were eligible	Alternative treatment or no treatment	The review identified two randomised controlled trials. Burgener et al 2008 (n=43) evaluated a 20 week multifaceted program involving exercise, cognitive behavioural therapy and social support groups.[127] Logsdon et al 2010 (n=142) evaluated a 9 week structured social support group incorporating educational seminars, supportive discussion and strategies for enhancing communication. Both studies were at risk of bias due to unclear reporting of methodology.[128] Both studies measured levels of depression at follow-up; Logsdon et al found a positive effect, with lower levels of depression in the intervention group (effect size d=0.36; p<0.01) whereas Burgener et al found no effect. Logsdon et al examined quality of life in the person with dementia; the study found that	1. CA 2. Y 3. Y 4. Y 5.Y 6. Y 7. Y 8. Y 9. Y 10. N 11. N

						participants in the intervention group had significantly higher scores on the QoL-AD tool than those in the control group (effect size d=0.44; p<0.001).Finally, Burgener et al found that people in the intervention group reported higher scores (p<0.01).[127] The authors of the review concluded that support groups may be of benefit in reducing depression and improving quality of life and self-esteem however, only two studies were identified and both had methodological limitations.	

CA=Can't answer; NA=Not applicable, MCI=mild cognitive impairment; QoL-AD=Quality of life in Alzheimer's disease; RCT=Randomised controlled trial

Appraisal criteria: (1) 'a priori' design provided, (2) Duplicate study selection and data extraction, (3) Comprehensive literature search, (4) Grey literature search, (5) List of included and excluded studies provided, (6) Characteristics of included studies provided, (7) Scientific quality of the included studies assessed and documented, (8) Scientific quality of included studies used to formulate conclusions, (9) Methods to combine findings appropriate, (10) Publication bias assessed, (11) Conflict of interest included for review and each of the included studies.

Table 63 GRADE Evidence Profile: Educational interventions for the person with dementia

Quality assessment							Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Patient satisfaction with care								
0	No evidence available							
Level of distress								
0	No evidence available							
Knowledge regarding the condition								
0	No evidence available							

Table 64 GRADE Evidence Profile : Social support group interventions for the person with dementia

Quality assessment							Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Quality of life								
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	None	1 RCT found a positive effect in favour of intervention (effect size d=0.44; p<0.001) [128]	⊕⊕OO LOW
Depression								
2	randomised trials	serious[1]	serious[3]	no serious indirectness	serious[2]	None	1 [128] of 2 RCTs found a positive effect (effect size d=0.36; p<0.01) [127 128].	⊕OOO VERY LOW
Self esteem								
1	randomised trials	serious[1]	no serious inconsistency	serious[4]	serious[2]	None	1 RCT reported increased levels in the intervention group post treatment [127]	⊕OOO VERY LOW

[1] Methodology unclear in several instances due to poor reporting
[2] Total sample size <400
[3] Mixed findings amongst studies
[4] Intervention was multifaceted and therefore benefits may not be related to support groups

SRQ 9: Models of care

Clinical question

The research question as defined in the protocol and the associated PICO criteria are listed below in Table 65.

Table 65 PICO for SRQ9: Models of care

Clinical question: For people with dementia, what is the best way of organising services in terms of integration of care, consumer directed care, multidisciplinary assessment and case management?			
Population	**Intervention**	**Comparator**	**Outcome**
People with a diagnosis of dementia	integrated care, consumer directed care, multidisciplinary care, case management	The specified models of care compared with other models of care or usual care	Quality of life (person with dementia) ADL function Institutionalisation Behavioural and psychological symptoms Satisfaction with care

Note that literature relating to case management was identified in clinical question 17 (Support for carers, see page 316) and is not repeated here. One database search included search terms for all models of care (integrated care, consumer directed care and multidisciplinary care) and search results categorised into the individual models.

Literature review search strategies:

Searches for existing HTAs and Systematic reviews

Searches to identify existing Health Technology Assessment reports (HTAs) and systematic reviews were conducted in the databases specified in Table 66, using the search terms listed in the Guideline Technical Report Volume 2.

Table 66 Searches for existing HTAs and systematic reviews for SRQ9: Models of care

Database	Date searched	Period covered	Citations retrieved
HTA	26 June 2014	2005 to 2014	0
Cochrane (Cochrane reviews, Cochrane protocols, DARE)	26 June 2014	2005 to 2014	4
MEDLINE	26 June 2014	2005 to 2014	35
PsycInfo	26 June 2014	2005 to 2014	15
EMBASE	26 June 2014	2005 to 2014	14
PubMed	26 June 2014	2005 to 2014	22

The most recent, comprehensive and highest quality systematic review identified was conducted by Low and colleagues for integrated care and consumer directed care (searched until 2009) and Wolfs and colleagues for multidisciplinary care [129 130].

Searches for primary studies

Searches were conducted in the databases listed in Table 67 to identify primary studies published since the search period of the included reviews. The search terms used are listed in the Guideline Technical Report Volume 2.

Table 67 Searches for primary studies for SRQ9: Models of care

Database	Dates searched	Period covered	Citations retrieved
MEDLINE	26 June 2014	2005 to June 2014	97
PsycInfo	26 June 2014	2005 to June 2014	35
EMBASE	26 June 2014	2005 to June 2014	17
PubMed	26 June 2014	2005 to June 2014	19

Criteria for selecting studies for review:

Table 68 Inclusion and exclusion criteria for SRQ9: Models of care

Characteristic	Criteria
Study design	Inclusion: Randomised controlled trials Exclusion: Other study designs
Population	Inclusion: People with a diagnosis of dementia
Intervention	Inclusion: Integrated care: Bringing together of services across sectors or teams or the organisation of services to bring all services together at one time [131]. Consumer directed care: Interventions where consumers were explicitly given choice and/or control of services. Multidisciplinary assessment: Assessment of the person with suspected dementia or dementia by a team comprising two or more different types of health professional. Case management: Care which may involve one or more of the following elements: entry screening, assessment, planning, coordination, monitoring, review and exit/case closure planning[132].
Comparator	Inclusion: The specified models of care compared with other models of care or usual care
Outcomes	Inclusion: Quality of life (person with dementia), ADL function, Institutionalisation, BPSD, satisfaction with care
Publication type	English language

Search results:

Existing HTAs and systematic reviews

The most recent, comprehensive and highest quality systematic reviews/HTAs identified and included in the current update are shown in Table 69.

Table 69 Systematic reviews and HTA report included in the review for SRQ9: Models of care

Intervention	Included systematic reviews/HTAs
Integrated Care	Low et al 2011 [129]
Consumer directed care	Low et al 2011 [129]
Multidisciplinary care	Wolfs et al [130]

Primary studies

A total of 168 citations were retrieved in the electronic database searches. 31 studies were viewed in full text and 4 were included evidence update.

Evidence summary:

Integrated care:

The systematic review by Low and colleagues [129] did not identify any trials evaluating integrated care for people with dementia. A cluster randomised, controlled trial conducted since the Low et al systematic review was identified (Table 67). This trial by Bass and colleagues [133] involved Veterans in the United States (n=333) and evaluated the 'Partners in Dementia Care' intervention. Care in the intervention group was integrated across the local Veterans Health medical centre and the partnering Alzheimer's Association chapter. The services worked together using a shared electronic patient information system and regular case conferences. Reported benefits for the intervention group included significantly reduced relationship strain, reduced unmet need and reduced depression.

Consumer directed care:

The systematic review conducted by Low and colleagues [129] (Table 70) identified one non-randomised controlled trial that compared a form of consumer-directed care with usual care in 121 people with cognitive impairment (MMSE score <24/30) in Italy [134]. The method of allocation to intervention or control group was unclear. Baseline characteristics were similar although carers of participants in the control group reported lower levels of stress at baseline. The intervention group received vouchers to purchase care from health providers. Study participants were able to purchase a generous amount of additional care (4 to 24 hours of care per day) whereas the control group received usual care; thus, there was a discrepancy in the amount of care provided as opposed to differences in type of care (ie consumer directed versus agency directed). The study found that all outcomes were similar at 6 and 12 months. At 24 months there were lower rates of mortality in the intervention group; however, the control group had lower levels of disability and depression. The low methodological quality of the trial and study comparison (vouchers for care versus usual care which resulted in differences in the amount of care received) mean that the study is not helpful in considering a consumer-directed care model in Australia. We identified no randomised, controlled trials evaluating consumer directed care specifically for people with dementia published subsequent to the Low et al systematic review.

Multidisciplinary assessment:

The systematic review conducted by Wolfs and colleagues identified five studies which assessed the value of multidisciplinary teams in comparison to monodisciplinary approaches for people with dementia. [130] (Table 70) The studies were unable to be pooled and the authors concluded that the added value of multidisciplinary assessment for people with dementia was unclear. However, the

authors felt that multidisciplinary teams may be better able to identify issues such as depression and differentiate dementia subtypes, but the basis for this is unclear.

Three randomised, controlled trials published subsequently (Table 71) evaluated different approaches to multidisciplinary assessment for people with dementia. These studies found mixed results, thus results were not pooled. A study conducted in the United States by Bellantonio [135] found that there were no significant benefits associated with multidisciplinary assessment for older people with dementia moving into assisted living. The assessment team comprised a geriatrician or practice nurse, physiotherapist, dietitian and social worker. Although not statistically significant, people in the intervention group had reduced risk of hospitalisation or permanent relocation to a nursing facility. A large trial conducted by Stenvall and colleagues in Sweden [136 137] reported on the outcomes of multidisciplinary assessment for people with dementia after hip fracture. It should be noted that in addition to multidisciplinary assessment the people in the intervention group also received care on a specialised ward, systematic care and early mobilisation. The intervention group had fewer complications such as falls, delirium and urinary tract infections and shorter stay on the ward (mean 20 vs 32 days). There were no differences in mortality between groups however, at one year, people in the intervention group were more independent. Finally, Wolfs and colleagues [138 139] compared outcomes for people with dementia attending a multidisciplinary clinic with usual care. There was no statistically significant difference detected in quality of life, independence in performing daily activities, cognition or behavioural or psychological symptoms, although there was a trend towards improved quality of life in the intervention group.

Evidence statements	*GRADE Quality*	*Related recommendation*
One RCT evaluating the efficacy of an integrated care model found reduced levels of depression in a subgroup of participants with higher levels of cognitive impairment.[133] (Table 72)	Very low	EBR 54
A systematic review [129] identified one non-randomised controlled trial evaluating a form of consumer directed care that found no significant differences between groups on quality of life for the person with dementia, ADL function or BPSD.[41] (Table 73)	Very low	NA
Single RCTs evaluating the effects of multidisciplinary assessment found no difference between groups on ADL function (low), institutionalisation (low) or quality of life (low). [135-137] (Table 74)	Low	NA
A systematic review identified one RCT evaluating the effects of case management that showed significantly improved quality of life in the person with dementia (very low)[140] whereas an additional RCT found no effect on quality of life [141] One (of two) RCTs included in a systematic review reported a significant reduction in carer impact (very low).[140] One RCT found no significant difference between groups on institutionalisation (low).[140] (Table 176)	Low	EBR 55

Table 70 Evidence summary of systematic reviews for SRQ9: Models of care

Reference	Study Design/Level of Evidence	Types of studies included	Types of participants included	Intervention	Comparison	Results	Quality appraisal[1]
Low 2011 [129]	Systematic Review	Evaluation studies using quantitative outcomes	Community dwelling older people (majority aged 65 years and over)	Integrated care Consumer directed care Case management	Not specified	Integrated care: The authors did not identify any studies in which only people with dementia were included. Consumer directed care: There were no randomised controlled trials which examined the outcomes of consumer directed care for people with dementia. The authors identified one non-randomised controlled trial conducted with older people with a MMSE <24/30 (n=121) in Italy.[134] This study compared outcomes for a group which received vouchers to buy 4 to 24 hours per day of home care attendance from health providers versus a control group which received 'usual assistance' from health and aged care services. The study found that there was reduced mortality in the intervention group at 6 and 24 months (7 deaths compared with 20 deaths). At 24 months there were no differences in other outcomes. The review identified three randomised controlled trials that evaluated case management for people with dementia. Vickrey (2006) found that people in the intervention group had higher rates of health related quality of life [142]. There were no differences in caregiver quality of life outcomes. It should be noted that the intervention provided by Vickrey Eloniemi-Sulkava (2001) found that the rate of institutionalisation was lower in the first 6 months but benefits were not apparent at later assessment [143]. Miller (1999) found that after 3 years there were no differences in nursing home entry rates or family carer burden[144].	1. N 2. Y 3. N 4. N 5. N 6. Y 7. Y 8. Y 9. Y 10. N 11. N

Reference	Study Design/Level of Evidence	Types of studies included	Types of participants included	Intervention	Comparison	Results	Quality appraisal[1]
Wolfs 2006 [130]	Systematic Review	Controlled studies	Older people suspected of having dementia	Multidisciplinary assessment, diagnosis or evaluation	Not specified	The review identified five studies which reported on the value of the multidisciplinary team compared to monodisciplinary approaches. Health outcomes for patients were not reported. The review demonstrated substantial agreement on the diagnosis of dementia but not the diagnosis of subtypes. The added value of the multidisciplinary team in terms of diagnostic accuracy was not determined.	1. N 2. Y 3. N 4. N 5. N 6. Y 7. N 8. Y 9. Y 10. N 11. N

Abbreviations: Y=yes; N=no; CA=can't answer MMSE: Mini Mental State Examination

1. *Appraisal criteria: (1) 'A priori' design provided, (2) duplicate study selection and data extraction, (3) comprehensive literature search, (4) grey literature search, (5) list of included and excluded studies provided, (6) characteristics of included studies provided, (7) scientific quality of the included studies assessed and documented, (8) scientific quality of included studies used to formulate conclusions, (9) methods to combine findings appropriate, (10) publication bias assessed, (11) conflict of interest included for review and each of the included studies.*

Table 71 Evidence summary of randomised controlled trials for SRQ9: Models of care

Reference Country	Type	N(n)	Participants	Intervention Integrated care Multidisciplinary care Consumer directed care	Comparison	Main Outcomes	Measure/s	Length of follow up	Results/ Effect size	Comments Risk of bias[1]
Integrated care										
Bass 2014 [133] United States	RCT (cluster)	333	People with dementia Mean age 79 Gender 98% male	"Partners in Dementia Care" Care coordinators worked in the local Veterans Affairs medical center (health care) and the partnering Alzheimer's Association chapter (community service organisation). The care coordinators worked as a team with one shared electronic system and regular case conference meetings. The three main components of the intervention are: initial assessment, action plan and ongoing monitoring and reassessment	Usual care	Unmet need; embarrassment about memory problems; isolation; relationship strain; depression	Study specific questionnaire to measure unmet need; published questionnaires regarding embarrassment about memory problems and isolation; adapted caregiver strain questionnaire; Center for Epidemiologic Studies Depression Scale;	Months 6 and 12	The intervention group had significantly reduced relationship strain (P=0.05), depression (P=0.03), and unmet need (P=0.02) in comparison to the usual care group. Intervention recipients also had less embarrassment about memory (P=0.02).	1. Unclear 2. Unclear 3. N 4. Unclear 5. N 6. Unclear

Reference Country	Type	N(n)	Participants	Intervention Integrated care Multidisciplinary care Consumer directed care	Comparison	Main Outcomes	Measure/s	Length of follow up	Results/ Effect size	Comments Risk of bias[1]
Multidisciplinary assessment										
Bellantonio 2008 [135] United States	RCT	100	People with dementia Mean age 82 Gender 63% female	The intervention group received four systematic, multidisciplinary assessments conducted by a geriatrician or geriatrics practice nurse, a physical therapist, a dietitian, and a medical social worker during the first 9 months of their residence in assisted living.	Usual care	Institutionalisation	Institutionalisation; service utilisation; mortality; MMSE; Katz ADL Index; Behave-AD rating scale	Days 7, 30, 120 and 320 after being admitted to assisted living	55 residents experienced unanticipated transition; falls were the primary reason for transition. The intervention reduced the risk of unanticipated transitions (reduced by 13%), permanent relocation to a nursing facility (11%), ED visits (12%), hospitalisation (45%) and death (63%) but these results were not statistically significant.	1. Unclear 2. Y 3. N 4. Unclear 5. Y 6. Y

Reference Country	Type	N(n)	Participants	Intervention Integrated care Multidisciplinary care Consumer directed care	Comparison	Main Outcomes	Measure/s	Length of follow up	Results/ Effect size	Comments Risk of bias[1]
Stenvall 2007 and 2012 [136 137] Sweden	RCT	64[(2)]	People with dementia Mean age 81 in intervention group and 83 in control group	Specialised ward involving comprehensive geriatric assessment and rehabilitation**.** Prevention, detection and treatment of postoperative complications such as delirium, falls, pain, decubital ulcers and malnutrition were actively and systematically implemented. Early mobilisation with daily training was provided by physiotherapists, occupational therapists and care staff during the hospital stay. In addition, a multidisciplinary team assessed the patients 4 months post-op.	Usual care (treatment on an orthopaedic ward)	Post-operative complicat-ions and functional recovery	Walking ability (from the Clinical Outcome Variables); Staircase of ADL including the Katz ADL index; MMSE; Organic Brain Syndrome Scale; Geriatric Depression Scale	On discharg e and at 4 months and 12 months post-operativ ely	People with dementia randomised to the intervention group had significantly fewer issues such as urinary tract infections, nutritional problems, falls and post-operative delirium. At four months, a higher proportion of people in the intervention group were able to walk independently compared to those in the control group (p=0.005). There were no significant differences between groups in levels of independence however, at one year, there was an effect in favour of the intervention group. There were no differences in mortality between groups. Length of stay averaged 20 days in the intervention group and 32 days in the control group.	1. Unclear 2. Yes 3. No 4. No 5. Unclear 6. Y

Reference Country	Type	N(n)	Participants	Intervention Integrated care Multidisciplinary care Consumer directed care	Comparison	Main Outcomes	Measure/s	Length of follow up	Results/ Effect size	Comments Risk of bias[1]
Wolfs 2008 and 2009 [138 139] The Netherlands	RCT	230	People with dementia Mean age 77 Gender 60% female control group; 66% female intervention group	Diagnostic Observation Centre for Psychogeriatric Patient. Combines the hospital based approach of a memory clinic with the care oriented approach of a regional community mental health team and aims to provide GPs with detailed diagnostic and therapeutic advice for patients with cognitive disorders. The Centre has expertise in old age psychiatry, geriatric medicine, neuropsychology, physiotherapy, occupational therapy, geriatric nursing, mental health nursing.	Usual care (GP, regional memory clinic or mental health community service)	Quality of life of the person with dementia and their family carer	EQ5D; SF36; MMSE; Global Deterioration Scale; Neuropsychiatric Inventory; Instrumental Activities of Daily Living scale; Cornell Scale for depression in dementia.	Months 6 and 12 after baseline assess	The mean score on the social functioning component of SF-36 significantly higher in intervention group than usual care group at 6 months. No other difference in mean scores between the groups. Patients in intervention group had mean 1.5 point increase in QOL at 6 months whereas patients in the control group reported a mean 4 point decline. Compared with patients receiving usual care, patients who visited the diagnostic facility gained a mean 0.05 QALY at the extra cost of euro65. The incremental cost per QALY amounted to euro1267.	1. Y 2. N 3. N 4. N 5. Y 6. Y

Abbreviations: RCT: Randomised controlled trial; MMSE: Mini Mental State Examination; ADL: activities of daily living; ED: emergency department; QOL: quality of life; QALY: quality adjusted life year

1. Risk of bias: (1) Random sequence generation, (2) Allocation concealment, (3) Blinding of participants and personnel, (4) Blinding of outcome assessment, (5) Incomplete outcome data, (6) Selective reporting
2. Note that this study presents subgroup analysis of a larger trial and looks only at the people in the trial with dementia

Table 72 GRADE Evidence Profile: Integrated care for people with dementia

Quality assessment							Effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**		
Quality of life (person with dementia)								
0	No evidence available					none		
ADL function								
0	No evidence available					none		
Institutionalisation								
0	No evidence available					none		
Behavioural and psychological problems								
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	1 RCT showed reduced depression within the intervention group in people with higher levels of cognitive impairment [133]	⊕OOO VERY LOW
Satisfaction with care								
0	No evidence available					none		

[1] Aspects of methodology unclear due to poor reporting
[2] Population unlikely to be representative of people with dementia (all Veterans and majority were male)
[3] Total sample size <400

Table 73 GRADE Evidence Profile: Consumer directed care for people with dementia

Quality assessment							Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Quality of life (person with dementia)								
1	observational studies	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	Non randomised trial identified within a systematic review [129]showed no significant differences in outcome [134]	⊕OOO VERY LOW
ADL function								
1	observational studies	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	Non randomised trial identified within a systematic review [129] showed no significant differences in outcome [134]	⊕OOO VERY LOW
Institutionalisation								
0	No evidence available					none		
Behavioural and psychological symptoms								
1	observational studies	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	Non randomised trial identified within a systematic review [129]showed no significant differences in outcome [134]	⊕OOO VERY LOW
Satisfaction with care								
0	No evidence available					none		

[1] Non-randomised trial
[2] Study took place in Italy. Intervention involved provision of vouchers to buy care.
[3] Sample size <400

Table 74 GRADE Evidence Profile: Multidisciplinary assessment for people with dementia

Quality assessment							Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Quality of life (person with dementia)								
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	1 RCT found no significant difference in outcome between groups but trend towards higher increased quality of life in the intervention group [135]	⊕⊕OO LOW
ADL function								
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	1 RCT (Stenvall) found no significant differences between groups [136]	⊕⊕OO LOW
Institutionalisation								
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	1 RCT found no significant differences between groups although there was a trend towards reduced risk of institutionalisation in the intervention group [135]	⊕⊕OO LOW
Behavioural and psychological symptoms								
0	No evidence available					None		
Satisfaction with care								
0	No evidence available					none		

[1] Poor reporting - methodology unclear for several domains
[2] Total sample size <400

SRQ10: Staff training

Clinical question

The research question as defined in the protocol and the associated PICO criteria are listed below.

Table 75 PICO for SRQ10: Staff training

Clinical question: What models of training for health and social care staff have positive outcomes for people with dementia?			
Population	**Intervention**	**Comparator**	**Outcome**
Health and aged care staff	Training	No training or 'standard training'	BPSD QOL (person with dementia) ADL function Restraint use Cognition

Literature review search strategies:

Searches for existing HTAs and Systematic reviews

Searches to identify existing Health Technology Assessment reports (HTAs) and systematic reviews were conducted in the databases specified in Table 76, using the search terms listed in the Guideline Technical Report Volume 2.

Table 76 Searches for existing HTAs and systematic review SRQ10: Staff training

Database	Date searched	Period covered	Citations retrieved
HTA	17 July 2014	2005 to 2014	3
Cochrane (Cochrane reviews, Cochrane protocols, DARE)	17 July 2014	2005 to 2014	23
MEDLINE	17 July 2014	2005 to 2014	168
PsycInfo	17 July 2014	2005 to 2014	59
EMBASE	17 July 2014	2005 to 2014	33
PubMed	17 July 2014	2005 to 2014	48

The most recent, comprehensive and highest quality systematic review/HTA identified was Olazaran [140] which included a search to September 2008 (Table 79).

Searches for additional primary studies

Searches were conducted in the databases listed in Table 77 to identify additional primary studies published since the search period of the included review. The search terms used are listed in the Guideline Technical Report Volume 2.

Table 77 Searches for primary studies SRQ10: Staff training

Database	Dates searched	Period covered	Citations retrieved
MEDLINE	22 July 2014	2008 to 2014	410
PsycInfo	22 July 2014	2008 to 2014	128
EMBASE	22 July 2014	2008 to 2014	86
PubMed	22 July 2014	2008 to 2014	0

Criteria for selecting studies for review:

Table 78 Inclusion and exclusion criteria for SRQ10: Staff training

Characteristic	Criteria
Study design	Inclusion: Randomised controlled trials Exclusion: Studies of other design
Population	Inclusion: Health or aged care staff in hospital, community or residential settings
Comparator	Inclusion: No training or 'standard training' (eg existing inservice program)
Outcomes	Inclusion: Patient outcomes: BPSD, QOL (person with dementia), ADL function, restraint use, cognition Exclusion: Staff outcomes
Publication type	English language

Search results:

Primary studies

A total of 624 citations were retrieved in the electronic database searches. 35 studies were viewed in full text and 15 were included evidence update (Table 80).

Evidence summary:

The systematic review conducted by Olazaran and colleagues [140] searched for all non-pharmacological interventions designed to improve outcomes for people with dementia. One of the categories of interventions they described was 'professional caregiver' interventions. The authors searched for randomised controlled trials published prior to September 2008. They identified ten RCTs [145-154]; data from these trials are presented in the GRADE evidence profiles. Olazaran and colleagues reported that professional caregiver training was found to reduce behavioural and psychological symptoms of dementia in four studies (effect size 0.223, 95%CI 0.017 to 0.428) and reduce restraint use in two studies (effect size not reported).

The 15 RCTs that were published after 2008 (subsequent to the review by Olazaran (Table 80))[155-169] varied in terms of the interventions, participants and outcomes measured. In order to identify areas where staff training is likely to be most beneficial, training interventions were categorised into the following four categories: broad training; training to enhance communication and interactions between the professional caregiver and the person with dementia; training in the management of behavioural and psychological symptoms of dementia; and, other training models.

Intervention approaches

Training that was broad in nature was associated with reduced restraint use. There was mixed evidence that training staff in communicating more effectively with the person with dementia resulted in reduced behavioural and psychological symptoms, improved quality of life and reduced restraint use with some studies indicating positive effects and others finding no effect. Training staff to manage behavioural and psychological symptoms of dementia was associated with a reduction of symptoms in 4 studies and reduced restraint use in 3 studies.

Setting

The majority of studies were conducted in residential care facilities. Training was most often provided for the care staff working within the facility. The results of the studies suggest that staff training can result in reduced restraint use in residential care facilities. The format of training varied. Studies that found that training led to reduced restraint use typically involved several training sessions which were often delivered over three to six months. The total duration of training in the studies was approximately eight hours of training. Training was most commonly provided face-to-face. We were unable to identify any studies which took place in the hospital setting.

Few studies were conducted within primary care settings. Donath and colleagues found that training general practitioners in dementia care and the needs of caregivers and asking GPs to recommend family carer support and counselling could increase family carer participation in support groups and counselling [156].

The findings of this evidence update also demonstrate that training in communication with the person with dementia (including person centered care) and active training and problem solving to manage BPSD were effective in reducing BPSD. However, the GRADE rating was low due to mixed findings amongst studies and risk of bias present in some studies included within the body of evidence. Studies that found a reduction in BPSD post staff training also involved at least eight hours of training and incorporated active learning techniques and resources (for example 'how to' cards)[162].

Many of the studies reported problems in uptake of intervention, highlighting that compliance is an issue in staff training interventions.

Evidence statements	*GRADE Quality*	*Related recommendation*
Two RCTs have found that providing broad but comprehensive training in dementia care can result in reduced restraint use in residential care facilities (moderate).[155 157] One RCT found that providing broad but comprehensive training in dementia care had no significant impact on BPSD or quality of life of the person with dementia (moderate).[155] (Table 81)	**Moderate**	**EBR 59, 60**
Two (of six) RCTs [158 170] have found that training staff in providing person-centred care and communicating effectively with the person with dementia can reduce BPSD (low) [145 146 158 159 170 171]. One (of two) [159]RCTs found that training staff in providing person-centred care and communicating effectively with the person with dementia improved the quality of life of the person with dementia (proxy rated) (low).[158 159] (Table 82)	Low	EBR 59,60, 81

Evidence statements	*GRADE Quality*	*Related recommendation*
Four (of 10) RCTs [148 162 165 172]found that training staff to manage BPSD resulted in reduced BPSD (low).[147 148 154 162-167 172] Three RCTs found that training staff to manage BPSD resulted in reduced restraint use (low).[147 154 165] One RCT found no significant differences between groups on quality of life of the person with dementia (low).[167] (Table 83)	Low	EBR 59,60

Table 79 Evidence summary of included systematic reviews for SRQ10: Staff training

Reference	Study Design/Level of Evidence	Types of studies included	Types of participants included	Intervention	Comparison	Results	Quality appraisal[1]
Olazaran 2010 [140]	Systematic Review	Randomised controlled trials published in a peer-reviewed journal	All participants had cognitive impairment or dementia with at least 80% due to Alzheimer's disease and related disorders Health and aged care staff (recipients of training)	The review included all non-pharmacological interventions for the person with dementia and/or the families and carer. We included non-pharmacological interventions that were directed at the professional carer in the GRADE Evidence Profiles.	Alternative intervention or no intervention	The review included 10 RCTs that evaluated interventions involving the professional carer[145-148 151 154 170-175]. Authors conclusions: Professional caregiver training was found to reduce behaviours of concern (based on four studies with a total effect size 0.22; 95% CI0.017 to 0.43) and reduce use of physical restraints (based on two studies with a total effect size -0.284; 95%CI -0.529 to -0.039)	1. CA 2. N 3. Y 4. N 5. Y 6. N 7. Y 8. Y 9. Y 10. N 11. N

1. *Appraisal criteria: (1) 'a priori' design provided, (2) Duplicate study selection and data extraction, (3) Comprehensive literature search, (4) Grey literature search, (5) List of included and excluded studies provided, (6) Characteristics of included studies provided, (7) Scientific quality of the included studies assessed and documented, (8) Scientific quality of included studies used to formulate conclusions, (9) Methods to combine findings appropriate, (10) Publication bias assessed, (11) Conflict of interest included for review and each of the included studies. Y=yes, N=no, CA=can't answer CI: confidence interval; CBA: controlled before and after study; CCT: controlled clinical trials; ITS: interrupted time series; RCT: randomised controlled trial*

Table 80 Evidence summary of randomised controlled trials published since the search of the included systematic review SRQ10: Staff training

Reference Country	Type	Participants	Intervention	Compar-ison	Main Outcomes	Measure/s	Length follow up	Results/ Effect size	Risk of bias[1]
Broad training (eg covers condition, symptoms, management)									
Beer 2011 [155] Australia	Cluster RCT	N=351 people with MMSE ≤24/30 living in residential aged care facilities + Care staff GPs (N=55) Mean age control group 84, intervention group 86 Clusters: 39 aged care facilities	Care facilities and GPs were independently randomised to intervention or control An educational program was developed; the main topics were communication, personal care and activities, positive values, behaviours of concern, pain management, depression and delirium and effective working between GPs and aged care facilities. GPs could participate in face-to-face education and self-directed packages.	Usual care	Quality of life of the person with dementia	Quality of Life – Alzheimer's disease Scale (self -rated, staff and next of kin rated); Alzheimer's Disease Related Quality of Life Scale; Neuropsychiatric Inventory; Brief Pain Inventory; PAIN_AD, use of restraints	4 weeks and 6 months after the end of the educational intervention	Adherence to the education intervention was low, particularly amongst GPs Neither GP education nor care staff education was associated with significant changes in self rated or informant rated quality of life. There were no significant changes on the Neuropsychiatric Inventory. At 4 weeks, participants in the GP education group had decreased restraint use (adjusted OR 0.22, 95% CI 0.09 to 0.54) and reduced scores on the Brief Pain Inventory (adjusted OR 0.31; 95% CI 0.13 to 0.75).	1. Low 2. Low 3. Low 4. Low 5. Low 6. Low

Reference Country	Type	Participants	Intervention	Compar-ison	Main Outcomes	Measure/s	Length follow up	Results/ Effect size	Risk of bias[1]
Donath 2010 [156] Germany	Cluster RCT	N=390 people with dementia Average age of the person with dementia was 80; 68% were female. Mean MMSE was 19. N=129 General Practitioners Clusters: 303 medical practitioners	Training was provided based on current Guidelines for Diagnostics and Treatment of Dementia for General Practitioners and guidelines for drug therapy and support for families and carers. All GPs were provided with 180 minutes of training which covered dementia epidemiology, etiology and knowledge and capability for dementia, early symptoms, physical examination, lab diagnostics, imaging and screening. GPs in Arms B and C received an additional 140 minute unit of training. This addressed drug and non-drug therapy, available health care services and information and counselling of the informal caregivers of dementia patients. GPs in Arms B and C additionally recommended support groups and family counselling to families and carers.	General dementia training	Process outcomes	Use of physical examination, lab diagnostics, imaging and referral to a specialist; prescription of cholinesterase inhibitors; contact between families and carers and a professional counsellor or support group; service utilisation	2 years after interventi on	Diagnostic behaviours of GPs were consistent with guideline recommendations. The utilisation of support groups and counselling increased and was 4 to 5 times higher than the control group however, utilisation of other support services remained low. There were no differences between groups in time to institutionalisation or care costs.	1. Low 2. Low 3. High 4. Low 5. High 6. Low

Reference Country	Type	Participants	Intervention	Compar-ison	Main Outcomes	Measure/s	Length follow up	Results/ Effect size	Risk of bias[1]
Pellfolk 2010 [157] Sweden	Cluster RCT	N=191 residents of nursing units with dementia Mean age intervention group 81, control group 84 Gender intervention group 64% female, control group 77% female N=184 staff Mean age 44 intervention group, 42 control group, 90% female, mean years working in geriatric care 14 Clusters: 40 group dwelling nursing units	The education program for nursing staff was conducted for 6 months. The themes of the education program were: dementia (types, symptoms, diagnosis, treatment); delirium; falls prevention; use of physical restraints (adverse effects, alternatives, legislation); caring for people with dementia (interaction and communication techniques); complications (BPSD). One person from each unit spent 2 days in training while the remaining staff watched six 30 minute videotaped lectures.	Usual care	Staff knowledge and attitudes	Staff knowledge (study specific scale); Perceptions of Restraints Use Questionnaire; physical restraint use; Multidimensional Dementia Assessment Scale; ADL score; cognitive scale; falls risk rated by staff on a visual analogue scale;	Following intervention	Staff in the intervention group had more knowledge at follow up but no differences in attitudes towards restraint. Further exploration of results revealed that staff in intervention group were less prone to using restraints and their estimated knowledge of dementia care had increased significantly but knowledge regarding legislation regulating use of restraints had not increased. Intervention units had increased subjective and objective knowledge and changed attitudes whereas only subjective knowledge had increased in the control units Residents in the intervention group were less likely to be physically restrained (OR 0.21, 95%CI 0.08 to 0.57). Cognitive scores were higher in the intervention group (mean 11.1 vs mean 9.1). There were no significant differences between groups regarding falls or use of benzodiazepines or neuroleptics.	1. Low 2. Unclear 3. Low 4. Unclear 5. High 6. Low

Reference Country	Type	Participants	Intervention	Compar-ison	Main Outcomes	Measure/s	Length follow up	Results/ Effect size	Risk of bias[1]
Training to enhance communication and interactions between the professional caregiver and the person with dementia									
Chenoweth 2009 [158] Jeon 2012 [176] Australia	Cluster RCT	N=289 residents of 15 aged care facilities Mean age 83 DCM group, 84 PCC group, 85 usual care group Gender 83% female DCM group, 76% female PCC group, 73% female control group Clusters: 15 aged care facilities	3-armed trial of DCM: 2 care staff at each site trained & conducted DCM with 2 researchers, 6 hrs/day for 2 days. Observations Included: positive and negative care delivery, ie positive events & personal detractions, & wellbeing scores within 24 DCM behavioural categories. Person centred care (PCC) intervention: 2 day training provided by 2 care staff from each site. Topics included: understanding behaviour as communication, recognising feelings persist despite cognitive impairment, acknowledging feelings during social interactions, and focusing on unique ways that residents express feelings and needs to change usual care. Training sessions explored how staff actions contribute to behaviours. Site visits and telephone contacts were also made to assist implementation of PCC.	Usual care	Agitation	Cohen Mansfield Agitation Inventory (CMAI); Quality of life in late stage dementia; TESS-NH;	Post intervention and 4 months after the end of intervention	At follow up CMAI score was lower in sites providing mapping (mean difference 10·9, 95% CI 0·7–21·1; p=0·04) and person-centred care (13·6, 3·3–23·9; p=0·01). Compared with usual care, fewer falls were recorded in sites that used mapping (mean difference in change in proportion of residents with falls from baseline to followup 0·24, 0·08–0·40; p=0·02) but there were more falls with person-centred care (0·15, 0·02–0·28; p=0·03). There were no other significant effects.	1. Low 2. Low 3. Low 4. Low 5. Low 6. Low

Reference Country	Type	Participants	Intervention	Compar-ison	Main Outcomes	Measure/s	Length follow up	Results/ Effect size	Risk of bias[1]
Clare 2013 [159] UK	Cluster RCT	N=32 care staff from 4 residential facilities. Majority of staff were female and mean age 39 years. N=32 residents from 4 residential facilities. Most were female and mean age was 82 in intervention group and 85 in control group. Residents had spent approx. 3 years in the care home. Clusters: 4 residential facilities	The intervention took place over 8 weeks. In the first two weeks, care staff participated in two 90 minute training sessions. Staff were trained to consider the nature of residents' awareness and instructed in the use of the 'AwareCare' observational measure of awareness in severe dementia and trained in communicating with severely impaired residents. Staff were then asked to carry out observations and supported with supervision and individual support.	Usual care	Quality of life of the person with dementia	Quality of Life in Late-stage Dementia scale (rated by a family member where available and by a member of the care staff). Measures of the person with dementia: Positive Response Schedule (wellbeing); Guy's Advanced Dementia Schedule (cognitive functioning); Behavioural Assessment Scale of Later Life (behaviour) Measures of the care staff: Maslach Burnout Inventory (wellbeing); GHQ12; Approaches to Dementia Questionnaire	Following intervention	Residents in the intervention group were rated by family members to have a significantly improved quality of life (effect size 0.72, p=0.022). Staff members did not rate the residents quality of life as significantly improved. There were no other significant differences between groups on the other outcomes.	1.Low 2. Low 3. Low 4. Low 5. Low 6. Low

Reference Country	Type	Participants	Intervention	Compar-ison	Main Outcomes	Measure/s	Length follow up	Results/ Effect size	Risk of bias[1]
Kuske 2009 [160] Germany	Cluster RCT	N=210 nursing home residents N=96 care staff Clusters: 6 nursing homes	Three month training program in dementia care. The objective of the training program was to improve the interaction between caregivers and residents. The training aimed to improve knowledge and competencies in dementia care. Instructional and problem-based learning principles were applied. Methods of delivery included presentation, videotapes, handouts, brainstorming, games and discussion.	Wait list control or relaxation group	Staff knowledge and competencies in dementia care	Person with dementia: Use of physical restraints; Use of sedatives Staff: Knowledge and competencies in dealing with BPSD (GEROLF questionnaire); Penn State Health Care-giving Questionnaire; Maslach Burnout Inventory; level of health complaints	Following intervention and at 6 months	Caregivers in the intervention group reported significantly greater scores on the knowledge questionnaire than those in the control group following intervention. Caregivers in the intervention group reported significantly improved competence on the GEROLF questionnaire. Use of restraints did not increase within the intervention group whereas it did increase for the relaxation and control group. There were no significant differences between groups in sedative use.	1. Low 2. Low 3. Low 4. Unclear 5. Low 6. Unclear

Reference Country	Type	Participants	Intervention	Compar-ison	Main Outcomes	Measure/s	Length follow up	Results/ Effect size	Risk of bias[1]
Van der Kooji 2013 [161] Netherlands	RCT	N=124 professional carers in nursing home wards Mean age 30, gender 90% female intervention, 83% female control	Intervention involved training coach-consultants and staff in emotion oriented care and use of a model care plan. Integrated Emotion Oriented Care was described in terms of content and methods that caregivers could use to make contact and to communicate empathically, verbally and non-verbally with people with dementia. General advice was given on how to attune to the experience world of people with dementia in different stages of the disease and during different care activities, such as washing, dressing, helping to eat, toileting, recreational activities and having a conversation, using elements of psychosocial methods, such as Validation, Snoezelen and Reminiscence	Usual care	Implementation of the intervention	Self report questionnaire: 'Emotion oriented skills in the interaction with elderly people with dementia'; participant observation; time spent by care personnel on different types of care tasks	At 7 months	Carers in the intervention group reported higher scores in 'expertise' and 'knowledge of patient'. Observations suggested that carers in the intervention group started to work in a more emotion-oriented way	1. Unclear 2. Unclear 3. High 4. High 5. Unclear 6. Unclear

Reference Country	Type	Participants	Intervention	Compar-ison	Main Outcomes	Measure/s	Length follow up	Results/ Effect size	Risk of bias[1]
Training in the management of behavioural and psychological symptoms of dementia									
Deudon 2009 [162] France	Cluster RCT	N=306 nursing home residents Mean age 86, 77% female in intervention group, 79% female in control group; mean MMSE score 9 in intervention group, 12 in control group Clusters: 16 nursing homes	Program: 90 mins teaching re dementia, BPSD & use of 'how to' instruction cards. Instruction cards (presented in article) summarised practical advice on dealing with BPSD. The cards addressed (1) what to do when faced with opposition, denial of care, agitation, aggression, hallucinations or screaming, (2) how to avoid or decrease emergence of BPSD and (3) recommendations on non-pharmacological interventions. Remainder of program: individual sessions where trainers provided constructive feedback on dealing with BPSD & provided coaching. The total training time was 24 hrs.	Usual care	Behaviour al and Psychologi cal Symptoms of Dementia	Neuropsychiatric inventory; Cohen-Mansfield Agitation Inventory (CMAI; observational scale	Followin g interven tion and 3 months after interven tion	Between baseline and post intervention assessment there was a significant decrease in global CMAI scores (-7.8 points per week; p,0.001); and Physically Non Aggressive behaviour, Verbally Non Aggressive behaviour and Verbally Aggressive subscale scores in the intervention group but not the control group. Between baseline and 3 month follow up. there was similarly a significant decrease in global CMAI scores (-6.52 points). Scores on the observational scale decreased significantly in the intervention group but not the control group(-0.71; p<0.001).	1. Unclear 2. Unclear 3. Low 4. Low 5. Low 6. Unclear

Reference Country	Type	Participants	Intervention	Compar-ison	Main Outcomes	Measure/s	Length follow up	Results/ Effect size	Risk of bias[1]
Leone 2013 [163] France	RCT	N=230 nursing home residents Average age was 88 80% were female Mean MMSE was 12	The intervention was designed to manage apathy in people with dementia. The education involved a 2 hour training session on Alzheimer's disease and BPSD. Information was summarised on index cards. These contained 'Do's and Don'ts' when faced with apathy or depression and what to do to avoid or decrease BPSD especially during ADLs. The cards also provided recommendations for non-pharmacological interventions. Staff then received a weekly 4 hour training for a month. It consisted of methods and practical advice for dealing with apathy and depression. Staff were taught how to deal with ADLs, promote patient autonomy and increase their sense of competence. Time was also spent teaching staff how to structure activities for residents.	Usual care	Behavioural and Psychological Symptoms of Dementia	Staff: Qualitative data; Nursing Home Behavioural Symptom Management Questionnaire; Apathy Inventory-Clinician version; Group Observational Scale; Individual Observational Scale Person with dementia: Katz ADL Scale; Neuropsychiatric Inventory – Nursing Home;	Post intervention and 3 months following intervention	Post intervention, the affective subgroup and psychotic subgroup within the intervention group had significantly higher scores on the Neuropsychiatric Inventory. There were no significant changes at 3 month follow up or changes in the amount of psychotropic drugs used. The intervention group had significantly lower scores in the apathy assessment (emotional blunting dimension). Several activities of daily living were improved (going to the toilet and continence).	1. Unclear 2. Unclear 3. Low 4. Low 5. Low 6. Unclear

Reference Country	Type	Participants	Intervention	Compar-ison	Main Outcomes	Measure/s	Length follow up	Results/ Effect size	Risk of bias[1]
McCurry 2012 [164] US	RCT	N=47 residents of community residential homes Mean age 87; Female 60% N=37 Care staff Mean age 48, 89% female	Four session Sleep Education Program for care staff which covered sleep problems in dementia, sleep scheduling, napping, physical activity, diet, environment, developing a sleep plan, using an ABC approach to problem-solve challenges, developing individualised pleasant activities	Usual care	Resident sleep	Sleep wake activity (wrist actigraphy), Cornell Scale for Depression in Dementia; Revised Memory and Behaviour Problems Checklist; Epworth Sleepiness Scale	1 and 6 months post interven tion	Following intervention there were no significant differences in actigraphic measures of resident sleep. Measures over 6 months showed significantly greater percent of 'lights out' time asleep (effect size 0.70) and total sleep time (effect size 0.72) in the intervention group. Caregivers in the intervention group reported reductions in the frequency and disturbance levels associated with sleep related target behaviours. The intervention group were significantly less depressed at follow up. There were no differences in sleepiness or BPSD.	1. Unclear 2. Unclear 3. Low 4. Low 5. Low 6. Low

Reference Country	Type	Participants	Intervention	Compar-ison	Main Outcomes	Measure/s	Length follow up	Results/ Effect size	Risk of bias[1]
Testad 2010 [165] Norway	Cluster RCT	N=145 nursing home residents Median age 86, gender 75% female intervention, 73% female control Clusters: 4 nursing homes	Education and training program "Relation Related Care"provides a practical framework for staff to reduce agitation and use of restraint in the interaction with residents with dementia. The education consists of a 2 day seminar and monthly group guidance for 6 months. The education focusses on predisposing factors, enabling factors and reinforcing factors.	Usual care	Restraint use and agitation	Restraint use (based on interview data); Cohen Mansfield Agitation Inventory; use of antipsychotics	Post intervention and 6 months after the end of intervention	There were short term effects on restraint use (intervention group had significantly better proportions of those that started, remained unchanged and stopped) however these effects were not sustained 6 months after intervention. Residents in the intervention group had significantly reduced scores on the agitation inventory. Use of antipsychotic drugs remained relatively stable in both groups.	1.Unclear 2. Unclear 3. High 4. Low 5. High 6. Unclear
Verkaik 2011 [166] Netherlands	Cluster RCT	N=97 nursing home residents Clusters: 18 nursing home wards	Nursing staff were trained in using a guideline with residents diagnosed with depression. Key elements of the guideline were increasing individualised pleasant activities and decreasing unpleasant events. The education included 9 hours of training and homework provided over 11 weeks.	Usual care	Severity of depression	Cornell Depression Scale; Depression Rating Scale; FACE observation scale; medical data	Post intervention and 10-12 weeks following intervention	Depression scores (on the DRS) were significantly reduced in the intervention group (from 4.56 to 3.79 at 10-12 week follow up). There were no significant differences between groups in scores on the Cornell scale or on mood.	1.Unclear 2. Low 3. High 4. Low 5.Low 6. Unclear

Reference Country	Type	Participants	Intervention	Compar-ison	Main Outcomes	Measure/s	Length follow up	Results/ Effect size	Risk of bias[1]
Visser 2008 [167] Australia	Cluster RCT	N=52 staff from aged care facilities. Mean age 44, 94% female Clusters: 3 aged care facilities	The education program consisted of eight units that were run twice a week for 1-1.5 hours. Units were designed to provide staff with information about dementia and BPSD. The first three sessions were didactic. These were followed by five workshops on individualised care planning, problem solving and developing strategies to manage behaviours. The education was complemented by a peer support program.	Usual care	Behavioural and Psychological Symptoms of Dementia	Cohen Mansfield Agitation Inventory; Alzheimer's Disease Related Quality of Life; staff attitudes questionnaire; Maslach Burnout Inventory	Following intervention and 3 and 6 months after intervention	There were no differences between groups on the CMAI or quality of life tool at any of the follow up assessments. The intervention group that received education plus peer support reported improved perceived skills and knowledge post intervention and at 3 and 6 month follow up.	1. Low 2. Low 3. High 4. Low 5. Low 6. Low

Reference Country	Type	Participants	Intervention	Compar-ison	Main Outcomes	Measure/s	Length follow up	Results/ Effect size	Risk of bias[1]
Other training models									
Resnick 2009 [168 177] United States	RCT	N=523 Nursing assistants from 12 nursing homes Mean age 38, 93% female. Mean 12 years' experience as a nursing assistant	The Res-Care Intervention was developed to help nursing assistants change their philosophy of long-term care from one focused on providing care for residents to one geared toward optimizing function in each resident by encouraging each individual to engage in all activities at his or her highest functional level. Education was provided for 6 weeks (30 minutes a week). The education covered: Philosophy of Restorative Care; motivating residents to participate in functional activities; interventions (Transfers, ambulation, and exercise training activities, bathing, dressing, feeding, communication, and bowel/bladder training). Classes were interactive and involved role play and discussion.	Single 30 min education session on managing behavioral problems in nursing homes	Staff knowledge of restorative care.	Theoretical Testing of Restorative Care Nursing;	Post educatio n	Following education, nursing assistants at the intervention sites increased their knowledge of Restorative Care. Note that an additional part of this study investigated outcomes for nursing home residents however the sample included all older people and not just those with dementia and therefore results are not presented here.	1. Unclear 2. Unclear 3. High 4. High 5. Low 6. Unclear

Reference Country	Type	Participants	Intervention	Compar-ison	Main Outcomes	Measure/s	Length follow up	Results/ Effect size	Risk of bias[1]
Spijker 2011 [169] Netherlands	RCT	N=301 patient-caregiver dyads Mean age 80; gender 70% intervention group, 64% control group	The Systematic Care Program for Dementia involves training professionals in the systematic assessment and interpretation of the family carer's sense of competence and depressive symptoms and strategies in how to deal with deficiencies. The training program involves 3 sessions (2 hours each) had 3 components: screening, psychosocial support and transfer to regular healthcare.	Usual care	Institution alisation	Resource Utilisation in Dementia Questionnaire; process outcomes	12 month follow up	There were no significant effects on institutionalisation or time until institutionalisation.	1. Unclear 2. Low 3. High 4. Low 5. High 6. Unclear

Abbreviations: DCM: Dementia care mapping; hrs: hours; RCT: Randomised controlled trial; GP: general practitioner; OR: odds ratio; CI: confidence interval; MMSE: Mini Mental State Examination; CMAI: Cohen Mansfield Agitation Inventory; PCC: person centred care; DCM: Dementia Care Mapping; BPSD: behavioural and psychological symptoms of dementia; DRS: depression rating scale

1. Risk of bias: (1) Random sequence generation, (2) Allocation concealment, (3) Blinding of participants and personnel, (4) Blinding of outcome assessment, (5) Incomplete outcome data, (6) Selective reporting

Table 81 GRADE Evidence Profile: Staff training programs that cover a broad content

Quality assessment							Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Behavioural and psychological symptoms								
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	RCT (Beer) showed no significant differences between groups [155]	⊕⊕⊕O MODERATE
Quality of life of the person with dementia								
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	RCT (Beer) showed no significant differences between groups [155]	⊕⊕⊕O MODERATE
Activities of daily living function								
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	RCT (Pellfolk) showed that there was a non-significant trend towards improvements in the intervention group [157]	⊕⊕OO LOW
Cognition								
1	randomised trials	serious[1]	no serious inconsistency	serious[4]	serious[3]	none	RCT (Pellofolk) found that participants in the intervention group had higher scores than those in the control group at follow up [157]	⊕OOO VERY LOW
Use of restraints								
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Both studies reported reduced use of restraints in the intervention group: Beer [155]: (adjusted OR 0.22, 95% CI 0.09 to 0.54) Pellfolk [157]: (OR 0.21, 95%CI 0.08 to 0.57)	⊕⊕⊕O MODERATE

[1] Methodology unclear in multiple studies due to poor reporting
[2] Mixed findings across studies
[3] Total sample size <400
[4] Surrogate outcome

Table 82 GRADE Evidence Profile: Training in communication for staff and interactions with the person with dementia

Quality assessment							Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Behavioural and psychological symptoms								
6	randomised trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision[3]	none	2 RCTs (Chenoweth, McCallion) [158 178] found a significant reduction in BPSD in the intervention group as below: Chenoweth mean difference on CMAI 13·6, p=0·01; McCallion effect size not reported) 4 RCTs [145 146 152 159] found no significant effects	⊕⊕OO LOW
Quality of life of the person with dementia								
2	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	serious[3]	none	1 RCT (Clare) found that people in the intervention group were rated by family members to have sig improvement (effect size 0.72, p=0.022)[159] 1 RCT (Chenoweth) found no effect [158]	⊕⊕OO LOW
Activities of daily living function								
1	randomised trials	serious[1]	no serious inconsistency[2]	no serious indirectness	serious[3]	none	1 RCT (Schrijnemaekers) found no sig effects [171]	⊕⊕OO LOW
Cognition								
0	randomised trials					none		
Use of restraints								
2	randomised trials	serious[1]	serious[2]	no serious indirectness	serious[3]	None	1 RCT (Kuske) found that use of restraints did not increase within the intervention group whereas it did increase for the control group [160] 1 RCT (McCallion) found no sig effects [178]	⊕OOO VERY LOW

[1] Methodology unclear in multiple studies due to poor reporting
[2] Mixed findings across studies
[3] Total sample size <400
[4] Surrogate outcome

Table 83 GRADE Evidence Profile: Training staff in the management of BPSD

Quality assessment							Effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**		
Behavioural and psychological symptoms								
10	randomised trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision[3]	none	4 RCTs found a significant reduction in BPSD in the intervention group (Deudon found a mean reduction on the CMAI of 7.8 points per week [162]; Kovach reported a decrease in levels of agitation (effect size 0.7) [148]; Teri found a mean reduction of 1.1 points on the RMBPC[172]; Testad 2010 also had significant effect (effect size not reported) [165] 1 RCT found a significant increase in BPSD in the intervention subgroup – Leone [163] 5 RCTs reported no significant effects related to intervention (McCurry, Verkaik, Visser, Huizing, Testad 2005)[147 154 164 166 167]	⊕⊕OO LOW
Quality of life of the person with dementia								
1	randomised trials	serious[1]	no serious inconsistency[2]	no serious indirectness	serious[3]	none	1 RCT found no significant differences (Visser) [167]	⊕⊕OO LOW
Activities of daily living function								
1	randomised trials	serious[1]	no serious inconsistency[2]	no serious indirectness	serious[3]	none	1 RCT found that ability to manage several activities of daily living were sig improved (going to the toilet and continence) (Leone) [163]	⊕⊕OO LOW
Cognition (person with dementia)								
0	randomised trials							
Use of restraints								
3	randomised trials	serious[1]	no serious inconsistency[2]	no serious indirectness	serious[3]	none	3 RCTs found reduced restraint use (Testad 2010 found short term reductions in restraint use [165]; Huizing found restraint use in intervention group consistent whereas restraint use increased in the control group (56%-70%)[147]; Testad 2005 found sig difference between groups in restraint use (decrease by 54% in the treatment group) [154]	⊕⊕OO LOW

[1] Methodology unclear in multiple studies due to poor reporting
[2] Mixed findings across studies
[3] Total sample size <400
[4] Surrogate outcome

Table 84 GRADE Evidence Profile: Other training approaches

Quality assessment							Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Behavioural and psychological symptoms								
0	No evidence available							
Quality of life of the person with dementia								
0	No evidence available							
Activities of daily living function								
0	No evidence available							
Cognition								
0	No evidence available							
Use of restraints								
0	No evidence available							

[1] Methodology unclear in multiple studies due to poor reporting
[2] Mixed findings across studies
[3] Total sample size <400
[4] Surrogate outcome

§ This evidence profile represents the findings of studies included in the review that did not fit with categories presented above. This evidence profile represents the studies conducted by Resnick (2009), Spijker (2011) and Richardson (2002). None of these studies examined the outcomes of interest and instead focussed on acquisition of knowledge.

SRQ11: Promoting independence

Clinical question

The research question as defined in the protocol and the associated PICO criteria are listed below in Table 85.

Table 85 PICO for SRQ11: Promoting independence

Clinical question: For people with dementia, are there strategies for promoting functional independence that produce benefits/harms?			
Population	**Intervention**	**Comparator**	**Outcome**
People with all forms of dementia	Intervention focussed on promoting independence (occupational therapy, exercise, electronic assistive technology, falls prevention intervention)	Standard care	ADL function Number of falls Quality of life (person with dementia) Carer impact Harms

Literature review search strategies:

Searches for existing HTAs and Systematic reviews

Searches to identify existing Health Technology Assessment reports (HTAs) and systematic reviews were conducted in the databases specified in Table 86, using the search terms listed in the Guideline Technical Report Volume 2.

Table 86 Searches for existing HTAs and systematic review for SRQ11: Promoting independence

Database	Date searched	Period covered	Citations retrieved
HTA	23 October 2014	2005 to 2014	12
Cochrane (Cochrane reviews, Cochrane protocols, DARE)	23 October 2014	2005 to 2014	59
MEDLINE	23 October 2014	2005 to 2014	297
PsycInfo	23 October 2014	2005 to 2014	242
EMBASE	23 October 2014	2005 to 2014	57
PubMed	23 October 2014	2005 to 2014	50

The most recent, comprehensive and highest quality systematic reviews/HTAs identified were conducted by McLaren and colleagues [179], Forbes and colleagues [180], Bharucha and colleauges [181] and Winter and colleagues [182] (Table 90).

Searches for primary studies

Searches were conducted in the databases listed in Table 87 to identify additional primary studies published since the search periods of the included review. The search terms used are listed in the Guideline Technical Report Volume 2.

Table 87 Searches for primary studies/randomised controlled trials for SRQ11: Promoting independence

Database	Dates searched	Period covered	Citations retrieved
MEDLINE	23 October 2014	2005 to 2014	281
PsycInfo	23 October 2014	2005 to 2014	307
EMBASE	23 October 2014	2005 to 2014	65
PubMed	23 October 2014	2005 to 2014	1

Criteria for selecting studies for review:

Table 88 Inclusion and exclusion criteria for SRQ11: Promoting independence

Characteristic	Criteria
Study design	Inclusion: Randomised controlled trials, systematic reviews of randomised controlled trials Exclusion: Other study designs
Population	Inclusion: People with all forms of dementia
Intervention	Inclusion: occupational therapy, exercise, electronic assistive technology, falls prevention intervention
Comparator	Inclusion: Usual care or alternative intervention
Outcomes	ADL function, Number of falls, Quality of life (person with dementia), Carer impact, Harms
Publication type	English language

Search results:

Existing HTAs and systematic reviews

The most recent, comprehensive and highest quality systematic reviews/HTAs identified and included in the current update are show in Table 89.

Table 89 Systematic reviews and HTA report included for SRQ11: Promoting independence

Intervention	Included systematic reviews/HTAs
Occupational therapy	McClaren and colleagues [179]
Exercise	Forbes and colleagues [180]
Falls prevention	Winter and colleagues [182]
Assistive technology	Bharucha and colleagues [181]

Primary studies

A total of 654 citations were retrieved in the electronic database searches. 35 studies were viewed in full text and 8 were included evidence update (Table 91).

Evidence summary:

Occupational Therapy

We identified a systematic review conducted by McLaren and colleagues that examined the effects of non-pharmacological interventions (including occupational therapy) for people with dementia living in the community [179]. The review conducted a search up until 2012 and identified seven RCTs evaluating occupational therapy interventions for people with dementia [183-191]. These seven RCTs were extracted and data included in the GRADE Evidence Profile. As the review was restricted to studies with participants living in the community, we searched for RCTs in which occupational therapy was provided for people with dementia in a residential care setting; we identified one RCT conducted by Wenborn and colleagues [192]. We also searched for RCTs that were published following the search involved in the McLaren review. We identified one further RCT conducted by Kumar and colleagues that was included in the evidence update [193] (Table 91).

Interventions in the included studies ranged in dose from one to ten consultations. Occupational therapy programs conducted in the community varied however, there were common elements. Occupational therapy intervention commonly involved family/carer education, environmental modification, engagement in meaningful activities, individualised problem solving and task simplification.

Overall, the studies were of moderate quality. The GRADE Evidence Profile shows that occupational therapy for people with dementia living in the community was found to improve ADL function (SMD 0.17, 95%CI 0.02 to 0.33) and improve quality of life in the person with dementia (SMD 0.62, 95%CI 0.43 to 0.81).

Exercise

We identified a Cochrane Review that examined the efficacy of exercise in improving outcomes for people with dementia [180]. The authors identified 16 RCTs which were generally of moderate quality. The search was for studies listed up until August 2012. We identified a further two RCTs that were published after the search date of the Cochrane Review and included the studies in the analysis [194 195] (Table 91). Four of the 18 RCTs took place in participants' home settings whereas the remaining studies took place in residential care settings. Participants in the included studies ranged from those with mild to severe dementia. The frequency of exercise intervention ranged from twice a week to daily. The duration of the intervention program ranged from two weeks to 12 months.

The GRADE Evidence Profile shows that exercise was found to be associated with higher levels of independence in ADLs (SMD 0.68, 95%CI 0.08 to 1.27). Six of the studies reported that there were no adverse effects associated with the intervention.

Technologies to promote functional independence in the person with dementia

We identified a systematic review that examined the use of technology based interventions for people with early stage Alzheimer's Disease [181]. The review stated that they identified one RCT; however, when the study was obtained in full text it was determined that it was not a randomised trial. We conducted a search for new RCTs and identified two RCTs that involved technologies designed to promote independence in people with dementia [196 197]. The technologies included a falls prevention and management intervention involving night lighting and personal call alarms and a monitoring platform that monitored the health status of the person with dementia and their family carer via self-reporting. The falls prevention technology intervention was associated with reduced

falls in the intervention group. The study evaluating the monitoring device found that there were no significant differences between groups in terms of carer impact.

Falls prevention

We identified a systematic review that examined falls prevention interventions that included subgroups of people with cognitive impairment [182]. The review searched up until 2011. They were unable to identify any randomised trials that solely examined the efficacy of interventions for people with dementia. We identified a further two RCTs that involved interventions to reduce falls in people with dementia [196 198]. One of the studies examined the efficacy of an occupational therapy and physiotherapy program whereas the other study examined the efficacy of falls prevention and management technology (night light and personal call alarm). Both studies found that the intervention was associated with a reduced rate of falls with one study reporting an incidence rate ratio of 0.34 and the other study reporting a relative risk of 0.51.

Evidence statements	*GRADE Quality*	*Related recommendations*
Pooling of four RCTs demonstrated that occupational therapy was effective in improving ADL function (low) [183 186 187 190] and self-reported quality of life (moderate) [185 187 189 190 193] in community dwelling people with dementia. Pooling of four RCTs found no significant reduction in carer impact following occupational therapy (moderate).[183-186] (Table 92)	Low-moderate	EBR 67
A systematic review [180] pooled six RCTs evaluating an exercise intervention and showed a significant improvement in ADL function (low).[180] The systematic review [180] found one RCT that reported no significant differences between groups on self-reported quality of life after exercise intervention (low).[180] The systematic review found one (of two) RCTs associated with significantly reduced carer impact following an exercise program for the person with dementia (very low).[180] Six RCTs within the systematic review that reported on harms associated with exercise did not report any adverse events associated with intervention (moderate).[180] (Table 93)	Low	EBR 68
One RCT evaluating a technology intervention using a health status monitoring platform found no significant differences between groups in terms of carer impact [197]. (Table 94)	Low	NA
One RCT evaluating a falls prevention intervention found no significant differences between groups on ADL function (low) [198]. Two RCTs found that falls prevention interventions led to reduced incidence of falls (low) [196 198] . (Table 95)	Low	NA

Table 90 Evidence summary of included systematic reviews for SRQ11: Promoting independence

Reference	Study Design	Types of studies included	Types of participants included	Intervention	Comparison	Results	Quality appraisal[1]
Occupational therapy for people with dementia living in the community							
McLaren 2013 [179]	Systematic Review	RCTs	Community dwelling dementia patients with a primary caregiver	Any non-pharmacological intervention that had at least one primary outcome measuring any domain of functional limitations or disability was included.	Not specified	The study identified seven RCTs which evaluated the effects of occupational therapy on functional outcome. [183-191] Two of the studies were judged as being of high quality (with a low risk of bias). Five of the studies were judged as being of moderate quality with a medium risk of bias. The authors concluded that there was good evidence for occupational therapy with six of the studies reporting positive, significant increases in functional abilities or quality of life. The authors presented effect sizes for occupational therapy which ranged from 0.048 to 2.5.	1. CA 2. CA 3. N 4. N 5. N 6. Y 7. Y 8. Y 9. CA 10. N 11. N

Reference	Study Design	Types of studies included	Types of participants included	Intervention	Comparison	Results	Quality appraisal[1]
Exercise							
Forbes 2013 [180]	Systematic Review	RCTs	The majority of participants in the trials had to be older people (over 65 years of age) and diagnosed as having dementia using accepted criteria	Exercise interventions included exercise programs offered over any length of time with the aim of improving health outcomes in older people with dementia or improving family carer impact. The exercise could be any combination of aerobic, strength or balance training	Usual care or social contact/activities	See results in line below	1. Y 2. Y 3. Y 4. Y 5. Y 6. Y 7. Y 8. Y 9. Y 10. Y 11. N
Results: The authors included 16 RCTs involving 937 participants. Trials were generally of moderate quality. Outcome: ADL function Results: Six trials involving 289 participants were pooled. The overall effect was significant and in favour of intervention (SMD 0.68, 95%CI 0.08 to 1.27) Outcome: Number of falls Results: Not reported Outcome: Quality of life Results: None of the studies reported outcomes for QOL of the person with dementia Outcome: Carer impact Results: Data was only available for one trial. This trial reported a significant reduction in carer burden Outcome: Harms Results: Five trials addressed potential adverse events. None of the trials revealed any serious adverse events that could be attributed to the exercise intervention.							

Reference	Study Design	Types of studies included	Types of participants included	Intervention	Comparison	Results	Quality appraisal[1]
Technologies							
Bharucha 2009 [181]	Systematic Review	All study types	People with Early-Stage Alzheimer's Disease or Mild Cognitive Impairment	Research articles testing technology interventions in community settings including supportive facilities such as assisted living.	Not specified	See results in line below	1. CA 2. CA 3. Y 4. Y 5. N 6. N 7. N 8. N 9. CA 10. N 11. N
Results No randomised controlled trials were included in the review and the authors presented a narrative summary of the literature published to date. The authors identified 58 technologies with potential applications to dementia care. Technologies included 11 cognitive aids, 15 environmental sensors, 10 physiological sensors and 22 advanced integrated sensor systems. Clinical studies specifically involving people with dementia were limited to the following three devices: (1) Cognitive Orthosis for Activities in the Home (COACH): A system designed to guide people with dementia through the steps of handwashing. A study conducted with 10 participants showed that the system increased the successful completion of handwashing steps by 25%. (2) CareWatch: a sensor system that alerts the caregiver when the person gets out of bed or attempts to leave the house. A RCT evaluating CareWatch is currently underway. (3) CareMedia: A monitoring system designed to monitor the activities of residents in residential care facilities.							

Reference	Study Design	Types of studies included	Types of participants included	Intervention	Comparison	Results	Quality appraisal[1]
Falls prevention							
Winter 2013 [182]	Systematic Review	Controlled trials	Older people (at least 75% of the sample were aged 65 years or more) Community dwelling At least a subgroup of participants had cognitive impairment confirmed by an established test	Non-pharmacological interventions	Not specified	The review identified no RCTs that were conducted with people with dementia. Overall, the authors identified 11 studies involving 1928 participants with cognitive impairment. Study designs included pre and post studies without a control group. The authors reported that seven of the included studies found that intervention decreased falls risk. Of these, two showed a significant improvement in physical performance measures specifically in a cognitively impaired group. The authors concluded that there is currently conflicting evidence and inconclusive results for falls prevention interventions in people with cognitive impairment.	1. CA 2. Y 3. Y 4. N 5. N 6. Y 7. Y 8. Y 9. Y 10. N 11. N

Abbreviations: Y=yes, N=no, CA=can't answer, ADL: activities of daily living; QOL: quality of life; SMD: standardised mean difference

1. Appraisal criteria: (1) 'a priori' design provided, (2) Duplicate study selection and data extraction, (3) Comprehensive literature search, (4) Grey literature search, (5) List of included and excluded studies provided, (6) Characteristics of included studies provided, (7) Scientific quality of the included studies assessed and documented, (8) Scientific quality of included studies used to formulate conclusions, (9) Methods to combine findings appropriate, (10) Publication bias assessed, (11) Conflict of interest included for review and each of the included studies.

Table 91 Evidence summary of randomised controlled trials published subsequent to the included systematic review and included in the evidence update for SRQ11: Promoting independence

Reference Country	Type	N	Participants Age Gender Other	Intervention	Comparison	Main Outcomes	Measures	Length of follow up	Results/ Effect size[a]	Risk of bias[1]
Occupational therapy for people living in residential settings										
Wenborn 2013 [199] United Kingdom	Cluster RCT	210	Mean age 84, Gender: 64% female in intervention group, 71% female in control group Mean MMSE: 6/30	An occupational therapy program designed to enable care home staff to increase activity provision. Included assessment of the environment, educating staff regarding getting to know residents interests and abilities and planning activities.	Usual care	QOL	QOL-AD; MMSE; Clifton Assessment Procedures for the Elderly - Behaviour Rating Scale; Challenging Behaviour Scale; Cornell Scale for Depression in Dementia; Rating Anxiety in Dementia; Clinical Dementia Rating Scale	4 and 12 weeks after the intervention was completed	There were no significant differences between groups for any of the patient outcomes.	1. Unclear 2. Unclear 3. High 4. Low 5. Low 6. Low
Occupational therapy studies for people in the community										
Kumar 2014 [193] India	RCT	77	Mean age 69 Gender: 20% female The majority of participants had 'mild' dementia	The intervention, included a total of 10 treatment session of 70 minutes duration for 5 weeks. Each session contained: relaxation, physical exercise, practice of activities of daily living, practice of household tasks, cognitive exercise and recreational activities	Usual care	Quality of life	WHOQOL-BREF;	Post intervention	The overall quality of life (WHOQOL-BREF) improved significantly in the experimental group ($p < 0.001$) showing the effectiveness of program; whereas in the control group it significantly declined ($p = 0.011$) (effect size = 0.97)	1. Low 2. Low 3. High 4. Unclear 5. Unclear 6. Unclear

Reference Country	Type	N	Participants Age Gender Other	Intervention	Comparison	Main Outcomes	Measures	Length of follow up	Results/ Effect size[a]	Risk of bias[1]
Exercise										
Suttanon 2012 [195] Australia	RCT	40	Mean age 82 Gender: 63% female Mean MMSE: 21 in intervention group, 22 in control group	Six-month individualised home-based exercise program supervised by a physiotherapist. The program included standing balance and strengthening exercises and a graduated walking program and was based on an existing home exercise program (the Otago Program). The total number of home visits was 6.	Education program related to dementia and ageing	Balance, mobility, falls and falls risk	Laboratory measures of gait performance; Functional Reach Test; Step Test; Timed Chair Stands; Timed Up and Go Test; Human Activity Profile; incidence rate of falls; Falls Risk for Older People; Physiological Profile Assessment; Zarit Carer Burden Index; Assessment of Quality of Life	Post intervention	There were significant improvements in the exercise group relative to the control group for the measures of Functional Reach (effect size=0.05) and the Falls Risk for Older People – Community version (FROP-Com) score (effect size=0.06). The intervention group improved more on the Step Test, the modified Clinical Test of Sensory Interaction of Balance (mCTISB) and the Timed Up and Go Test with dual (manual) task however, the differences between groups were not statistically significant. There were no adverse events reported	1. Low 2. Low 3. High 4. Low 5. High 6. Low
Hauer 2012 [194] Germany	RCT	122	Mean age intervention group 82, control group 83 Gender 74% female intervention group, 73% female in control group Mean MMSE 22/30	The intervention group underwent a regimen of progressive resistance and functional training in groups of four to six participants for 3 months (2 hours, twice a week) supervised by a qualified Instructor The functional training focused on basic activity of daily living related motor functions including sitting down and standing up from a chair, standing (static and dynamic postural control) and walking.	All participants met two times per week for 1 hour of supervised motor placebo group training. Typical activities were flexibility exercise, calisthenics, low-intensity training with hand-held weights, and ball games while seated.	Physical function	Increase in maximum strength (1RM); five chair stand; Short Physical Performance Battery; stair climbing; Performance Oriented Motor Assessment; Timed Up and Go Test; Physical Activity Questionnaire for the Elderly	Months 3 (post intervention) and 6	The intervention group showed significant improvements in maximum strength (effect size=0.43) and five chair stands (effect size=0.15). Participants in the intervention group also improved significantly on walking speed (effect size=0.15).	1. Low 2. Low 3. Low 4. Low 5. Low 6. Low

Reference Country	Type	N	Participants Age Gender Other	Intervention	Comparison	Main Outcomes	Measures	Length of follow up	Results/ Effect size[a]	Risk of bias[1]
Technology										
Torkamani 2014 [197] UK, Spain, Greece	RCT	60	Mean age 78 Gender 45% female Mean MMSE 19/30	The intervention group were provided with the ALADDIN platform and an internet connection and laptop were provided where necessary. The carers were trained so that they could navigate the system and complete 'MY TASKS' monitoring of the person with dementia and their own mental state and burden. Being the primary users of ALADDIN, the carers chose the schedule of their tasks. The system was monitored twice daily by the clinical teams. The intervention duration was 6 months.	Usual care	Carer impact	Caregiver measures: Zarit Burden Interview; Neuropsychiatric Inventory; Beck Depression Inventory; Zung Depression Self Rating Scale; EQ5D; Quality of Life Scale; Assessments of the person with dementia were used solely to describe the sample	At months 3 (midpoint) and 6 (post intervention)	No significant differences between groups in carer burden or carer depression. There was a significant improvement in caregiver quality of life (4.1% gain in the intervention group versus 1.2% loss in the control group)	1. Unclear 2. Unclear 3. High 4. Unclear 5. Unclear 6. Unclear
Tchalla 2013 [196] France	RCT	96	Mean age 87; Gender 77% women; Median MMSE 21/30	Fall reduction program plus 'Home Based Technologies-tele-assistance' program (HBTec-TS). The HBTec in this study was a nightlight path for preventing falls at home. It requires a wire sensor installed on the floor. The nightlight path is a device installed near the bed that turns on automatically when the person sets foot on the ground. The tele-assistance service involves a remote intercom, an electronic bracelet and a central hotline providing telephone support at all times. The service helps to coordinate aid to someone who has fallen at home.	Fall reduction program	Number of falls	Geriatric Assessment;	1 year follow up	16 (32.7%) elderly people fell in the group with HBTec-TS versus 30 (63.8%) in the group without HBTec-TS. The use of HBTec-TS was significantly associated with a reduction in the number of indoor falls among elderly people with mild-to-moderate AD (OR = 0.37, 95% CI = 0.15–0.88, p = 0.03.	1. Unclear 2. Unclear 3. High 4. Unclear 5. Low 6. Unclear

Reference Country	Type	N	Participants Age Gender Other	Intervention	Comparison	Main Outcomes	Measures	Length of follow up	Results/ Effect size[a]	Risk of bias[1]
Falls prevention										
Wesson 2013 [198] Australia	RCT	22	Mean age 79 in intervention group; 81 in control group Gender: 46% women in intervention group; 36% female in control group Mean MMSE 24.5/30 in intervention group; 22.5/30 in control group	A home hazard reduction and balance and strength exercise fall prevention program. The program was tailored to participant's individual cognitive levels and implemented as a carer-supported intervention. The duration was 12 weeks and was based in the person's home. Intervention was provided by occupational therapists and physiotherapists.	Usual care. Written information on falls prevention and home safety.	Feasibility	Person with dementia: Interview for Deterioration of Daily Activities in Dementia; Cornell Scale for Depression in Dementia; Agitated Behaviours in Dementia Scale; Incidental and Planned Exercise Questionnaire; Physiological Profile Assessment; Hill Step Test; near-tandem test of standing balance with eyes closed; Falls Efficacy Scale International; Iconographical Falls Efficacy Scale; Falls calendar Carer: Zarit Burden Interview; Task Management Strategy Index	Post interventi on	There were fewer falls in the intervention group than in the control group (5 falls vs 11 falls; IRR=0.34 (95%CI 0.06 to 1.91)) There were no significant differences between group on the physiological and functional outcomes for the person with dementia. There were trends towards improved physical activity levels and reduced agitation in the intervention group. There was a trend towards increased carer impact in the intervention group. No serious adverse events reported	1. Low 2. Low 3. High 4. Low 5. Low 6. Low

Reference Country	Type	N	Participants Age Gender Other	Intervention	Comparison	Main Outcomes	Measures	Length of follow up	Results/ Effect size[a]	Risk of bias[1]
Tchalla 2013 [196] France	RCT	96	Mean age 87; Gender 77% women; Median MMSE 21/30	Fall reduction program plus 'Home Based Technologies-tele-assistance' program (HBTec-TS). The HBTec in this study was a nightlight path for preventing falls at home. It requires a wire sensor installed on the floor. The nightlight path is a device installed near the bed that turns on automatically when the person sets foot on the ground. The tele-assistance service involves a remote intercom, an electronic bracelet and a central hotline providing telephone support at all times. The service helps to coordinate aid to someone who has fallen at home.	Fall reduction program	Number of falls	Geriatric Assessment;	1 year follow up	16 (32.7%) elderly people fell in the group with HBTec-TS versus 30 (63.8%) in the group without HBTec-TS. The use of HBTec-TS was significantly associated with a reduction in the number of indoor falls among elderly people with mild-to-moderate AD (OR = 0.37, 95% CI = 0.15–0.88, p = 0.03.	1. Unclear 2. Unclear 3. High 4. Unclear 5. Low 6. Unclear

Abbreviations: RCT: randomised controlled trial; QOL: quality of life; AD: Alzheimer's disease; OR: odds ratio; IRR: Incidence rate ratio

Risk of bias: (1) Random sequence generation, (2) Allocation concealment, (3) Blinding of participants and personnel, (4) Blinding of outcome assessment, (5) Incomplete outcome data, (6) Selective reporting

Table 92 GRADE Evidence Profile: Occupational therapy for people with dementia

Quality assessment							Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
ADL function								
4	randomised trials	serious[1]	inconsistency[2]	no serious indirectness	no serious imprecision	none	4 RCTs with 684 community dwelling participants were pooled (Gitlin 2001; Gitlin 2003; Gitlin 2010; Graff 2006) [183 186 187 190]. There was an overall positive effect on ADL function in favour of intervention (SMD 0.17, 95%CI 0.02 to 0.33)	⊕⊕OO LOW
Number of falls								
0	No evidence available					None		
Quality of life (person with dementia)								
5	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	None	4 RCTs with 456 community dwelling participants were pooled (Gitlin 08; Gitlin 2010; Graff 2006; Kumar 2013) [185 187 189 190 193]. There was an overall positive effect on self-reported quality of life (SMD 0.62, 95%CI 0.43 to 0.81). 1 RCT (Wenborn) found no significant differences between groups in participants living in residential care. [199]	⊕⊕⊕O MODERATE
Carer impact								
5	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	4 RCTs with 547 community dwelling participants were pooled (Gitlin 01; Gitlin 05; Gitlin 08; Gitlin 03) [183-186]. There was a non significant trend towards reduced family carer upset in the intervention group (SMD -0.15, 95%CI -0.32 to 0.02). Data from one RCT (Nobili) was unable to be pooled. Results showed a trend towards reduced family carer stress in the intervention group though this was not significant (p=0.6) [191]	⊕⊕⊕O MODERATE
Harms								
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[3]	None	2 RCTs (Gitlin 2010; Graff 2006) reported that they did not identify any harms associated with the intervention [190] [187]	⊕⊕⊕O MODERATE

[1] Aspects of methodology poorly reported in multiple studies
[2] Mixed findings across studies
[3] Total sample size <400

Table 93 GRADE evidence profile: Exercise for people with dementia

Quality assessment							Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
ADL function								
6	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	None	Six trials involving 289 participants were pooled. The overall effect was significant and in favour of intervention (SMD 0.68, 95%CI 0.08 to 1.27) [180]	⊕⊕OO LOW
Number of falls								
0	No evidence available					None		
Quality of life (person with dementia)								
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[1]	None	1 RCT (Suttanon) found no significant differences between groups [195]	⊕⊕OO LOW
Carer impact								
2	randomised trials	serious[1]	serious[2]	no serious indirectness	serious[3]	None	1 RCT found a significant reduction in impact in the intervention group (MD -15.30, 95% CI -24.73 to -5.87). [180] 1 RCT (Suttanon) found no significant differences between groups [195]	⊕OOO VERY LOW
Harms								
6	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	None	Six studies reported that there were no adverse events associated with the intervention [180 195]	⊕⊕⊕O MODERATE

[1] Aspects of methodology poorly reported in multiple studies
[2] Mixed findings across studies
[3] Total sample size <400

Table 94 GRADE Evidence Profile: Assistive technologies for people with dementia

Quality assessment							Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
ADL function								
0	No evidence available					none		
Number of falls								
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	1 RCT (Tchalla) found a significant reduction in the number of indoor falls in the intervention group (OR = 0.37, 95% CI 0.15 to 0.88) [196]	⊕⊕OO LOW
Quality of life (person with dementia)								
0	No evidence available					none		
Carer impact								
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	1 RCT (Torkamani) found no significant differences between groups in carer impact [197]	⊕⊕OO LOW
Harms								
0	No evidence available					none		

[1] Aspects of methodology poorly reported in multiple studies
[2] Mixed findings across studies
[3] Total sample size <400

Table 95 GRADE Evidence Profile: Falls prevention for people with dementia

Quality assessment							Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
ADL function								
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	1 RCT (Wesson) found no significant differences between groups [198]	⊕⊕OO LOW
Number of falls								
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	2 RCTs found reduced falls in the intervention group Wesson (5 falls vs 11 falls; IRR=0.34 (95%CI 0.06 to 1.91)) [198] Tchalla (relative risk reduction 48.8%, (95%CI 19.3 to 67.6)) [196]	⊕⊕OO LOW
Quality of life (person with dementia)								
0	No evidence available					none		
Carer impact								
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	1 RCT (Wesson) found a trend towards increased carer impact in the intervention group (mean scores 19.14/88 in intervention group versus mean 11.64/88 in control group) [198]	⊕⊕OO LOW
Harms								
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	1 RCT (Wesson) reported no harms associated with the intervention [198]	⊕⊕OO LOW

[1] Aspects of methodology poorly reported
[2] Mixed findings across studies
[3] Total sample size <400

SRQ12: Cognitive training and rehabilitation

Clinical question

The research question as defined in the protocol and the associated PICO criteria are listed below in Table 96.

Table 96 PICO for SRQ12: Cognitive training and rehabilitation

Clinical question: For people with dementia, do cognitive rehabilitation interventions produce benefits?			
Population	**Intervention**	**Comparator**	**Outcome**
People with all forms of dementia	Cognitive stimulation therapy, cognitive training or cognitive rehabilitation	Standard care	Cognition (assessed with a global measurement tool) ADL function Self-reported QOL Carer impact Harms

Literature review search strategies:

Searches for existing HTAs and Systematic reviews

Searches to identify existing Health Technology Assessment reports (HTAs) and systematic reviews were conducted in the databases specified in Table 97, using the search terms listed in the Guideline Technical Report Volume 2.

Table 97 Searches for existing HTAs and systematic review for SRQ12: Cognitive training and rehabilitation

Database	Date searched	Period covered	Citations retrieved
HTA	24 October 2014	2005 to 2014	5
Cochrane (Cochrane reviews, Cochrane protocols, DARE)	24 October 2014	2005 to 2014	4
MEDLINE	24 October 2014	2005 to 2014	65
PsycInfo	24 October 2014	2005 to 2014	48
EMBASE	24 October 2014	2005 to 2014	22
PubMed	24 October 2014	2005 to 2014	11

Cognitive stimulation therapy

The most recent, comprehensive and high quality systematic review was published by Woods and colleagues [200]. Their Cochrane review included studies indexed before December 2011.

Cognitive training

The most recent, comprehensive and high quality systematic review was published by Bahar Fuchs and colleagues [201]. Their Cochrane review included studies indexed before November 2012.

Cognitive rehabilitation

The Cochrane review conducted by Bahar Fuchs and colleagues [201] also included studies of cognitive rehabilitation indexed before November 2012.

Searches for additional primary studies

Searches were conducted in the databases listed in Table 98 to identify additional primary studies published since the search period of the included review. The search terms used are listed in the Guideline Technical Report Volume 2.

Table 98 Searches for primary studies for SRQ12: Cognitive training and rehabilitation

Database	Dates searched	Period covered	Citations retrieved
MEDLINE	24 October 2014	2012-October 2014	62
PsycInfo	24 October 2014	2012-October 2014	61
EMBASE	24 October 2014	2012-October 2014	24
PubMed	24 October 2014	2012-October 2014	0

Criteria for selecting studies for review:

Table 99 Inclusion and exclusion criteria for review for SRQ12: Cognitive training and rehabilitation

Characteristic	Criteria
Study design	Inclusion: Randomised controlled trials
Population	Inclusion: People with a diagnosis of dementia
Intervention	Inclusion: (1) Cognitive stimulation therapy: engagement in a 'range of group activities and discussions aimed at general enhancement of cognitive and social functioning'[202] . (2) Cognitive training: Intervention 'typically involves guided practice on a set of standard tasks designed to reflect particular cognitive functions, such as memory, attention, language or executive function'[202] . (3) Cognitive rehabilitation: An 'individualised approach to helping people with cognitive impairments in which those affected, and their families, work together with health care professionals to identify personally-relevant goals and devise strategies for addressing these. The emphasis is not on enhancing performance on cognitive tasks but on improving functioning in the everyday context' [202] .
Comparator	Standard care
Outcomes	Inclusion: Cognition (assessed with a global measurement tool), ADL function, Self-reported QOL, Carer impact, Harms
Publication type	English language

Search results:

Existing HTAs and systematic reviews

Cognitive stimulation therapy

We identified a Cochrane Review published in 2012 by Woods and colleagues that examined the efficacy of cognitive stimulation therapy [200] (Table 101). Their search for trials in December 2011 identified 15 RCTs which were generally low in quality and heterogeneous in terms of the participants involved and the intensity and duration of intervention provided. Nine of the 15 studies were based in residential care or hospitals and the remaining six studies recruited people living in

the community. The authors found a benefit on cognitive function, measured using global tools such as the ADAS-Cog, associated with cognitive stimulation (SMD 0.41, 95%CI 0.25 to 0.57). Secondary analysis involving smaller numbers of studies and participants showed benefits for self-reported quality of life and wellbeing (SMD 0.38, 95%CI 0.11 to 0.65). No differences were found relating to activities of daily living or behavioural and psychological symptoms of dementia. Overall, the authors concluded that there was consistent evidence that cognitive stimulation programs benefit cognition in people with mild to moderate dementia. However, the Committee indicated that there were significant flaws in the analysis of one of the main contributing trials in this review and that these flaws had affected the findings of the review.

Cognitive training

We identified a Cochrane Review published by Bahar Fuchs and colleagues (2013) that examined the efficacy of both cognitive training and cognitive rehabilitation [201](Table 101). Their search in November 2012 identified 11 RCTs evaluating cognitive training which were of low to moderate quality. In general, participants were in the mild stages of dementia with average MMSE scores of 20-25/30. Cognitive training was not associated with beneficial effects in relation to any of the reported outcomes. However, it should be noted that some of the trials did report statistically significant positive effects on specific measures of cognition [203].

Cognitive rehabilitation

The Cochrane Review conducted by Bahar Fuchs and colleagues [201] included one RCT of high quality evaluating cognitive rehabilitation [204]. The intervention in the study focused on addressing personally meaningful goals and delivering individualised intervention which involved providing practical aids and strategies, techniques for learning new information, practice in maintaining attention and techniques for stress management. The intervention was associated with improved performance of individual goals measured by the Canadian Occupational Performance Measure (effect size = 0.44) and a result that approached significance towards increased self-reported quality of life (effect size=0.19). There were 69 participants in the study.

Table 100 Systematic reviews and HTA report included in the review for SRQ12: Cognitive training and rehabilitation

Intervention	Included systematic reviews/HTAs
Cognitive stimulation therapy	Woods and colleagues [200]
Cognitive training	Bahar Fuchs and colleagues [201]
Cognitive rehabilitation	Bahr Fuchs and colleagues [201]

Primary studies

A total of 147 citations were retrieved in the electronic database searches. 18 studies were viewed in full text and 2 were included evidence update (Table 102).

Evidence summary

Cognitive stimulation therapy

Our search revealed one RCT published following the Cochrane Review [205 206]. The high quality trial (involving 236 participants with moderate severity dementia) examined whether a 'maintenance cognitive stimulation therapy' program following a standard cognitive stimulation

therapy program was beneficial. The trial found that the intervention group reported better outcomes on ADL function and quality of life although effect sizes were small

Cognitive training

We identified one RCT published following the search date of the Bahar Fuchs review [207]. The RCT involved 19 people and was of low quality. The study compared two forms of cognitive training (computer led versus therapists led) and a control group. The authors reported that participants in the therapist led training group had significantly lower levels of depression at follow-up than those in the control group. There were no other significant differences between groups.

Cognitive rehabilitation

No relevant studies identified.

Evidence statements	*GRADE Quality*	*Related recommendations*
A systematic review [200] pooled 14 RCTs investigating cognitive stimulation therapy and found a significant effect on global cognition (low). Pooling of four RCTs in the review found no significant difference between groups on ADL function (mod).[200] Pooling of four RCTs found a significant effect on quality of life (low).[200] (Table 103)	Low-Moderate	NA
A systematic review [201] pooled six RCTs investigating cognitive training and found no significant effect on global cognition. Pooling of four RCTs within the review found no significant effects on ADL function.[201] (Table 104)	Low	NA
A systematic review [201] found one RCT investigating cognitive rehabilitation that reported no significant differences between groups on ADL function, quality of life or carer impact.[204] (Table 105)	Moderate	NA

Table 101 Evidence summary of included systematic reviews for SRQ12: Cognitive training and rehabilitation

Reference	Study Design	Types of studies included	Types of participants included	Intervention	Comparison	Results	Quality appraisal[1]
Cognitive stimulation							
Woods 2012 [200]	Systematic Review	RCTs published in English in a peer-reviewed journal	People with all forms of dementia at all levels of severity	'Cognitive stimulation': defined as engagement in a range of activities and discussions (usually in a group) aimed at general enhancement of cognitive and social functioning; Participants attended regular therapy sessions (involving a group or family caregiver) for a minimum period of 4 weeks	'No treatment', 'standard treatment', or placebo.	See summary in box below	1. Y 2. Y 3. Y 4. Y 5. Y 6. Y 7. Y 8. Y 9. Y 10. Y 11. N
Results of the Woods review: 15 RCTs were included. The quality of studies in general was low. Outcome: Cognition Result: Analysis showed a significant improvement on this outcome following treatment compared to control groups. The SMD was 0.41 (95% CI 0.25 to 0.57) based on 14 studies with 658 participants. Outcome: ADL function Result: Analysis showed improved ADL function in the intervention group however this was not statistically significant (SMD 0.21 (95%CI -0.05 to 0.47) Outcome: Self-reported QOL Result: Analysis showed a significant improvement on this outcome following treatment compared to control groups. The SMD was 0.38 (95% CI: 0.11 to 0.65) based on 4 studies with 219 participants Outcome: Carer impact Result: Analysis showed no significant improvement in carer stress or burden based on two studies with 147 participants (SMD -0.03 (95% CI -0.35 to 0.29) Outcome: Harms Result: None reported							

Abbreviations: ADL – Activities of Daily Living; CI – confidence interval; N – No; QOL – Quality of Life; RCTs – randomised-controlled trials; SMD – standardised mean difference;Y – Yes;

Reference	Study Design	Types of studies included	Types of participants included	Intervention	Comparison	Results	Quality appraisal[1]
Cognitive training and rehabilitation							
Bahar-Fuchs 2013 [201]	Systematic Review	RCTs published in English where adequate data was provided or could be obtained.	People with a medical diagnosis of dementia. Data was excluded from participants for whom dementia was known to have an aetiology other than Alzheimer's disease or cerebrovascular pathology.	Cognitive training or cognitive rehabilitation. Cognitive training focuses on guided practice on a set of tasks that reflect particular cognitive functions, such as memory, attention or problem-solving. Cognitive rehabilitation focuses on identifying and addressing individual needs and goals, which may require strategies for taking in new information or compensatory methods such as using memory aids.	'No treatment', 'standard treatment', 'wait list control', 'active control' which does not involve cognitive training or cognitive rehabilitation	See summary in box below.	1. Y 2. CA 3. Y 4. Y 5. Y 6. Y 7. Y 8. Y 9. Y 10. N 11. N

The authors identified 11 RCTs that reported on cognitive training interventions and one RCT that reported on cognitive rehabilitation [204]. The overall quality of cognitive training trials was low to moderate. The quality of the cognitive rehabilitation RCT was high.

Cognitive training

Outcome: Cognition. Result: Data from six studies (with 173 participants) was pooled and found no significant effect on global measures of cognition (SMD 0.10, 95%CI -0.21 to 0.40)
Outcome: ADL function Result: Data from four studies (with 107 participants) was pooled. The result was not significant (SMD 0.00, 95% CI -0.38 to 0.38)
Outcome: Self-reported QOL Result: None of the included studies reported on outcomes for self-reported quality of life
Outcome: Carer impact Result: Two studies (with 66 participants) reported outcomes for carer impact. The result was not significant (SMD 0.11, 95% CI -0.38 to 0.61)
Outcome: Harms: Result: None reported

Cognitive rehabilitation

Outcome: Cognition Result: Tool to measure global cognition not used
Outcome: ADL function Result: Assessed using the Independent Living Skills Health and Safety subscale. No sig diff between groups (intervention mean 29.84 (4.55) vs control mean 30.85 (4.28)
Outcome: Self-reported QOL Result: Assessed using the Qol-AD. No significant differences between groups (intervention mean 38.05 (5.11) vs control mean 36.86 (7.2)
Outcome: Carer impact Result: Assessed using the Relatives' Stress Scale. No significant differences between groups (intervention mean 23.08 (12.21) vs control mean 26 (11.2)
Outcome: Harms Result: None reported

Abbreviations: ADL – Activities of Daily Living; CA – can't answer; CI – confidence interval; N – No; QOL – Quality of Life; RCTs – randomised-controlled trials; sig diff – significant difference; SMD – standardised mean difference; Y – Yes;

Appraisal criteria: (1) 'a priori' design provided, (2) Duplicate study selection and data extraction, (3) Comprehensive literature search, (4) Grey literature search, (5) List of included and excluded studies provided, (6) Characteristics of included studies provided, (7) Scientific quality of the included studies assessed and documented, (8) Scientific quality of included studies used to formulate conclusions, (9) Methods to combine findings appropriate, (10) Publication bias assessed, (11) Conflict of interest included for review and each of the included studies.

Table 102 Evidence summary of randomised controlled trials published subsequently to the included systematic reviews for SRQ12: Cognitive training and rehabilitation

Reference Country	Type	N	Participants Age Gender Other	Intervention	Comparison	Main Outcomes	Measures	Length of follow up	Results/ Effect size	Risk of bias[1]
Cognitive stimulation training										
Orrell 2014 Aguirre 2014 [205 206] UK	RCT	236	Age: (mean) 83 Gender: 65% F intervention 62% F control MMSE: (mean) 18/30	The intervention group participated in a cognitive stimulation therapy program followed by a 24-week maintenance CST program. Each maintenance CST session has a specific theme or activity (i.e. current affairs, my life, word games) within a consistent structure including orientation-based activity, refreshments and a group song. Sessions were 1 hour in duration and conducted once a week	Standard cognitive stimulation program then treatment as usual. Treatment as usual varied across the 18 centres but other activities were generally available to both groups	Cognition; QOL	ADAS-Cog; QOL-AD; MMSE; DEMQOL; Neuro-psychiatric Inventory; AD Cooperative Study – ADL scale	Months 3 and 6	At 3 months, the intervention group had improved significantly in ADL function (effect size 0.11). At 6 months the intervention group had improved significantly in self-reported QOL (effect size 0.12). There were no significant effects on the other outcome measures. The intervention subgroup taking AChEIs showed cognitive benefits (on the MMSE) at 3 (P = 0.03) and 6 months (P = 0.03)	1. Low 2. Low 3. High 4. Low 5. Low 6. Low

Reference Country	Type	N	Participants Age Gender Other	Intervention	Comparison	Main Outcomes	Measures	Length of follow up	Results/ Effect size	Risk of bias[1]
Cognitive training										
Lee 2013 [207] Hong Kong	RCT	19	Age: (mean) 78 Gender 68% F MMSE: (mean) 15/30 computer group; 17/30 therapist led group; 18/30 control group	Arm 1: computer based memory training program. Arm 2: therapist led memory training program. Dose of both programs was 12 sessions of individualised 30 minute errorless learning memory training. Both programs were structured with training components including: basic training on various memory types; memory strategies for using mnemonics (like chunking, organization, and categorization) and learning principles, and also on name/face association; advanced memory training on application of strategies to ADL, including home-making, habit training, money management, shopping, and community-living skills.	Wait list control group	Cognition	MMSE; Mattis Dementia Rating Scale; Hong Kong List Learning Test; Brief Assessment of Prospective Memory-Short Form; Geriatric Depression Scale-Short Form; Chinese Modified Barthel Index; Hong Kong Lawton Instrumental Activities of Daily Living Scale	Post intervention and 3 months post intervention	The authors reported that there was a significant difference between groups on the Geriatric Depression Scale with best results in the therapist led group (N.B. Lack of statistical significance observed by reviewers when calculating the mean difference in RevMan).	1. Unclear 2. Unclear 3. High 4. Low 5. Unclear 6. Unclear

Abbreviations: ADAS-Cog – Alzheimer's Diesease Assessment Scale – Cognition; ADL – Activities of Daily Living; CA – can't answer; CI – confidence interval; CST – cognitive stimulation training ; MMSE mini mental state examiniation; N – No; QOL – Quality of Life; RCT – randomised-controlled trial; SMD – standardised mean difference; Y – Yes;

1. Risk of bias: (1) Random sequence generation, (2) Allocation concealment, (3) Blinding of participants and personnel, (4) Blinding of outcome assessment, (5) Incomplete outcome data, (6) Selective reporting

Table 103 GRADE Evidence Profile Cognitive stimulation therapy for people with dementia

Quality Assessment							Effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**		
Cognition (assessed with a global cognition measurement tool)								
15	Randomised trials	Serious[1]	No serious inconsistency	Serious[3]	No serious imprecision	None	Pooling of 14 RCTs found positive benefits in favour of intervention: SMD 0.41 (95% CI 0.25 to 0.57).[200] One additional RCT (Orrell) found no significant differences between groups. [205 206]	⊕⊕OO LOW
ADL function								
5	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[4]	None	Pooling of 4 RCTs found no significant impact on ADL function: (SMD 0.21 (95%CI -0.05 to 0.47)[200] One additional RCT (Orrell) found a small significant effect on ADL midway through intervention (effect size 0.11) [205 206]	⊕⊕OO LOW
Self-reported QOL								
5	Randomised trials	Serious[1]	Serious[2]	No serious indirectness	Serious[4]	None	Pooling of 4 RCTs found positive benefits in favour of intervention: SMD 0.38 (95%CI 0.11 to 0.65)[200] One additional RCT (Orrell) found a small significant effect on ADL post intervention (effect size 0.12) [205 206]	⊕OOO VERY LOW
Carer impact								
2	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[4]	None	Pooling of 2 RCTs found no significant impact on carer impact (SMD -0.03 (95% CI -0.35 to 0.29) [200]	⊕⊕OO LOW

Quality Assessment							Effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**		
Harms								
0	No evidence available					None		

Abbreviations: ADL – Activities of Daily Living; QOL – Quality of Life; RCT – randomised-controlled trial; SMD – standardised mean difference; SR – Systematic Review;

[1] *Aspects of methodology poorly reported in multiple studies*

[2] *Mixed findings across studies*

[3] *Surrogate outcome*

[4] *Total sample size <400*

Table 104 GRADE Evidence Profile: Cognitive training for people with dementia

Quality Assessment							Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Cognition (assessed with a global cognition measurement tool)								
7	Randomised trials	Serious[1]	Serious[2]	Serious[3]	Serious[4]	None	Pooling of 6 RCTs in found no significant differences between groups (SMD 0.10, 95%CI -0.21 to 0.40) [201] One additional trial (Lee) found no significant differences between groups [207]	⊕OOO VERY LOW
ADL function								
5	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[4]	None	Pooling of 4 RCTs found there were no significant differences between groups (SMD 0.00, 95% CI -0.38 to 0.38) [201] One additional trial (Lee) found no significant differences between groups [207]	⊕⊕OO LOW
Self-reported QOL								
0	No evidence available					None		
Carer impact								
2	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[4]	None	Pooling of 2 RCTs found there were no significant differences between groups (SMD 0.11, 95% CI -0.38 to 0.61) [201]	⊕⊕OO LOW
Harms								
0	No evidence available					None		

Abbreviations: CI – confidence interval; SMD – standardised mean difference; SR – Systematic Review;

[1] Aspects of methodology poorly reported in multiple studies

[2] Mixed findings across studies

[3] Surrogate outcome

[4] Total sample size <400

Table 105 GRADE Evidence Profile: Cognitive rehabilitation for people with dementia

Quality Assessment							Effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**		
Cognition (assessed with a global cognition measurement tool)								
0	No evidence available					None		
ADL function								
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[4]	None	1 RCT (Clare) found no significant differences between groups [204]	⊕⊕⊕O MODERATE
Self-reported QOL								
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[4]	None	1 RCT (Clare) found no significant differences between groups [204]	⊕⊕⊕O MODERATE
Carer impact								
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[4]	None	1 RCT (Clare) found no significant differences between groups [204]	⊕⊕⊕O MODERATE
Harms								
0	No evidence available					None		

Abbreviations: RCT – randomised-controlled trial;

[1] Aspects of methodology poorly reported in multiple studies

[2] Mixed findings across studies

[3] Surrogate outcome

[4] Total sample size <400

SRQ13: Acetylcholinesterase inhibitors and memantine

Clinical question

The research question as defined in the protocol and the associated PICO criteria are listed below in Table 106.

Table 106 PICO for SRQ13: Acetylcholinesterase inhibitors and memantine

Clinical question: For people with dementia/mild cognitive impairment*, do acetylcholinesterase inhibiting drugs/memantine produce benefits/harms?			
Population	**Intervention**	**Comparator**	**Outcome**
a. Examined by dementia subtypes: - *Alzheimer's disease:* studies were included if they reported a population comprising adults with AD. Trials that included participants with mixed dementia were included if the predominant dementia was AD. - *Vascular dementia* - *Dementia with Lewy Bodies* - *Parkinson's Disease Dementia* *b.* Mild cognitive impairment*	Donepezil, Galantamine, Rivastigmine, Memantine (for Alzheimer's disease) Combination therapy (acetylcholinesterase inhibitor plus memantine)*	Placebo or usual care	Cognition ADL function BPSD QOL Adverse events

*Combination therapy and mild cognitive impairment were added as components of the systematic review in response to feedback received during public consultation.

Literature review search strategies:

Searches for existing HTAs and Systematic reviews

Searches to identify existing HTAs and systematic reviews were conducted in the databases specified in Table 107, using the search terms listed in the Guideline Technical Report Volume 2.

Table 107 Searches for existing HTAs and systematic review for SRQ13: Acetylcholinesterase inhibitors and memantine

Database	Date searched	Search re-run	Period covered	Citations retrieved
Population: dementia				
HTA	5 October 2014	9 March 2015	2005 to March 2015	28
Cochrane (Cochrane reviews, Cochrane protocols, DARE)	5 October 2014	9 March 2015	2005 to March 2015	84
MEDLINE	5 October 2014	9 March 2015	2005 to March 2015	168
PsycInfo	5 October 2014	9 March 2015	2005 to March 2015	72
EMBASE	5 October 2014	9 March 2015	2005 to March 2015	32
PubMed	5 October 2014	9 March 2015	2005 to March 2015	9
Population: mild cognitive impairment – searches for HTAs, systematic reviews and RCTs				
HTA	15 July 2015	N/A	2005 to Dec 2014	1
Cochrane (Cochrane reviews, Cochrane protocols, DARE)	15 July 2015	N/A	2005 to Dec 2014	13
MEDLINE	15 July 2015	N/A	2005 to Dec 2014	257
PsycInfo	15 July 2015	N/A	2005 to Dec 2014	180
EMBASE	15 July 2015	N/A	2005 to Dec 2014	35
PubMed	16 July 2015	N/A	2005 to Dec 2014	0

The most recent, comprehensive and highest quality systematic review/HTA identified examining acetylcholinesterase inhibitors/memantine for mild to moderately severe Alzheimer's disease was a NICE technology appraisal which searched for evidence in March 2010. An additional systematic review including people with severe Alzheimer's disease was included [208].

Four additional systematic reviews were included that evaluated acetylcholinesterase inhibitors for people with other types of dementia: Parkinson's disease dementia or Dementia with Lewy Bodies [209], Donepezil for vascular dementia [210], Rivastigmine for vascular dementia [211] and Galantamine for vascular dementia [212].

Following public consultation, a systematic review by Tricco et al. (2013) was identified and included as the most recent systematic review of acetylcholinesterase inhibitors/memantine for mild cognitive impairment.[213]

Searches for additional primary studies

Searches were conducted in the databases listed in Table 108 to identify additional primary studies published since the search period of the included reviews for the use of acetylcholinesterase inhibitors/memantine in people with dementia. The search terms used are listed in the Guideline Technical Report Volume 2.

Searches for primary studies conducted in people with MCI were combined with the search for existing HTAs/systematic reviews, as shown in Table 107.

Table 108 Searches for primary studies/randomised controlled trials for SRQ13: Acetylcholinesterase inhibitors and memantine, population dementia

Database	Dates searched	Period covered	Citations retrieved
MEDLINE	25 September 2014	2009 – September 2014	183
PsycInfo	25 September 2014	2009 – September 2014	146
EMBASE	25 September 2014	2009 – September 2014	43
PubMed	25 September 2014	2009 – September 2014	0

Criteria for selecting studies for review

Table 109 Inclusion and exclusion criteria for SRQ13: Acetylcholinesterase inhibitors and memantine

Characteristic	Criteria
Study design	Inclusion: Randomised controlled trials
Population	Inclusion: *Dementia:* Alzheimer's disease: Studies were included if they reported a population comprising adults with AD. Trials that included participants with mixed dementia were included if the predominant dementia was AD. Parkinson's disease dementia Dementia with Lewy Bodies Vascular dementia *Mild cognitive impairment:* Studies were included if they reported a population comprising adults with mild cognitive impairment Exclusion: *Mild cognitive impairment:* People with subjective memory loss were excluded
Intervention	Inclusion: Donepezil, Galantamine, Rivastigmine, Memantine (for Alzheimer's disease), combination therapy Exclusion: *Mild cognitive impairment:* Studies of combination therapy were excluded
Comparator	Inclusion: Placebo or usual care
Outcomes	Inclusion: Cognition, ADL function, BPSD, QOL, Adverse events
Publication type	English language

Search results:

Table 110 Systematic reviews and HTA report included in the review for SRQ13: Acetylcholinesterase inhibitors and memantine

Intervention	Included systematic reviews/HTAs
Acetylcholinesterase inhibitors/memantine for mild to moderately severe AD	Bond 2012 (NICE HTA) [214]
Acetylcholinesterase inhibitors for severe AD	Di Santo [208]
Acetylcholinesterase inhibitors for PDD and DLB	Wang 2015 [209]
Donepezil for vascular dementia	Malouf 2003 [210]
Rivastigmine for vascular dementia	Birks 2013 [211]
Galantamine for vascular dementia	Birks 2013 [212]
Combination therapy for AD	Schmidt 2015 [215]
Acetylcholinesterase inhibitors/memantine for mild cognitive impairment	Tricco 2013 [213]

Primary studies

For the population of dementia, a total of 372 citations were retrieved in the electronic database searches; 253 studies were viewed in full text and 9 were included in the evidence update. In the review for mild cognitive impairment, a total of 486 citations were retrieved in the database searches; two were viewed in full text. One systematic review and no additional primary studies were included in the evidence update.

Evidence summary:

Acetylcholinesterase inhibitors/memantine for mild to moderately severe Alzheimer's disease (or mixed dementia where the primary type is Alzheimer's disease).

The NICE Guideline was amended in 2012 to reflect the updated NICE technology appraisal of donepezil, galantamine, rivastigmine and memantine for Alzheimer's disease.[214] The appraisal summarised evidence from RCTs published before March 2010. The review included four systematic reviews and 17 RCTs (Table 111). The quality of trials ranged from low quality to high quality; however, overall the authors of the review reported that the quality of the trials was 'disappointing'. The authors concluded that cholinesterase inhibitors were beneficial although there was debate regarding the magnitude of effect .[214] The NICE Guideline Committee used this information to make a recommendation that donepezil, galantamine, rivastigmine were recommended as options for managing mild to moderate Alzheimer's disease and that memantine was recommended as an option for managing people with moderate to severe Alzheimer's disease.

This evidence update involved a search for RCTs published from 2010 onwards. A total of nine RCTs meeting the inclusion criteria were identified. One new RCT examined the effect of donepezil vs placebo [216], one new RCT examined the effect of galantamine vs placebo[217], one RCT already included in the technology appraisal reported new data on rivastigmine patches [218] and six new RCTs examined the effects of memantine vs placebo [219-224] (Table 112).

Donepezil versus placebo

The NICE technology appraisal identified 19 RCTs investigating the effectiveness of donepezil compared with placebo. This evidence update identified one additional low-moderate quality RCT [216] (see Table 111, Table 112). Overall, meta-analysis of cognitive outcomes showed a significant benefit from donepezil at 24 weeks (10 RCTs; SMD=0.40 (95%CI 0.29 to 0.50). Benefits were also seen on functional outcome at 24 weeks (5 RCTs; SMD=0.30 (95%CI 0.14 to 0.45). Pooling of four RCTs found that there was no significant improvement associated with donepezil on BPSD (measured using the Neuropsychiatric Inventory) at 12 weeks (SMD=WMD -2.25 (95%CI -5.11 to 0.61) or 24 weeks (SMD=WMD -3.12 (95%CI -8.17 to 1.93)). One trial reporting outcomes at 60 weeks did not find a significant effect. Only two RCTs measured effects on quality of life and findings were mixed with one study reporting significant improvement associated with donepezil and the other reporting no significant differences between groups. These RCTs were not pooled. Adverse events associated with donepezil were common. Adverse event data from eleven trials were examined in the NICE HTA; of these, there were no statistical comparisons of overall event rates (total, serious or drug-related) in three trials; seven found no significant differences between trial arms and one demonstrated significantly higher overall event rates in the donepezil arm. The most frequently reported symptoms were nausea and vomiting (4 to 24% of participants), diarrhoea (4 to 17%), headache and dizziness (3 to 13%), agitation (0 to 13%). In general, the proportion of withdrawals due to adverse events was similar across intervention and control groups. Three studies which compared 5mg and 10mg doses of donepezil found higher rates of withdrawal in the group receiving 10 mg. See Table 113

Rivastigmine versus placebo

The NICE technology appraisal identified seven RCTs investigating the effectiveness of rivastigmine compared with placebo. This evidence update identified additional information (tolerability of rivastigmine patches) for one of the seven RCTs already included in the technology appraisal (see Table 111, Table 112).[225] Overall, pooling of cognitive outcome data found a significant effect at 24-26 weeks based on 4 studies (SMD = 0.28 (95% CI 0.14 to 0.42). In addition, there was a significant effect on ADL function (SMD = 0.21 (95% CI 0.12 to 0.29), based on 3 studies). There were mixed findings for the effect of taking rivastigmine on BPSD with one study reporting a significant effect and the other reporting no effect. Overall, there was a high percentage of adverse events, ranging from 51% to 91% in the treatment groups and from 46% to 76% in control groups. The main adverse events were gastrointestinal: the lower dose (9.5 mg/day) transdermal patch produced fewer side effects than the capsule (12 mg/day). Two studies that reported rates of any adverse event found a significant increase in the rivastigmine arm. One study reporting overall serious adverse event rates did not find any significant difference between rivastigmine and placebo [214]. See Table 114

Galantamine versus placebo

The NICE technology appraisal identified eight RCTs investigating the effectiveness of galantamine versus placebo. This evidence update identified one additional RCT.[217] (see Table 111, Table 112) Overall, meta-analysis showed a significant effect on cognition (WMD=-2.39, 95%CI -2.8 to -1.97), measured by the ADAScog at 12-16 weeks). Results from the additional RCT were in accord with this. A significant effect was also seen on ADL function (SMD=0.27, 95%CI 0.18 to 0.34, based on 4 studies) and a reduction in BPSD measured using the Neuropsychiatric Inventory (based on 2 studies). Overall, there was a high percentage of adverse events in both treatment and control groups although more people in the galantamine treatment group experienced adverse events. The main adverse events were gastrointestinal, dizziness and headaches. Withdrawals due to adverse events resulted in a loss of between 6 and 44% of galantamine participants (compared to 5 to 9% of

placebo subjects), with differences following a dose–response relationship. Testing of serious adverse event rates for the three studies reporting this found no statistically significant difference between groups. Testing found that three of four published studies had significantly higher withdrawals due to adverse events for galantamine in contrast to placebo. See Table 115

Memantine versus placebo

The NICE technology appraisal identified two RCTs investigating the effectiveness of memantine versus placebo in subjects with moderately severe to severe AD. In one of the RCTs, subjects were enrolled in the study after at least 6 months donepezil treatment; memantine was administered in addition to ongoing donepezil therapy [226]. This evidence update identified an additional six RCTs [219-224]. (see Table 111, Table 112) While one RCT reported that there was a significant effect of memantine on cognition (measured using the SMMSE at 12 weeks), six RCTs reported no significant differences between groups on cognition at follow up assessments ranging from 24-52 weeks. Two studies were pooled and found a significant effect on function at 24 weeks whereas an additional study found no differences between groups on function. Six studies measured the effects of memantine on BPSD; Three studies reporting BPSD outcomes measured by the NPI at 24 weeks were pooled, showing a significant reduction in favour of memantine (WMD -1.23, 95%CI -1.5 to -0.97). One other RCT found significant difference between groups in favour of memantine on the NPI at 12 weeks .[227] Two RCTs with longer follow-up of one to two years found no significant difference in BPSD (as measured by the NPI) between groups. Overall, the studies identified similar numbers and types of adverse events across groups. The main adverse events were agitation, hypertension, falls, dizziness and headache. See Table 116

Comparisons of cholinesterase inhibitors

While this evidence update did not include studies comparing the efficacy of cholinesterase inhibitors it is useful to note that the NICE technology appraisal identified seven RCTs that involved head-to-head comparisons and did not recommend use of one cholinesterase inhibitor over another.[214]

Acetylcholinesterase inhibitors for severe Alzheimer's disease

A systematic review examining the efficacy of acetylcholinesterase inhibitors by dementia severity was included in the evidence update as a source of studies in people with severe dementia (Table 111).[208] The review included six RCTs conducted in people with severe dementia. The trials were generally large in terms of sample size and were assessed as being at low risk of bias. All six trials found a positive effect on cognition. There were mixed results for impact on ADL function (with two of four studies reporting positive results) and one of five RCTs found a positive effect on BPSD. See Table 117

Acetylcholinesterase inhibitors for Parkinson's disease dementia and Dementia with Lewy Bodies

Wang and colleagues completed a systematic review for people with PDD and DLB arguing that clinical and neuropathological symptoms were highly similar in both conditions and thus they may be the same condition or within a spectrum of disorders [209] (Table 111). The authors included ten trials in the analysis. Most studies were of moderate to high quality. The review included people who were on average mild to moderate in terms of severity of dementia. The meta-analysis revealed statistically significant positive effects on cognition. Studies examining the impact of BPSD were mixed: meta-analysis failed to find an overall significant result however, two of the five studies within the analysis reported significant reductions (on doses of 10mg Donepezil and 12 mg Rivastigmine). One trial found a small but significant improvement in ADL function. There were more

adverse events in the groups receiving the acetylcholinesterase inhibitors; these included anorexia, nausea, vomiting, diarrhoea, aggravation of Parkinson and psychiatric symptoms, tremor, fall, somnolence, insomnia, pain, hallucination, confusion, dizziness, urinary tract infection and respiratory tract infection. See Table 118

Acetylcholinesterase inhibitors for people with vascular dementia

Three Cochrane reviews looked at the efficacy of donepezil, rivastigmine and galantamine for people with vascular cognitive impairment [210-212] (Table 111). An additional RCT investigating donepezil was also included - it was published after the associated Cochrane review [228](Table 112). The trials predominantly included people with a diagnosis of probable vascular dementia. The trials were generally large and at low risk of bias. However, most were conducted or supported by the pharmaceutical company. Use of acetylcholinesterase inhibitors was consistently associated with small but significant improvements in cognitive function and ADL function. There was little evidence for an effect on BPSD and people taking the medications experienced significantly more adverse effects than those taking the placebo. The studies suggest there is more evidence supporting donepezil and galantamine than rivastigmine. (See Table 119, Table 120, Table 121)

Acetylcholinesterase inhibitors used in combination with memantine

In response to comments received during the public consultation phase of guideline development, evidence on the use of combination therapy with an acetylcholinesterase inhibitor and memantine in comparison to acetylcholinesterase inhibitor monotherapy (ie. an acetylcholinesterase inhibitor alone) was considered. The 2012 NICE HTA identified two studies of combination therapy.[214] Pooled data from these studies failed to show any additional benefit on functional, behavioural or global outcomes. The search for systematic reviews and HTAs was updated to July 2015 and a more recent meta-analysis of combination therapy in people with moderate to severe Alzheimer's disease including data from two newer trials was identified and included for review (Table 111).[215]

The 2015 meta-analysis pooled data from the four trials to demonstrate significant benefits of combination therapy in comparison to acetylcholinesterase inhibitor monotherapy for cognition (SMD -0.27, 95% CI -0.37 to -0.17) and behaviour (SMD -0.19; 95% CI -0.31 to -0.07). No significant effect on activities of daily living was observed (SMD -0.08, 95%CI -0.18 to 0.02). The pooled estimate of serious adverse event rates was not significantly different between treatments (Risk Difference –0.02; 95%CI –0.06 to 0.02). The authors used GRADE to rate the quality of the evidence for each outcome; the quality ranged from low to high. The overall quality of the evidence, based upon the lowest quality of the critical outcomes, is considered to be low. Note that the GRADE Evidence Profile has not been reproduced here but can be found in the 2015 meta-analysis published by Schmidt and colleagues.

Acetylcholinesterase inhibitors or memantine for mild cognitive impairment

During the public consultation phase it was raised that there was existing evidence that supported a recommendation (a practice point) against the use of cholinesterase inhibitors for people with mild cognitive impairment.

The 2006 NICE Guideline conducted a systematic review of studies of acetylcholinesterase inhibitors and memantine to March 2006. Two randomised placebo controlled trials of donepezil and two trials of galantamine for the treatment of amnestic mild cognitive impairment were included. It was concluded that these studies failed to show benefits that outweighed potential adverse events for both of these drugs and it was recommended that acetylcholinesterase inhibitors should not be used

in people with Mild Cognitive Impairment. The 2012 NICE HTA did not assess the effectiveness of acetylcholinesterase inhibitors or memantine in people with mild cognitive impairment. [214]

This evidence update involved a search for HTAs and systematic reviews of the effectiveness of acetylcholinesterase inhibitors or memantine in people with mild cognitive impairment published from 2005 onwards. One systematic review of studies published to November 2011 by Tricco and colleagues was included (Table 111).[213] The review included eight placebo controlled trials enrolling between 51 and 1058 people with mild cognitive impairment, published to 2007. Seven studies were of acetylcholinesterase inhibitors. The single study of memantine only contributed serious adverse event rates to the review. No additional randomised controlled trials published after the search dates of the Tricco were identified. The use of acetylcholinesterase inhibitors showed no significant changes in cognition, activities of daily living, behavioural and psychological symptoms of dementia, mortality or serious adverse events. Treatment was however associated with a significant increase in individual adverse event rates, including nausea and diarrhoea, vomiting and headache. The studies did not support a role for acetylcholinesterase inhibitors in treating people with mild cognitive impairment. See Table 122.

Evidence statements	*GRADE Quality*	*Related recommendations*
Pooling of nine studies (out of 10) found a significant effect on cognition at 24 weeks in people with mild to moderate Alzheimer's disease taking donepezil.[214] (Table 113)	Low	EBR 69
Pooling of four RCTs found that there was no significant improvement associated with donepezil on BPSD (measured using the Neuropsychiatric Inventory) at 12 weeks or 24 weeks in people with mild to moderate Alzheimer's disease.[214](Table 113)	Moderate	EBR 69
Pooling of four RCTs of rivistagmine found a significant improvement in cognition at 24 weeks.[214] (Table 114)	Low	EBR 69
One small RCT of rivistagmine found a significant benefit on BPSD, while a larger RCT did not.[214] (Table 114)	Moderate	EBR 69
Pooling of seven RCTs of galantamine found a significant improvement in cognition at 12 to 16 weeks.[214] (Table 115)	Low	EBR 69
Two pooled studies of galantamine found a significant improvement in BPSD (measured using the Neuropsychiatric Inventory) in people with mild to moderate Alzheimer's disease; this was not associated with an increase in the number of serious adverse events.[214] (Table 115)	Moderate	EBR 69
In people with moderately severe to severe Alzheimer's disease; pooled data from three RCTs of memantine found a significant improvement in BPSD (measured using the Neuropsychiatric	Moderate	EBR 71

Evidence statements	*GRADE Quality*	*Related recommendations*
Inventory) at 24 weeks.[214 229] Two RCTs reporting longer-term outcomes (at one to two years) did not find a significant effect.[220 224] There were no significant differences in adverse events between memantine treatment and placebo .[214] [219 220 223 227 229] (Table 116)		
Six RCTs found that acetylcholinesterase inhibitors were associated with significantly improved cognitive function in people with severe Alzheimer's disease[208]. Two (of four) RCTs found a significant improvement on ADL function[208]. One (of five) RCTs showed a significant reduction in BPSD.[208] (Table 117)	Moderate	EBR 69
Pooling of nine RCTs in a systematic review showed a significant improvement in cognitive function amongst people with Dementia with Lewy Bodies and Parkinson's Disease dementia taking acetylcholinesterase inhibitors [209]; One of the RCTs in the review measured impact on ADL function and found a significant improvement.[209] (Table 118)	Low	EBR 72
Systematic reviews [210-212] and one additional study [228] found that six (of eight) RCTs found a statistically significant improvement in cognition in people with vascular dementia taking acetylcholinesterase inhibitors compared to those taking a placebo; Three (of seven) RCTs found a positive impact on ADL function.[210-212 228] (Table 119, Table 120, Table 121)	Low	EBR 72
Pooled data from four RCTs of combination therapy of an acetylcholinesterase inhibitor and memantine, in comparison to acetylcholinesterase inhibitor monotherapy, found a significant improvement in cognition and behaviour, with no significant difference in activities of daily living or the rate of serious adverse events at 24 to 30 weeks.[215]	Low	EBR 73
A systematic review [213] reported that in people with mild cognitive impairment, pooled data from placebo-controlled RCTs of acetylcholinesterase inhibitors did not find any significant effect on cognition (8 RCTs), behaviour (1 RCT), activities of daily living (2 RCTs), overall mortality (3 RCTs) or serious adverse events (4 RCTs). Treatment was associated with a significant increase in the rates of nausea and diarrhoea (4 RCTs), vomiting (3 RCTs) and headache (2 RCTs). [213] (Table 122)	Low	EBR 75

Resource requirements

The three acetylcholinesterase inhibitors and memantine are reimbursed through the Pharmaceutical Benefits Scheme (PBS) and are available in a variety of formulations and doses and are produced by a number of manufacturers.

Reimbursement through the PBS for the three acetylcholinesterase inhibitors is for mild to moderately severe Alzheimer's disease (MMSE ≥10). Reimbursement for memantine is for moderately severe Alzheimer's disease (MMSE 10-14). The maximum price paid by consumers is $37.70.

The drugs (their trade names) and the relevant PBS codes are:

- Acetylcholinesterase inhibitors:
    - o donepezil (Aricept®), PBS Codes: 2479L, 2532G, 8495D, 8496E (max$37.70)
    - o galantamine (Reminyl®, Galantyl®), PBS Codes: 2463P, 2531F, 2537M, 8770N, 8771P, 8772Q (max $37.70 for 28 units)
    - o rivastigmine (Exelon®), PBS Codes: 2475G, 2476H, 2477J, 2493F, 2494G, 2526Y, 2551G, 8497F, 8498G, 8499H, 8500J, 8563Q, 9161E, 9162F (max $37.70 for 28 units)
- Memantine (Memanxa®, Ebixa®, APO-Memantine®) (PBS Codes: 1956Y, 2492E, 2513G, 9306T). [230]

There are also a number of generic products available at lower prices.

People who are unable to register the relevant score on the MMSE or SMMSE for reasons other than their Alzheimer's disease can be assessed using the Clinicians Interview Based Impression of Severity (CIBIS) scale. For people with non-Alzheimer's disease dementias, or Alzheimer's disease of a different severity, the full cost is paid by the consumer.

Table 111 Evidence summary of systematic reviews & HTA for SRQ13: Acetylcholinesterase inhibitors and memantine

Reference	Study Design/Level of Evidence	Types of studies included	Types of participants included	Intervention	Comparison	Results	Quality appraisal[1]
Alzheimer's disease							
Bond 2012 [214]	Health Technology Assessment	RCTs	People with mild to moderately severe Alzheimer's disease	Donepezil, rivastigmine, galantamine, memantine	Placebo	The authors identified four SRs and 17 RCTs. The authors concluded that "The additional clinical effectiveness evidence identified continues to suggest clinical benefit from the AChEIs in alleviating AD symptoms, although there is debate about the magnitude of the effect. Although there is also new evidence on the effectiveness of memantine, it remains less supportive of this drug's use than the evidence for AChEIs". The quality of included trials was 'disappointing'. "The conclusions concerning cost-effectiveness are quite different from the previous assessment. This is because both the changes in effectiveness and costs between drug use and non-drug use underlying the ICERs are very small. This leads to highly uncertain results, which are very sensitive to change".	1. Y 2. Y 3. Y 4. Y 5. Y 6. Y 7. Y 8. Y 9. Y 10. Y 11. Y

Results:

Donepezil vs placebo

19 RCTs in mild to moderately severe AD.

Cognition at 24 weeks: SMD 0.395 (95%CI 0.293 to 0.497) based on 9 studies

ADL function at 24 weeks: SMD 0.298 (95%CI 0.144 to 0.452) based on 5 studies

BPSD (NPI measured) at 12 weeks: WMD -2.249 (95%CI -5.105 to 0.606) based on 4 studies; at 24 weeks SMD=WMD -3.12 (95%CI -8.17 to 1.93)

QOL: results not pooled and mixed findings. One study found an increase in QOL whereas the other didn't

Adverse events:

Eleven trials reported adverse events; of these, four did not report statistical comparisons of overall event rates, four found no significant differences between trial arms and two demonstrated significantly higher event rates in the donepezil arm.

The most frequently reported symptoms were nausea and vomiting (4 to 24% of participants), diarrhoea (4 to 17%), headache and dizziness (3 to 13%), agitation (0 to 13%). The following adverse events were reported significantly more often in the donepezil than the placebo arm in included studies: anorexia, diarrhoea, dyspepsia, nausea, urinary tract infection, vomiting, fatigue, muscle cramps, dizziness, insomnia, pain.

The SR reported that: "Adverse events affected participants receiving donepezil more than those on placebo, and higher doses of donepezil increased the incidence of people suffering from adverse events. Nausea, vomiting and diarrhoea were the main adverse events. Most were described as mild to moderate. Withdrawals due to adverse events generally resulted in similar losses between the low-dose donepezil groups and placebo; however, higher doses of donepezil tended to lead to more withdrawals". Eleven trials reported adverse events; of these, four did not report statistical comparisons of overall event rates, four found no significant differences between trial arms and two demonstrated significantly higher event rates in the donepezil arm .

Rivastigmine vs placebo

Cognition at 24 weeks: SMD 0.28 (95%CI 0.14 to 0.42) based on 4 studies

ADL function at 24 weeks: SMD 0.21 (95%CI 0.12 to 0.29) based on 3 studies

BPSD: results not pooled and mixed findings. One study reported benefit associated with treatment whereas the other didn't

QOL: no studies

Adverse events: 2 studies reporting rates of any adverse event found a significant increase with rivastigmine (Feldman, Winblad 2007). One study found no significant difference between rivastigmine and placebo for overall serious AE rates (Feldman 2007). The SR reported that overall, there was a high percentage of any AEs, from 51% to 91% in the treatment groups and 46% to 76% in control groups. The main AEs were gastrointestinal: the lower dose (9.5 mg/day) transdermal patch had fewer AEs than the capsule (12 mg/day). Two studies reporting rates of any AE found a significant increase in the rivastigmine arm (Feldman, Winblad 2007). One study reporting overall serious AE rates did not find any significant difference between rivastigmine and placebo (Feldman 2007).

Reference	Study Design/Level of Evidence	Types of studies included	Types of participants included	Intervention	Comparison	Results	Quality appraisal[1]
Galantamine vs placebo Cognition (ADAS-Cog) at 12-16 weeks: WMD -2.39 (95%CI -2.8 to -1.97) based on 7 studies ADL function at 21 weeks: SMD 0.27 (95%CI 0.18 to 0.34) based on 4 studies BPSD (NPI measured) at 16-21 weeks: WMD -1.46 (95%CI -2.59 to -0.34) based on 2 studies QOL: no studies Adverse events: High percentage of any AE reported. One RCT (Brodaty) galantamine 79% vs placebo 70%. One RCT (Rockwood) galantamine 84% vs placebo 62%. Withdrawals due to adverse events: galantamine 6 to 44%, placebo 5 to 9%, with differences following a dose–response relationship . *Memantine vs placebo* 2 multicentre RCTs of 20mg/day memantine conducted in moderately severe to severe AD (Reisberg, Tariot), over 24-28 weeks. In 1 RCT subjects received ongoing donepezil therapy, subjects enrolled in the study after ≥6 months donepezil treatment (Tariot). Cognition: WMD 3.254 (95%CI -2.233 to 8.741) based on 2 studies ADL function at 24 weeks: WMD 1.41 (95%CI 0.04 to 2.78) based on 2 studies BPSD (NPI measured) at 24 weeks: WMD -1.608 (95%CI -4.739 to 1.523) based on 2 studies QOL: no studies Adverse events: Overall the studies identified similar numbers and types of adverse events across groups. The main AEs were agitation, hypertension, falls, dizziness, headache.							
Di Santo 2013 [208]	Systematic Review	RCTs	People with Alzheimer's disease **(includes severe AD)**	Donepezil, rivastigmine, galantamine, memantine	Placebo	The authors identified 34 RCTs meeting the inclusion criteria. Of these, 6 RCTs examined efficacy in people with severe dementia (Winblad 2006, Black 2007, Homma 2008, Feldman 2001, Lopez-Pousa 2005, Burns 2009). All 6 RCTs showed a significant effect on cognition in favour of cholinesterase inhibitors. Two (of four) RCTs found a significant effect on function and one (of five) RCTs found an effect on global BPSD. They concluded that the efficacy of the acetylcholinesterase inhibitors was independent of dementia severity on cognition.	1. CA 2. CA 3. Y 4. Y 5. N 6. N 7. N 8. CA 9. Y 10. N 11. N
Results: Composite size effect on cognition (noting that lower scores indicate higher cognitive function) Winblad 2006: -0.32, (95%CI -0.5 to -0.14) Black 2007: -0.32 (95%CI -0.53 to -0.10) Homma 2008: -0.71 (95%CI -0.92 to -0.51) Feldman 2001: -0.43 (95%CI -0.60 to -0.26) Lopez-Pousa 2005: -0.30 (95%CI -0.57 to -0.03) Burns 2009: -0.22 (95%CI -0.43 to -0.02) Composite size effect on function Winblad 2006: -0.28 (95%CI -0.53 to -0.03) Black 2007:-0.11 (95%CI -0.34 to 0.12) Homma 2008: -0.18 (95%CI -0.46 to 0.10) Feldman 2001: -0.31 (95%CI -0.41 to -0.21)							

Reference	Study Design/Level of Evidence	Types of studies included	Types of participants included	Intervention	Comparison	Results	Quality appraisal[1]
Composite size effect on global BPSD Winblad 2006: -0.14 (95%CI -0.39 to 0.11) Black 2007: 0.08 (95%CI -0.14 to 0.31) Homma 2008: 0.03 (95%CI -0.16 to 0.23) Feldman 2001: -0.39 (95%CI -0.63 to -0.15) Lopez-Pousa 2005: -0.11 (95%CI -0.38 to 0.16) * Note: The authors did not assess the risk of bias for the included studies so we sourced the 6 RCTs involving people with severe dementia and completed risk of bias assessment. Overall, the studies were deemed to be at low risk of bias when assessed with the Cochrane Risk of Bias tool although most were funded by pharmaceutical companies							
Parkinson's disease dementia; dementia with Lewy bodies							
Wang 2015 [209]	Systematic Review	Placebo controlled double blind RCTs	Parkinson's disease dementia; dementia with Lewy bodies; CIND-PD	Acetylcholine sterase inhibitors and memantine	Placebo	The authors completed a search up until May 2013. The authors included ten trials in the meta-analysis (5 donepezil, 2 rivastigmine, 3 memantine). Study quality was assessed using the Cochrane Risk of Bias tool and studies were mostly moderate to high quality with the exception of two studies (Leroi 2004 and Leroi 2009) where quality was unclear due to poor reporting. The average MMSE at baseline ranged from 17.9 to 21.7 across trials indicating mild to moderate severity.	1. CA 2. Y 3. Y 4. Y 5. N 6. Y 7. Y 8. Y 9. Y 10. Y 11. N
Cognition: Donepezil and rivastigmine produced significant effects on mean MMSE change scores in meta-analysis, and WMDs were 2.57 points (95% CI 0.90 to 4.23) on donepezil 5 mg, 1.31 (95% CI 0.09 to 2.53) on donepezil 10 mg, 1.04 (95% CI 0.43 to 1.65) on rivastigmine 12 mg. BPSD: Of five RCT examining the effect on global NPI score, there was a trend towards reduced BPSD in all studies however, this was only statistically significant in two trials (Donepezil 10mg and Rivastigmine 12mg). ADL: One trial of rivastigmine (12mg) found a small but statistically significant result on ADL: SMD of 0.21 (95%CI 0.02 to 0.40) Safety: the number of drop outs was significantly higher in rivastigmine 12mg treated groups than that in the placebo-treated groups (177/421 vs 42/240, RR 1.59, 95%CI 1.16 to 2.19). The number of drop outs for adverse events was not significantly greater in rivastigmine than placebo (69/421 vs 21/240, RR 1.69, 95%CI 0.84 to 3.41). Adverse events were inconsistently reported. Common adverse events were anorexia, nausea, vomiting, diarrhoea, aggravation of Parkinson and psychiatric symptoms (tremor, fall, somnolence, insomnia, pain, hallucination, confusion), dizziness, UTI, respiratory tract infection. Most AEs were mild or moderate. Rivastigmine groups experienced significantly more AEs than placebo (357/421 vs 173/240, RR 1.19, 95%CI 1.04 to 1.36).							

Reference	Study Design/Level of Evidence	Types of studies included	Types of participants included	Intervention	Comparison	Results	Quality appraisal[1]
Vascular dementia							
Birks 2013 [211]	Systematic review	RCTs	People with vascular cognitive impairment	Rivastigmine	Placebo	The search was completed in February 2013. Three RCTs (with 800 participants) were included in the review. Two trials were smaller and one trial larger (n=710). Average MMSE scores ranged from 13/20 to 23.9/30 indicating that patients with a wide spectrum of severity were included. Results were not pooled due to heterogeneity of severity of dementia. Two of the studies (Ballard and Narasimhalu) were deemed to be at low risk of bias whereas the remaining study (Mok) was deemed to be at high risk of bias.	1. Y 2. CA 3. Y 4. Y 5.NA 6. Y 7. Y 8. Y 9. Y 10. CA 11. Y
Results: Ballard 2008 included people with mild to moderate vascular dementia and found a small but significant effect on the MMSE in the intervention group ((MD 0.60, 95% CI 0.11 to 1.09). There were no significant differences between groups on ADL function or BPSD. This study showed a significant difference in withdrawals before the end of treatment, with more participants withdrawing from the rivastigmine group than from the placebo group (rivastigmine 90/365, placebo 48/345, OR 2.02, 95% CI 1.38 to 2.98, P value 0.0003). A greater number of some adverse effects (nausea, vomiting, diarrhoea and anorexia) were documented in the rivastigmine group than in the placebo group. Mok 2007 involved participants with an average MMSE of 13/30 indicating moderate to severe dementia. There were no statistically significant differences between groups on cognition, ADL function or BPSD or adverse events. Narasimhalu 2010 involved participants with mean MMSE scores around 23/20 indicating mild severity dementia. There were no significant differences between groups in cognition, BPSD or ADL function. There were no significant differences between groups in adverse events. The authors concluded that only one trial found beneficial effects and that rivastigmine was associated with a larger number of adverse events							
Birks 2013 [212]	Systematic review	RCTs	People with vascular cognitive impairment	Galantamine	Placebo	The search was completed in January 2013. The authors included two trials (with 1378 participants) that were both deemed to be at low risk of bias. Both trials were of six months duration and were testing a galantamine dose of 16-24 mg/day in two divided doses. Trials were not pooled	1. Y 2. Y 3. Y 4. Y 5.Y 6. Y 7. Y 8. Y 9. Y 10. CA 11. Y
GAL-INT-6 trial: beneficial effect found on cognition (ADAS-cog/11 MD -2.29, 95%CI -3.46 to -1.12), BPSD (NPI MD -2.06, 95%CI -4.09 to -0.03) and ADL function (DAD-ADL 4.10, 95%CI 1.25 to 6.95). There were significantly more adverse events in the galantamine group relative to the placebo group. The main events reported were nausea and vomiting. GAL-INT-26 trial: beneficial effect found on cognition (ADAS-cog/11 MD -1.5, 95%CI -2.39 to -0.61). Negative effect on BPSD associated with intervention and with benefits seen in the placebo group (MD 1.8, 95%CI 0.29 to 3.31). There were significantly more AEs in the intervention group.							
Malouf 2009 [210]	Systematic review	RCTs	People with vascular cognitive impairment	Donepezil	Placebo	The search was completed in 2003 and the review edited in 2009 with no change to conclusions. The review included two RCTs (with 1219 participants with mild to moderate cognitive decline). Donepezil was administered at 5 or 10 mg a day.	1. Y 2. Y 3. Y 4. Y 5.Y

Reference	Study Design/Level of Evidence	Types of studies included	Types of participants included	Intervention	Comparison	Results	Quality appraisal[1]
							6. Y 7. Y 8. Y 9. Y 10. CA 11. Y
Cognition: Both studies found beneficial effect at 12 and 24 weeks on the ADAS-Cog and MMSE MMSE: donepezil (5 mg/day) at 24 weeks (WMD 0.83, 95% CI 0.38 to 1.29, P = 0.0004) (completers); donepezil (10 mg/day) at 24 weeks (WMD 1.08, 95%CI 0.62 to 1.55, P < 0.00001) (completers) ADL: Both studies found beneficial effect on ADL function. Adverse events: Donepezil was well tolerated. There were a broad range of adverse events reported and most AEs were transient (eg nausea, diarrhoea, anorexia and cramp). AEs were more frequent on the 10mg dose relative to the 5mg dose.							
Combination therapy							
Schmidt 2015 EFNS [215]	Systematic review	RCTs	Moderate to severe AD	ChEI plus memantine	ChEI alone	The search was completed in June 2014. The authors included four trials (with 1549 patients with moderate to severe Alzheimer's disease) of 24 to 30 weeks duration . Three studies compared 20mg per day with placebo in patients on a stable dose of AChEI. The remaining study used 28mg memantine extended release which is equivalent to 20mg. The studies were assessed as being at low risk of bias according to GRADE.	1. CA 2. CA 3. Y 4. Y 5. Y 6. Y 7. Y 8. Y 9. Y 10. Y 11. N
Results and GRADE assessment (as assessed by EFNS authors): Cognition: Pooled data from 4 trials showed significant benefit of combination therapy vs AChEI alone (SMD -0.27; 95% CI -0.37 to -0.17), as measured by the ADAS-Cog and SIB; **GRADE Quality: moderate**. ADL: Non significant change in pooled data from 4 trials (SMD -0.08; 95%CI -0.18 to 0.02) as measured on the ADCS-ADL and BADLS; **GRADE Quality: low**. Behaviour and mood: Pooled data from 4 trials showed significant benefit of combination therapy as measured by the NPI (SMD -0.19; 95%CI -0.31 to -0.07); **GRADE Quality: high**. Serious adverse events: No significant differences in serious adverse events rates (RD -0.02; 95%CI -0.06 to 0.02); **GRADE Quality: low**.							
Mild cognitive impairment							
Tricco 2015 [213]	Systematic review	RCTs	Diagnosis of MCI	Donepezil, rivastigmine, galantamine or memantine	Other cognitive enhancers, placebo or supportive care	The search was completed in November 2011. The review included 8 placebo controlled RCTs conducted between 1999 and 2007; 2 of galantamine (16-24 mg), 4 of donepezil (5-10mg), 1 of rivastigmine (3-12mg) and 1 of memantine (10-20mg). The duration of the studies ranged from 19 to 208 weeks. Three studies had a low risk of bias, 1 study had a high risk of bias for one item and 4 studies had an unclear risk of bias for at least 2 criteria.	1. Y 2. Y 3. Y 4. Y 5. Y 6. Y 7. Y 8. Y 9. Y 10. Y 11. Y

Reference	Study Design/Level of Evidence	Types of studies included	Types of participants included	Intervention	Comparison	Results	Quality appraisal[1]
Tricco et al (2015) cont[d] Cognition: Donepezil vs placebo showed no difference in cognition by MMSE at median of 36 weeks follow-up (3 RCTs, MD 0.14, 95%CI -0.22 to 0.50). Donepezil or galantamine vs placebo showed no sig diff on ADAS-Cog in pooled analysis after median 24 weeks (5 RCTs, MD -0.07, 95%CI -0.16 to 0.01) BPSD: Donepezil vs placebo no sig diff on NPI at 48 weeks (MD 0.8, 95%CI -0.59 to 2.19) Function (ADL): Galantamine vs placebo no significant difference in ADL after 96 weeks (2 RCTs, MD 0.30, 95%CI 0.26 to 0.86) Mortality (overall): No sig diff vs placebo after median 156 weeks (3 RCTs, donepezil, rivastigmine or galantamine RR = 1.84, 95%CI 0.41 to 8.20). Mortality (treatment related): No sig diff donepezil vs placebo (1 RCT, RR = 2.97, 95%CI 0.31 to 28.4) Adverse events: No significant difference for serious adverse events treatment vs placebo, median 48 weeks, (4 RCTs, RR = 0.97, 95%CI 0.86 to 1.10) Significantly greater individual adverse event rates treatment vs placebo after 126 weeks for nausea (4 RCTs donepezil, rivastigmine or galantamine, RR = 3.04, 95%CI 2.52 to 3.66) and diarrhoea (4 RCTs donepezil, rivastigmine or galantamine, RR 2.33, 95%CI 1.74 to 3.13), vomiting (median 208 weeks, 3 RCTs, RR = 4.40, 95%CI 3.21 to 6.03), headaches (median 152 weeks, 2 RCTs, RR = 1.27, 95%CI 1.04 to 1.53) Significantly greater bradycardia vs placebo (1 RCT galantamine, 96 weeks, RR = 1.52, 95%CI 1.04 to 2.22), but significantly fewer falls (1 RCT galantamine, 96 weeks, RR =0.71, 95%CI 0.52 to 0.98).							

Abbreviations: ADAS-Cog = Alzheimer's Disease Assessment Scale – Cognitive Subscale; AChEI = acetylcholinesterase inhibitor(s); ADL=Activities of Daily living; AE = adverse event; BADLS = Bristol Activities of Daily Living Scale; BPSD=behavioural and psychological symptoms of dementia; QOL=quality of life; NPI=Neuropsychiatric Inventory; RD = risk difference; SIB = severe impairment battery.

1. AMSTAR: Appraisal criteria: (1) 'A priori' design provided, (2) duplicate study selection and data extraction, (3) comprehensive literature search, (4) grey literature search, (5) list of included and excluded studies provided, (6) characteristics of included studies provided, (7) scientific quality of the included studies assessed and documented, (8) scientific quality of included studies used to formulate conclusions, (9) methods to combine findings appropriate, (10) publication bias assessed, (11) conflict of interest included for review and each of the included studies.

Y=yes; N=no; CA=can't answer, SR=systematic review; RCT=randomised controlled trial, AD=Alzheimer's disease; SMD=standardised mean difference; WMD=weighted mean difference; AE=adverse event;

Table 112 Evidence summary of randomised controlled trials for SRQ13: Acetylcholinesterase inhibitors and memantine

Reference Country	Type	N	Participants	Intervention	Comparison	Main Outcomes	Measure/s	Length of follow up	Results/ Effect size	Risk of bias[1]
Donepezil										
Maher-Edwards 2011 [216]	RCT	198	Patients with mild-to-moderate probable AD (MMSE scores 12–26)	Three arm trial: Donepezil at 10 mg/day (n=67); Comparator drug: SB-742457 at 35 mg/day (n=68)	Placebo, (n=61)	Cognition	CIBIC+ score; ADAS-Cog score	Week 0, 8,16, 24	Drug-placebo treatment differences in CIBIC+ score at week 24 were non-significant (-0.28 (90% CI: -0.61, 0.05)) for donepezil. Drug-placebo treatment differences (90% CI) in change from baseline ADAS-Cog score at week 24 were non-significant (-1.2 (-3.0, 0.6)) for donepezil. All treatments were generally safe and well tolerated. Four patients on donepezil prematurely withdrew due to adverse events. Two patients died from the donepezil treatment group. Adverse events: Nasopharyngitis, urinary tract infection, upper abdominal pain, headache and nausea.	1. Low 2. Unclear 3. Unclear 4. Unclear 5. Low 6. Low

Reference Country	Type	N	Participants	Intervention	Comparison	Main Outcomes	Measure/s	Length of follow up	Results/ Effect size	Risk of bias[1]
Roman 2010 [228]	RCT	974	Patients with probable or possible vascular dementia Intervention group mean age 73.4, 61% male; control group mean age 72.3, 54% male Mean MMSE 23.5 in both groups	Donepezil 5 mg/day	Placebo	Cognition	Vascular AD Assessment Scale-Cognitive Subscale (V-ADAScog); Clinician's Interview–Based Impression of Change plus carer interview (CIBIC-Plus); ADAS-cog; Mini Mental State Examination (MMSE); executive clock-drawing task; Executive Interview (EXIT25); Disability Assessment for Dementia (DAD); and Clinical Dementia Rating-Sum of Boxes (CDR-SB).	weeks 6, 12, 18, and 24	Patients treated with donepezil showed significant improvement compared with those taking placebo on the V-ADAS-cog at end point and at all time points except week 6. The least-squares mean change from the baseline total score at end point was1.03±0.25 (donepezil group) and 0.12±0.35 (placebo group), indicating a slight improvement in those receiving donepezil and relative stability in the placebo group. No difference between donepezil and placebo was demonstrated for CIBIC-Plus at end point. Significant treatment differences favouring donepezil were demonstrated at end point for the ADAS-cog and Mini Mental State Examination. DAD scores showed significantly greater improvement in the donepezil group at week 24 mean difference=2.24; 95% CI, 0.36 to 4.12; *P*<0.02) and a trend at end point (*P*<0.06). At end point, a treatment difference favouring donepezil was demonstrated on the NCT. No significant differences were observed on the CLOX, EXIT25, Clinical Dementia Rating-Sum of Boxes, or Maze.	1. Unclear 2. Unclear 3. Low 4.Low 5. High 6. Low
Rivastigmine										
Cummings 2010 (USA) [225] Note: Continuation of #140 in HTA	RCT	1195	Patients aged 50–85 years with Mini-MMSE of 10–20 and diagnoses of dementia of the Alzheimer type and probable AD	Rivastigmine Active patch treatment (4.6 mg/24 h or 9.5 mg/ 24 h) (n=574)	Placebo patches (5 cm2/10 cm2) (n=579)	Skin tolerability	Adverse reactions	52 weeks	Overall, the data support a favourable skin tolerability profile for the rivastigmine transdermal patch, and provide reassurance that the benefits of rivastigmine patch therapy for patients with AD are not confounded by significant skin irritation problems.	1. Unclear 2. Unclear 3. Unclear 4. Unclear 5. Low 6. Low

Reference Country	Type	N	Participants	Intervention	Comparison	Main Outcomes	Measure/s	Length of follow up	Results/ Effect size	Risk of bias[1]
Galantamine										
Hager 2014 [217]	RCT	2045	Adult outpatients, aged 45 to 90 years (inclusive), with mild to moderate, probable or possible AD; and patient with or without cerebrovascular disease, having a CT or MRI of the head performed since the diagnosis of AD, and before inclusion in the study, a MMSE score of 10–26, and a responsible caregiver.	Galantamine oral extended release capsules equivalent to 8 mg, 16 mg and 24 mg (n=1024)	Matching placebo and dose (n=1021)	Safety ; efficacy	Mortality was assessed; primary efficacy end point was cognitive change from baseline to month 24, as measured by the MMSE score	Post treatment follow-up phase of 30 days; 2-year study	Mortality rate signif lower for galantamine vs placebo (hazard ratio [HR] =0.58; 95% confidence interval [CI]: 0.37; 0.89) (*P*=0.011). Cognitive impairment, based on the mean (SD) change in MMSE scores, baseline to month 24, signif worsened in placebo (−2.14 [4.34]) vs galantamine group (−1.41 [4.05]) (*P*<0.001). Functional impairment, based on mean (SD) change in the Disability Assessment in Dementia score, at month 24 significantly worsened in the placebo (−10.81 [18.27]) versus the galantamine group (−8.16 [17.25]) (*P*=0.002). Incidences of treatment-emergent adverse events were 54.0% for the galantamine and 48.6% for the placebo group. Adverse events: Nausea, headache, vertigo, insomnia, hypertension, vomiting, weight decreased, decreased appetite, diarrhea, nasopharyngitis, agitation, fatigue and anxiety. Except for gastrointestinal galantamine-associated adverse effects, the adverse events incidences were similar to placebo.	1. Low 2. Low 3. Low 4. Low 5. Low 6. High
Memantine										
Ashford 2011 (USA) [219]	RCT	13	Mild to moderately patients with a probable AD diagnosis and their caregivers; Mean age 76; 0.38% female; MMSE score (19.9 ± 4.8 and 21.8 ± 3.1)	A one-year course of Memantine	Placebo	Changes on MRI ; Changes in cognitive and function scale scores.	Change from the baseline to the final study visit in the MRS NAA/Cr ratio of the inferior parietal region; change from the baseline to the final study visit in the ADAS-cog measure..	Brief visits at months 1, 3, 6 and 9	This pilot study failed to demonstrate a benefit of memantine on the primary outcome measure, the inferior parietal NAA/Cr ratio, or the secondary outcome measures. First, the placebo and treatment groups' inferior parietal region NAA/Cr ratio did not differ significantly at baseline (treatment group M = 1.47 ± 0.11; placebo group M = 1.38 ± 0.10; p > .1) or follow-up (treatment group M = 1.62 ± 0.14; placebo group M= 1.41 ± 0.10; p = 0. 09). Second, the two groups' ADAS-cog scores also did not differ significantly at baseline (treatment group M = 44.67 ± 10.30; placebo group M = 49.17 ± 8.37; p > .1) or follow up (treatment group M = 45.75 ± 7.99; placebo group M = 50.39 ± 8.88; p > .1). Adverse events were not reported.	1. Unclear 2. Unclear 3.High 4. Low 5. Low 6. Low

Reference Country	Type	N	Participants	Intervention	Comparison	Main Outcomes	Measure/s	Length of follow up	Results/ Effect size	Risk of bias[1]
Dysken 2014 (USA) [220]	RCT	613	Patients with mild to moderate AD; MMSE 12-26	20mg/d of memantine (n=155); 2000 IU/d of alpha tocopherol (n=152); the combination (n=154)	Placebo (n = 152)	ADL function	ADCS-ADL Inventory score (range, 0-78). Secondary measures: MMSE; ADASCog; NPI; Caregiver Activity Survey	Mean (SD) follow-up time of 2.27 (1.22) years	No significant differences in the groups receiving memantine alone or memantine plus alpha tocopherol. ADCS-ADL scale: Mean difference of memantine compared with placebo (95% CI): 1.98 (−0.24 to 4.20). Unadjusted *P* value: 0.08. Adjusted *P* value: 0.4. 3 (1%) withdrew because of an adverse event possibly related to the study medication.	1. Low 2. Unclear 3. Unclear 4. Unclear 5. Low 6. Low
Fox 2012 (UK) [227]	RCT	153	Participants with AD and clinically significant agitation from residential care or hospitals. Diagnosis of probable AD; with a SMMSE score of ≤19, Hachinski Score ≤4, being aged ≥45, and a history ≥two weeks of clinically significant agitation (requiring treatment) with a CMAI score of ≥45.	Twice daily memantine 10 mg (titrated in 5 mg increments over four weeks)	Placebo	Agitation	CMAI;12 weeks CMAI; 6 and 12 weeks NPI, Clinical Global Impression Change (CGI-C), Standardized Mini Mental State Examination, Severe Impairment Battery.	Follow-up at weeks 2, 4, 6 and 12.	Memantine did not affect significant agitation in people with in moderate-to-severe AD. No significant differences in the primary outcome, 6 weeks CMAI, between memantine and placebo or CGI-C or adverse events at 6 or 12 weeks. NPI mean difference favoured memantine at weeks 6 (-6.9; -12.2 to -1.6; p = 0.012) and 12 (-9.6; -15.0 to -4.3 p = 0.0005). Memantine was significantly better than placebo for cognition (mean effect of memantine at 12 weeks (1.4 points on SSMSE(95%CI 0.4 to 2.4) There were 4 serious adverse events (3 memantine and 1 placebo). The levels of adverse events were similar for memantine and placebo Adverse events: Headache, fatigue, somnolence, confusion, hallucinations, constipation, vomiting, dizziness, abnormal gait, death.	1. Low 2. Low 3. Low 4. Unclear 5. Low 6. Low

Reference Country	Type	N	Participants	Intervention	Comparison	Main Outcomes	Measure/s	Length of follow up	Results/ Effect size	Risk of bias[1]
Herrmann 2013 [229]	RCT	369	Patients with moderate-to-severe AD with NPI total score ≥13 and NPI agitation/aggression score ≥1; average = 75; ave MMSE = 12	20-mg memantine	Placebo	Co-primary outcome measures were behaviour, measured by total NPI score, and cognition, using the SIB. Secondary outcome measures were CIBIC-Plus, the 19-item ADCS-ADL total score and the CMAI total score.	Primary efficacy: ANCOVA of change baseline to Week 24 in NPI and SIB total Efficacy analysed using mixed-effect model repeated measure and ANCOVA based on observed cases. Secondary efficacy analyses: ANCOVA of change baseline to Week 24 in ADCS-ADL19 score and NPI sub-items. Descriptive analyses of total scores and changes baseline to Week 24 were CMAI and CIBIC-Plus.	The NPI was assessed at the screening, baseline, Week 4, Week 8, Week 12, Week 18, and Week 24 visits.	This study was prematurely terminated due to recruitment problems. There were no statistically significant differences between memantine and placebo in mean change from baseline in NPI, SIB, or any of the secondary outcome measures. Analysis was by ANCOVA with treatment and center as factors and baseline score as covariate. Behaviour improved in both groups (total NPI change scores −3.90 ± 1.24 for memantine and −5.13 ± 1.23 for placebo). Memantine was generally well tolerated and patient retention in both treatment arms was good. 10 participants who received memantine discontinued intervention due to adverse events. Approx 3/4 all patients had AEs, the incidence of which was similar in treatment and control groups. The incidence of *severe AE*s was 3% placebo and 9% memantine. AEs *related* to the study drug by the investigator was 30% placebo and 36% memantine. The incidence of adverse events that contributed to withdrawal was 5% in the placebo group and 8% in the memantine group.	1. Low 2. Unclear 3. Low 4. Low 5.Low 6. Low
Herrmann 2013 Cont[d]									The only adverse event that contributed to withdrawal in more than two patients in either treatment group was *agitation*, which contributed to withdrawal in one patient in the placebo group and three patients in the memantine group. Adverse events with an incidence ≥5%: Falls, agitation, weight decreased, somnolence, nausea.	

Reference Country	Type	N	Participants	Intervention	Comparison	Main Outcomes	Measure/s	Length of follow up	Results/ Effect size	Risk of bias[1]
Saxton 2012 [223]	RCT	265	Patients with AD; MMSE 10–19	Memantine (10 mg bid) (n=136)	Placebo (n=129)	functional communication abilities; treatment-emergent adverse events	Functional Linguistic Communication Inventory (FCLI); American Speech-Language-Hearing Association Functional Assessment of Communication Skills for Adults	12 weeks	In moderate AD, memantine treatment improved functional communication, as recognized by caregivers. After 12 weeks, non-signif improvement on FCLI with memantine (placebo: −0.6; memantine: 0.7; $p = 0.070$, LOCF; $n = 133$) and signif improvement on ASHA FACS (placebo: −5.3; memantine: 0.5; $p = 0.022$), vs placebo ($n = 124$). Potentially clinically significant AEs occurring more frequently with memantine: weight increase of≥7% (2.3% vs. 0%), weight decrease of ≥7% (2.3% vs. 0%), and DBP≥180mmHg that also represented a change of at least 20mm Hg over baseline (1.5% vs. 0%). Memantine had a low incidence of adverse events (only dizziness and restlessness were notably higher with memantine) Adverse events: Dizziness, upper respiratory tract infection, fall, hypertension, oedema, peripheral headache, restlessness diarrhoea, nausea, agitation, syncope	1. Low 2. Low 3.Unclear 4. Unclear 5. Low 6. Low

Reference Country	Type	N	Participants	Intervention	Comparison	Main Outcomes	Measure/s	Length of follow up	Results/ Effect size	Risk of bias[1]
Wilkinson 2012 [224]	RCT	278	Patients with probable AD; mean age 74; MMSE) score ≥12 and ≤20 at screening and baseline	Memantine (n=134) Up-titrated to the target dose of 20 mg/day over 4 weeks	Placebo (n=144)	Rate of total brain atrophy (TBA); several cognitive and behavioural scales	Serial MRI using the Brain Boundary Shift Integral (BBSI);	52 weeks; MRI scans collected over at weeks 4, 42, and 52	In the primary efficacy analysis, the differences in TBA rates no sig diff memantine (15.2 mL/year) vs placebo (15.3 mL/year) (−0.04 mL/year [(95% CI: −2.60, 2.52), p = 0.98]). AEs considered related to the investigational medicinal product by the investigator: 32% memantine vs 22% placebo. Memantine AEs: 5 patients had severe, related adverse events (atrial fibrillation and cardiac failure, visual acuity reduced, constipation, ankle fracture and fall, delusion). Placebo AEs: 6 patients had severe, related adverse events (fall and femoral neck fracture, convulsion, somnolence and urinary incontinence, anxiety, hypotension, abnormal behaviour). The incidence of AEs that contributed to withdrawal was11%in the memantine group and8%in the placebo group. The AEs were distributed across many symptoms and diagnoses with no apparent trend.	1. Low 2. Low 3. Low 4. Low 5. Low 6. Low

Abbreviations: AE=Adverse Events; RCT=randomised controlled trial; CIBIC= Clinicians Global Impression of Change; ADAS-Cog= The Alzheimer's Disease Assessment Scale – Cognitive section; AD=Alzheimer's disease; MMSE=Mini Mental State Examination; SD=Standard Deviation; CI=Confidence Interval; CMAI=Cohen Mansfield Agitation Inventory; SSMSE=Standardised Mini Mental State Examination; NPI=Neuropsychiatric Inventory; SIB= Severe Impairment Battery; LOCF= Last observation carried forward; signif = significant(ly); DBP = diastolic blood pressure

Risk of bias: (1) Random sequence generation, (2) Allocation concealment, (3) Blinding of participants and personnel, (4) Blinding of outcome assessment, (5) Incomplete outcome data, (6) Selective reporting

Table 113 GRADE Evidence Profile: Donepezil for Alzheimer's disease

Quality assessment							Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Cognition (follow-up 24 to 26 weeks); assessed with: cognitive outcome measures (pooled))								
10	randomised trials	serious[1]	no serious inconsistency	serious[3]	no serious imprecision	None	Pooling of 9 studies found a positive effect : SMD=0.395 (95%CI 0.293 to 0.497) in favour of donepezil [214] An additional RCT (Maher-Edwards, N=198) found no significant differences between groups on the ADASCog [216]	⊕⊕OO LOW
ADL function (follow-up mean 24 weeks)								
5	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	None	Pooling of 5 studies found a positive effect: SMD=0.298 (95%CI 0.144 to 0.452) in favour of donepezil[214]	⊕⊕⊕O MODERATE
BPSD (NPI at 12 to 60 weeks)								
4	randomised trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision	None	Pooling of 4 studies at 12 weeks WMD -2.249 (95%CI -5.105 to 0.606) (non-significant) or 24 weeks (SMD=WMD -3.12 (95%CI -8.17 to 1.93) [214]	⊕⊕OO LOW
QOL								
2	randomised trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision	None	Studies were not pooled by Bond and colleagues (for reasons not stated). One study found a significantly difference in QOL between groups at 12 weeks (in favour of the placebo group). The other study found no sig difference between groups. [214]	⊕⊕OO LOW
Adverse events								
12	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	None	Bond and colleagues reported : "Adverse events affected participants receiving donepezil more than those on placebo; higher doses of donepezil increased the incidence of people suffering from adverse events. Nausea, vomiting and diarrhoea were the main adverse events. Most were described as mild to moderate. Withdrawals due to adverse events generally resulted in similar losses between the low-dose donepezil groups and placebo; however, higher doses of donepezil tended to lead to more withdrawals" [214]	⊕⊕⊕O MODERATE

1 Risk of bias present in at least one study or unclear details due to poor reporting

2 Mixed findings between studies

3 Downgraded due to surrogate outcome (cognition)

Table 114 GRADE Evidence Profile: Rivastigmine for Alzheimer's disease

Quality assessment							Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Cognition (follow-up mean 24-26 weeks; assessed with: cognitive outcomes)								
4	randomised trials	serious[1]	no serious inconsistency	Serious[3]	no serious imprecision	none	Pooling of 4 studies found a positive effect: SMD = 0.28 (95% CI 0.14 to 0.42) in favour of rivastigmine [214]	⊕⊕OO LOW
ADL function (follow-up mean 24-26 weeks; assessed with: Functional outcomes)								
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Pooling of 3 studies found a positive effect: SMD = 0.21 (95% CI 0.12 to 0.29) in favour of rivastigmine [214]	⊕⊕⊕O MODERATE
BPSD (follow-up 12-24 weeks)								
2	randomised trials	Serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Studies were not pooled due to heterogeneity. One small study (N=66) found a significant benefit associated with rivastigmine whereas the larger study (N=529) found no significant difference between groups. [214]	⊕⊕⊕O MODERATE
QOL								
0	No evidence available					none		
Adverse events								
7	randomised trials	Serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Bond and colleagues reported that overall, there was a high percentage of any AEs, ranging from 51% to 91% in the treatment groups and from 46% to 76% in control groups. The main AEs were gastrointestinal: the lower dose (9.5 mg/day) transdermal patch produced fewer side effects than the capsule (12 mg/day). [214] Additional data from the Cummings study published since the SR found that skin tolerability for the rivastigmine transdermal patch was high. [225]	⊕⊕⊕O MODERATE

1 Risk of bias present in at least one study or unclear details due to poor reporting

2 Mixed findings between studies

3 Downgraded due to surrogate outcome (cognition)

Table 115 GRADE Evidence Profile: Galantamine for Alzheimer's disease

Quality assessment							Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Cognition (follow-up mean 12-16 weeks; assessed with: ADAS-Cog)								
8	randomised trials	serious[1]	no serious inconsistency	Serious[3]	no serious imprecision	none	Pooling of 7 studies found a significant effect : WMD=-2.39 (95%CI -2.8 to -1.97) in favour of galantamine [214] An additional RCT (Hager) found a significant difference between groups in MMSE at 6 months (diff=-0.48 (95%CI -0.73 to -0.22))[217]	⊕⊕OO LOW
ADL function (follow-up mean 21-26 weeks; assessed with: Functional outcome measure)								
5	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Pooling of 4 studies: SMD=0.27 (95%CI 0.18 to 0.34) found a significant effect in favour of galantamine[214] An additional RCT (Hager) found greater functional decline in the placebo group at 12 months relative to the control group (-6.5 points vs -4.55 points on the DAD)[217]	⊕⊕⊕O MODERATE
BPSD (follow-up mean 16-26 weeks; assessed with: NPI)								
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	Pooling of 2 studies found a significant effect: WMD=-1.46 (-2.59 to -0.34) in favour of galantamine[214]	⊕⊕⊕⊕ HIGH
QOL								
0	No evidence available					none		
Adverse events								
9	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	High percentage of any AE reported. Three published RCTs reporting serious adverse event rates found no significant differences between groups. Three of four published studies had significantly higher withdrawals due to adverse events for galantamine in contrast to placebo. One RCT (Brodaty) galantamine 79% vs placebo 70% (sourced from [214]) One RCT (Rockwood) galantamine 84% vs placebo 62% (sourced from [214]) One RCT (Hager) found difference in mortality (3.1% in galantamine group vs 4.9% in placebo group). There were 54% of people with Treatment Emergent AEs in the galantamine group and 49% of people with Treatment Emergent AEs in the placebo group. [217]	⊕⊕⊕O MODERATE

1 Risk of bias present in at least one study or unclear details due to poor reporting
2 Mixed findings between studies
3 Downgraded due to surrogate outcome (cognition)

Table 116 GRADE Evidence Profile: Memantine for Alzheimer's disease

Quality assessment							Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Cognition								
7	randomised trials	serious[1]	no serious inconsistency	serious[3]	no serious imprecision	none	Pooling of 3 studies (Bond et al, Hermann) found a non-significant effect on cognition at 21-24 weeks (WMD 1.8 (95%CI-1.8 to 5.4) on the Severe Impairment Battery).[214 229] Other studies could not be pooled due to the way in which data was reported: One RCT (Fox, N=153)[221] found significant difference between groups on the SMMSE at 12 weeks (1.4 (95%CI 0.4 to 2.4) Three RCTs (Ashford; Dysken;; Wilkinson) found no significant differences between groups at follow-ups at 52 weeks and 2 years). [219 220 224]	⊕⊕OO LOW
ADL function (24-28 weeks)								
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Pooling of two studies: WMD = 1.41 (95%CI 0.04 to 2.78) in favour of memantine at 24 weeks [214] One RCT (Dysken) found no significant differences between groups on the ADCS-ADL at a follow up of 2 years[220]	⊕⊕⊕O MODERATE

Quality assessment							Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
BPSD								
6	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Pooling of 3 studies (2 from Bond et al plus Hermmann) found a significant reduction in favour of memantine (WMD -1.23, 95%CI -1.5 to -0.97) on the NPI at 24 weeks. [214 229] Two RCTs (Dysken; Wilkinson) found no significant differences between groups at follow-ups on the NPI (ranging from 1-2 years)[220 224] One RCT (Fox) found significant difference between groups in favour of memantine (-9.6 points, 95%CI -15.0 to -4.3) on the NPI at 12 weeks [227]	⊕⊕⊕O MODERATE
QOL								
0	No evidence available					none		
Adverse events								
6	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Overall the studies identified similar numbers and types of adverse events across groups. The main AEs were agitation, hypertension, falls, dizziness, headache	⊕⊕⊕O MODERATE

1 Risk of bias present in at least one study or unclear details due to poor reporting

2 Mixed findings between studies

3 Downgraded due to surrogate outcome (cognition)

Table 117 GRADE Evidence Profile: Acetylcholinesterase inhibitors for severe dementia

Quality assessment							Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Cognition								
6	randomised trials	no serious risk of bias	no serious inconsistency	Serious[3]	no serious imprecision	none	All RCTs found a statistically significant effect on cognition in favour of acetylcholinesterase inhibitors. Composite effect sizes ranged from 0.22 to 0.71[208]	⊕⊕⊕O MODERATE
ADL function								
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	2 of the four RCTs in the review [208]reported a significant effect on ADL function in favour of acetylcholinesterase inhibitors. Effect sizes for these two RCTs finding a positive effect were: Winblad 2006: composite size effect = -0.28 (95%CI -0.53 to -0.03) sourced from [208] Feldman 2001: composite size effect = -0.31 (95%CI -0.41 to -0.21) sourced from [208]	⊕⊕⊕⊕ HIGH
BPSD								
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	One of the five RCTs found a significant reduction in global BPSD associated with acetylcholinesterase inhibitors. Feldman 2001: composite size effect: -0.39 (95%CI -0.63 to -0.15) sourced from [208]	⊕⊕⊕⊕ HIGH
QOL								
0	No evidence available					none		

1 Risk of bias present in at least one study or unclear details due to poor reporting
2 Mixed findings between studies
3 Downgraded due to surrogate outcome (cognition)

Table 118 GRADE Evidence Profile: Acetylcholinesterase inhibitors for Parkinson's disease dementia and Dementia with Lewy Bodies

Quality assessment							Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Cognition								
9	Randomised trials	Serious[1]	Serious[2]	serious[3]	no serious imprecision	none	Donepezil and rivastigmine produced significant effects on mean MMSE change scores in meta-analysis, and WMDs were 2.57 points (95% CI 0.90 to 4.23) on donepezil 5 mg, 1.31 (95% CI 0.09 to 2.53) on donepezil 10 mg, 1.04 (95% CI 0.43 to 1.65) on rivastigmine 12 mg. [209]	⊕OOO VERY LOW
ADL function								
1	Randomised trial	no serious risk of bias	no serious inconsistency	Serious[4]	no serious imprecision	None	One trial of rivastigmine (12mg) found a small but statistically significant result on ADL: SMD of 0.21 (95%CI 0.02 to 0.40) [209]	⊕⊕⊕O MODERATE
BPSD								
5	Randomised trials	Serious[1]	no serious inconsistency	serious[4]	no serious imprecision	None	Of five RCT examining the effect on global NPI score, there was a trend towards reduced BPSD in all studies however, this was only statistically significant in two trials (Donepezil 10mg and Rivastigmine 12mg). [209]	⊕⊕OO LOW
QOL								
0	No evidence available							
Adverse events								
10	Randomised trials	Serious[1]	No serious inconsistency	Serious[4]	No serious imprecision		Rivastigmine groups experienced significantly more AEs than placebo (357/421 vs 173/240, RR 1.19, 95%CI 1.04 to 1.36).[209]	⊕⊕OO LOW

1 Risk of bias present in at least one study or unclear details due to poor reporting
2 Mixed findings between studies
3 Downgraded due to surrogate outcome (cognition)
4 Downgraded (population included PDD CIND)

Table 119 GRADE Evidence Profile: Donepezil for vascular dementia

Quality assessment							Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Cognition								
3	Randomised trials	Serious[1]	No serious inconsistency	Serious[3]	No serious imprecision	none	Pooling of two studies found a significant positive effect on the MMSE at 24 weeks (WMD: 0.83, 95%CI 0.38 to 1.29) [210] Another RCT (Roman) found a statistically significant result in favour of donepezil (difference in least squares mean 0.472 (95%CI 0.05, 0.89)[228]	⊕⊕OO LOW
ADL function								
3	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	none	Pooling of two studies found a significant improvement in favour of donepezil (5mg)l at 24 weeks WMD-0.97 [95%CI -1.80 to -0.14][210] Another RCT (Roman) found a trend towards improved ADL function in the donepezil group at 24 weeks (P=0.06). [228]	⊕⊕⊕O MODERATE
BPSD								
0	None							
QOL								
0	None							
Adverse events								
3	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision		There were significantly more adverse events in the donepezil group for digestive system side effects, anorexia, diarrhoea, nausea, insomnia, skin carcinoma, leg cramps, abnormal dreams and rhinitis.[210]	⊕⊕⊕O MODERATE

1 Risk of bias present in at least one study or unclear details due to poor reporting
2 Mixed findings between studies
3 Downgraded due to surrogate outcome (cognition)

Table 120 GRADE Evidence Profile: Rivastigmine for vascular dementia

Quality assessment							Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Cognition								
3	Randomised trials	Serious[1]	Serious[2]	Serious[3]	No serious imprecision	none	A systematic review [211] reported that one RCT found a small but significant effect on cognition on the MMSE (MD 0.60, 95%CI 0.11 to 1.09)]. Two RCTs found no significant differences between groups	⊕OOO VERY LOW
ADL function								
3	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	none	A systematic review [211] reported that three RCTs found no significant differences between groups on ADL function	⊕⊕⊕O MODERATE
BPSD								
3	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	A systematic review [211] reported that three RCTs found no significant differences between groups	⊕⊕⊕O MODERATE
QOL								
0	No evidence available							
Adverse events								
3	Randomised trials	Serious[1]	Serious[2]	No serious indirectness	No serious imprecision	None	One RCT reported significantly more adverse events in the treatment group (nausea, vomiting, diarrhoea, anorexia) Two RCTs found no significant differences between groups (All sourced via [211])	⊕⊕OO LOW

1 Risk of bias present in at least one study or unclear details due to poor reporting
2 Mixed findings between studies
3 Downgraded due to surrogate outcome (cognition)

Table 121 GRADE Evidence Profile: Galantamine for vascular dementia

Quality assessment							Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Cognition								
2	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[3]	No serious imprecision	None	A systematic review [212] reported that two RCTs found significant improvements in cognition GAL-INT-6 trial: MD-2.29 (95%CI -3.46 to -1.12) GAL-INT-26 trial: MD -1.5 (95%CI -2.39 to -0.61)	⊕⊕⊕O MODERATE
ADL function								
1	Randomised trial	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	A systematic review [212] found one RCT found a significant improvement in function MD 4.10 (95%CI 1.25, 6.95)	⊕⊕⊕O MODERATE
BPSD								
2	Randomised trials	No serious risk of bias	Serious[2]	No serious indirectness	No serious imprecision	None	A systematic review [212] found the two RCTs had opposite results: one RCT found reduced BPSD in the intervention group whereas the other RCT found reduced BPSD in the placebo group	⊕⊕⊕O MODERATE
QOL								
0	No evidence available							
Adverse events								
2	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	A systematic review found [212] both RCTs reported significantly more adverse events in the group treated with galantamine. The main AEs were nausea and vomiting.	⊕⊕⊕⊕ HIGH

1 Risk of bias present in at least one study or unclear details due to poor reporting
2 Mixed findings between studies
3 Downgraded due to surrogate outcome (cognition)

Table 122 GRADE Evidence Profile: Acetylcholinesterase inhibitors or memantine for mild cognitive impairment

Quality assessment							Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Cognition								
6	Randomised trials	Serious[1]	No serious inconsistency	Serious[2]	No serious imprecision	none	A systematic review [213] found no significant difference in cognition on MMSE (3 RCTs donepezil at median 36 weeks) or ADAS-Cog (5 RCTs donepezil or galantamine at median 24 weeks)	⊕⊕OO LOW
ADL function								
2	Randomised trials	Serious[3]	No serious inconsistency	No serious indirectness	No serious imprecision	none	A systematic review [213] found two RCTs of galantamine found no significant differences between groups on ADL function at 96 weeks	⊕⊕⊕O MODERATE
BPSD								
1	Randomised trials	Serious[4]	No serious inconsistency	No serious indirectness	No serious imprecision	None	One RCT of donepezil found no significant difference on NPI at 48 weeks.[213]	⊕⊕⊕O MODERATE
QOL								
0	No evidence available							
Adverse events – overall mortality								
3	Randomised trials	Serious[5]	Serious[6]	No serious indirectness	No serious imprecision	None	Pooled estimate from 3 RCTs of donepezil, galantamine and rivastigmine shows no significant effect of treatment at median 156 weeks.[213]	⊕⊕OO LOW
Adverse events – serious adverse events								
4	Randomised trials	Serious[7]	No serious inconsistency	No serious indirectness	No serious imprecision	None	Pooled estimate from 3 RCTs of donepezil, galantamine and rivastigmine shows no significant effect of treatment.[213]	⊕⊕⊕O MODERATE
Adverse events – individual events								
4	Randomised trials	Serious	No serious inconsistency	No serious indirectness	No serious imprecision	None	Pooled estimates show a significant increase in nausea and diarrhoea (4 RCTs), vomiting (3 RCTs) and headache (2 RCTs) at a median of 48 weeks[213]	⊕⊕⊕O MODERATE

[1] All studies had unclear random sequence generation, 2 had unclear allocation concealment, 2 unclear blinding, 2 incomplete outcome data and 4 selective outcome reporting.
[2] Cognition is considered a surrogate outcome; [3] Unclear random sequence generation; [4] Unclear selective outcome reporting
[5] 2 studies unclear randomisation, 1 study unclear allocation concealement, blinding and unclear incomplete and selective outcome reporting
[6] I2 = 80%, confidence intervals of the estimate from 2 studies do not overlap
[7] Unclear random sequence generation in 2 studies, unclear outcome data and reporting in 2 studies

SRQ 14: Souvenaid®

Clinical question

The research question as defined in the protocol and the associated PICO criteria are listed below.

Table 123 PICO for SRQ 14: Souvenaid®

Clinical question: For people with dementia, does Souvenaid® produce benefits/harms?			
Population	**Intervention**	**Comparator**	**Outcome**
People with all forms of dementia **Setting:** all settings	Souvenaid	Placebo or no intervention	Cognition (global measure) Activities of daily living Quality of life (person with dementia) Number of people who suffered at least one adverse event by follow up Memory*

***Memory was added as a outcome following completion of the systematic review, in response to feedback received during public consultation.**

Literature review search strategies:

Searches for existing HTAs and Systematic reviews or randomised controlled trials

A concurrent search for systematic reviews, HTAs and randomised controlled trials was run. Searches to identify existing Health Technology Assessment reports (HTAs), systematic reviews and randomised controlled trials were conducted in the databases specified in Table 124, using the search terms listed in the Guideline Technical Report Volume 2.

Table 124 Searches for existing HTAs and systematic review and randomised controlled trials SRQ 14: Souvenaid®

Database	Date searched	Period covered	Citations retrieved
HTA	3 April 2014	2005 to 2014	0
Cochrane (Cochrane reviews, Cochrane protocols, DARE)	3 April 2014	2005 to 2014	0
MEDLINE	3 April 2014	2005 to 2014	4
PsycInfo	3 April 2014	2005 to 2014	3
EMBASE	3 April 2014	2005 to 2014	3
PubMed	3 April 2014	2005 to 2014	7

No systematic reviews meeting the inclusion criteria were identified.

Criteria for selecting studies for review:

Table 125 Inclusion and exclusion criteria for review for SRQ 14: Souvenaid®

Characteristic	Criteria
Study design	Inclusion: Randomised controlled trials
Population	Inclusion: People with all forms of dementia
Intervention	Inclusion: Souvenaid®
Comparator	Inclusion: Placebo or no intervention
Outcomes	Inclusion: Cognition (global measure), Activities of daily living, Quality of life (person with dementia), memory* Number of people who suffered at least one adverse event by follow up
Publication type	English language

*Memory was added as a outcome following completion of the systematic review, in response to feedback received during public consultation.

Search results:

Primary studies

A total of 17 citations were retrieved in the electronic database searches. 5 papers were viewed in full text and 3 studies were included evidence update (Table 126).

Evidence summary

Souvenaid® is a relatively new product and the NICE guideline committee did not search for evidence related to its effectiveness. This evidence update revealed three randomised controlled trials comprising 1,011 patients which were included in the review [231-235] (Evidence Summary Table 126). All three studies were sponsored by the manufacturer. The three trials were appraised as being at low risk of bias in terms of their methodological quality (Evidence Summary Table 126). Two of the included studies recruited participants with mild Alzheimer's disease [231-234]. Most of the outcomes from these studies could not be pooled due to the way in which data was reported; however, it was possible to calculate a pooled risk ratio for adverse events. The third study recruited patients with mild-to-moderate Alzheimer's disease who were all taking cholinesterase inhibitors and/or memantine [235]; outcomes of this study are presented separately (GRADE Evidence Profile Table 128).

In the Souvenir I study, conducted in patients with mild Alzheimer's disease, a greater proportion of the group receiving treatment showed an improvement in delayed verbal recall (40% vs 25%, P=0.026), a component of the Wechsler Memory Scale, however the mean change was similar between groups.[233] It was necessary to substitute the planned statistical analysis for a non-parametric analysis as approximately 40% of the patients scored zero at baseline. There were no significant differences between groups in the immediate verbal recall test or in global cognitive function, independence in activities of daily living or quality of life. In a subgroup of patients with very mild AD (MMSE 24-26), there was a significant improvement in both delayed verbal recall and immediate verbal recall.

In the Souvenir II study, the change in memory domain NTB z-score from baseline to week 24 did not significantly differ between active versus control group (P=0.09).[234] The 24-week trajectory over

time was reported to significantly differ (P=0.023, Cohen's d=0.21). There was no significant change in the NTB executive function domain z-score at 12 or 24 weeks. The modified NTB total composite z-score showed a trend for effect over the 24-week trajectory over time (P=0.053), with a significant difference in change from baseline to week 24 (P=0.035). This outcome comprised the NTB plus two additional tasks (the ADAS-cog orientation score plus the letter digit substitution test). The findings could not be pooled with those from the Souvenir I study. There was no difference in functional ability between groups.

Results of these studies suggest that some people with mild Alzheimer's disease who drank Souvenaid® were more likely to experience small improvements in some aspects of their memory function (see GRADE Evidence Profile Table 127).

The S-Connect study was conducted in people with mild-to-moderate Alzheimer's disease who were all taking cholinesterase inhibitors and/or memantine [199] At 24 weeks there was no significant difference in ADAS-cog score between study groups (between-group difference of 0.37 points, standard error=0.57, P=0.513). There were no significant differences between groups on the ADSC-ADL or Clinical Dementia Rating. Adverse event rates were similar in both groups (see GRADE Evidence Profile Table 128).

The studies found that Souvenaid® was well tolerated and no significant adverse events were associated with taking the supplement.

There are two ongoing trials of Souvenaid. The LipiDiDiet study is a randomised controlled trial which will examine the effects of Souvenaid taken over 2 years in patients with prodromal Alzheimer's disease on a modified version of the Neuropsychological Test Battery (NTB), in addition to other outcomes. The study has received funding from the European Union. AWARE is an open-label observational study of the use of Souvenaid in patients with early Alzheimer's disease over 12 months and was expected to close in October 2014 (Nederlands Trial Register, NTR3855). This study will examine the effects of Souvenaid on the function of people with dementia as assessed by the caregiver.

Resource requirements

Souvenaid® is not listed on the Australian Therapeutic Goods Register and is not considered by any Australian regulatory body to be a therapeutic good. Souvenaid® should be considered as a dietary supplement. There is no government subsidy available for Souvenaid, so the full cost must be borne by the consumer. As at May 2015, Souvenaid® can be purchased at a concession rate of $3.07 per bottle, or approximately $92 per month.

Formulation of recommendation

The evidence for Souvenaid® had not previously been considered by NICE; recommendations were formulated using the GRADE evidence-to-decision framework and automated voting on the outcomes of cognition, quality of life, activities of daily living and adverse events. Guideline Adaptation Committee members Professors Henry Brodaty, Dimity Pond and Associate Professor Mark Yates left the meeting for discussions. The committee considered the evidence for the benefits, harms and cost to consumers for (a) people with mild to moderate Alzheimer's Disease taking acetylcholinesterase inhibitors and/or memantine or (b) people with mild Alzheimer's Disease. The committee considered that the cost of Souvenaid® was substantial and could increase inequities. On the basis of a lack of convincing evidence for benefit or harm and the cost, the committee formulated a weak negative recommendation: "It is suggested that health care practitioners do not recommend the use of Souvenaid® for people with dementia ." This

recommendation was the subject of many submissions in the public consultation phase. Many consumers and clinicians interpreted this recommendation to be stronger than intended (that is, that clinicians should tell patients not to use Souvenaid). This was not the intention of the recommendation. Feedback indicated that the committee had undervalued memory as an important outcome for people with mild AD and that the product can be made available at a lower price. Small changes were made to the evidence summaries including revising the cost information, adding more detail and incorporating memory as an important outcome. The committee reviewed the evidence further and agreed to remove the recommendation on the basis that the current recommendation was being interpreted as more negative than intended and that the evidence was insufficient to support a recommendation in support of Souvenaid.

The NHMRC advised that a recommendation should be provided. Upon further discussion amongst the Committee, the Committee agreed upon a recommendation based on the critical outcomes (quality of life, ADL) according to GRADE methodology. Evidence for memory was considered as an important (but not critical) outcome for people with mild Alzheimer's disease overall. One member of the Committee favoured a recommendation, based on the memory outcome, articulating that, when asked about the effects of Souvenaid® by consumers, health professionals may advise that there is some evidence that suggests that Souvenaid® may have small benefits for some aspects of memory function in some people with mild Alzheimer's disease who are not using acetylcholinesterase inhibitors. However, the remainder of the committee favoured the included recommendation stating that there is insufficient evidence to draw conclusions for the group with mild Alzheimer's disease.

Evidence statements	*GRADE Quality*	*Rec*
One RCT showed that there were no statistically significant benefits associated with taking Souvenaid® on ADL function (high) or cognition (moderate) in patients with mild to moderately severe Alzheimer's disease taking cholinesterase inhibitors and/or memantine.[235] (Table 128)	Moderate	76
There were no statistically significant benefits associated with taking Souvenaid® on quality of life (1 RCT, moderate) or ADL function (2 RCTs, high) in patients with mild Alzheimer's disease.[233 234] One RCT reported no significant effect on cognition in patients with mild Alzheimer's disease at 12 weeks, while another RCT reported a significant effect at 24 weeks (moderate).[233 234] A significant improvement in memory was demonstrated in a subgroup of people with very mild Alzheimer's disease (MMSE 24-26) in one RCT.[233] Amongst all patients with mild Alzheimer's disease, statistically significant differences were shown in some analyses of some memory outcome measures but not others in two RCTs.[233 234] (Table 127)	Moderate-High	76
In three RCTs, the total number of adverse events did not differ significantly between those taking Souvenaid® and those taking placebo (high).[231-235] (Table 127, Table 128)	High	76

NA – Not Applicable. Due to the uncertainty in the body of evidence for the effectiveness of Souvenaid no recommendation was made.

Table 126 Evidence Table for included randomised controlled trials of Souvenaid®

Reference Country	Study Design	N(n)	Participants	Intervention	Comparison	Main Outcomes	Measure/s	Length of follow up	Results/ Effect size	Risk of bias[1]
Scheltens 2010 [233] Kamphuis 2011[2] [232] 'Souvenir I Study' 5 countries (Europe and United States)	RCT	225 Drop-outs were balanced across groups and reasons for withdrawal similar 13 patients excluded from analysis due to a site violation 200 patients were included in the 12 week intention-to-treat efficacy population	Age: (mean) 73.7 Gender: 50% M Mild AD (Mean MMSE 23.9)	Souvenaid® Once daily for 12 weeks	Control drink (isocaloric, isonitrogenic, similar in flavour and appearance, identical packaging) Once daily for 12 weeks	Cognitive function	Delayed verbal recall test of the Wechsler Memory Scale revised; 13 item modified ADAS-cog; MMSE; Immediate verbal memory test of the WMS; Clinician interview based impression of change plus caregiver Input; 12 item Neuro-psychiatric Inventory; Alzheimer's Disease Co-operative Study ADL; Quality of Life in Alzheimer's Disease; plasma homocysteine and vitamins C and E; erythrocyte membrane fatty acid profile; adverse events.	Assessments at weeks 6 and 12 Participants were invited to participate in a 12 week extension study if AD drug treatment was not required according to the treating physician These participants were assessed at week 24	At 12 weeks, 40% of active group showed improvement in delayed verbal recall versus 24% in control group (P=0.026); the mean change was similar between groups. Planned analysis substituted for non-parametric as approx. 40% scored 0 at baseline. Proportion scoring 0 in each arm NR. There were no significant differences between groups in the immediate verbal recall test. Subgroup analysis showed people with very mild AD (MMSE 24-26, n=120) had a significant improvement in delayed verbal recall and immediate verbal recall. No change in the ADAS-cog, NPI, MMSE, ADL or QOL between groups. Increased BMI in the active group at Week 24. There was no significant between-group difference in adverse events. Adverse events were most commonly gastrointestinal complaints and not considered to be related to the study product. 27 of the adverse events reported were considered serious.	1. Low 2. Unclear 3. Low 4. Low 5. Low 6. Low

Reference Country	Study Design	N(n)	Participants	Intervention	Comparison	Main Outcomes	Measure/s	Length of follow up	Results/ Effect size	Risk of bias[1]
Scheltens 2012 [234] De Waal 2014[3] [231] 'Souvenir II Study' Europe	RCT	259	Age: (mean) 73.2 Control 74.4 Active Gender: 64% M Control 68% M Active Very mild AD (drug naive) (MMSE mean 25)	Souvenaid® Once daily for 24 weeks	Control drink (isocaloric, isonitrogenic, similar in flavour and appearance, identical packaging) Once daily for 24 weeks	Cognitive function	Memory function domain score (NTB, 4 items); Executive function domain score (NTB 5 items plus ADAS-cog orientation score and Letter digit substitution test); Disability Assessment for Dementia (DAD) scale; Nutritional blood parameters; EEG (for179 participants); Adverse events reviewed by independent committee	Assessments at 12 and 24 weeks	The change from baseline to week 24 in z-score for the NTB memory domain did not significantly differ between active versus control group (P=0.09; Cohen's d=0.21, 95% CI −0.06 to 0.49), but a 24-week trajectory over time was reported to significantly differ (P=0.023,). There was no significant change in the NTB executive function domain score at 12 or 24 weeks. The modified NTB total composite z-score showed a trend for effect over the 24-week trajectory over time (P=0.053), with a significant difference in change from baseline to week 24 (P=0.035). No significant differences in DAD on non-parametric testing. EEG found some differences in functional connectivity in favour of the active group. Similar numbers of adverse events in both groups thought to be unrelated to study product. 18 of the adverse events were considered serious.	1. Low 2. Low 3. Low 4. Low 5. Low 6. Low

Reference Country	Study Design	N(n)	Participants	Intervention	Comparison	Main Outcomes	Measure/s	Length of follow up	Results/ Effect size	Risk of bias[1]
Shah 2013 [235] United States	RCT 'S Connect Study'	527 Early withdrawals (n=76) balanced across groups	Age: (mean) 76.7 Gender: 48% M Mild-to-moderate AD taking stable doses of cholinesterase inhibitors and/or memantine Mean baseline MMSE = 19.5 (SD 3.1)	Souvenaid® Once daily for 24 weeks	Control drink (isocaloric, isonitrogenic, similar in flavour and appearance, identical packaging) Once daily for 24 weeks	Cognitive function	ADAS-cog; Cognitive test battery (Digit Span, Concept Shifting Test, Letter Digit Substitution, Category Fluency); Alzheimer's Disease Cooperative Study ADL scale; Adverse events reviewed by independent committee; Nutritional blood parameters	Assessments at 12 and 24 weeks	No significant differences between groups in ADAS-cog scores. No significant differences between groups on cognitive test battery or ADL scale. There was a significant difference in uptake of docosahexaenoic acid and eicosapentaenoic acid into the erythrocyte membranes, increased plasma vitamin E levels and decreased homocysteine levels for the intervention group compared with the control group at 24 weeks. No group differences in adverse event rates; events included gastrointestinal symptoms, headache, dizziness, anxiety, and respiratory illnesses. AEs thought to be unrelated to study product.	1. Unclear 2. Low 3. Low 4.Low 5.Low 6.Low

Abbreviations: AD –Alzheimer's Disease ; ADAS-cog – Alzheimer's Disease Assessment Scale-Cognition; ADL - Activities of Daily Living; AEs – Adverse Events; MMSE – mini mental state examination; NR – not reported; RCT – randomised-controlled trial;

1. Risk of bias: (1) Random sequence generation, (2) Allocation concealment, (3) Blinding of participants and personnel, (4) Blinding of outcome assessment, (5) Incomplete outcome data, (6) Selective reporting
2. Reports findings of the same study as Scheltens 2010
3. Reports findings of the same study as Scheltens 2012

Table 127 GRADE Evidence Profile: Souvenaid® versus placebo for people with mild Alzheimer's disease

Quality Assessment						No of patients			Effect[6]	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consider-ations	Souvenaid	Control		
Cognition (global measure) (follow-up 12-24 weeks; measured with: Modified Alzheimer's Disease Assessment Scale–cognitive subscale; range of scores: 0-85; Better indicated by lower values), or modified NTB composite z-score										
2	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	None	N=101 (n=101) N=130 (n=83)	N=99 (n=99) N=129 (n=89)	1RCT: modified ADAS-Cog @ 12 weeks: MD 0.1 higher (2.05 lower to 2.25 higher) [233] 1 RCT: Modified NTB composite Z-score mean change baseline - 24 weeks 0.04 (SD 0.29) vs Souvenaid 0.12 (SD 0.28), P=0.03; trajectory over 24 weeks P=0.05 [234]	⊕⊕⊕⊖ MODERATE
Memory (follow-up 12-24 weeks; measured with Wechsler Memory Scale-revised (scale 0-25 better indicated by higher values) or memory domain of Neuropsychological Test Battery[5]										
2	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	None	N=101 (n=100) N=130 (n=103)	N=99 (n=98) N=129 (n=103)	1 RCT WMS-r delayed recall: No sig diff in mean change baseline – 12 weeks, signif greater proportion improved from baseline with Souvenaid (40% vs 24%, P=0.02), No sig diff in WMS-r immediate. [233] 1 RCT NTB memory domain z-score: change baseline – 24 weeks control 0.11 (SD 0.46) vs Souvenaid 0.20 (SD 0.40),P = 0.09; 24-week trajectory P=0.02 [234]	⊕⊕⊕⊖ MODERATE
Function: Activities of Daily Living function (follow-up 12-24 weeks; measured with: Alzheimer's disease Co-operative Study—Activities of Daily Living, range of scores: 0-78 and Disability Assessment for Dementia scale, range of scores 0-100; better indicated by higher values)										
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	None	N=101 (n=101) N=130 (n NR)	N=99 (n=99) N=129 (n NR)	1 RCT: modified ADAS-Cog: MD 0.3 higher (2.77 lower to 3.37 higher) [233] 1 RCT DAD no statistically significant difference: [234]	⊕⊕⊕⊕ HIGH
Quality of life (follow-up 12 weeks; measured with: Quality of Life in Alzheimer's disease; range of scores: 13-52; Better indicated by higher values)										
1[4]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	None	101	99	MD 0.8 higher (0.38 lower to 1.98 higher) [233]	⊕⊕⊕⊖ MODERATE

Quality Assessment						No of patients			Effect[6]	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consider-ations	Souvenaid	Control		
Number of people who suffered at least one adverse event by follow up (follow-up 12 or 24 weeks)										
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	None	125/243 (51.4%)	127/241 (52.7%)	RR 0.99 (0.72 to 1.35) [233 234] 5 fewer per 1000 (from 148 fewer to 184 more)	⊕⊕⊕⊕ HIGH

Abbreviations: CI – confidence interval; MD – mean difference; NR – not reported; RR – risk ratio; signif – significant; signif diff – significant difference; WMS-r –Weschler Memory Scale- revised

[1] Surrogate outcome used - downgraded by 1

[2] Total population size <400 - downgraded by 1

[3] Heterogeneity: Tau^2=0.04; Chi^2 =3.20, df=1 (P=0.07), I^2 = 69%

[4] Information relates to study conducted by Scheltens et al (2010)

[5] This outcome added for mild AD in response to public feedback[6] Outcomes could not be pooled

Table 128 GRADE Evidence Profile: Souvenaid® versus placebo for people with mild-to-moderate Alzheimer's disease taking acetylcholinesterase inhibitors and/or memantine

Quality Assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Souvenaid	Control	Relative (95% CI)	Absolute	
Cognition (global measure) (follow-up 24 weeks; measured with: The Alzheimer's Disease Assessment Scale - Cognition; range of scores: 0-70; Better indicated by lower values)											
1	randomised trials	no serious risk of bias	no serious inconsistency	serious1	no serious imprecision	none	220	208	-	MD 1.02 lower (3.15 lower to 1.11 higher)	⊕⊕⊕⊖ MODERATE
Activities of Daily Living function (measured with: Alzheimer's Disease Cooperative Study – ADL Scale; range of scores: 0-78; Better indicated by higher values)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	228	223	-	MD 0.51 higher (2.4 lower to 3.42 higher)	⊕⊕⊕⊕ HIGH
Quality of life - not reported											
0	-	-	-	-	-	none	-	-	-	-	
Number of people who suffered at least one adverse event by 24 weeks (follow-up 24 weeks)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	150/265 (56.6%)	165/262 (63%)	RR 1.11 (0.97 to 1.28)	64 more per 1000 (from 17 fewer to 158 more)	⊕⊕⊕⊕ HIGH

Abbreviations: ADL – Activities of Daily Living; CI – confidence interval; MD – mean difference; RR – risk ratio;

[1] Surrogate outcome used - downgraded by 1

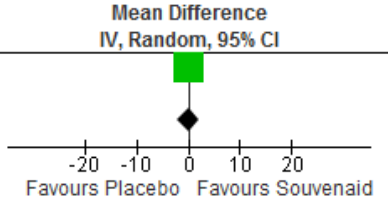
Forest plots

1. Souvenaid versus placebo for people with mild Alzheimer's disease

Outcome 1.1 Cognition (global measure)

Study or Subgroup	Souvenaid Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Scheltens 2010	25.9	7.7	101	25.8	7.8	99	100.0%	0.10 [-2.05, 2.25]
Total (95% CI)			**101**			**99**	**100.0%**	**0.10 [-2.05, 2.25]**

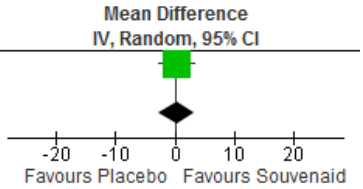
Heterogeneity: Not applicable
Test for overall effect: Z = 0.09 (P = 0.93)



Outcome 1.2 Activities of Daily Living function

Study or Subgroup	Souvenaid Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Scheltens 2010	-62.3	10.7	101	-62.6	11.4	99	100.0%	0.30 [-2.77, 3.37]
Total (95% CI)			**101**			**99**	**100.0%**	**0.30 [-2.77, 3.37]**

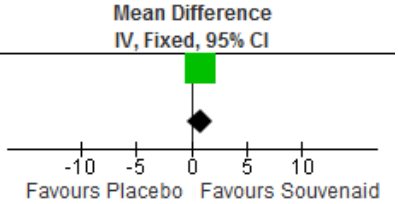
Heterogeneity: Not applicable
Test for overall effect: Z = 0.19 (P = 0.85)



Outcome 1.3 Quality of life

Study or Subgroup	Souvenaid Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Scheltens 2010	-34.8	4.2	101	-35.6	4.3	99	100.0%	0.80 [-0.38, 1.98]
Total (95% CI)			**101**			**99**	**100.0%**	**0.80 [-0.38, 1.98]**

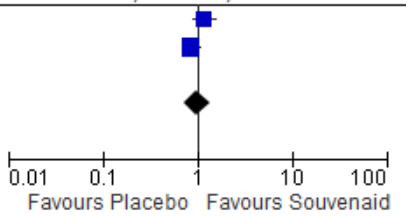
Heterogeneity: Not applicable
Test for overall effect: Z = 1.33 (P = 0.18)



Outcome 1.4 Number of people who suffered at least one adverse event by follow up

Study or Subgroup	Souvenaid Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Scheltens 2010	58	113	49	112	46.3%	1.17 [0.89, 1.55]
Scheltens 2012	67	130	78	129	53.7%	0.85 [0.69, 1.06]
Total (95% CI)		**243**		**241**	**100.0%**	**0.99 [0.72, 1.35]**
Total events	125		127			

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 3.20$, df = 1 (P = 0.07); $I^2 = 69\%$
Test for overall effect: Z = 0.07 (P = 0.94)

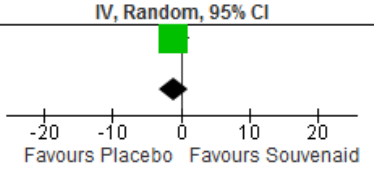


2. Souvenaid versus placebo for people with mild-to-moderate Alzheimer's disease taking cholinesterase inhibitors and/or memantine

Outcome 2.1 Cognition (global measure)

Study or Subgroup	Placebo Mean	SD	Total	Souvenaid Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Shah 2013	24.42	10.95	208	25.44	11.56	220	100.0%	-1.02 [-3.15, 1.11]
Total (95% CI)			**208**			**220**	**100.0%**	**-1.02 [-3.15, 1.11]**

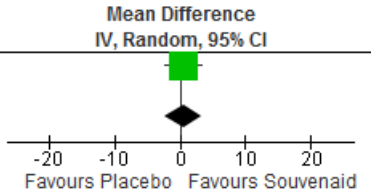
Heterogeneity: Not applicable
Test for overall effect: Z = 0.94 (P = 0.35)



Outcome 2.2 Activities of Daily Living function

Study or Subgroup	Placebo Mean	Placebo SD	Placebo Total	Souvenaid Mean	Souvenaid SD	Souvenaid Total	Weight	Mean Difference IV, Random, 95% CI
Shah 2013	-54.15	15.91	223	-54.66	15.56	228	100.0%	0.51 [-2.40, 3.42]
Total (95% CI)			**223**			**228**	**100.0%**	**0.51 [-2.40, 3.42]**

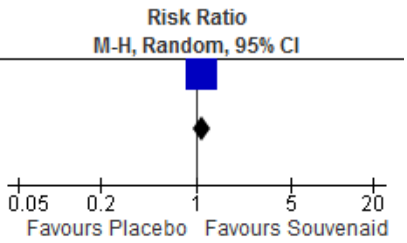
Heterogeneity: Not applicable
Test for overall effect: Z = 0.34 (P = 0.73)



Outcome 2.3 Number of people who suffered at least one adverse event by 24 weeks

Study or Subgroup	Placebo Events	Placebo Total	Souvenaid Events	Souvenaid Total	Weight	Risk Ratio M-H, Random, 95% CI
Shah 2013	165	262	150	265	100.0%	1.11 [0.97, 1.28]
Total (95% CI)		**262**		**265**	**100.0%**	**1.11 [0.97, 1.28]**
Total events	165		150			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.49 (P = 0.14)



Abbreviations: CI – confidence interval; IV - ; SD –standard deviation;

SRQ 15: Non-pharmacological interventions for BPSD

Clinical question

The research question as defined in the protocol and the associated PICO criteria are listed below.

Table 129 PICO for SRQ 15: Non-pharmacological interventions for BPSD

Clinical question: For people with behavioural and psychological symptoms of dementia, do non-pharmacological interventions produce benefits?			
Population	**Intervention**	**Comparator**	**Outcome**
People with behavioural and psychological symptoms of dementia	Non-pharmacological interventions aimed at decreasing BPSD	No intervention or alternative intervention	BPSD Depression Carer impact Institutionalisation Quality of life (person with dementia)

Literature review search strategies:

Searches for existing HTAs and Systematic reviews

Searches to identify existing Health Technology Assessment reports (HTAs) and systematic reviews were conducted in the databases specified in Table 130, using the search terms listed in the Guideline Technical Report Volume 2.

Table 130 Searches for existing HTAs and systematic reviews for SRQ 15: Non-pharmacological interventions for BPSD

Database	Date searched	Period covered	Citations retrieved
HTA	25 August 2014	2005 to 2014	22
Cochrane (Cochrane reviews, Cochrane protocols, DARE)	25 August 2014	2005 to 2014	71
MEDLINE	25 August 2014	2005 to 2014	532
PsycInfo	25 August 2014	2005 to 2014	467
EMBASE	25 August 2014	2005 to 2014	122
PubMed	25 August 2014	2005 to 2014	95

A number of systematic reviews were identified as described in Table 133.

Searches for additional primary studies

Searches were conducted in the databases listed in Table 131 to identify additional primary studies published since the search period of the included reviews. The search terms used are listed in the Guideline Technical Report Volume 2.

Table 131 Searches for primary studies/randomised controlled trials for SRQ 15: Non-pharmacological interventions for BPSD

Database	Dates searched	Period covered	Citations retrieved
MEDLINE	27 August 2014	2008 to 2014	645
PsycInfo	27 August 2014	2008 to 2014	594
EMBASE	27 August 2014	2008 to 2014	155
PubMed	27 August 2014	2008 to 2014	50

Criteria for selecting studies for review

Table 132 Inclusion and exclusion criteria for SRQ 15: Non-pharmacological interventions for BPSD

Characteristic	Criteria
Study design	Inclusion: Randomised controlled trials Exclusion: Other study designs
Population	Inclusion: People with dementia and BPSD
Intervention	Inclusion: Behavioural management intervention, cognitive stimulation, physical exercise, music, reminiscence, massage and touch, recreation therapy, light therapy, aromatherapy, multisensory stimulation, support and psychotherapy, animal assisted therapy, multicomponent therapy
Comparator	Inclusion: Alternative or no intervention (usual care)
Outcomes	Inclusion: BPSD, Depression, Carer impact, Institutionalisation, Quality of life (person with dementia)
Publication type	English language

Search results

Existing HTAs and systematic reviews

The most recent, comprehensive and highest quality systematic reviews/HTAs identified and included in the current update are show in Table 133.

Table 133 Systematic reviews and HTA report included in the review for SRQ 15: Non-pharmacological interventions for BPSD

Intervention	Included systematic reviews/HTAs
Behavioural management	Olazaran and colleagues 2010 [140]
Reminiscence therapy	Olazaran and colleagues 2010 [140]
Massage	Olazaran and colleagues 2010 [140]
Recreation therapy	Olazaran and colleagues 2010 [140]
Multisensory stimulation	Olazaran and colleagues 2010 [140]
Support and psychotherapy	Olazaran and colleagues 2010 [140]
Multicomponent interventions	Olazaran and colleagues 2010 [140]
Cognitive stimulation	Woods and colleagues 2012 [200]
Exercise	Forbes and colleagues 2013 [180]
Music therapy	Ueda and colleagues 2013 [236]
Light therapy	Forbes and colleagues 2014 [237]
Aromatherapy	Forrester and colleagues 2014 [238]
Animal assisted therapy	Bernabei and colleagues 2013 [239]

Primary studies

A total of 1444 citations were retrieved in the electronic database searches. 116 studies were viewed in full text and 34 were included evidence update (Table 135).

Evidence summary

This evidence update identified many studies and systematic reviews published since the NICE Guidelines, addressing a wide range of interventions. Intervention approaches were classified into categories. Results are presented by intervention approach below. Previous evidence summaries in these guidelines on staff training interventions and caregiver interventions are also relevant here as both intervention approaches were associated with reducing behavioural and psychological symptoms of dementia.

Behavioural management interventions

Behavioural management interventions tend to commence with a detailed assessment and individualised management plan which may include changes to the environment, the way in which care is delivered and training and support for family carers or professional caregivers. Several interventions use the A-B-C (antecedents-behaviour-consequence) model to assist in developing a management plan. We included the systematic review published by Olazaran and colleagues who examined all non-pharmacological interventions for people with dementia [140] (Table 134). The systematic review identified 11 randomised-controlled trials evaluating behavioural interventions. One of the trials was published in Spanish and therefore excluded [240]. We extracted the remaining ten randomised-controlled trials for inclusion in the GRADE evidence profiles [153 241-249]. We identified no additional trials published after the search date of the Olazaran review.

Overall, there were mixed findings in the studies. Of the nine randomised-controlled trials that provided data on the impact of behavioural interventions on behavioural and psychological

symptoms of dementia, three of these reported significant improvements in favour of the intervention group and an additional study reported a trend towards a positive effect in the intervention group[140]. Of the seven studies reporting on carer impact, three of these reported reduced impact in the intervention group with reasonable effect sizes[140].

Cognitive stimulation

We identified a high quality systematic review by Woods and colleagues (2012) [200] examining the effectiveness of cognitive stimulation for dementia(Table 134). The review searched for randomised-controlled trials listed on ALOIS (an open access register of dementia studies established by the Cochrane Group) prior to December 2011. The authors included 15 randomised-controlled trials in their review. We extracted the 15 trials for inclusion in the GRADE evidence profiles. Our search for studies published since then identified no further randomised-controlled trials. The results of the review suggested that cognitive stimulation was not associated with a reduction in behavioural and psychological symptoms of dementia or the other outcomes of interest.

Physical exercise

A Cochrane review published by Forbes and colleagues in 2013 was included in the review [180] (Table 134). The review searched ALOIS for studies listed prior to August 2012. The authors identified 16 randomised-controlled trials with 937 participants. We extracted the 16 trials for inclusion in the GRADE evidence profiles however, not all of these studies reported outcomes for behavioural and psychological symptoms of dementia. Trials were highly heterogeneous in terms of the participants involved, the duration and the frequency of exercise. Only two trials involved people living at home. We identified an additional trial that measured the effects of exercise on depression among people with dementia however the authors did not report the outcome results in the paper [194]. This trial conducted by Hauer (2012) is presented in Table 135. Results of studies included in the GRADE Evidence Profile suggest that there is currently a lack of evidence to support exercise programs in reducing behavioural and psychological symptoms of dementia.

Music

A systematic review published in 2013 by Ueda and colleagues was included in the review (see Table 134) [236]. The review searched electronic databases for studies indexed prior to February 2011. They identified 10 randomised-controlled trials. We extracted the 10 trials for inclusion in the GRADE evidence profiles. We identified a further six trials that evaluated the effectiveness of music for behavioural and psychological symptoms of dementia. (see Table 135) [250-256]. The results show that there are nine trials that have reported that music therapy (including listening and singing and dancing) can reduce behavioural and psychological symptoms of dementia and four randomised-controlled trials that have found that music therapy can reduce depressive symptoms in people with dementia.

Reminiscence

We included the systematic review published by Olazaran and colleagues who examined all non-pharmacological interventions for people with dementia [140] (Table 134). The systematic review identified six randomised-controlled trials evaluating reminiscence interventions [257-262]. We extracted the six trials for inclusion in the GRADE evidence profiles. In addition, we identified an additional three randomised-controlled trials that were published after the search date of the Olazaran review [263-265](Table 135). There are two trials that suggest that reminiscence therapy may be helpful in reducing behavioural and psychological symptoms of dementia and reducing depressive symptoms.

Massage and touch

We included the systematic review published by Olazaran and colleagues who examined all non-pharmacological interventions for people with dementia [140] (Table 134). The systematic review identified four randomised-controlled trials evaluating massage and touch [266-269]. We extracted the four trials for inclusion in the GRADE evidence profiles. In addition, we identified an additional three trials that were published after the search date of the Olazaran review [270-272](Table 135). There are five randomised-controlled trials that have reported that massage is effective in reducing agitation although they did not demonstrate long term effects.

Recreation therapy

We included the systematic review published by Olazaran and colleagues who examined all non-pharmacological interventions for people with dementia [140] (Table 134). The systematic review identified 4 randomised-controlled trials evaluating recreation therapy [273-276]. We extracted the four trials for inclusion in the GRADE evidence profiles. In addition, we identified an additional 11 randomised-controlled trials that were published after the search date of the Olazaran review [166 192 255 256 277-285] (Table 135). The evidence for recreation (involving use of prescribed activities rather than tailored activities) therapy does not currently suggest that it leads to reduced behavioural and psychological symptoms of dementia, depression or quality of life in the person with dementia.

Light therapy

We included a Cochrane systematic review that looked at the effect of light therapy on a number of outcomes including BPSD [237] (Table 134). The Cochrane review published by Forbes and colleagues included six RCTs that evaluated light therapy for behavioural and psychological symptoms of dementia. The search date within this review was January 2014 and we were unable to identify any subsequently published studies. The authors of the review were unable to find positive effects of light therapy on behavioural and psychological symptoms of dementia.

Aromatherapy

We identified a Cochrane review published by Forrester and colleagues in 2014 that looked at the effects of aromatherapy on behavioural and psychological symptoms of dementia. [238] (Table 134). The review searched for studies up until January 2014 and included two randomised-controlled trials that examined the effectiveness of aromatherapy on reducing behavioural and psychological symptoms of dementia. We extracted the two trials for inclusion in the GRADE evidence profiles. We were unable to identify any subsequently published studies. Studies had mixed findings and at present there is a lack of evidence to support aromatherapy in reducing behavioural and psychological symptoms of dementia.

Multisensory stimulation

We included the systematic review published by Olazaran and colleagues who examined all non-pharmacological interventions for people with dementia [140] (Table 134) . The systematic review identified three randomised-controlled trials evaluating multisensory stimulation [286-288]. We extracted the three trials for inclusion in the GRADE evidence profiles. We were unable to identify any subsequently published studies. There is currently insufficient evidence to suggest that multisensory stimulation may be associated with reduced behavioural and psychological symptoms of dementia.

Support and psychotherapy

We included the systematic review published by Olazaran and colleagues who examined all non-pharmacological interventions for people with dementia [140] (Table 134). The systematic review

identified three randomised-controlled trials evaluating support and psychotherapy [289-291]. We extracted the three trials for inclusion in the GRADE evidence profiles. In addition, we identified an additional two trials that were published after the search date of the Olazaran review [292 293] (Table 135). There are currently few studies and results are mixed with one trial finding that intensive counselling (30 minutes, three times a week for 16 weeks) was associated with a reduction in depressive symptoms and another trial which was also intensive associated with increased quality of life in participants.

Animal assisted therapy

We identified a systematic review published by Bernabei and colleagues that looked at the effects of animal assisted therapy for older people affected by dementia or psychiatric disorders (see Table 134) [239]. The review searched for studies published before February 2012 and was unable to identify any randomised-controlled trials. We identified two trials that examined the effect of animal assisted therapy for people with dementia published following the review [294 295] (Table 135). There is currently insufficient evidence to draw conclusions regarding the effectiveness of animal assisted therapy on reducing behavioural and psychological symptoms of dementia.

Multicomponent

We included the systematic review published by Olazaran and colleagues who examined all non-pharmacological interventions for people with dementia [140] (Table 134). The systematic review identified five randomised-controlled trials evaluating multicomponent interventions that examined effect on behavioural and psychological symptoms of dementia [127 296-299]. We extracted the randomised-controlled trials for inclusion in the GRADE evidence profiles. We identified a further six trials that met the inclusion criteria [300-305] (Table 135). Interventions that involved multiple components were frequently associated with positive results; five trials found a reduction in behavioural and psychological symptoms of dementia, four trials found significant reductions in depressive symptoms, two trials found reduced carer impact and four trials reported improved quality of life in the person with dementia. These findings suggest that an approach that is tailored to the abilities and preferences of the person with dementia and involves multiple intervention approaches may be most beneficial.

Evidence statements	*GRADE Quality*	*Related recommendations*
Five RCTs found that multicomponent interventions significantly reduced global BPSD (moderate)[297 300 302 304 305] whereas one RCT found no significant difference. [299] Four RCTs [296 298 303 305] found that multicomponent interventions significantly reduced levels of depression in the intervention group whereas one RCT found no effect (low).[127] (Table 148)	Low-moderate	EBR 84
Three (of nine) RCTs included in a systematic review [140] found that behavioural management interventions reduced global BPSD (low). Three (of seven) RCTs reported reduced carer impact associated with the intervention (low).[140] (Table 136)	Low	EBR 84
A systematic review [200] which pooled eight RCTs evaluating the effects of cognitive stimulation therapy found no significant overall effect on BPSD (low). Pooling of five RCTs found no significant effect on mood (very low).[265] (Table 137)	Very low-low	NA

Evidence statements	*GRADE Quality*	*Related recommendations*
A systematic review [180] that pooled four RCTs evaluating the effects of exercise on global BPSD found no significant effects (low). Pooling of six RCTs found no significant effect on depression (low).[180] One RCT reported a reduction in carer impact (moderate).[180] (Table 138)	Low-moderate	NA
A systematic review that pooled six trials investigating the effects of music therapy found a significant reduction in global BPSD.[236] A further three RCTs also reported a reduction in agitation associated with music therapy [251 253 255] whereas two RCTs found no significant results (low).[254 306] A systematic review which pooled four RCTs found a significant reduction in depression whereas a further study found no significant differences between groups (low).[236 250] (Table 139)	Low	EBR 84
Two (of five) RCTs included in a systematic review [140] found a significant reduction in global BPSD associated with reminiscence therapy (very low).[140] Two RCTs found significantly reduced levels of depression (low).[258 263] (Table 140)	Very low-low	EBR 84
Five RCTs reported reductions in agitation following massage (low).[267-269 271 272] (**Table 141**)	Low	EBR 84
Three [255 256 279 280] (of 11) RCTs found that recreation therapy led to reduced global BPSD (low). One [277] (of six) RCTs reported reduced levels of depression (low). (Table 142)	Low	NA

Evidence statements	*GRADE Quality*	*Related recommendations*
A systematic review [237] which pooled six RCTs investigating light therapy found no significant effect on global BPSD (low) and pooling of five RCTs found no effect on depression (very low).[237] (Table 143)	Very low-low	NA
A systematic review [238] found that one (of two) RCTs reported that aromatherapy was associated with reduced global BPSD (very low). (Table 144)	Very low	NA
A systematic review [140] reported that one (of two) RCTs reported that multisensory stimulation was associated with reduced agitation (very low).(Table 145)	Very low	NA
One RCT [293] examining support and psychotherapy reported reduced levels of depression associated with the intervention (very low) whereas two other RCTs found no significant treatment effect.[289 292] One RCT reported improved quality of life in the intervention group (low).[292] (Table 146)	Very low-low	EBR 84
One RCT reported no effect of animal-assisted therapy in reducing global BPSD [307] whereas another study reported a trend towards reduced symptoms (very low).[294] (Table 147)	Very low	NA

Table 134 Evidence summary of included systematic reviews for SRQ 15: Non-pharmacological interventions for BPSD

Reference	Study Design	Types of studies included	Types of participants included	Intervention	Comparison	Results	Quality appraisal[1]
Non-pharmacological intervention for BPSD (a number of approaches)							
Olazaran 2010 [140]	Systematic Review	RCTs	Dementia	All non-pharmacological interventions. Included behavioural interventions	Not specified	See summary in box below	1. CA 2. N 3. Y 4. N 5. Y 6. N 7. Y 8. Y 9. Y 10. N 11. N
Results: *Behavioural interventions:* 11 RCTs identified. 2 studies high quality, rest at risk of bias. Pooling 5 studies: effect size 0.565 (95%CI 0.209 to 0.921) in reducing BPSD. *Reminiscence therapy:* 6 RCTs involving reminiscence therapy identified. All at risk of bias. No pooling. Of the three studies that examined effect on behaviour, two of these were found to have positive results. Of the four studies that examined effect on mood, two of these were found to have positive results. *Massage:* Four RCTs included. All at risk of bias. All four of the studies found significant effects in reducing BPSD in the intervention group. *Recreation therapy:* 4 RCTs included in the review. The authors reported that all were at risk of bias. One of the three studies that examined impact on BPSD found a positive result in favour of the intervention group. The study that examined effect on mood did not find a significant effect in favour of intervention. *Multisensory stimulation:* 3 RCTs included. All at risk of bias. 2 of 3 studies examining impact on behavioural symptoms found a positive result. 1 study examined effect on mood; no signif effect. *Support and psychotherapy:* 3 RCTs included. All at risk of bias. 1 study examined BPSD; unable to find any positive effects. 2 studies examined mood; 1 study found a significant effect. *Multicomponent interventions:* 5 interventions identified were multicomponent in nature and designed to reduce BPSD. Results were not pooled. Results are presented in the GRADE Evidence Profile.							

Reference	Study Design	Types of studies included	Types of participants included	Intervention	Comparison	Results	Quality appraisal[1]
Cognitive stimulation for BPSD							
Woods 2012 [200]	Systematic Review	Randomised-controlled trials published in English in a peer-reviewed journal	People with all forms of dementia at all levels of severity	'Cognitive stimulation': defined as engagement in a range of activities and discussions (usually in a group) aimed at general enhancement of cognitive and social functioning; Participants attended regular therapy sessions (involving a group or family caregiver) for a minimum period of 4 weeks	'no treatment', 'standard treatment', or placebo.	See summary in box below	1. Y 2. Y 3. Y 4. Y 5. Y 6. Y 7. Y 8. Y 9. Y 10. Y 11. N

Results: 15 RCTs included

Outcome: behaviour
Results: The authors found no differences between intervention and control groups in behaviour (SMD 0.13, 95%CI -0.07 to 0.32) based on 8 studies with 416 participants.

Outcome: self-reported measure of mood
Results: Cognitive stimulation was not associated with significant improvement in mood (SMD 0.22, 95%CI -0.09 to 0.53) measured using a self-report tool and based on 5 studies with 201 participants

Outcome: self-reported QOL
Results: Analysis showed a significant improvement on this outcome following treatment compared to control groups. The SMD was 0.38 (95% CI: 0.11, 0.65), P = 0.006 based on 4 studies with 219 participants

Reference	Study Design	Types of studies included	Types of participants included	Intervention	Comparison	Results	Quality appraisal[1]
Exercise for BPSD							
Forbes 2013 [180]	Systematic Review	RCTs	The majority of participants in the trials had to be older people (over 65 years of age) and diagnosed as having dementia using accepted criteria	Exercise interventions included exercise programs offered over any length of time with the aim of improving health outcomes in older people with dementia or improving family carer impact. The exercise could be any combination of aerobic, strength or balance training	Usual care or social contact/activities	See summary in box below	1. Y 2. Y 3. Y 4. Y 5. Y 6. Y 7. Y 8. Y 9. Y 10. Y 11. N
Results: 16 RCTs with 937 participants included. **Outcome:** Behavioural and psychological symptoms of dementia **Results:** Four trials (110 participants) examined the impact of exercise on challenging behaviours The review authors were unable to pool data in a meta-analysis. Three of the studies reported no significant effect on behavioural symptoms. The remaining trial reported that participants in the exercise group showed improvements in behaviour. **Outcome:** depression **Results:** Six studies (341 participants) examined the impact on depression. Five of the studies were pooled in a meta-analysis. The results were not significant (MD - 0.14, 95% CI -0.36 to 0.07; I2=0%) **Outcome:** carer impact **Results:** Data was only available for one trial. This trial reported a significant reduction in carer burden None of the studies reported outcomes for QOL of the person with dementia							

Reference	Study Design	Types of studies included	Types of participants included	Intervention	Comparison	Results	Quality appraisal[1]
Music therapy for BPSD							
Ueda 2013 [236]	Systematic Review	RCTs, Clinical Controlled Trials, cohort studies or clinical trials	People diagnosed with any type of dementia occurring with Parkinson's Disease or Alzheimer's Disease, vascular dementia, fronto-temporal dementia, or other types	Music therapy: The music types that were used for intervention had to be a single music-related experience or a combination of music-related experiences such as singing, listening, performing, rhythmic exercising, and/or improvising	Not stated	See summary in box below	1. CA 2. Y 3. Y 4. N 5. N 6. Y 7. Y 8. Y 9. Y 10. Y 11. N
Results: 20 studies included **Outcome:** Depression **Result:** Nine studies (with 250 participants) reported a SMD of -0.32, 95%CI -0.68 to -0.04; I2=44%) **Outcome:** Behavioural and psychological symptoms of dementia **Result:** 11 studies (with 397 participants) found a SMD of -0.49; 95%CI -0.82 to -0.17; I2=58%) The authors pooled RCTs and CCTs. Sensitivity analysis showed no difference between the pooled result of all studies and RCTs alone.							

Reference	Study Design	Types of studies included	Types of participants included	Intervention	Comparison	Results	Quality appraisal[1]
Light therapy for BPSD							
Forbes 2014 [237]	Systematic Review	RCTs	Participants had to have a diagnosis of dementia according to accepted criteria	The review authors included any intervention involving the use of bright light. Acceptable control interventions were usual care, possibly with dim red light or dim, low-frequency blinking light at less than 300 lux.	Not stated	See summary in box below	1. Y 2. Y 3. Y 4. Y 5. Y 6. Y 7. Y 8. Y 9. Y 10. Y 11. N
Results: 11 RCTs met the inclusion criteria. As a group, studies were deemed to be at risk of bias. **Outcome:** Agitation **Results:** Six studies measured agitation; four of which were pooled. Light therapy administered during the morning, evening, or all day for between 10 days to 10 weeks had no effect on agitation (SMD-0.01, 95%CI -0.31 to 0.29, I2 = 16%, P = 0.95, n = 250) **Outcome:** Psychiatric disturbance **Results:** Data from two studies were pooled. No effect on the NPI score was observed after 6 to 10 weeks of treatment (MD2.22, 95%CI -6.48 to 10.91, P = 0.62, n= 157) **Outcome:** Depression **Results:** Five studies measured depression. Three studies were pooled. No effect on depression was seen following 2 to 10 weeks of light therapy (SMD 0.09, 95% CI - 0.54 to 0.73, P = 0.78, n = 161)							

Reference	Study Design	Types of studies included	Types of participants included	Intervention	Comparison	Results	Quality appraisal[1]
Aromatherapy for BPSD							
Forrester 2014 [238]	Systematic Review	RCTs	Participants in the included studies were to have a diagnosis of dementia of any type and severity, based on diagnostic criteria	Trials using fragrance from plants in an intervention defined as aromatherapy for people with dementia. All doses, frequencies, and fragrances were considered	Placebo aromatherapy	See summary in box below	1. Y 2. Y 3. Y 4. Y 5. Y 6. Y 7. Y 8. Y 9. Y 10. Y 11. N

Results of the Forrester review: Seven RCTs were included in the review. All of the included studies were considered to be at risk of bias.

Outcome: behavioural symptoms
Results: Data were not pooled due to heterogeneity. 1 study showed a statistically significant treatment effect in favour of the aromatherapy after 4-weeks treatment (n = 71, MD -15.8, 95% CI -24.4 to -7.2). An additional study found no significant differences between groups.

Outcome: Quality of life
Results: 1 RCT measured QOL. There was no statistically significant difference in quality of life between the participants receiving aromatherapy and those receiving placebo (n = 63, MD 19.00, 95% CI -23.12 to 61.12)

Authors conclusion: The benefits of aromatherapy for people with dementia are equivocal from the seven trials included in the review

Reference	Study Design	Types of studies included	Types of participants included	Intervention	Comparison	Results	Quality appraisal[1]
Animal assisted therapy							
Bernabei 2013 [239]	Systematic Review	Studies of all designs	People aged 65 years and over	Animal assisted therapy	Not specified	See summary in box below	1. CA 2. CA 3. Y 4. N 5. N 6. Y 7. N 8. N 9. Y 10. N 11. N
The authors identified 18 studies which involved people with dementia. They were unable to identify any RCTs and thus provided a narrative synthesis of study results. The authors concluded that animal assisted interventions were found to have positive influences on people with dementia by reducing the degree of agitation and by improving degree and quality of social interaction. Few studies have assessed the effects of AAI on mood.							

Abbreviations: AAI – animal assisted interventions; CA – ; RCTs – randomised-controlled trials; BPSD - behavioural and psychological symptoms of dementia; CA - ; N – No; RCTs – randomised-controlled trials; Y – Yes; CI – confidence interval ; I2 - ; MD – mean difference; P - ; QOL – Quality of Life; RCTs – randomised-controlled trials; SMD – standardised mean difference; MD – mean difference;

Table 135 Evidence summary of randomised controlled trials published subsequently to the included systematic reviews for SRQ 15: Non-pharmacological interventions for BPSD

Reference Country	Type	N	Participants	Intervention	Comparison	Main Outcomes	Measures	Length of follow up	Results/Effect size[a]	Risk of bias[1]
Exercise										
Hauer 2012 [194] Germany	RCT	122	Mean age: 82 Gender: 74% female in intervention group; 73% female in control group	Progressive resistance and functional training. Resistance training was targeted at functionally relevant muscle groups at a submaximal intensity in groups of four to six participants for 3 months (2 hours, twice a week) supervised by a qualified instructor. Participants were also trained to perform basic activity of daily living (ADL)-related motor functions such as walking, climbing stairs, sitting down and standing up, progressing to advanced levels of functional tasks.	All participants assigned to the control group met two times per week for 1 hour of supervised motor placebo group training. Typical activities were flexibility exercise, calisthenics, low-intensity training with hand-held weights, and ball games while seated	Physical function	Short Physical Performance Battery; stair climbing; Performance Oriented Motor Assessment; Timed Up and Go Test; cumulative illness rating scale; ADLs; social status; falls; Geriatric Depression Scale; Falls Efficacy Scale International; 12 item Short Form Health Survey; Attitude to Falls Related Intervention Scale	Post interven-tion and 3 months following interven-tion	Physical function improved in the intervention group b. Results related to effect on depression were not reported in the paper.	1. Low 2. Low 3. Low 4. Low 5. Low 6. Unclear

Reference Country	Type	N	Participants	Intervention	Comparison	Main Outcomes	Measures	Length of follow up	Results/Effect size[a]	Risk of bias[1]
Music										
Cooke 2010 [306] Australia	Crossover RCT	47	Most participants were in the 75-94 year old age bracket (mean age not provided) 70% of participants were female	Live group music program delivered by two musicians. Each music session involved 30 minutes of musician-led familiar song singing and 10 minutes of pre-recorded instrumental music for active listening. Sessions were held three mornings a week for eight weeks.	Group reading sessions: led by a facilitator and interactive in nature. Included reading local news stories, short stories, telling jokes and undertaking quiz activities.	Agitation and anxiety	Cohen Mansfield Agitation Inventory; Rating of Anxiety in Dementia; Dementia Quality of Life; Geriatric Depression Scale	Post-intervention	There were no significant differences between groups on any of the measures.	1. Low 2. Unclear 3. High 4. Low 5. Low 6. Unclear
Lin 2011 [251] Taiwan	RCT	104	Mean age was 81 years in the intervention group and 82 in the control group 53% of participants were female	Intervention group received a 12 x 30 minute group music intervention program over 6 weeks.	Normal daily activities	Agitation	MMSE; Cohen Mansfield Agitation Inventory	Post interven-tion and 1 month following the end of intervention	Results showed that the intervention group had significantly reduced agitation at all three follow ups whereas the levels of agitation in the control group remained the same (effect size=0.2 post intervention)	1. Low 2. Unclear 3. High 4. Unclear 5. Low 6. Unclear
Nair 2011 [252] Australia	Crossover RCT	75	Mean age in intervention group was 86; mean age in control group was 82 Gender: 75% female	During the intervention weeks, a selection of Baroque music was played from 3pm to 7pm on a CD player in the common area of the wards at a volume sufficient to be heard throughout the common area but not in the individual rooms	Usual care	BPSD	Behaviour observation chart	Post interven-tion	There were more behavioural disturbances during the weeks when the Baroque music was played (0.2 more episodes per week, P=0.01)	1. Unclear 2. Unclear 3. High 4. High 5. Unclear 6. Unclear

Reference Country	Type	N	Participants	Intervention	Comparison	Main Outcomes	Measures	Length of follow up	Results/Effect size[a]	Risk of bias[1]
Ridder 2013 [253] Denmark	Crossover RCT	42	Mean age intervention group was 80; mean age control group was 82	Individual music therapy was given fortnightly over 6 weeks (total=12 sessions) by qualified music therapists. Therapy included singing, dancing, listening and talking.	Usual care	Agitation and quality of life	Cohen Mansfield Agitation Inventory; prescription of medication; Alzheimer's Disease Related Quality of Life	Post interven-tion and 7 weeks post end of interventio n	During standard care frequency of agitation increased slightly vs decreased during music therapy (non-signif MD between groups=3.41 points on CMAIfr). Music therapy had signif reduction in agitation disruptiveness vs standard care (MD =6.77 points, ES = 0.50, p=0.027). QOL: no sig diff. The prescription of psychotropic medication increased signif more often during standard care vs music therapy.	1. Unclear 2. Unclear 3. High 4. Low 5. Low 6. Unclear

Reference Country	Type	N	Participants	Intervention	Comparison	Main Outcomes	Measures	Length of follow up	Results/Effect size[a]	Risk of bias[1]
Sung 2012 [254] Taiwan	RCT	55	Mean age 81 intervention group; mean age 80 for control group Gender 66%	30-min music intervention using percussion instruments with familiar music in a group setting in mid-afternoon twice weekly for 6weeks	Usual care	Agitation	Cohen Mansfield Agitation Inventory; Rating of Anxiety in Dementia	Assessments at Week 4 and Week 6	Both the intervention and control groups reported reduced agitation and anxiety over time. The music intervention group experienced significantly reduced levels of anxiety (effect size=0.35). Mean agitation scores between the two groups were not significantly different at follow up.	1. Low 2. Unclear 3. High 4. High 5. Unclear 6. Unclear
Vink 2013 [255] Vink 2014 [256] The Netherlands	RCT	77	Mean age 82, gender 70% female	Music therapy twice weekly for 4 months. Music therapy sessions lasted for 40 minutes and were provided by a trained music therapist. Included a welcome song and music selected, sung or played by the therapist. If possible, the participant sung, danced or played a musical instrument.	Recreational therapy twice weekly for 4 months. Sessions were 40 minutes, and consisted of activities such as handwork, shuffleboard, cooking and puzzles provided by OTs	Agitation	Cohen Mansfield Agitation Inventory;	1 hour before session; 1 hour after session; 2 hours after session and 4 hours after session	In both groups, the intervention resulted in a decrease in agitated behaviours from 1 h before to 4 h after each session. The difference between groups non-signif	1. Unclear 2. Low 3. High 4. High 5. High 6. Unclear

Reference Country	Type	N	Participants	Intervention	Comparison	Main Outcomes	Measures	Length of follow up	Results/Effect size[a]	Risk of bias[1]
Reminiscence therapy										
Hsieh 2010 [263]	RCT	61	Mean age 78; gender 41% female	A reminiscence group therapy program consisting of 12 sessions, 40–50 minutes per week, was implemented for the residents in the intervention group	Usual care	Depression and apathy	Clinical Dementia Rating Scale; Geriatric Depression Scale; Apathy Evaluation Scale; Neuropsychiatric Inventory	3 months	The intervention group reported reduced depression (effect size d=0.7, p=0.003) and apathy (effect size d=0.04, p=0.002) in comparison to the control group.	1. Unclear 2. Unclear 3. High 4. Unclear 5. Unclear 6. Unclear
Serrani 2012 [264]	RCT	135	Mean age 85 in intervention group, 86 in active control group, 86 in passive control group Gender ranged from 60-70% female across the groups	Individual treatment in which each participant received 24 bi-weekly sessions lasting one hour each, over a period of 12 weeks. The patients joined a peer group where the coordinators offered memory triggers, such as photographs, recordings and newspaper clippings used to promote personal and shared memories. Sometimes, caregivers or family members were allowed to be included alongside their relatives with dementia. Then, a general discussion followed, fostering the emergence of shared concepts and reframing the patient's initiative to improve both cognitive capacities and relationship abilities.	The active control group received participated in activities focussed towards social interaction and being enjoyable, planned work and turn taking. The passive control activities focussed on social interaction and being enjoyable.	Quality of life	Self-reported quality of life scale; Social Engagement Scale; Zarit Burden Interview; Wellbeing Ill-being Scale; ADL scale	Post interven-tion and six months post interven-tion	Significantly greater increase in QOL in the intervention group over time (effect size= 2.2). The intervention group improved significantly more in terms of social engagement than the control groups. Family carers reported reduced carer impact in the intervention group however, the difference between groups non-signif.	1. Unclear 2. Unclear 3. High 4. Low 5. Low 6. Unclear

Reference Country	Type	N	Participants	Intervention	Comparison	Main Outcomes	Measures	Length of follow up	Results/Effect size[a]	Risk of bias[1]
Woods 2012 [200] UK	RCT	488	Mean age 78; 50% female	The intervention consisted of joint reminiscence groups held weekly for 12 consecutive weeks, followed by monthly maintenance sessions for a further 7 months. The sessions followed a treatment manual, and were led by two trained facilitators. Each session lasted 2 hours and focused on a different theme, including childhood, schooldays, working life, marriage, and holidays and journeys. Dyads were encouraged to contribute with materials brought from home. Subsequent maintenance sessions were held monthly and followed a similar pattern. Each session blended work in large and small groups, and a range of activities including art, cooking, physical re-enactment of memories, singing and oral reminiscence.	Usual care	Quality of life for the person with dementia	Person with dementia: QoL-AD; Family carer: GHQ28; Relatives Stress Scale; GDS	Months 3 and 10	There were no differences in outcome between intervention and control patients at primary or secondary outcomes at the 10 month end point or at the 3 month assessment. Carers in the intervention group reported a significant increase in anxiety at the 10 month end point.	1. Low 2. Low 3. High 4. Low 5. High 6. Low

Reference Country	Type	N	Participants	Intervention	Comparison	Main Outcomes	Measures	Length of follow up	Results/Effect size[a]	Risk of bias[1]
Massage and touch										
Hicks-Moore 2008 [271] Canada	RCT	41	Mean 85 years; 78% female Nursing home residents	10 minutes of listening to favourite music + 10 minutes of hand massage + 10 minutes of massage plus music.	Usual care	Agitation	Cohen Mansfield Agitation Inventory	Immediate-ly post interven-tion and one hour follow up	The authors report that participants in the intervention group were significantly less agitated one hour post intervention.	1. Unclear 2. Unclear 3. High 4. High 5. High 6. Unclear
Harris 2012 [270] United States	RCT	40	Mean age 86; Female 78% Mean MMSE: 10.6/30 Nursing home residents	Slow stroke back massage intervention. The intervention group had a 3 minute massage at bedtime for two nights prior to sleep time. Conversation was kept to a minimum.	Usual care	Sleep	Actigraph sleep variables: night-time sleep, sleep latency, sleep efficiency, wake after sleep onset, daytime inactivity	Data collected for 48 hours post interven-tion	While descriptive statistics suggested increase in minutes of night time sleep in the intervention group (mean additional 36 minutes) there were no statistically significant differences between groups.	1. Low 2. Unclear 3. High 4. Low 5. Low 6. Unclear

Reference Country	Type	N	Participants	Intervention	Comparison	Main Outcomes	Measures	Length of follow up	Results/Effect size[a]	Risk of bias[1]
Rodriguez-Mansilla 2013 [272] Spain	RCT	120	Mean age 85 in intervention group, 82 in control group Gender: 23% female in both groups Nursing home residents	The massage therapy group received a relaxing massage by a physiotherapist every day from Monday to Friday. The massage was applied in the back and lower limbs for 20 min. The massage techniques used were superficial effleurage and deep kneading with moisturising cream. The study was performed over five months, with three months of experimental treatment and two months with no treatment	Ear acupuncture group Control group	BPSD	Questionnaire to measure behavioural alterations, sleep disturbance, participation in therapy and eating designed by the research team.	Taken monthly over the 5 month study period	In the third month, the massage intervention group significantly improved in scores of behavioural alterations, sleep, therapy participation and eating relative to the control group (P<0.001). At 5 months there were no differences between the massage group and control group in behaviour or sleep.	1. Unclear 2. Unclear 3. Unclear 4. Low 5. Unclear 6. Unclear

Reference Country	Type	N	Participants	Intervention	Comparison	Main Outcomes	Measures	Length of follow up	Results/Effect size[a]	Risk of bias[1]
Recreation therapy										
Cheng 2012 [277] Hong Kong	Cluster RCT	36	Mean age 81 in Tai Chi group, 82 in Mahjong group, 83 in control group, Gender: 75% female in control and Mahjong groups, 50% female in Tai Chi Group Nursing home residents	Participants in each group performed the activities in small groups for an hour three times a week for 12 consecutive weeks. Tai Chi intervention (details lacking in the paper) Mahjong intervention (details lacking in the paper)	Handicrafts	Depressive symptoms	Geriatric Depression Scale; physiological measures including cholesterol, blood glucose and blood pressure; Barthel Index	Months 3 and 6	The Mahjong group reported reduced levels of depression at 3 months (effect size d=1.05) however, this was not maintained at 6 months. There were no significant reductions in depression in the control or Tai Chi group.	1. Unclear 2. Unclear 3. High 4. Unclear 5. Unclear 6. Unclear
Ferrero-Arias 2011 [278] Spain	Crossover RCT	146	Mean age 84, 74% female Nursing home or day care residents	Occupational therapy sessions were held on weekdays, lasted for 50 minutes, and followed a 3-day rotation scheme to avoid boredom: day 1 music therapy, day 2 art therapy, day 3 psychomotor activity and mime, day 4 music therapy again, and so on until 20 sessions had been completed.	Activities of their own choice in the day room (e.g. listen to music, watch TV, read)	Apathy	Neuropsychiatric Inventory Questionnaire; Dementia Apathy Interview and Rating Scale	Week 4 and 8	Signif diff intervention vs control periods, by the apathy scale, (effect size=0.39). No signif diff with NPI-Q scale, although clear improvement trend in the "apathy" question on this scale	1. Unclear 2. Low 3. High 4. Low 5. Unclear 6. Unclear

Reference Country	Type	N	Participants	Intervention	Comparison	Main Outcomes	Measures	Length of follow up	Results/Effect size[a]	Risk of bias[1]
George 2011 [279]	RCT	15	Mean age 86 in intervention group, 81 in control group	Intergenerational volunteering with children aged 5-14 years. In alternating weeks, participants served as mentors during hour-long visits with kindergarten classroom in which they interacted with children and engaged in singing and small group reading and writing activities and 6th grade classroom where they participated in life history reminiscence sessions. Total 20 hours of volunteering for the 5 month study.	Successful Aging seminar with total duration of 12 hours.	QOL	Mini Mental State Examination; Beck Anxiety Inventory; Beck Depression Inventory; Sense of Purpose and Sense of Usefulness questionnaires	Post intervention	Significant decrease in stress on anxiety inventory in intervention group whereas the control group increased (effect size Hedges g= 1.18, p=0.049). no signif diff in cognition, depression or sense of purpose.	1. Unclear 2. Unclear 3. High 4. Unclear 5. Unclear 6. Unclear
Hattori 2011 [280] Japan	RCT	39	Mean age 75 in intervention group, 73 in control group Gender 54% female Mean MMSE 25 in intervention group, 22 in control group	Art therapy intervention was performed once weekly for 12 weeks. The primary task was to colour abstract patterns with pastel crayons or water-based paint	Learning therapy using calculation	Apathy and cognition	MMSE; Logical memory subscale of the Wechsler Memory Scale Revised; Geriatric Depression Scale; Apathy Scale; SF8 to measure QOL; Dementia Behaviour Disturbance Scale; Barthel Index; Zarit Burden Interview	Post intervention	Comparisons between before and after each therapy revealed signif improvement in Apathy Scale in art therapy group (effect size Cohen's d=0.12, P = 0.0014) and in the MMSE score in the control group (P = 0.0015) but no signif diff in other items	1. Unclear 2. Unclear 3. High 4. Unclear 5. Low 6. Unclear

Reference Country	Type	N	Participants	Intervention	Comparison	Main Outcomes	Measures	Length of follow up	Results/Effect size[a]	Risk of bias[1]
Houser 2014 [281] United States	Cluster RCT	20	Mean age 86 in intervention group, 84 in control group Gender: 75% women	"TimeSlips": a creative storytelling program A staged picture is distributed (e.g., an elephant sitting next to a girl on a park bench), and facilitators encourage input from all participants as a collective narrative is formed. Responses are recorded verbatim and woven into a story that is read back to the group. The process offers an avenue for community interaction, creativity, and self-worth and often engenders laughter. The Principal Investigator facilitated each one-hour TimeSlips session twice per week for 6 weeks	Usual care	BPSD	Behavioural observations (using Care Tracker data collection tool)	During the interven-tion period	Between-group comparisons did not reveal statistically significant differences in mood and behavioural symptoms. No differences in psychotropic drug prescriptions were found	1. Low 2. Unclear 3. High 4. Unclear 5. Unclear 6. Unclear

Reference Country	Type	N	Participants	Intervention	Comparison	Main Outcomes	Measures	Length of follow up	Results/Effect size[a]	Risk of bias[1]
Kolanowski 2011 [282] United States	RCT	128	Mean ages in the four groups ranged from 85-87 Gender: percentage of females in the groups ranged from 74% to 81% Mean MMSE ranged from 13 to 16	Program incorporating three weeks of activities provided twice daily. Four intervention groups as follows: Functional Level group: Activities were specifically adjusted to their skill level but opposite their personality style of interest. The selection of activities was determined according to their physical and cognitive capabilities Personality style of interest group: Prescribed activities specifically adjusted to their interest and deliberately selected to be functionally challenging for them Functional level + interest group: Prescribed activities that were specifically adjusted to their functional level and personality style of interest Active control group: Prescribed activities that were functionally challenging and opposite their personality style of interest	There were four comparative groups	BPSD	Rating of agitation, passivity, engagement and mood made via video recordings; Cohen Mansfield Agitation Inventory; Passivity in Dementia Scale; activity engagement; Philadelphia Geriatric Center Affect Rating Scale; Dementia Mood Picture Test	Post interven-tion	All outcomes demonstrated improvement during intervention regardless of group assignment (data not shown) with the exception of mood, which became more negative in Active Control Group. Agitation (full scale score), passivity, anxiety and self-reported mood did not differ according to group. There was less agitation and passivity in groups with a component adjusted to PSI	1. Low 2. Low 3. Low 4. Low 5. Low 6. Low

Reference Country	Type	N	Participants	Intervention	Comparison	Main Outcomes	Measures	Length of follow up	Results/Effect size[a]	Risk of bias[1]
Lam 2010 [283] Hong Kong	RCT	74	Mean age 83 in the intervention group, 84 in the control group Gender 68% female in the intervention group, 81% female in the control group Mean MMSE 14/30 in both groups	Functional Enhancement Program: Delivered as group sessions of 4–6 persons under the supervision of experienced occupational therapists. Individual functional profiles were mapped, abilities were enhanced to compensate for the areas of deficiency. Secondly, training activities were selected from activities considered as important by the participants. Thirdly, the training adopted a cognitive-behavioural approach. Positive emotional experiences were enforced and rehearsed throughout the sessions	General occupational therapy activities appropriate to the severity of cognitive impairment	BPSD	Chinese Disability Assessment for Dementia (DAD); Assessment of Motor and Process Skills; Cornell Scale for Depression in Dementia; Neuropsychiatric Inventory; Mini Mental State Examination;	1 month post interven-tion and 4 months post interven-tion	Both groups improved on the AMPS process skills at 1 month post intervention. The DAD scores did not differ significantly from baseline. There were no significant group differences in the changes in DAD, AMPS, and CSDD scores after controlling for the effects of Age, educational level, and CIRS total scores	1. Unclear 2. Unclear 3. Low 4. Low 5. Unclear 6. Unclear
Luk 2011 [284] Hong Kong	RCT	14	Mean age 85; 93% female Mean MMSE 13.4/30 Nursing home residents	The intervention was a 30-min twice-weekly horticultural activity conducted in an outdoor garden for 6 weeks. Each session had a different theme such as fertilizing, seeding, flower arranging, and planting.	The control condition was designed to provide sensory stimulation and social interaction using activities such as origami, doing puzzles, drawing, and making collages	Agitation	Cohen-Mansfield Agitation Inventory	Post interven-tion	No significant difference was observed in agitation between the experimental and control group post-intervention. Nor were there significant within-group changes in agitation pre- and post-intervention.	1. Unclear 2. Unclear 3. Low 4. Low 5. Unclear 6. Unclear

Reference Country	Type	N	Participants	Intervention	Comparison	Main Outcomes	Measures	Length of follow up	Results/Effect size[a]	Risk of bias[1]
Van der Ploeg 2013 [285] Australia	Crossover RCT	44	Mean age 78 years; 68% female Nursing home residents	Both conditions were delivered for 30 minutes twice weekly, giving a total of four Montessori and four control sessions. Personalized one-to-one interaction activities based on Montessori principles. Activity facilitators selected up to ten activities per participant based on discussion with the family about participants' former interests and hobbies. Typical selections included listening and singing along to favorite music, looking at and sorting pictures, arranging flowers, sorting dry pastas, folding towels, screwing nuts and bolts together, planting seeds, and making puzzles.	Facilitators engaged participants in social interaction by means of general conversation or conversation based on newspaper stories and pictures	BPSD	Behavioural observations; Philadelphia Geriatric Center Affect Rating Scale; Menorah Park Engagement Scale; Mini Mental State Examination; Clinical Dementia Rating	Post intervention	During both the Montessori and control sessions, agitation scores were nearly halved and sessions were spent predominantly with interested affect and constructive or passive engagement. There were no significant differences between group in terms of agitation at follow up.	1. Low 2. Unclear 3. Low 4. High 5. Unclear 6. Unclear
Vink 2013 [255] Vink 2014 [256] The Netherlands	RCT	77	Mean age 82, gender 70% female	Music therapy twice weekly for 4 months. Music therapy sessions lasted for 40 minutes and were provided by a trained music therapist. Included a welcome song and music selected, sung or played by the therapist. If possible, the person sung, danced or played a musical instrument.	Recreational therapy twice weekly for 4 months. Sessions were 40 minutes, and consisted of activities such as handwork, shuffleboard, cooking and puzzles provided by occupational therapists	Agitation	Cohen Mansfield agitation inventory;	1 hour before session; 1 hour after session; 2 hour after session and 4 hour after session	In both groups, intervention decreased agitated behaviours from 1 h before to 4 h after each session. Difference between groups not statistically significant.	1. Unclear 2. Low 3. High 4. High 5. High 6. Unclear

Reference Country	Type	N	Participants	Intervention	Comparison	Main Outcomes	Measures	Length of follow up	Results/Effect size[a]	Risk of bias[1]
Wenborn 2013 [199] United Kingdom	Cluster RCT	210	Mean age 84, Gender: 64% female in intervention group, 71% female in control group Mean MMSE: 6/30	An occupational therapy programme designed to enable care home staff to increase activity provision. Included assessment of the environment, educating staff re getting to know residents interests and abilities, planning activities.	Usual care	QOL	QOL-AD; MMSE; Clifton Assessment Procedures for the Elderly - Behaviour Rating Scale; Challenging Behaviour Scale; CSDD; Rating Anxiety in Dementia; Clinical Dementia Rating Scale	4 and 12 weeks after the interven-tion was completed	There were no significant differences between groups for any of the patient outcomes.	1. Unclear 2. Unclear 3. High 4. Low 5. Low 6. Low
Support and psychotherapy										
Stanley 2013 [292] United States	RCT	32	Mean age 79, Gender 59% female	The 'Peaceful Mind' program included up to 12 weekly in-home sessions during the initial 3 months and up to 8 brief telephone sessions during months 3-6 involving self-monitoring for anxiety, deep breathing and optional skills (coping self-statements, behavioural activation, sleep management).	Usual care	Patient anxiety	NPI anxiety scale; Rating Anxiety in Dementia Scale; Penn State Worry Questionnaire; Geriatric Anxiety Inventory; Geriatric Depression Scale; QOL-AD Family carer: PHQ-9	Months 3 and 6	Patients in the intervention group had significantly greater improvements in anxiety than those in the usual care group at 3 months (effect size =0.99). There were significantly greater improvements on the QOL-AD from baseline to 3 months in the intervention group (effect size=1.05). There were no significant differences between groups on the other outcome measures	1. Unclear 2. Unclear 3. High 4. Low 5. High 6. Unclear

Reference Country	Type	N	Participants	Intervention	Comparison	Main Outcomes	Measures	Length of follow up	Results/Effect size[a]	Risk of bias[1]
Tappen 2009 [293] United States	RCT	30	Mean age intervention group 84; Mean age control group 90 Gender: 90% female Mean MMSE was 10.6 in intervention group and 12.26 in the control group Nursing home residents	Thirty-minute modified counselling sessions (Therapeutic Conversation) were provided three times per week for 16 weeks to participants in the treatment group. The goals were to: Form and maintain a supportive relationship; Provide the opportunity for the individual to express his or her feelings and concerns; Reduce isolation; Improve self-esteem; Improve mood; Reduce anxiety; Maintain verbal abilities; Maintain dignity.	Usual care	Mood	Dementia Mood Assessment Scale; Alzheimer's Disease and Related Disorders Mood Scale; Montgomery Asberg Depression Rating Scale;	Post interven-tion	Treatment group participants evidenced a significant decline in sadness (effect size=0.78) and apathy (effect size=0.49), as measured on the subscales of the AD-RD Mood Scale, whereas control group participants remained at the same level. Treatment group participants also evidenced a significant decline in depressive symptomatology as measured by the MADRS (effect size=0.47).	1. Unclear 2. Unclear 3. High 4. Low 5. Low 6. Unclear
Animal assisted therapy										
Dabelko 2014 [294] United States	Crossover RCT	16	Mean age 78, gender: 56% female Mean MMSE 20.8/30	A multi-component intervention was implemented comprised of opportunities for grooming, painting, and leading horses	Usual care	BPSD	Observations of behaviours and affect; Nursing Home Behaviour Problem Scale Scores	At 11:30am and end of day each day for 4 days	Trend towards the overall mean number of problem behaviours decreasing after farm visit. Pre-test scores on the farm days vs ADS days were also lower, suggesting fewer behaviour problems present with anticipation of horse interaction.	1. Unclear 2. Unclear 3. High 4. High 5. Unclear 6. Unclear

Reference Country	Type	N	Participants	Intervention	Comparison	Main Outcomes	Measures	Length of follow up	Results/Effect size[a]	Risk of bias[1]
Travers 2013 [307] Australia	RCT	67	Mean age 85 years; gender 70% female in the intervention group, 86% female in the control group Nursing home residents	Dog assisted therapy: Group sessions. Participants offered the dog a small food treat, petted and talked to the dog. There was discussion regarding the dog. Listen to short story or poem about dogs.	Human therapist only therapy: Group sessions with introductions, discussions. Listen to short stories or poems (human related)	Mood and QOL	QOL-AD; SF36; Geriatric Depression Scale; MOSES	Post interven-tion	Quality of life in people participating in dog assisted therapy was higher in the intervention group at one facility (effect size d=1.01, P=0.02) and lower or constant at the other two sites. There were no significant effects on any of the other outcome measures	1. Low 2. Unclear 3. High 4. Low 5. Low 6. Unclear
Multicomponent interventions										
Bakker 2011 [300] The Netherlands	RCT	168	Mean age 80 in intervention group, 82 in control group Gender: 67% female in intervention group, 61% female in control group	Integrative reactivation and rehabilitation program The program had a duration of 13 weeks, with clinical admission to a 15 bed specialised unit in a psychiatric skilled nursing home. The multidisciplinary team developed a personal package of interventions for each patient and caregiver. Interventions included: assessment, counselling, life review, interpersonal therapy, cognitive behavioural therapy, behavioural therapy, support in accepting behaviour, regression approach, rehabilitation, support from a social worker on discharge, psychoeducation and family therapy	Usual multi-disciplinary nursing home care	BPSD	Neuropsychiatric Inventory; Caregiver Burden; Caregiver Competence List; SF20; EQ5D and EQVAS; Global Deterioration Scale	Post interven-tion and after 6 months of follow-up	There was a significant reduction in caregiver rated behaviours of concern (measured via the NPI) in favour of the intervention group with a moderate effect size (d=0.53, p=0.003). No significant effects were found for the nurse rated NPI. Caregiver burden was significantly reduced in the intervention group (d=0.63, p=0.001). There were no significant differences in QOL between groups.	1. Unclear 2. Unclear 3. High 4. High 5. Low 6. Unclear

Reference Country	Type	N	Participants	Intervention	Comparison	Main Outcomes	Measures	Length of follow up	Results/Effect size[a]	Risk of bias[1]
Brooker 2011 [301] United Kingdom	Cluster RCT	293	Mean age 81 in intervention group, 82 in control group Gender: 77% female in intervention group and 74% in control group Mean MMSE 19 in intervention group, 20 in control group	Enriched Opportunities Programme (EOP). The "EOP Locksmith" worked with around 20–30 residents per scheme to identify types of occupation and activity that were the most likely keys to unlock the potential for well-being and to help them achieve their goals. Individualised casework also ensured that any potential problems were dealt with quickly. This involved active liaison with primary and secondary health and care teams when appropriate. The EOP Locksmith worked closely with all the direct staff-team in order to identify problems and solutions, to offer guidance and model positive ways of assisting residents with dementia. The EOP Locksmith took the lead on ensuring that a programme of activity was available and accessible for their client group. The programme was designed to be stimulating, tailored to the capabilities of the individual residents and encouraged integration with the local community.	Appointment of an additional staff member to focus on activity within the housing scheme	QOL, depression	QOL-AD; Geriatric Depression Scale; perception of social support; total number of activities; occupational diversity; number and type of relocation to alternative care environment (e.g., care home); mortality rate; number of hospital in-patient days; and use of community health resources	Months 6, 12 and 18	Signif group–time interaction for participants' self-perceived QOL (p=0.001), step increase in baseline score at 6 mo, maintained fairly consistently at 12 & 18 mo with intervention. Over 3 periods, increase ave 4.0 units (14%, p=0.001). Self-rating depressive symptoms by GDS showed signif group–time interaction (p=0.003). Reduction in GDS at baseline of 25% at 6 & 12 mo and 37% reduction at 18 mo in intervention group (all p<0.001). 42% decrease in hospital inpatient days in intervention sites vs 52% increase in control sites over 18-mo. Intervention group half as likely to relocate to care homes vs control schemes (22 people versus 11 people moved.	1. Low 2. Low 3. High 4. High 5. Low 6. Unclear

Reference Country	Type	N	Participants	Intervention	Comparison	Main Outcomes	Measures	Length of follow up	Results/Effect size[a]	Risk of bias[1]
Cohen-Mansfield 2012 [302] Israel	RCT	125	Mean age 86; Gender 74% female Mean MMSE 8/30 Nursing home residents	A decision tree protocol (TREA protocol) was used to uncover possible reasons for agitated behaviours, relying on data derived from observations and assessments. An unmet need was hypothesised, a corresponding treatment category was identified and the specifics of the treatment were chosen to fit the person's past identity, preferences and abilities. Unmet needs (loneliness, depression, boredom and discomfort) were addressed via interventions such as robotic animal assisted therapy, personal interaction, family videos, lifelike baby doll, group activities, arts and crafts, physical activities, games, massage, and music. Treatment lasted 2 weeks.	Staff education in services describing agitation and possible solutions	Agitation	Agitation Behaviour Mapping Instrument; Lawton's Modified Behaviour Stream;	Observations recorded within the first and last 3 days of this period	The intervention group showed a significant decline in total, physical nonaggressive and verbal agitation during treatment. The effect size was -0.451 for verbal, -0.896 for physical nonaggressive and -0.913 for total agitation. The intervention group showed significant increases in pleasure and interest from baseline to the treatment condition, whereas the control group remained constant.	1. Unclear 2. Unclear 3. Low 4. High 5. High 6. Low

Reference Country	Type	N	Participants	Intervention	Comparison	Main Outcomes	Measures	Length of follow up	Results/Effect size[a]	Risk of bias[1]
Hilgeman 2014 [303] United States	RCT	19 carer / person with dementia dyads	Mean 83 years, Gender: 68% women	Individuals received four in-home sessions over 4–6 weeks from trained interventionists. The intervention combined one self-adjusting, future planning component and one self-maintaining, reminiscence-based component to maximize coping and enhance quality of life and well-being in the early stages of dementia. The intervention maximized prevalent coping strategies to impact emotional and health-related outcomes. Over the course of four sessions, individuals were guided through a reminiscence activity to complete a tangible product (e.g. scrapbook, recipe book, family tree, memory box, framed memorabilia, etc.) with the support of the interventionist and/or family. In addition, one of the four sessions transitioned from the reminiscence activity focus of 'what it has meant to live well in the past' to a discussion focused on 'what it will mean to live well in the future.' Individuals were provided with information about common treatment options, review myths about how care decisions are made, asked to document care preferences through interview-style. They also rehearse communicating their preferences to important loved ones.	A minimal support-based intervention focused on empathic listening and supportive reflection. Two calls were made over a 4-week period and lasted at least 10 minutes but no more than 30.	Depression	Cornell Scale for Depression in Dementia; QOL-AD; Bath Assessment of Subjective Quality of Life in Dementia; Meaning in Life Scale; Emotional Support and Anticipated Support Scales; EQ5D; Decisional Conflict Scale	Post intervention	Participants in the intervention group reported less depressive symptomatology post intervention than those in the control group (effect size Cohen's d=0.37). They also reported increased QOL on the BASQID (effect size=0.18). Other emotional outcomes did not appear to be affected. Participants in the intervention group reported significantly improved mobility, decisional conflict and coping.	1. Unclear 2. Unclear 3. Low 4. Unclear 5. Low 6. Unclear

Reference Country	Type	N	Participants	Intervention	Comparison	Main Outcomes	Measures	Length of follow up	Results/Effect size[a]	Risk of bias[1]
Lin 2009 [304] Taiwan	Crossover RCT	133	Mean age 80; Gender: 26% female Mean MMSE ranged from 6.9 to 8.0 in the three intervention groups Nursing home residents	Participants randomised to acupressure, Montessori activities and presence (companionship) Acupressure: Five acupoints were chosen to treat the agitation behaviours associated with dementia. Included acupressure applied to each point for 2 minutes. Completed 6 days per week for 4 weeks. Montessori: The activity programs during the period of study were scheduled six times a week for 4 weeks. The Montessori based activity program for persons with dementia has five major categories of activities associated with daily living: scooping, pouring, squeezing, fine motor skills, environmental care, and personal care.	Presence: A research team member who was not one of the data collectors would become a subject's companion for a 15-minute period each day for 6 days a week	Agitation	Cohen Mansfield Agitation Inventory; Ease of Care Inventory; Apparent Affect Rating Scale	Pre and post each type of interven-tion	Post intervention, acupressure and Montessori-based-activities groups had signif decrease in agitated behaviours, aggressive behaviours, and physically non-aggressive behaviours than the presence group. Ease-of-care ratings for the acupressure and Montessori-based-activities groups were significantly better than for the presence group. In terms of apparent affect, positive affect in the Montessori-based-activities group was significantly better than in the presence group	1. Unclear 2. Unclear 3. Low 4. Low 5. Unclear 6. Unclear

Reference Country	Type	N	Participants	Intervention	Comparison	Main Outcomes	Measures	Length of follow up	Results/Effect size[a]	Risk of bias[1]
Maci 2012 [305] Italy	RCT	14	Mean age 75 in intervention group, 70 in control group 57% female	The treatment group underwent a program lasting 3 months and consisting of cognitive stimulation, physical activity, and socialisation. In particular, every morning, 5 days a week from Monday to Friday, patients were driven from their homes to a gymnasium, where they stayed from 9:30 AM to 12:30 PM, before being driven back home. Patients were also encouraged to socialise through group discussions. On the way, music was played (old Italian songs that all patients knew), and one of the research staff stimulated the patients to interact with each other, singing all together, or talking about everyday life.	Usual care	QOL, mood	MMSE; Frontal Assessment Battery; ADL; Instrumental Activities of Daily Living; Clinical Dementia Rating scale; CSDD; Cornell-Brown Scale for QOL in Dementia; Apathy Evaluation Scale; QOL-AD; Hamilton anxiety rating scale. Family carers: Caregiver Burden Inventory; Beck Depression Inventory; and QoL-AD (version for the caregiver)	Post interven-tion	No significant changes in cognitive performances were observed. There was a significant improvement in apathy (effect size=3.22), anxiety (effect size=0.74), depression (effect size=2.56), and QOL (effect size=1.6) after the treatment in the intervention group. There was a reduction in caregiver burden in the intervention group (effect size = 0.49)	1. Unclear 2. Unclear 3. High 4. Low 5. Unclear 6. Unclear

Abbreviations: ADL – Activities of Daily Living; MMSE – mini mental state examination; QOL- Quality of Life- AD – Alzheimer's Disease; RCT – randomised-controlled trials; BPSD – behavioural and psychological symptoms of dementia; CI – confidence; MMSE – mini mental state examination; RCT – randomised-controlled trial; CMAlfr - ; I2 - ; MD – mean difference; n - ; P - ;signif – significant; OT – occupational therapy. GDS - ;GHQ28 - ; AMPS – Assessment for Motor and Process Skills; CIRS - ; CSDD – Cornell Scale for Depression in Dementia; PSI - ; MADRS - Montgomery Asberg Depression Rating Scale; MMSE – mini mental state examination; QOL-AD – Quality of Life-Alzheimer's Disease; PHQ-9 - ;NPI – Neuropsychiatric Inventory; ES –effect size. BASQID – Bath Assessment of Subjective Quality of Life in Dementia;
Risk of bias: (1) Random sequence generation, (2) Allocation concealment, (3) Blinding of participants and personnel, (4) Blinding of outcome assessment, (5) Incomplete outcome data, (6) Selective reporting

a. Effect sizes are reported using Cohen's d unless stated otherwise

b. Detailed results not reported as not an outcome of interest for this systematic review.

Table 136 GRADE Evidence Profile: Behavioural interventions for behavioural and psychological symptoms of dementia (BPSD)

Quality assessment							Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Behavioural and psychological symptoms								
9	randomised trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	A systematic review [140] involving 9 RCTs reported that: 5 studies reported that there were no significant differences between groups and 3 studies reported positive results: The results of the three positive studies were: Bourgeois: The intervention group had significantly less symptoms relative to the control group (effect size=0.26)[241] Teri (1997): significant reduction in depressive symptoms (effect size = 1.0)[249] Teri (2005): significant reduction in caregiver reaction to behaviours [172] One study (Gonyea) found a trend towards a reduction in BPSD in the intervention group (p=0.10)	⊕⊕OO LOW
Carer impact								
7	randomised trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	A systematic review [140] identified 7 studies: 4 studies reported that there were no significant differences between groups. 3 studies reported positive results. The results of the three positive studies were: Bourgeois: Caregivers in the intervention group had a small significant reduction in strain at 3 months (effect size 0.65) [241] Teri (2005): Sig reduction in burden (effect size=0.54)[172] Robinson: The intervention group had improved outcomes in relation to objective burden (effect size=1.94) [247]	⊕⊕OO LOW
Institutionalisation								
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	A systematic review [140] found 1 study (Farran) reported no significant differences between groups[243]	⊕⊕OO LOW
Quality of life of the person with dementia								
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	A systematic review [140] found 1 study (Teri 2005) reported that patients in the intervention group had a significant improvement (effect size=0.4)[172]	⊕⊕OO LOW

[1] *Aspects of methodology poorly reported in multiple studies* [2] *Mixed findings across studies* [3] *Total sample size <400*

Table 137 GRADE Evidence Profile: Cognitive stimulation for behavioural and psychological symptoms of dementia (BPSD)

Quality assessment							Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Behavioural and psychological symptoms								
8	randomised trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	There were no differences between intervention and control groups (SMD 0.13, 95%CI -0.07 to 0.32) based on 8 studies with 416 participants.[200]	⊕⊕OO LOW
Depression								
5	randomised trials	serious[3]	serious[2]	no serious indirectness	serious[4]	none	Intervention was not associated with a significant improvement in mood (SMD 0.22, 95%CI -0.09 to 0.53) based on 5 studies with 201 participants[200]	⊕OOO VERY LOW
Carer impact								
0	no evidence available					none		
Institutionalisation								
0	no evidence available					none		
Quality of life of the person with dementia								
4	randomised trials	serious[1]	serious[3]	no serious indirectness	serious[3]	none	There was a significant improvement on this outcome following treatment compared to control groups. The SMD was 0.38 (95% CI: 0.11, 0.65) [200]	⊕OOO VERY LOW

Abbreviations: CI – confidence interval; RCTs – randomised-controlled trials; SMD – standardised mean difference; SR – Systematic review

[1] *Aspects of methodology poorly reported in multiple studies*

[2] *Mixed findings across studies*

[3] *Total sample size <400*

Table 138 GRADE Evidence Profile: Exercise for behavioural and psychological symptoms of dementia (BPSD)

Quality assessment							Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Behavioural and psychological symptoms								
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	A systematic review identified four studies.[180]Three of the studies reported no significant effect on behavioural symptoms. The remaining trial reported that participants in the exercise group showed improvements in behaviour. [180]	⊕⊕OO LOW
Depression								
7	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	Five of these studies were pooled in a meta-analysis within the review[180]. The results were not significant (MD - 0.14, 95% CI -0.36 to 0.07; I2=0%) [180]	⊕⊕OO LOW
Carer impact								
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	The RCT included in the review reported a significant reduction in carer burden ([180])	⊕⊕⊕O MODERATE
Institutionalisation								
0	no evidence available					none		
Quality of life of the person with dementia								
0	no evidence available					none		

Abbreviations: CI – confidence interval; MD – mean difference; RCTs – randomised-controlled trials; SR – Systematic review

[1] *Aspects of methodology poorly reported in multiple studies*

[2] *Total sample size <400*

Table 139 GRADE Evidence Profile: Music therapy for behavioural and psychological symptoms of dementia (BPSD)

Quality assessment							Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Behavioural and psychological symptoms of dementia								
6	randomised trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	Pooling of 11 studies (non randomised and randomised) in a systematic review found a SMD of -0.49; 95%CI -0.82 to -0.17; I2=58%)*5[236]* 3 additional RCTs reported a positive result: Lin[251]: significant reduction in agitation in the intervention group Ridder[253]: reduced agitation disruptiveness in the intervention group (effect size 0.50) Vink 2013[255]: the intervention and control groups both had significantly reduced agitation (music therapy vs recreation therapy) 1 RCT (Nair)[252] reported more behavioural disturbances in the intervention group 2 additional studies found no significant effects compared to usual care [254 306]	⊕⊕OO LOW
Depression								
5	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	Pooling of 9 studies (randomised and non-randomised) in a systematic review found a SMD of -0.32, 95%CI -0.68 to -0.04; I2=44%) [236] 1 RCT (Cooke) found no significant differences between groups [306]	⊕⊕OO LOW
Carer impact								
0	no evidence available					none		
Institutionalisation								
0	no evidence available					none		
Quality of life of the person with dementia								
1 RCT	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	1 RCT found no significant differences between groups [253]	⊕⊕OO LOW

Abbreviations: CI – confidence interval; SMD – standardised mean difference; RCTs – randomised-controlled trials; SR – Systematic review
[1] Aspects of methodology poorly reported in multiple studies *[2] Mixed findings across studies* *[3] Total sample size <400*
[5] The SR pooled RCTs and CTs in the meta-analysis. They conducted a subgroup analysis based on design and found there were no differences in the effects between the two comparisons .Thus, their meta-analysis findings are presented here.

Table 140 GRADE Evidence Profile: Reminiscence therapy for behavioural and psychological symptoms of dementia (BPSD)

Quality assessment							Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Behavioural and psychological problems								
5	randomised trials	serious[1]	serious[2]	no serious indirectness	serious[3]		A systematic review [140] found 3 RCTs found no significant differences between groups and 2 RCTs reported improvements: The results of these two RCTs were: 1 RCT (Thorgrimsen) found a trend towards reduced BPSD in the intervention group[262] 1 RCT (Tadaka) found significant reductions in withdrawal in the intervention group in comparison to control group (effect size=0.70)[261]	⊕OOO VERY LOW
Depression								
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]		2 RCTs found significantly reduced levels of depression Haight: effect size d=0.82[258] Hsieh: effect size d=0.7 [263]	⊕⊕OO LOW
Carer impact								
3	randomised trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision		2 RCTs included in a systematic review found no significant differences between groups [140] 1 RCT (Woods) published since that review found that carers in the intervention group reported a significant increase in anxiety at the 10 month end point. [265]	⊕⊕OO LOW
Institutionalisation								
0	no evidence available					None		
Quality of life of the person with dementia								
3	randomised trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision		2 RCTs included in a systematic review found no significant differences between groups [140] 1 RCT (Serrani) published since that review found there was a significantly greater increase in QOL in the intervention group over time (effect size=2.2) than the control	⊕⊕OO LOW

							groups[264]	

Abbreviations: BPSD – behavioural and psychological symptoms of dementia; d - ;QOL – Quality of Life; RCTs – randomised-controlled trials;
[1] *Aspects of methodology poorly reported in multiple studies* [2] *Mixed findings across studies* [3] *Total sample size <400*

Table 141 GRADE Evidence Profile: Massage for dementia

Quality assessment							Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Behavioural and psychological symptoms of dementia								
5	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	5 RCTs (Hawranik; Remington; Woods; Hicks-Moore; Rodriguez Mansilla) reported significantly reduced levels of agitation post intervention. [265 267 268 271 272]. The effect size in the study conducted by Woods et al was 0.49. Effect sizes in other studies not able to be calculated based on data reported	⊕⊕OO LOW
Depression								
0	no evidence available					none		
Carer impact								
0	no evidence available					none		
Institutionalisation								
0	no evidence available					none		
Quality of life of the person with dementia								
0	no evidence available					none		

Abbreviations: RCTs – randomised-controlled trials;

[1] *Aspects of methodology poorly reported in multiple studies*

[2] *Total sample size <400*

Table 142 GRADE Evidence Profile: Recreation therapy for dementia

Quality assessment							Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Behavioural and psychological symptoms of dementia								
11	randomised trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	8 RCTs found no significant differences between groups ([274 278 281-284]) 3 RCTs found positive results for the intervention group George[279]: reduced anxiety in intervention group (effect size Hedges g=1.18) Hattori[280]: significant reduction in apathy (d=0.12) Vink 2013[255]: significant reduction in agitation in both the intervention group and the control group which received music therapy	⊕⊕OO LOW
Depression								
6	randomised trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	5 RCTs found no significant differences between groups ([192 279-281 283]) 1 RCT (Cheng 2012) found significantly reduced levels of depression post intervention (effect size=1.05)[277]	⊕⊕OO LOW
Carer impact								
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	1 RCT found no significant differences between groups[280]	⊕⊕OO LOW
Institutionalisation								
0	no evidence available					none		
Quality of life of the person with dementia								
2	randomised trials	serious[1]	serious[2]	no serious indirectness	serious[3]	none	2 RCTs found no significant differences between groups [192 280]	⊕OOO VERY LOW

Abbreviations: d - ; g - ; RCTs – randomised-controlled trials;
[1] *Aspects of methodology poorly reported in multiple studies* [2] *Mixed findings across studies* [3] *Total sample size <400*

Table 143 GRADE Evidence Profile: Light therapy for dementia

Quality assessment							Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Behavioural and psychological symptoms of dementia								
6	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	A systematic review found light therapy administered during the morning, evening, or all day for between 10 days to 10 weeks had no effect on agitation (SMD-0.01, 95%CI -0.31 to 0.29, I^2 = 16%, P = 0.95, n = 250)[237]	⊕⊕OO LOW
Depression								
5	randomised trials	serious[1]	serious[2]	no serious indirectness	serious[3]	none	No effect on depression was seen following 2 to 10 weeks of light therapy (SMD 0.09, 95% CI - 0.54 to 0.73, P = 0.78, n = 161) when studies were pooled in a systematic review[237]	⊕OOO VERY LOW
Carer impact								
0	no evidence available					none		
Institutionalisation								
0	no evidence available					none		
Quality of life of the person with dementia								
0	no evidence available					none		

Abbreviations: CI – confidence interval; n - ; P - ; SMD – standardised mean difference; RCTs – randomised-controlled trials; SR – Systematic review

[1] *Aspects of methodology poorly reported in multiple studies* [2] *Mixed findings across studies* [3] *Total sample size <400*

Table 144 GRADE Evidence Profile: Aromatherapy for dementia

Quality assessment							Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Behavioural and psychological symptoms of dementia								
2	randomised trials	serious[1]	serious	no serious indirectness	serious[2]	none	A systematic review [238] found 1 RCT (Ballard 2002) showed a statistically significant treatment effect (MD -15.8, 95% CI -24.4 to -7.2) whereas one RCT (Burns 2011) found no significant differences between groups.	⊕OOO VERY LOW
Depression								
0	no evidence available					none		
Carer impact								
0	no evidence available					none		
Institutionalisation								
0	no evidence available					none		
Quality of life of the person with dementia								
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	1 RCT included in a systematic review found no significant differences between groups ([238])	⊕⊕OO LOW

Abbreviations: CI – confidence interval; MD – mean difference; RCTs – randomised-controlled trials; SR – Systematic review

[1] *Risk of bias*

[2] *Total sample size <400*

Table 145 GRADE Evidence Profile: Multisensory stimulation for dementia

Quality assessment							Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Behavioural and psychological symptoms of dementia								
2	randomised trials	serious[1]	serious[2]	no serious indirectness	serious[3]	none	A systematic review [140] found 1 RCT (Baker[286]) which found no significant differences between groups and 1 RCT (Staal) which found reduced agitation levels over time (effect size d=0.82 post intervention)[288]	⊕OOO VERY LOW
Depression								
0	no evidence available					none		
Carer impact								
0	no evidence available					none		
Institutionalisation								
0	no evidence available					none		
Quality of life of the person with dementia								
0	no evidence available					none		

Abbreviations: d - ; RCTs – randomised-controlled trials;
[1] Aspects of methodology poorly reported in multiple studies
[2] Mixed findings across studies
[3] Total sample size <400

Table 146 GRADE Evidence Profile: Support and psychotherapy

Quality assessment							Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Behavioural and psychological symptoms of dementia								
1	randomised trials	serious[1]	serious[2]	no serious indirectness	serious[3]	none	1 RCT included in a systematic review found no significant differences between groups ([140])	⊕OOO VERY LOW
Depression								
3	randomised trials	serious[1]	serious[2]	no serious indirectness	serious[3]	none	2 RCTs found no significant differences between groups [289 292] 1 RCT (Tappen) found a significant decline in depressive symptomatology in the intervention group (p = 0.02). [293]	⊕OOO VERY LOW
Carer impact								
0	no evidence available					none		
Institutionalisation								
0	no evidence available					none		
Quality of life of the person with dementia								
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	1 RCT (Stanley 2013) found significantly greater improvements from baseline to 3 months in the intervention group (d=1.05).[292]	⊕⊕OO LOW

Abbreviations: d - ; MD – mean difference; p - ; RCTs – randomised-controlled trials;
[1] Aspects of methodology poorly reported in multiple studies
[2] Mixed findings across studies
[3] Total sample size <400

Table 147 GRADE Evidence Profile: Animal assisted therapy for dementia

Quality assessment							Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Behavioural and psychological symptoms of dementia								
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	1 RCT (Dabelko) showed a trend towards the overall mean number of problem behaviours tending to decrease after therapy [294] 1 RCT found no significant effects [307]	⊕⊕OO LOW
Depression								
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	1 RCT found no significant effects [307]	⊕⊕OO LOW
Carer impact								
0	no evidence available					none		
Institutionalisation								
0	no evidence available					none		
Quality of life of the person with dementia								
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	Intervention was associated with increased quality of life at one of the facilities in the study (effect size d=1.01, P=0.02) [307]	⊕⊕OO LOW

Abbreviations: d - ; P - ; RCTs – randomised-controlled trials;
[1] Aspects of methodology poorly reported in multiple studies
[2] Mixed findings across studies
[3] Total sample size <400

Table 148 GRADE Evidence Profile: Multicomponent interventions for BPSD

Quality assessment							Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Behavioural and psychological symptoms of dementia								
6	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1 RCT found no sig differences between groups[299] 5 RCTs reported significant benefits associated with intervention[a] Sung 2006[297] and Lin [304]reported significant reductions in agitation (unable to calculate effect size) Bakker: significant reduction in caregiver rated BPSD in favour of the intervention group (effect size=0.53, p=0.001)[300] Cohen Mansfield: significant reduction in agitation (effect size = 0.913)[302] Maci: significant reduction in apathy in the intervention group (effect size=3.22) [305]	⊕⊕⊕O MODERATE
Depression								
5	randomised trials	serious[3]	serious[3]	no serious indirectness	serious[4]	none	1 RCT found no sig differences between groups [127] 4 RCTs found significant reductions in depression in the intervention group[b]: McCurry (change 0.28 points versus 0.06 points) [296] Teri 2003: effect size d=0.27 [298] Brooker 2011: significant (25%) decrease in depression measures post intervention [301] Hilgeman 2014: significant reduction in depression (effect size =0.37) [303] Maci 2012 reported significant reduction in depression (effect size=2.56) [305]	⊕OOO VERY LOW
Carer impact								
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	2 RCTs reported significant reductions in carer impact[c] Maci 2012: reduction in caregiver burden in the intervention group (effect size= 0.49)[305] Bakker 2011: significant reduction in caregiver burden (effect size=0.63) [300]	⊕⊕OO LOW
Institutionalisation								
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	1 RCT (Brooker) found that overall, there was a 42% decrease in hospital inpatient days in the intervention sites over the 18-month period. [301]	⊕⊕OO LOW

Quality assessment							Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Quality of life of the person with dementia								
5	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	1 RCT found no significant differences between groups[300] 4 RCTs reported positive results[d]: Teri 2003 significant improvement in QOL in the intervention group (effect size d=0.28)[298] Brooker: reported significant (14%) increase in QOL in the intervention group [301] Hilgeman: improved QOL in the intervention group (effect size=0.18)[303] Maci: improved QOL in the intervention group (effect size=1.6) [305]	⊕⊕OO LOW

Abbreviations: d - ; MD – mean difference; QOL – Quality of Life; RCTs – randomised-controlled trials;

[1] *Aspects of methodology poorly reported in multiple studies*

[2] *Mixed findings across studies*

[3] *Total sample size <400*

a. *Studies that reported positive results varied greatly in their intervention approaches. Interventions found to be effective included: music plus movement; acupressure plus Montessori activities; cognitive stimulation plus physical activity plus socialisation; multifaceted interventions with a focus on support and therapy; and personalised interventions selected based on a decision tree.*

b. *Studies that reported positive results varied greatly in their intervention approaches. Interventions found to be effective included: meaningful activities plus case management; reminiscence therapy plus counselling; cognitive stimulation plus physical activity plus socialisation; and exercise plus caregiver education plus light therapy.*

c. *Studies that reported positive results varied greatly in their intervention approaches. Interventions found to be effective included: cognitive stimulation plus physical activity plus socialisation; and multifaceted interventions with a focus on support and therapy*

d. *Studies that reported positive results varied greatly in their intervention approaches. Interventions found to be effective included: meaningful activities plus case management; cognitive stimulation plus physical activity plus socialisation; reminiscence therapy plus counselling.*

SRQ 16: Pharmacological interventions for BPSD

Clinical question

The research question as defined in the protocol and the associated PICO criteria are listed below.

Clinical question: For people with behavioural and psychological symptoms of dementia, does appropriate drug treatment when compared to placebo produce benefits/harm?

Population	Intervention	Comparator	Outcomes
People with behavioural and psychological symptoms of dementia (BPSD)	- Antipsychotics (aripiprazole, olanzapine, quetiapine, risperidone, haloperidol) - Anxiolytics/Hypnotics (Benzodiazepines [sustained action: diazepam; shorter-acting compounds: lorazepam and oxazepam, clonazepam]) - Antimanic drugs [e.g. carbamazepine, valproate] - Acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine) + memantine - Antidepressants (SSRIs [citalopram or es-citalopram or fluoxetine or fluvoxamine or paroxetine or sertraline] and SNRIs [venlafaxine or duloxetine or desvenlafaxine or mirtazapine] and atypical antidepressants [mirtazaline]), mirtazapine, mianserin, moclobemide, agomelatine, reboxetine - Analgesics OR any of the above medications in combination with non-drug intervention EXCLUDED: Tricyclic antidepressants, anti-androgens, testosterone, supplements (thiamine, gingko-bilboa), synthetic cannabinoids, psychostimulants (eg. methyphenidate), adjunctive treatments	Placebo OR placebo in combination with non-drug intervention	Primary outcomes: BPSD Secondary outcomes: Quality of life of the person with dementia Institutionalisation Adverse effects (including cognition for antidepressants) Pain (analgesics)

Literature review search strategies:

Searches for existing HTAs and Systematic reviews

Searches to identify existing Health Technology Assessment reports (HTAs) and systematic reviews were conducted in the databases specified in Table 149, using the search terms listed in the Guideline Technical Report Volume 2.

Table 149 Searches for existing HTAs and systematic review for SRQ 16: Pharmacological interventions for BPSD - antipsychotics, antidepressants, mood stabilisers, anxiolytics and melatonin

Database	Date searched	Period covered	Citations retrieved
HTA & NHSEED	17 Nov 2014	2005 to 2014	20
Cochrane (Cochrane reviews, Cochrane protocols, DARE)	17 Nov 2014	2005 to 2014	311
MEDLINE	18 Nov 2014	2005 to 2014	103
PsycInfo	18 Nov 2014	2005 to 2014	76
EMBASE	18 Nov 2014	2005 to 2014	59
PubMed	17 Nov 2014	2005 to 2014	12

Table 150 Searches for existing HTAs and systematic review for SRQ 16: Pharmacological interventions for BPSD - analgesics

Database	Date searched	Period covered	Citations retrieved
HTA & NHSEED	12 September	2005 to 2014	0
Cochrane (Cochrane reviews, Cochrane protocols, DARE)	12 September	2005 to 2014	12
MEDLINE	12 September	2005 to 2014	67
PsycInfo	12 September	2005 to 2014	32
EMBASE	12 September	2005 to 2014	16
PubMed	12 September	2005 to 2014	1

Searches for additional primary studies

Searches were conducted in the databases listed in Table 151 to identify additional primary studies published since the search period of the included systematic reviews. The search terms used are listed in the Guideline Technical Report Volume 2.

Table 151 Searches for randomised controlled trials review for SRQ 16: Pharmacological interventions for BPSD - antipsychotics, antidepressants, mood stabilisers, anxiolytics, melatonin and analgesics

Database	Dates searched	Period covered	Citations retrieved
MEDLINE	1 Dec 2014 12 Jan 2015 12 Sept 2014	Various, by class[§] Non-SSRI, non-TCA antidepressants: 2005-2008 Analgesics: 1 Jan 2011 to 12 September 2014	124 15 32
PsycInfo	1 Dec 2014 12 Jan 2015 12 Sept 2014	Various, by class[§] Non-SSRI, non-TCA antidepressants: 2005-2008 Analgesics: 1 Jan 2011 to 12 September 2014	118 12 15
EMBASE	1 Dec 2014 12 Jan 2015 12 Sept 2014	Various, by class[§] Non-SSRI, non-TCA antidepressants: 2005-2008 Analgesics: 1 Jan 2011 to 12 September 2014	66 4 20
PubMed	1 Dec 2014 1 Dec 2014 12 Sept 2014	Various, by class[§] Non-SSRI, non-TCA antidepressants: 2005-2008 Analgesics: 1 Jan 2011 to 12 September 2014	0 0 7

[§] Antipsychotics searched from 2011-current, haloperidol 2005-2014, non-tricyclic antidepressants 2009-2014, mood stabilisers 2011-2014, anxiolytics 2005-2014, melatonin 2009-2014.

Criteria for selecting studies for review:

Table 152 Inclusion and exclusion criteria for review of drugs for the treatment of BPSD

Characteristic	Criteria
Study design	Inclusion: Systematic reviews, randomised controlled trials
Population	Inclusion: People with BPSD Exclusion: People with Huntington's Disease
Intervention	Inclusion: Antipsychotics, Anxiolytics, Mood stabilisers, Antidepressants (SSRIs [citalopram or es-citalopram or fluoxetine or fluvoxamine or paroxetine or sertraline] and SNRIs [venlafaxine or duloxetine or desvenlafaxine or mirtazapine] and atypical antidepressants [mirtazaline]) - Analgesics (any form of pharmacological pain relief [over the counter or by prescription] adhering to protocol for pain management) OR any of the above medications in combination with non-drug intervention EXCLUDED: Tri-cyclic antidepressants, anti-androgens, testosterone, supplements (thiamine, gingko-bilboa), synthetic cannabinoids, psychostimulants (eg. methyphenidate), adjunctive treatments
Comparator	Inclusion: Placebo with or without non-pharmacological interventions Inclusion (analgesics): Placebo or no pain relief or usual care
Outcomes	Inclusion: BPSD, Secondary outcomes: Quality of life of the person with dementia, Institutionalisation, Adverse effects (including cognition for antidepressants), Pain (analgesics)
Publication type	English language

Search results:

Existing HTAs and systematic reviews

The most recent, comprehensive and highest quality systematic reviews/HTAs identified and included in the current update are show in Table 153; the related Evidence Summaries are presented in

Table 155

Table 153 Systematic reviews and HTA report included in the review of drugs for the treatment of BPSD

Drug class	Included systematic reviews/HTAs
Antipsychotics	*Atypicals*: Maglione et al. 2011 (AHRQ HTA) [308 309] *Haloperidol:* Lonergan 2001 [310]
Antidepressants	*Depression:* Sepehry et al. 2012 (SSRIs/SNRIs) [311] *Agitation:* Seitz et al. 2011 [312], Cooper et al. 2013 (QOL) [313]
Mood stabilisers	Seitz et al. 2013 [314]
Anxiolytics	Nil
Melatonin	*Sleep:* McCleery et al. 2014 [315] *Other:* Jansen et al. 2011 [316]
Analgesia	Pieper et al. 2013 [317]
Acetyl –cholinesterase inhibitors	NICE Technology appraisal [214]

Primary studies

Antipsychotics, antidepressants, mood stabilisers, anxiolytics and melatonin: A total of 339 citations were retrieved in the electronic database searches. After exclusion of duplicate citations, 246 were reviewed by abstract and title. Twelve studies were viewed in full text and two studies were included in the evidence update (see Table 154); the related Evidence Summaries are presented in Table 156.

Table 154 Primary studies included in the review of drugs for the treatment of BPSD

Drug class	Original studies published subsequent to included systematic review	Original studies included in lieu of an existing systematic review
Antipsychotics	Nil	N/A
Antidepressants	Agitation: CiTAD (Porsteinsson et al. 2014) [318]	Depression (Non-SSRI/SNRIs): Banerjee (2011) [319]
Mood stabilisers	Nil	N/A
Anxiolytics	N/A	Nil RCTs for BPSD
Melatonin	Nil	N/A
Analgesia	Nil	N/A

Evidence summary:

The NICE Guidelines Committee recommended that pharmacological treatment for BPSD should not be offered as a first line treatment unless the person with dementia is severely distressed or there is an immediate risk of harm to the person or others.

This evidence update has considered pharmacological interventions for BPSD in the following categories: antipsychotics, antidepressants, acetylcholinesterase inhibitors and memantine, anxiolytics, mood stablisers and melatonin. The studies included as the source of evidence for this review are summarised in Table 154 and the Evidence Summaries are presented in

Table 155.

Analgesia

The use of analgesia to treat BPSD is a relatively new approach to care. The NICE Guideline Committee did not specifically look for evidence on the efficacy of analgesics on BPSD.

This evidence update searched for systematic reviews published since 2005. A systematic review conducted by Pieper and colleagues was identified (Evidence Summary

Table 155).[317] The systematic review searched for studies up until March 2012. Our search for studies published after this date failed to reveal any additional RCTs meeting our inclusion criteria. The GRADE Evidence Profile is presented in Table 157.

The systematic review conducted by Pieper and colleagues identified three RCTs that examined the effect of pharmacological treatment of pain on behaviour.[320-322] All three studies recruited participants with moderate to severe dementia residing in nursing homes. Two of the studies examined the effectiveness of regular paracetamol [320 321] whereas the third study examined the effectiveness of analgesic medication prescribed based on the use of a step-wise protocol [323]. Two of the three studies reported improved outcomes for people with dementia. [321 322]

Antipsychotics

Atypical antipsychotics:

The NICE Guideline Committee conducted a systematic review and identified 11 RCTs for their efficacy review and two meta-analyses for their safety review. Based on these trials, the Committee recommended that antipsychotics should not be prescribed to people with mild-to-moderate cognitive symptoms with Alzheimer's disease, vascular dementia, mixed dementias or DLB. It was recommended that antipsychotics should only be offered to people with Alzheimer's disease, vascular dementia, mixed dementias or DLB with severe non-cognitive symptoms following a number of specific procedures and assessments (see details above).

> This evidence update identified a 2011 review of off-label use of antipsychotics conducted Agency for Healthcare Research and Quality (AHRQ), which included a meta-analysis of 17 conducted over a 6-12 week follow-up (Evidence Summary

Table 155).[308 309] The analysis demonstrated that atypical antipsychotics had small but statistically significant positive effects on BPSD overall, agitation and psychosis. In meta-analyses of individual medications, risperidone demonstrated a statistically significant positive effect on psychosis, but aripiprazole, olanzapine and quetiapine did not. Risperidone and olanzapine had a statistically significant positive effect on agitation, with weaker evidence for effectiveness for aripiprazole and no statistically significant difference was seen with quetiapine (Evidence Summary

Table 155).[308 309]

A systematic review of studies reporting on the quality of life of people with dementia [313] identified a large randomised controlled trial that found no difference in carer-rated quality of life for subjects receiving atypical antipsychotic treatment compared to placebo (the Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease, CATIE-AD).[324] This was not considered a critical outcome for use in cases of severe BPSD (i.e., psychosis and/or agitation/aggression causing significant distress to themselves or others) .

The 2011 AHRQ review also considered a 2005 meta-analysis of 15 published and unpublished studies of atypical antipsychotic use in dementia, which indicated a statistically significant increased risk of mortality (3.5% atypical antipsychotics vs 2.3% placebo; OR 1.54, 95%CI 1.06 to 2.23).[325] This meta-analysis contains unpublished data not available to other authors and is therefore still considered the most comprehensive analysis available. In the 2011 AHRQ review there was a statistically significant increased risk of cardiovascular events for olanzapine (OR 2.33, 95%CI 1.08 to 5.61) and risperidone (OR 2.08, 95%CI 1.38 to 3.22), but not quetiapine or aripiprazole. The authors found consistency between this meta-analysis and FDA analyses as well as between published and unpublished trials. The risk of cerebrovascular accident was increased with risperidone (OR = 4.69, 95%CI 1.87 to 14.14).

The GRADE Evidence Profile for atypical antipsychotics for the management of BPSD is presented in Table 158.

Intramuscular atypical antipsychotics:

The NICE guideline committee recommended IM olanzapine for behavioural control in situations where there is a significant risk of harm, based on trial evidence considered of moderate quality (Meehan 2002; NICE Appendix GRADE Evidence profile Tables 16.41 & 16.42, reproduced in Table 159; associated Forest plots NICE Appendix 20 pp 130-140).[326]

The 2011 AHRQ report included one additional study of IM aripiprazole. However, this antipsychotic is not available in this formulation in Australia, hence the data were not included in this evidence update [327].

A search for randomised controlled trials published 2011 to November 2014 did not identify any additional studies of atypical antipsychotics for BPSD.

Classical antipsychotics:

The NICE Guideline Committee considered evidence for haloperidol compared to placebo from a 2002 Cochrane review of haloperidol for agitation in dementia. The Cochrane authors updated the searches to June 2010, with no additional studies identified.[310] This evidence update identified the Cochrane Review as being the most recent high quality systematic review meeting the inclusion criteria. The Cochrane review included five randomised, placebo-controlled trials were. This evidence update did not identify any additional studies published to November 2014.

Haloperidol decreased behavioural symptoms, aggressive behaviour and agitation. The NICE guideline committee also considered safety data from a 2005 meta-analysis of published and unpublished studies of the risk of death associated with antipsychotic use in dementia.[325] This study showed an increase in the risk of death at a rate similar to that of atypical antipsychotics, although it was not statistically significant (2 trials, OR 1.68, 95%CI 0.72 to 3.92, P = 0.23; RR 2.07, 95%CI 0.78 to 5.51, P=0.15).[325] Data from an observational study indicated no significant

difference in the risk of cardiovascular events between haloperidol and atypical antipsychotics.[328] The overall quality of evidence was rated as moderate in the NICE Guideline; the GRADE Evidence Profile was not presented. On the basis of this evidence IM haloperidol was recommended by NICE for behavioural control in situations where there is a significant risk of harm due to behaviour that challenges. The Guideline Adaptation Committee did not include a recommendation for IM haloperidol as it was considered that olanzapine and lorazepam should be considered as first line IM treatments when necessary, rather than haloperidol. This was due to the less favourable adverse event profile of haloperidol.

Antidepressants

Dementia with concomitant depression

The NICE Guideline Committee considered evidence from a 2002 Cochrane systematic review by Bains et al. [329] This review included four small RCTs (two of SSRIs, two of TCAs) of 6 to 12 weeks treatment, which indicated a significant improvement in mood measured by the Cornell Scale for Depression and in the Clinical Global Impression. There were also significant increases in adverse events (of the nervous and gastrointestinal systems, and dryness of the mouth) in association with antidepressant use. On the basis of this review, NICE recommended that people with dementia who also have major depressive disorder should be offered antidepressant medication and that antidepressant drugs with anticholinergic effects (eg. tricyclic antidepressants) should be avoided.

This evidence update identified Sepehry et al (2012) as the most recent, comprehensive systematic review of antidepressants for depression in dementia (Evidence Summary

Table 155).[311] The Sepehry et al. review examined novel antidepressants (selective-serotonin reuptake inhibitors [SSRIs] and serotonin-noradrenaline reuptake inhibitors [SNRIs]) for people with Alzheimer's disease and depression and included 5 trials in a meta-analysis (

Table 155). [311 319 330-333] Therefore the Sepehry review did not consider other types of antidepressants (eg. mirtazapine, mianserin). To include any additional evidence from other antidepressant classes, the data from a third arm of an included trial examining mirtazapine has also been considered in the current evidence update (Evidence Summary Table 156). [319 334] Trials of tricyclic antidepressants were excluded. Pooled data from four RCTs and one pseudorandomised controlled trial of SSRIs failed to show a significant improvement in depression, global behavioural outcomes or quality of life in subjects with dementia and concomitant depression (

Table 155).[311 319] The findings of a trial including mirtazapine were consistent with the results of the SSRI meta-analysis. One small randomised controlled trial (the DIADS-1 trial, considered by NICE in the 2006 Guideline and included in the more recent Sepehry meta-analysis) demonstrated a significant improvement in depression according to one outcome measure (the Cornell Scale for Depression in Dementia), but not another (the Hamilton Depression Scale).[333] No significant effect on depression was found in the three other RCTs of SSRIs [319 330 332] nor a small pseudorandomised trial [331]. Cognition did not significantly differ between SSRIs and placebo in the pooled analysis.[311] This evidence update pooled serious adverse event rates from three of the included RCTs; no significant difference was seen (OR 1.42, 95%CI 0.80 to 2.53; see page 316). The remaining RCT reported no difference in total adverse events.[333]

The GRADE Evidence Profile is presented in Table 161.

Dementia with agitation/psychosis

The current evidence update identified Seitz et al (2011) as the most recent, comprehensive systematic review of antidepressants for agitation in dementia (Evidence Summary

Table 155).[312] Seitz et al (2011) identified two trials enabling pooling of reporting outcomes of agitation measured as change in the Cohen Mansfield Agitation Inventory (CMAI). The additional Citalopram for Agitation in Alzheimer Disease Study (CitAD) was identified in a search for more recent primary studies (Evidence Summary Table 156).[318] A significant improvement in reducing agitation has been demonstrated in the two large RCTs of SSRIs compared to placebo [318 335], with no significant impact on serious adverse events [318] or trial withdrawals (pooled data from four RCTs included in systematic review). [312] One very small pilot trial did not demonstrate a significant effect [336]; pooled data from this trial and one of the larger trials [335] demonstrated a significant improvement. [312] Evidence for an impact of SSRIs on global behavioural outcomes in studies reporting on treatment of agitation and psychosis in dementia is less consistent; however, the most recent and highest quality RCT did demonstrate a significant improvement over 9 weeks of treatment with citalopram using a number of different outcome measures (Evidence Summary

Table 155; GRADE Evidence Profile Table 160).[318] This recent RCT also demonstrated an increase in some adverse events, including an increase in cognitive decline and of QT interval on ECG in the subjects treated with citalopram.[318] (Note, no significant difference in cognition outcomes was seen in a pooled analysis of 5 studies of SSRIs for dementia and depression, nor in any of the individual studies, as described above). No studies reporting quality of life in people treated for agitation or psychosis in dementia were identified in a recent systematic review.[313] The GRADE Evidence Profile is presented in Table 160.

Mood stabilisers

NICE identified 5 RCTs with a total of 342 participants which examined mood stabilisers compared to placebo. The included studies demonstrated inconsistent effects for carbamazepine (two small studies). There were no significant improvements in BPSD for valproate, but adverse events were more frequent in the valproate group (three studies). No recommendations on the use of this class of drug were made by NICE.

Based on the assumption that mood stabilisers are typically used for people with severe dementia residing in residential care settings, we included a recent systematic review that examined pharmacological treatments in long term care. The review included four RCTs of mood stabilisers (Evidence Summary

Table 155).[314] One small, fair quality study of carbamazepine demonstrated a significant improvement in BPSD (on the Brief Psychiatric Rating Scale total) over six weeks (GRADE Evidence Profile Table 162).[337] No significant change in BPSD was observed in studies of divalproex or oxcarbazepine (GRADE Evidence Profiles Table 163 and Table 164).[338-340]

No additional RCTs of mood stabilisers for BPSD were identified in a search for primary studies published from 2011 to November 2014.

Anxiolytics/benzodiazepines

The NICE Guideline Committee recommended the use of IM lorazepam for behavioural control in situations where there is a significant risk of harm, based on a single study [326]. This trial provided moderate to high quality evidence of safety and effectiveness (see Table 166 reproduced from NICE Appendix GRADE Evidence profile Tables 16.43 & 16.44; associated Forest plots NICE Appendix 20 pp 130-140). The NICE committee also recommended against the use of IM diazepam for behavioural control.

No additional RCTs of anxiolytics for BPSD were identified.

Melatonin

The NICE Guideline Committee did not review the evidence for the use of melatonin for BPSD. This evidence update identified two Cochrane reviews that examined the effects of melatonin in people living with dementia; one for sleep disturbances in Alzheimer's disease (this did not address BPSD outcomes) [315] and another for dementia reporting BPSD outcomes [316].

The Cochrane review of pharmacological treatments for sleep disorders in AD identified three studies of melatonin and one study of ramelteon, a melatonin receptor-agonist (Mc Cleery et al 2014, Evidence Summary

Table 155).[315] No significant effects on major sleep outcomes or adverse events were found.

Another Cochrane review [316] of melatonin in dementia reporting a number of outcomes, excluding sleep, demonstrated positive effects on global BPSD across two studies (Jansen et al, 2011, Evidence Summary

Table 155).[341 342] The Cochrane reviewers conducted analysis of the longitudinal data from another trial for multiple outcomes including mood ratings.[343] Worsening of mood was observed at one year on the Philadelphia Geriatric Center Affect Rating Scale (positive); the effect was not statistically significant at 6 weeks or 2 years. There was no statistically significant effect on the Philadelphia Geriatric Center Affect Rating Scale (negative) or the overall Philadelphia Geriatric Center Morale Scale at 6 weeks, 1 year or 2 years, or other outcome measures of mood and behaviour (see

Table 155).[343] A regression analysis in the original paper reported a significant decrease in positive mood ratings and significant increase in negative mood ratings, considering data from multiple follow-up times and accounting for missing data. The number of adverse events did not significantly differ between treatment arms.

A search for RCTs of melatonin for dementia published to November 2014 did not identify any additional studies.

In summary, pooled data from two small studies indicated that melatonin may be useful in BPSD [341 342]. However there are also possible negative effects on mood [343] and unclear biological plausibility given the lack of effect on sleep.[315] Therefore there is uncertainty in the overall body of evidence for melatonin effectiveness and the Guideline Adaptation Committee decided that the evidence was inadequate to inform a recommendation.

The GRADE Evidence Profile is presented in Table 167.

Summary

In summary, evidence exists for a small improvement in BPSD with treatment with atypical antipsychotics; however, this is associated with a small but statistically significant increase in mortality, cardiovascular and cerebrovascular events. There is also evidence that analgesics can reduce BPSD without high risk of serious adverse events.

The most recent evidence indicates that antidepressants are unlikely to improve depression, but there is some evidence that SSRIs can improve agitation in people with dementia. There is uncertainty in the overall body of evidence for melatonin effectiveness. There is no convincing evidence for the use of mood stabilisers or anxiolytics.

Evidence statements	*GRADE Quality*	*Rec*
A systematic review [317] found that one of two RCTs examining the efficacy of analgesia to manage agitation reported a significant reduction in agitation and pain [322], with no significant change in adverse event rates in three RCTs [320-322]. (Table 157)	Low	EBR 81
A pooled analysis [311] of five studies (four RCTs and one pseudorandomised trial [[311 319 330-333]) indicated that antidepressants (SSRIs) do not have a statistically significant impact on depression in people with dementia overall. There were no significant effects on BPSD or quality of life (two RCTs) [319 344]. Serious adverse event rates did not significantly differ in a pooled analysis of threeRCTs (page 316). The systematic review [311] did not find a significant difference in cognition outcomes between SSRIs and placebo (five studies). The findings from an additional trial arm of mirtazapine were consistent. [319 334](Table 161)	Low	EBR 88

Evidence statements	*GRADE Quality*	*Rec*
Two large RCTs demonstrated a significant reduction in agitation with the use of selective serotonin update inhibitors (SSRIs) compared to placebo in patients with dementia [318 335]; one additional very small RCT showed no significant difference [336] (Quality: moderate). One high quality RCT found that there was no significant difference in the number of serious adverse events between SSRIs and placebo (Quality: moderate).[318] Pooled data found no significant difference in trial withdrawals due to adverse events (four RCTs).[312] SSRI use was associated with a decrease in cognition (one point on the MMSE) and an increase in the QT interval on ECG, which is considered a surrogate outcome for adverse events (one RCT, Quality: low).[318] (Table 160)	Moderate	EBR 86
A pooled analysis of 17 RCTs indicated that atypical antipsychotics are associated with a small but statistically significant improvement in global BPSD. [308 309] In meta-analyses of individual medications, risperidone demonstrated a statistically significant positive effect on psychosis (five RCTs), but aripiprazole (three RCTs), olanzapine (five RCTs) and quetiapine (three RCTs) did not. Risperidone (six RCTs) and olanzapine (four RCTs) had a statistically significant positive effect on agitation, with weaker evidence of effectiveness for aripiprazole (two RCTs); no statistically significant difference was seen with quetiapine (five RCTs).[308 309]This is associated with a statistically significant increase in mortality (3.5% atypical antipsychotics vs 2.3% placebo) in a meta-analysis of 15 trials.[325]. Separate meta-analyses demonstrated a significant increase in cardiovascular events with olanzapine (5 RCTs) and risperidone (6 RCTs) and cerebrovascular events with risperidone (3 RCTs). [308 309] There was no change in carer-rated quality of life in one RCT.[324] (Table 158)	Moderate	EBR 89, 91
One RCT provided evidence that intramuscular olanzapine can improve agitation two hours after treatment.[326] (Table 159)	Moderate	CBR 97
A systematic review [314] found a significant improvement in BPSD (as measured with the Brief Psychiatric Rating Scale) with carbamazepine over six weeks [337] (one RCT; Quality: low) (Table 162). No significant effect on BPSD was found with divalproex sodium (two RCTs) [338 340] or oxcarbazepine (one RCT) [339]. (Table 163, Table 164)	Low	NA
No RCTs were identified that reported on the effectiveness of anxiolytics for BPSD (excluding IM administration; Table 165). One RCT reported that intramuscular lorazepam significantly improved BPSD two hours after treatment.[326] (Table 166)	Moderate	CBR 97

Evidence statements	*GRADE Quality*	*Rec*
Pooled data from two small RCTs indicated that melatonin may be useful in BPSD.[341 342] There are also possible negative effects on mood (one RCT) [343]. There is uncertainty in the overall body of evidence for melatonin effectiveness. (Table 167)	Low	NA

Table 155 Evidence Summary of Included Systematic Reviews for SRQ 16: Pharmacological interventions for BPSD

Reference	Study Design	Types of studies included Search period	Types of participants included Relevant research question(s)	Intervention	Comparison	Relevant Result Relevant Concl
Multiple drug classes						
McCleery (2014)[315]	Systematic review	RCTs To May 2013	People with Alzheimer's disease and sleep disturbance To assess the effects, including common adverse effects, of any drug treatment versus placebo for sleep disorders in people with Alzheimer's disease	Any drug intended to improve sleep (no restrictions)	Placebo	3 studies of me trazodone, 1 st of benzodiazepi hypnotics ident Lack of evidenc problems in AD melatonin in th AD or for ramel moderate AD a
Effectiveness *Sleep outcomes* Melatonin (immediate- or slow-release) did not improve major sleep outcomes in AD (in meta-analysis of 2 studies), or other sleep outcomes in single studies. A phase 2 trial of ramelteon 8mg at night in subjects with mild to moderate dementia indicated no significant effect on total nocturnal sleep at one or eight week Adverse events No serious adverse effects of melatonin or ramelteon were reported						
Cooper (2013) [313]	Systematic review	RCTs reporting QoL or wellbeing To June 2011	People with dementia (any type) To review the effectiveness of all pharmacological interventions to improve quality of life and well-being in people with dementia.	Pharma-cological interventions	Placebo or comparator controlled	15 RCTs and on atypical antipsy of antimanics, a identified. Inclu variety of agent cholinesterase i No consistent e improves qualit dementia.
Antipsychotics 1 RCT (421 patients) of antipsychotics vs placebo (CATIE) in AD (MMSE mean 15.0, SD 5.8) showed no difference in QOL at 12 weeks (WMD 3.50, 95%CI -1.54 to 8						
Atypical antipsychotics						
Maglione (2011) [308 309] AHRQ	Systematic review	Clinical trials Observational studies >1,000 subjects for rare adverse events To May 2011	Off-label conditions including dementia What does the evidence show regarding the efficacy and comparative effectiveness of atypical antipsychotics for off-label indications? How do atypical antipsychotic medications compare with other drugs, including first generation antipsychotics, for treating off-label indications? What are the potential adverse effects and/or complications involved with off-label prescribing of atypical antipsychotics? How do they compare within the class and with other drugs used for the conditions?	Atypical antipsychotic (aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone, paliperidone, asenapine, iloperidone)	Placebo or another atypical antipsychotic or other pharmacotherapy	37 RCTs in dem controlled: 5 ar quetiapine, 8 ri reporting QoL i Aripiprazole, ol have efficacy as symptoms of de evidence). In dementia pat in mortality (sm significant), and in weight gain, extrapyramidal increase in ende

Reference	Study Design	Types of studies included Search period	Types of participants included Relevant research question(s)	Intervention	Comparison	Relevant Result Relevant Concl
Effectiveness *Overall BPSD* Pooled analysis of atypical antipsychotics overall (aripiprazole, olanzapine and risperidone compared to placebo, 17 studies, outcomes between 6 and 12 weeks), (95%CI 0.08 to 0.25). High confidence that risperidone is superior to placebo for overall symptoms SMD 0.19 (95%CI 0.00 to 0.38, substantial heterogeneity, sensitivity analysis based o Moderate confidence that aripiprazole is superior to placebo (SMD 0.20, 95%CI 0.04 to 0.35). Low level confidence that olanzapine or quetiapine are superior to placebo (olanzapine SMD 0.12, 95%CI 0.00 to 0.25; quetiapine SMD 0.13, 95%CI -0.03 to 0.28 r *Psychosis* Overall psychosis (16 studies of atypical antipsychotics) SMD 0.12 (95% CI 0.04, 0.19) Pooled analysis indicated risperidone was superior to placebo in decreasing psychosis symptoms (SMD 0.20, 95% CI 0.05 to 0.36, 5 RCTs, moderate level evidence 0.20, 95% CI −0.02 to 0.42, 3 trials), olanzapine (SMD 0.05, 95% CI −0.07 to 0.17, 5 trials), quetiapine (SMD −0.03, 95% CI −0.24 to 0.18, 3 trials). *Agitation* Overall agitation (17 studies of atypical antipsychotics) SMD 0.20 (95% CI 0.12 to 0.27) Pooled analysis indicated olanzapine (SMD 0.19, 95%CI 0.07 to 0.31; 4 trials) and risperidone (SMD 0.22, 95%CI 0.09 to 0.35; 6 trials) were superior to placebo, ef trials of aripiprazole reported positive results compared to placebo (low level evidence). No significant difference between quetiapine and placebo (5 studies).						
Maglione (2011) [308 309] AHRQ Cont[d] Adverse events (patients with dementia; comparison to placebo) *Mortality* The difference in risk for death was small but statistically significant for atypicals, according to a 2005 meta-analysis of 15 published and unpublished randomised Alzheimer's disease (death in 3.5% with antipsychotics vs 2.3% placebo, OR 1.54, 95%CI 1.06 to 2.23 [P<0.01], NNH = 100 (95%CI 53 to 1000), 14 trials were of 6-1 differential risks for individual atypical antipsychotics. No trials or large observational studies of ziprasidone in this population. Patients taking haloperidol had similar increased odds of mortality over those taking no antipsychotics in two trials, although it was not statistically significant. *Cardiovascular events (cardiovascular symptoms, edema or vasodilatation)/CVA* Occurred significantly more often in patients taking olanzapine (5 studies, OR 2.33, 95%CI 1.08 to 5.61; NNH 48) and risperidone (6 studies, OR 2.08, 95%CI 1.38 t Quetiapine (3 trials; N =254) and aripiprazole (1 trial, N = 121) were not statistically significantly associated with these symptoms. Cerebrovascular accident more common in risperidone than placebo (3 studies, OR = 3.12, 95%CI 1.32 to 8.21; NNH = 53, only drug associated with an increase in *Weight gain* More common in patients taking olanzapine (OR = 4.69, 95%CI 1.87 to 14.14) and risperidone (OR 3.40, 95%CI 1.08 to 12.75). People with dementia treated with weight gain of 1.0, 0.7 and 0.4 pounds on treatment vs a weight loss of 0.9 pounds per month on placebo (CATIE-AD trial). *Endocrine/diabetes* No difference in events for risperidone (1 trial). *Extrapyramidal symptoms* More common in patients taking risperidone (5 studies, OR 3.00, 95%CI 1.96 to 4.70, NNH = 20) or olanzapine (1 study, OR = 15.21 [95%CI 3.50 to 138.55], NNH = studies) or aripiprazole (4 studies). *Fatigue/sedation* More common in patients with dementia taking atypical antipsychotics according to meta-analysis (NNH 18 to 21 for each drug). *Urinary symptoms* Significantly more common in those taking atypical antipsychotics than placebo (NNH 16 to 36 for different drugs).						
Antidepressants for dementia and agitation/psychosis						
Seitz 2011 [312]	Systematic review	RCTs with primary outcome of treatment of psychosis, agitation or other NPS To Oct 2009	People with dementia (AD, vascular, mixed AD and vascular, DLB or dementia not otherwise specified), any age, any severity, in community or residential care. Not Parkinson's disease or FTD, not concomitant major depressive disorder. To assess the safety and efficacy of antidepressants in treating psychosis and agitation in older adults with dementia.	Antidepressants (SSRIs, TCAs, trazodone, others), daily orally administered	Placebo or other medications	9 included RCTs 2 studies SSRIs included in met antipsychotics, placebo or beha There are few s the treatment dementia. The citalopram are in symptoms of placebo in 2 stu reasonably well
Effectiveness (vs placebo) *Global BPSD* No significant effect of SSRI sertraline in one study according to change in total NPI score (MD 1.80, 95%CI -2.01 to 5.61, favours control) or BEHAVE-AD total scor sertraline).[335] Significant difference in behaviour (NBRS total) after controlling for baseline severity in one study of citalopram vs placebo (unadjusted MD not statistically signifi *Agitation* Significant reduction in agitation (CMAI total score) with SSRIs (MD -0.89, 95%CI -1.22 to -0.57, 2 studies; 1 small study of fluoxetine [336], result driven by 1 large Adverse events No difference in rates of trial withdrawal due to adverse events for SSRIs vs placebo (4 studies, RR = 1.07, 95%CI 0.55 to 2.11). No difference in trial withdrawals due to any cause for SSRIs vs placebo (3 studies, RR 0.91, 95%CI 0.65 to 1.26)						
Antidepressants for people with dementia and concomitant depression						

Reference	Study Design	Types of studies included Search period	Types of participants included Relevant research question(s)	Intervention	Comparison	Relevant Result Relevant Concl
Sepehry (2012) [311]	Systematic review	Randomised and non-randomised studies To July 2011	People with Alzheimer's disease and comorbid depression	Any novel antidepressa nt (SSRI/SNRI)	Placebo	5 SSRI trials (4 R pseudorandomi depression outc dose titration, c allowed in 2 stu Current evidenc efficacy of SSRI comorbid depre

Sepehry (2012) [311] cont[d]

Effectiveness

Global BPSD

2 RCTs reported no significant effect of sertraline on NPI (DIADS-1 trial effect size at 12 weeks 0.25, P = 0.32, mean reduction sertraline 9.4 vs placebo 3.1, no sig weeks follow-up = 2.02, 95%CI -2.94 to 6.97) [319].

Depression

No significant effect of SSRIs on depression (Effect size global depression -0.06 [95%CI -0.26 to 0.14], -0.10 [95%CI -0.34 to 0.13] in 2 pooled analyses, 5 studies [4 between randomised and non-randomised study], 4 sertraline, 1 fluoxetine). [319 330-333]

Quality of life

2 RCTs reported no significant difference in quality of life for SSRIs vs placebo.

Adverse events

Serious AEs: We conducted a pooled analysis across 3 RCTs comparing SSRIs to placebo that reported serious AEs and found no significant difference (OR 1.42, 95 (DIADS1) reported no significant difference in total AEs (SSRI 9/24 vs placebo 7/20; DIADS [333]).

The HTA-SADD trial reported the largest list of AEs for both treatment arms (86 SSRI, 58 placebo; see table 11 of original HTA report for details).[319]

Cognition

No significant difference in MMSE in pooled analysis of 5 studies (Effect Size 0.001, 95%CI -0.191 to 0.19).

Mood stabilisers

Seitz 2013 [314]	Systematic review	RCTs with parallel-group comparison and NPS as primary outcome To Feb 2011	Study populations with >50% residential care residents. To review of the efficacy and safety of pharmacological treatments for neuropsychological symptoms of dementia in residential care.	Any pharmaco-logical intervention[2]	Placebo, other mediation or non-pharmacological interventions	4 included stud carbamazepine, oxcarbazepine) There are few s than atypical an their use for BP NPI) in long-ter

Effectiveness-

Global BPSD

Carbamazepine: Statistically significant reduction in BPSD with carbamazepine (1 small RCT, N = 51, 6 weeks duration, change in total BPRS carbamazepine 300mg

Divalproex: No statistically significant change in BPSD (2 studies, 6 weeks duration, total BPRS change divalproex 375 mg/day -6.9 vs -5.9 placebo; N = 56 [338] an 153 [340].

Oxcarbazepine: no statistically significant effect (1 RCT, N = 23, 8 weeks duration, 300-900 mg/day; oxcarbazepine vs placebo change in total NPI-NH -5.8 vs -4.3, BARS -5.5 vs -3.2). [339]

Adverse events

Carbamazepine trial withdrawals 14.8%, withdrawals due to adverse events 3.7%, mortality 0%; placebo 0 withdrawals.[337]

No significant difference in withdrawals or mortality in 2 trials of divalproex sodium (375 mg/day and 800mg/day) vs placebo. [338 340]

Oxcarbazepine (300-900 mg/day) trial reported a significantly greater number of total withdrawals than placebo (28.8% oxcarbazepine vs 9.8% placebo, P<0.05; v mortality 0 vs 0) [339]

Melatonin

Jansen (2011) [316]	Systematic review	RCTs To June 2009	People with dementia of any severity, for managing cognitive, behavioural (excluding sleep) and mood disturbances. Clinical effectiveness of melatonin in the treatment of manifestations of dementia, relevant primary outcomes mood, behaviour, functions of daily living, and safety of melatonin use; secondary outcomes quality of life, morbidity, mortality, length of time to institutionalization, caregiver stress.	Melatonin, orally administered	Control group	2 included stud mood. No studi mortality or tim Meta-analysis s effective in trea

Reference	Study Design	Types of studies included Search period	Types of participants included Relevant research question(s)	Intervention	Comparison	Relevant Result Relevant Concl
Effectiveness *BPSD- Global* Significant improvement in BPSD (combined change of ADAS non-cognitive scale and NPI WMD -3.48, 95% CI - 4.89 to - 2.07; 2 studies [n=101 and n=20], 2.5 [sus [342 346] In one of these trials, the melatonin arm had a significantly greater NPI than in the placebo group at baseline. [342] In a separate, cluster randomised tr severity score and Multi Observation Scale for Elderly Subjects was not significantly different between 2.5mg melatonin and placebo at 6 weeks (n=97), 1 year (n= 1 RCT no significant effect of 10mg melatonin on NPI after 7 weeks. [342] *BPSD- agitation* CMAI not significantly different between 2.5mg melatonin and placebo at 6 weeks (n =86), 1 year (n = 49) or 2 years (n = 19) in cluster randomised trial. [343] *BPSD-depression* Cornell Depression Rating Scale Score not significantly different between 2.5mg melatonin and placebo at 6 weeks (n=86), 1 year (n = 49) or 2 years (n = 29) in clu *BPSD-Mood* The Cochrane reviewers conducted an analysis of longitudinal data from the Riemersma-van der Lek 2008 cluster randomised trial.[343] A worsening of mood wa Rating Scale, positive favours melatonin, WMD -1.60, 95%CI -3.14 to -0.06, 2.5mg melatonin, n= 49). There was no significant effect on the positive Philadelphia G or 2 years (n = 19), nor was there a significant effect on the negative Philadelphia Geriatric Center Affect Rating Scale or the Philadelphia Geriatric Center Morale longitudinal mixed effect regression analysis in the original paper found a significant decrease in positive mood ratings (-0.55, 95%CI -1.00 to -0.10), increasing ne increase in aggravated withdrawn behaviour (1.02, 95%CI 0.18 to 1.86). Adverse events The mean number of adverse events per person did not significantly differ between melatonin and placebo (1 RCT, 2.5mg, 7 weeks; Effect Size = 1.0, 95%CI -0.19 significantly less in the melatonin arm at 7 weeks (1 RCT, 2mg WMD -0.10 95% CI -0.18 to -0.02; 10 mg WMD -0.10 95% CI -0.16 to -0.04)[342]. Estimates of rates of individual adverse events did not differ between melatonin and placebo. [343]						
Analgesia						
Pieper et al 2013 [317]	Systematic Review	All study designs	People with a main diagnosis of dementia	Interventions targeting a reduction in the person's pain or distress and/or behaviour. Includes pain medication, analgesia, drug therapy	Not applicable	See belov Overall th pain med behaviou symptom suggeste analgesic compare and stepw was supp treatmen
Pieper et al 2013 [317] Results: The authors identified six studies that involved a pain intervention targeting behaviour in dementia. Three of these studies were RCTs that evaluated the pharmacological treatment (use of pain medication) and its effect on behaviour. Adverse events were not reported. The three studies were assessed as being of moderate to high quality although for all three studies there were incomplete descriptions of randomisation, allocati One RCT (Buffum et al. 2004) evaluated the efficacy of regularly scheduled analgesic medication for discomfort in 39 people with moderate to severe dementia in The conditions involved (1) 650mg/day of paracetamol as needed and a placebo administered four times a day, or (2) placebo as needed and 650mg/day of parac regularly scheduled, fixed dosages of paracetamol did not decrease discomfort. One RCT (Chibnall et al. 2005) recruited 25 people with moderate to severe dementia from two nursing homes.[321] Participants were randomly allocated to a co paracetamol) for 4 weeks and a 4 week placebo phase. Improvements were seen in patients taking paracetamol on several aspects measured using Dementia Car increased media engagement, work-like activities and social interaction. No reduction was found in agitation, measured using an agitation inventory. One large cluster RCT (Husebo et al. 2011) involved 352 people with moderate to severe dementia in nursing homes in Norway.[322] Patients were cluster randor an 8 week step-wise protocol of analgesic administration, with medication choice depending on prior treatment and assessment of pain. This approach was found and pain. Mean reduction in pain 1.3 points, (95%CI -0.8 to -1.7); effect size = 0.5. Mean reduction in agitation during the intervention phase (mean reduction 17% 10.3); effect size=0.33.						

Abbreviations: AD = Alzheimer's disease, ADL = activities of daily living, BEHAVE-AD = Behavioural Pathology in Alzheimer's Disease, BSRS = Brief Psychiatric Rating Scale, CA = can't answer, CMAI = Cohen-Mansfield Agitation Inventory, CVA = cerebrovascular accident, dem = dementia, FTD = frontotemporal dementia, n = No, mADCS-CGIC = modified Alzherimer's Disease Cooperative Study Clinical Global Impression of Change index, MD = mean difference, NBRS = Neurobehavioural Rating Scale, NNH = number needed to harm, NPI = Neuropsychiatric Inventory, NPS = neuropsychiatric symptom(s), QoL= quality of life, RCT = randomised controlled trial, SNRI = serotonin-noradrenaline (norepinephrine) reuptake inhibitor, SSRI = selective-serotonin reuptake inhibitor(s), WMD = weighted mean difference, Y = Yes.

1. Appraisal criteria: (1) 'a priori' design provided, (2) Duplicate study selection and data extraction, (3) Comprehensive literature search, (4) Grey literature search (considered screening reference lists of included studies as grey literature search), (5) List of included and excluded studies provided, (6) Characteristics of included studies provided, (7) Scientific quality of the included studies assessed and documented, (8) Scientific quality of included studies used to formulate conclusions, (9) Methods to combine findings appropriate, (10) Publication bias assessed, (11) Conflict of interest included for review and each of the included studies.
2. The search included antipsychotics, acetylcholinesterase inhibitors, antidepressants, anticonvulsants and benzodiazepines.

Table 156 Evidence summary of randomised controlled trials published since the search of the included systematic reviews for SRQ 16: Pharmacological interventions for BPSD

Reference Country Trial name	Study Type Recruitment	Participants Age Gender Other	Intervention	Comparison	Main Outcomes	Measure/s	Length of follow up	Relevant Res Effect size
Antidepressants for agitation/psychosis								
Porsteinsson 2014 [318] USA & Canada CiTAD	RCT Aug 2009 – Jan 2013	N = 186 subjects with probable AD and clinically significant agitation from 8 academic centres. Excluded those with raised corrected QT interval. Age mean (SD): 78 (8) Gender: 46% female MMSE score: 15.7 (6.7) NBRS agitation subscore: 7.6 (3.1) CMAI: 28.2 (6.7) NPI total score: 37.3 (17.5)	Citalopram for 9 weeks. Dose commenced at 10mg/d with planned titration to 30mg/d over 3 weeks	placebo	Behaviour, agitation	NBRS-A, mADCS-CGIC, CMAI, NPI, ADLs, caregiver distress, MMSE, adverse events	3,6, 9 weeks	Citalopram si behaviour ov See details be
Effectiveness *Global* NPI total difference −6.03 [95% CI: −10.75 to −1.32], p = 0.013 favouring citalopram. *Agitation* NBRS-A score crude difference 1.3 [95% CI: 2.6 to 3.5]; p = 0.010, favouring citalopram. Mixed model difference −0.93 [95% CI: −1.80 to −0.06] p = 0.036, favourin mADCS-CGIC OR 2.13 (95%CI 1.23 to 3.69), p=0.007 (odds ratio of being at or better than a given CGIC category, by proportional odds logistic regression). Proport baseline 40% citalopram vs 26% placebo. CMAI difference −2.38 [95% CI −4.13 to −0.63], p = 0.008 favouring citalopram (estimate from mixed-effects model, controlling for baseline score and MMSE) NPI agitation difference −0.78 [95% CI: −1.77 to 0.21], p = 0.123 (estimate from mixed-effects model, controlling for baseline score and MMSE) Safety Adherence: no significant difference Cognition: MMSE greater worsening with citalopram −1.05 points [95% CI: −1.97 to −0.13], p = 0.026 Get Up and Go: 0.79 (95%CI -1.26 to 2.83), favours placebo Serious adverse events: not significantly different (n = 8 citalopram vs n = 7 placebo). Adverse events: - deaths (0 citalopram, 1 placebo) more common with citalopram: - diarrhoea OR 2.37 (95%CI 1.10 to 5.10); fever (10% vs 2.3%, p = 0.03); anorexia OR 1.85 (95%CI 0.99 to 3.43); prolonged QT interval on ECG (12.5% vs 4.3%), gre ms; 95%CI 6.1-30.1; P = .004) More common with placebo: - weight loss >5% (1.3% vs 10.3%, P=0.02); insomnia OR 0.54 (95%CI 0.29 to 1.01)								
Antidepressants for depression – mirtazapine								
Banerjee 2011 [319 334] England HTA-SADD	RCT Dec 2006 – Jan 2010	N=326 Probable or possible AD by NINCDS-ADRA criteria with co-existing depression (≥8 CSDD, ≥4 weeks), from old-age psychiatry services in 9 UK NHS centres. Age mean (SD): placebo 79 (8.8) vs mirtazapine 79 (8.4) Gender: 64% vs 71% female	45 mg/day mirtazapine or 150mg/day sertraline	placebo	Reduction of depression	CSDD score, cost-effectiveness	13 & 39-weeks	No significant NB. The Sertr trial are consi review report **for table.**).

Reference Country Trial name	Study Type Recruitment	Participants Age Gender Other	Intervention	Comparison	Main Outcomes	Measure/s	Length of follow up	Relevant Res Effect size
Effectiveness [1] Mirtazapine mean dose 24mg/day (including withdrawals; 30mg/day for those remaining on mediation) Depression improved in both groups. No sig difference between groups. CSDD scores: 13 weeks -5.0 (SD 4.9) mirtazapine, -5.6 (SD 4.7) placebo; difference 0.01 (9 mirtazaline, -4.8 (SD 5.5) placebo; difference -0.66 (95%CI -2.12 to 0.79) NPI change, mirtazapine vs placebo: 13 weeks -3.56 (95%CI -8.07 to 0.96) QoL change, mirtazapine vs placebo (self-rated): DEMQOL -0.06 (95%CI -3.52 to 3.39); EQ5D 3.62 (95%CI -2.31 to 9.55) Withdrawals Week 39: 29% mirtazapine, 24% placebo Adverse events Overall no of participants (%, no. events), including definite, probable and possibly related to intervention: Mirtazapine 44 (41%, 96), sertraline 46 (43%, 86), plac P=0.017. Serious AEs at 13 weeks: Mirtazapine 14 vs sertraline 12 vs placebo 15 (no sig diff); Severe AEs at 13 weeks: Mirtazapine 10 vs sertraline 8 vs placebo 3 (p =0.003 mirtazapine 5 vs sertraline 5 vs placebo 5 (no sig diff) Cognition: no significant difference on MMSE at 13 (-0.27, 95%CI -1.48 to 0.94; P=0.66) or 39 weeks (–1.71, 95%CI –2.48 to 0.14; P=0.08). Most common with mirtazapine: psychological reactions (usually drowsiness and sedation) Cost-effectiveness (UK setting) Resource use: 0 to 39 weeks: mean hours/week of unpaid carers caring for people with dementia was 2x that in placebo than mirtazapine, significantly different (placebo mean 12.3 hours/week [SD 21.2]). 0 to 13 weeks: no significant differences in service use. Mean QALY gain at 39 weeks difference mirtazapine vs placebo 0.05 (95% CI −0.10 to 0.10), no sig diff. No significant differences in health and social care costs, or in total health social care and unpaid carer costs. Mirtazapine 80% greater likelihood of being more cost-effective (according to improvement in CSDD) than placebo if society willing to pay £5000 for a unit improv pay for improvement). 89% probability that mirtazapine was more cost-effective (according to QALYs) than placebo at a willingness to pay of £20,000 per QALY (c and informal care costs).								

Abbreviations: AD = Alzheimer's disease, ADL = activities of daily living, BEHAVE-AD = Behavioural Pathology in Alzheimer's Disease, BSRS = Brief Psychiatric Rating Scale, CA = can't answer, CMAI = Cohen-Mansfield Agitation Inventory, CSDD = Cornell scale for depression in dementia, dem = dementia, FTD = frontotemporal dementia, n = No, mADCS-CGIC = modified Alzherimer's Disease Cooperative Study Clinical Global Impression of Change index, MD = mean difference, NBRS = Neurobehavioural Rating Scale, NPI = Neuropsychiatric Inventory, NHS = National Health Service, NPS = neuropsychiatric symptom(s), OR = odds ratio, QoL – quality of life, RCT = randomised controlled trial, Y = Yes.

1. Sertraline results included in Sepehry (2012) systematic review and meta-analysis, see

Table 155

Table 157 GRADE Evidence Profile: Analgesia for behavioural and psychological symptoms of dementia (BPSD)

Quality assessment							Effect[3]	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Behavioural and psychological symptoms of dementia								
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	1 RCT (Chibnall) reported no significant differences between groups [321] 1 RCT (Husebo) reported a significant reduction in agitation during the intervention phase (mean reduction 17% (treatment effect estimate -7.0, 95%CI -3.7 to -10.3) effect size=0.33) [322]	⊕⊕OO LOW
Pain								
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	1 RCT (Buffum) reported no significant differences between groups. [320] 1 RCT (Husebo) reported a significant reduction in pain in the intervention group (mean reduction 1.3 points, (95%CI -0.8 to -1.7) effect size = 0.5) [322]	⊕⊕OO LOW
Quality of life (person with dementia)								
0	No evidence available					none		
Adverse effects								
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Three RCTs reported that there were no adverse effects related to the intervention. Across all three studies, one person receiving analgesia had an elevated liver function test. [320-322]	⊕⊕⊕O MODERATE

[1] Methodology unclear in several instances due to poor reporting

[2] Total sample size <400

[3] Results as reported in Evidence Summary

Table 155, in systematic review by Pieper et al 2013.

Table 158 GRADE Evidence Profile: Atypical antipsychotics for behavioural and psychological symptoms of dementia (BPSD)

Quality assessment							Effect	Quality[4]
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Behavioural and Psychological Symptoms of Dementia (follow-up 6-12 weeks)								
17	Placebo-controlled randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Pooled analysis of 17 RCTs favours treatment at 6-12 weeks [308 309], effect size small: Total/global scores SMD 0.17 [95%CI 0.08 to 0.25], psychosis SMD 0.12 [95% CI 0.04 to 0.19], agitation SMD 0.20 [95% CI 0.12 to 0.27].	⊕⊕⊕O MODERATE
Quality of Life of person with dementia (follow-up mean 12 weeks)								
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness[3]	serious[4]	none	1 RCT reported no change. Carer-rated QOL no difference at 12 weeks (WMD 3.50, 95%CI -1.54 to 8.54) [324]	⊕OOO VERY LOW
Adverse events - mortality (follow-up 6-24 weeks)								
15	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Small but significant increase in risk of death in pooled analysis. [325] Death in 3.5% with antipsychotics vs 2.3% placebo OR 1.54, 95%CI 1.06 to 2.23 [P<0.01], NNH = 100 (95%CI 53 to 1000)	⊕⊕⊕O MODERATE
Adverse events - Cardiovascular events (cardiovascular symptoms, edema or vasodilatation)								
11	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Significant increase in cardiovascular events with olanzapine and riperidone, not quetiapine or aripiprazole. [308 309] Olanzapine 5 RCTs, OR 2.33, 95%CI 1.08 to 5.61; NNH 48 Risperidone 6 RCTs, OR 2.08, 95%CI 1.38 to 3.22, NNH 34 Increase in cerebrovascular accident across 3 RCTs of Risperidone, OR = 3.12, 95%CI 1.32 to 8.21; NNH = 53	⊕⊕⊕O MODERATE

[1] Most studies were double blind. However, most studies had high attrition rates. Reporting of randomisation method, allocation concealment and blinding of outcome assessment was generally poor. No studies reported trial registration or publication of a trial protocol.

[2] Single blind, outcome assessors not blind and subjective measure, unclear reporting of randomisation, allocation concealment, and protocol/registration

[3] Carer-rated quality of life

[4] Wide confidence intervals

[5] Individual risk of bias assessment not available in published reports. Meta-analysis includes 9 unpublished trials hence novel risk assessment of all included trials not possible. The authors indicate that all trials were

randomised and double blind with no evidence of attrition bias but methods of randomisation or blinding were generally not reported (Schneider 2006)[347].

[6] Unclear which individual trials are included in the meta-analysis, appear to be a subset of 17 trials reporting effectiveness outcomes, risk of bias assessment based upon the assessment for effectiveness outcome (see footnote 1).

Table 159 GRADE Evidence Profile: IM olanzapine vs placebo for behavioural and psychological symptoms of dementia (BPSD, in situations where there is a significant risk of harm)[1]

Quality assessment							Effect	Quality[4]
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Psychotic symptoms (IM olanzapine 5mg, mean change in PANSS-EC score from baseline at 2 hour post first intramuscular injection)								
1	Placebo-controlled randomised trial	No serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[2]	none	SMD -0.49 (-0.83 to -0.14) [326]	⊕⊕⊕O MODERATE
Psychotic symptoms (IM olanzapine 5mg, mean change in PANSS-EC score from baseline at 24 hour post first intramuscular injection)								
1	randomised trial	No serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[2]	none	SMD -0.38 (-0.72 to -0.04) [326]	⊕⊕⊕O MODERATE
Agitated behaviour (IM olanzapine 5mg, mean change in CMAI score from baseline at 2 hour post first intramuscular injection)								
1	randomised trial	No serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[2]	none	SMD -0.32 (-0.67 to 0.02) [326]	⊕⊕⊕O MODERATE
Response to treatment (IM olanzapine 5mg, defined as at least 40% reduction from baseline to endpoint on PANSS-EC, Follow up: 2 hours)								
1	randomised trial	No serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	Response olanzapine 66.7% (44/66) Response placebo 37.3% (25/67) RR 1.79 (1.25 to 2.55) [326]	⊕⊕⊕⊕ HIGH
Leaving the study early for any reason (IM olanzapine 5mg)								
1	randomised trial	No serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[2]	none	Left early olanzapine 7.6% (5/66) Response placebo 11.9% (8/67) RR 0.63 (0.22 to 1.84) [326]	⊕⊕⊕O MODERATE
AE: accidental injury								
1	randomised trial	No serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[2]	none	olanzapine 3% vs placebo 0% RR 5.07 (0.25 to 103.73) [326]	⊕⊕⊕O MODERATE
AE: ECG abnormal								
1	randomised trial	No serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[2]	none	olanzapine 3% vs placebo 0% RR 5.07 (0.25 to 103.73) [326]	⊕⊕⊕O MODERATE

Quality assessment							Effect	Quality[4]
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
AE: Headache								
1	randomised trial	No serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[2]	none	olanzapine 3% vs placebo 0% RR 5.07 (0.25 to 103.73) [326]	⊕⊕⊕O MODERATE
AE: Hypertension								
1	randomised trial	No serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[2]	none	olanzapine 3% vs placebo 1.5% RR 2.03 (0.19 to 21.86) [326]	⊕⊕⊕O MODERATE
AE: Somnolence								
1	randomised trial	No serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[2]	none	olanzapine 3% vs placebo 3% RR 1.02 (0.15 to 7.00) [326]	⊕⊕⊕O MODERATE
AE: Vasodilation								
1	randomised trial	No serious risk of bias	no serious inconsistency[3]	no serious indirectness	serious imprecision[2]	none	olanzapine 3% vs placebo 0% RR 5.07 (0.25 to 103.73) [326]	⊕⊕⊕O MODERATE

[1] Reproduced from NICE Appendix 16, Tables 16.41 & 16.42

[2] Confidence interval compatible with both clinically significant and non-significant benefit, one trial of olanzapine IM 5mg N= 66 atypical antipsychotic, N=67 placebo

[3] I-squared > 50%

Table 160 GRADE Evidence Profile: Antidepressants for agitation and psychosis in dementia

Quality assessment							Effect[7]	Quality[4]
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Behavioural and Psychological Symptoms of Dementia - Global (follow-up 2.5 - 12 weeks)								
3	randomised trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	*Global outcomes:* SSRIs: 1 high quality RCT (CiTAD [318]) showed significant improvement in global BPSD (CiTAD, NPI difference −6.03 [95% CI: −10.75 to −1.32]), 1 RCT no difference [335], 1 RCT demonstrated a significant difference after controlling for baseline severity (unadjusted values not statistically significant) [345].	⊕⊕OO LOW
Behavioural and Psychological Symptoms of Dementia - Agitation (follow-up 6 - 8 weeks)								
3	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	SSRIs: Significant reduction in agitation in 2 individual RCTs. [318 335] Pooled value of 2 RCTs CMAI mean difference -0.89 (95%CI -1.22 to -0.57) [335 336]. 1 high quality RCT (CiTAD) also demonstrated significant reductions in agitation according to 4 different measures (CMAI difference −2.38 [95% CI −4.13 to −0.63], adjusted for baseline score and MMSE) [318].	⊕⊕⊕O MODERATE
Quality of Life of person with dementia								
0	No evidence available							
Adverse events - serious (follow-up 9 weeks)								
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	1 high quality RCT indicated no significant difference in serious adverse events or deaths. [318]	⊕⊕⊕O MODERATE
Adverse events - trial withdrawals								
4	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	No significant difference in trial withdrawals due to adverse events (4 RCTs), or due to any cause (3 RCTs). [312]	⊕⊕OO LOW
Adverse events – worsening of cognition (follow-up 9 weeks)								
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	No cognition outcomes reported in 3 RCTs included in systematic review. [312] 1 high quality RCT showed significant worsening of MMSE with SSRI vs placebo (−1.05 points, 95% CI: −1.97 to −0.13) [318]	⊕⊕⊕O MODERATE
Adverse events - cardiovascular (follow-up 9 weeks)								
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[6]	serious[5]	none	1 high quality RCT showed significant increase in QT interval on ECG with SSRI vs placebo [318]	⊕⊕OO LOW

1 Randomisation, allocation concealment, blinding unclear, incomplete outcome data in 1 study and unclear in 2 studies.

2 Some inconsistency between measures and studies

3 Unclear reporting for almost all domains in all 4 studies; incomplete outcome data for 2 of 4 studies.

4 Unclear reporting for all domains in 1 study, unclear methods and incomplete outcome data in 1 study
5 <400 subjects
6 QT interval is a surrogate for cardiovascular events
7Results from systematic review by Seitz et al 2011 [312] plus CiTAD trial [318].

Table 161 GRADE Evidence Profile: Antidepressants for depression in dementia

Quality assessment							Effect[6]	Quality[4]
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Behavioural and Psychological Symptoms of Dementia - Global (follow-up 12-39 weeks)								
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	2 RCTs reported no significant effect of SSRIs on NPI (DIADS & HTA-SADD)[319 333]. One of these RCTs also reported no significant effect of mirtazapine on NPI (HTA-SADD)[319].	⊕⊕OO LOW
Behavioural and Psychological Symptoms of Dementia - Depression (follow-up 6 to 39 weeks)								
5	4 randomised trials, 1 pseudorandomised trial	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Pooled analysis of 5 placebo-controlled trials indicated no significant effect of SSRIs on depression (effect size -0.06 [95%CI -0.26 to 0.14]). [311][[311 319 330-333] One of these RCTs also reported no significant effect of mirtazapine in a third arm (HTA-SADD).[319]	⊕⊕⊕O MODERATE
Quality of life (follow-up 24-39 weeks)								
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	2 RCTs reported no significant difference in quality of life for SSRIs vs placebo (HTA-SADD & DIADS-2). [319 344] One of these RCTs also reported no significant effect of mirtazapine in a third arm (HTA-SADD).[319]	⊕⊕OO LOW
Adverse events - serious AEs (follow-up 6 to 39 weeks)								
4	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Pooled analysis of 3 RCTs indicated no significant difference in serious AEs between SSRIs vs placebo (OR 1.42, 95%CI 0.80 to 2.53; page 316). 1 RCT reported no significant difference in total AEs (DIADS).[333]	⊕⊕⊕O MODERATE
Adverse events - cognition								
4 1	randomised trials observational study	very serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	No significant difference in MMSE in pooled analysis of 5 studies (Effect Size 0.001, 95%CI -0.191 to 0.19) [311]	⊕⊕OO LOW

[1] Unblinding and loss of randomisation to a proportion of patients in DIADS-2 [344] at 24 weeks

[2] <400 participants

[3] Attrition unbalanced and some unclear reporting in DIADS-1 trial, Magai study pseudorandomised but small study [331], unclear reporting of trial methods in Petracca [330].

[4] Attrition unbalanced and some unclear reporting in DIADS-1 trial, unclear reporting of trial methods in Petracca et al. 2001 [330], unblinding and loss of randomisation to a proportion of patients in DIADS-2 (Weintraub) at 24 weeks

[5] Rozzini (2010) observational study [348] not randomised or blinded. Attrition unbalanced and some unclear reporting in DIADS-1 trial, unclear reporting of trial methods in Petracca, unblinding and loss of randomisation to a proportion of patients in DIADS-2 at 24 weeks [344]

[6] Results from systematic review by Sepehry et al (2012) [311], plus mirtazapine arm of HTA-SADD trial [319].

Table 162 GRADE Evidence Profile: Mood stabiliser Carbamazepine for behavioural and psychological symptoms of dementia (BPSD) in long-term care

Quality assessment							Effect	Quality[4]
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
BPSD (follow-up 6 weeks; Better indicated by lower values)								
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	Total BPRS change -7.7 300mg/day carbamazepine vs -0.9 placebo [337]	⊕⊕OO LOW
Quality of Life								
0 RCTs	No evidence available							
Adverse events - mortality (follow-up 6 weeks)								
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	No mortality in either arm of trial [337]	⊕⊕OO LOW
Adverse events - total withdrawals (follow-up 6 weeks)								
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	No significant difference. [337]	⊕⊕⊕O MODERATE

[1] Unclear sequence generation and allocation concealment

[2] N=51

Table 163 GRADE Evidence Profile: Mood stabiliser Divalproex sodium for behavioural and psychological symptoms of dementia (BPSD) in long-term care

Quality assessment							Effect	Quality[4]
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
BPSD (follow-up 6 weeks; Better indicated by lower values)								
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	No significant difference in total BPRS change. [338 340]	⊕⊕OO LOW
Quality of Life								
0 RCTs	No evidence available							
Adverse events - mortality (follow-up 6 weeks)								
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	No mortality in either arm of trial. [338 340]	⊕⊕⊕O MODERATE
Adverse events - total withdrawals (follow-up 6 weeks)								
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	No significant difference. [338 340]	⊕⊕OO LOW

[1] Sequence generation and allocation concealment unclear in one study, blinding unclear in other

[2] N < 400 (total N= 209)

Table 164 GRADE Evidence Profile: Mood stabiliser Oxcarbazepine for behavioural and psychological symptoms of dementia (BPSD) in long-term care

Quality assessment							Effect	Quality[4]
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
BPSD (follow-up 8 weeks; Better indicated by lower values)								
1 RCT	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	No significant difference in total NPI-NH change (oxcarbazepine -5.8 vs placebo -4.3) [339]	⊕⊕OO LOW
Quality of Life								
0 RCTs	No evidence available							
Adverse events - mortality (follow-up 8 weeks)								
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	No mortality in either arm of trial [339]	⊕⊕⊕O MODERATE
Adverse events - withdrawals (follow-up 8 weeks)								
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	Significantly greater number of total withdrawals: 28.8% oxcarbazepine vs 9.8% placebo, P<0.05. No significant difference in withdrawals due to adverse events. [339]	⊕⊕OO LOW

[1] Unclear sequence generation, allocation concealment and blinding

[2] N < 400 (N= 103)

Table 165 GRADE Evidence Profile: Anxiolytics administered via a non-intravenous route for behavioural and psychological symptoms of dementia (BPSD)

Quality assessment							Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
BPSD								
0 RCTs	No evidence available							
Quality of Life								
0 RCTs	No evidence available							
Adverse events								
0 RCTs	No evidence available							

Table 166 GRADE Evidence Profile: IM lorazepam versus placebo for behavioural and psychological symptoms of dementia (BPSD, in situations where there is a significant risk of harm)[1]

Quality assessment							Effect	Quality[4]
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Psychotic symptoms (IM Lorazepam 1mg, mean change in PANSS-EC score from baseline at 2 hour post first intramuscular injection)								
1	Placebo-controlled randomised trial	No serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[2]	none	SMD -0.48 (-0.82 to -0.13) [326]	⊕⊕⊕O MODERATE
Psychotic symptoms (IM Lorazepam 1mg, mean change in PANSS-EC score from baseline at 24 hour post first intramuscular injection)								
1	randomised trial	No serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[2]	none	SMD -0.32 (-0.66 to 0.02) [326]	⊕⊕⊕O MODERATE
Agitated behaviour (IM Lorazepam 1mg, mean change in CMAI score from baseline at 2 hour post first intramuscular injection)								
1	randomised trial	No serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[2]	none	SMD -0.40 (-0.74 to -0.06) [326]	⊕⊕⊕O MODERATE
Response to treatment (IM Lorazepam 1mg, defined as at least 40% reduction from baseline to endpoint on PANSS-EC, Follow up: 2 hours)								
1	randomised trial	No serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	Response lorazepam 72.1%, Response placebo 37.3% RR 1.93 (1.37 to 2.72) [326]	⊕⊕⊕⊕ HIGH
Leaving the study early for any reason (IM Lorazepam 1mg)								
1	randomised trial	No serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[2]	none	Left early lorazepam 10.3%, Response placebo 11.9% RR 0.86 (0.33 to 2.24) [326]	⊕⊕⊕O MODERATE
AE: accidental injury								
1	randomised trial	No serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[2]	none	lorazepam 4.4% vs placebo 0% RR 6.90 (0.36 to 131.04) [326]	⊕⊕⊕O MODERATE
AE: ECG abnormal								
1	randomised trial	No serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[2]	none	lorazepam 0% vs placebo 0% RR not estimable [326]	⊕⊕⊕O MODERATE

AE: Headache								
1	randomised trial	No serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[2]	none	lorazepam 3% vs placebo 0% RR 5.07 (0.25 to 103.73) [326]	⊕⊕⊕O MODERATE
AE: Hypertension								
1	randomised trial	No serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[2]	none	lorazepam 2.9% vs placebo 1.5% RR 1.97 (0.18 to 21.22) [326]	⊕⊕⊕O MODERATE
AE: Somnolence								
1	randomised trial	No serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[2]	none	lorazepam 10.3% vs placebo 3% RR 3.45 (074 to 16.00) [326]	⊕⊕⊕O MODERATE
AE: Vasodilation								
1	randomised trial	No serious risk of bias	no serious inconsistency[3]	no serious indirectness	serious imprecision[2]	none	lorazepam 0% vs placebo 0% RR not estimable [326]	⊕⊕⊕O MODERATE

[1] Reproduced from NICE Appendix 16, Tables 16.43 & 16.44

[2] Confidence interval compatible with both clinically significant and non-significant benefit, one trial of lorazepam, N=68 benzodiazepine, N = 67 placebo

Table 167 GRADE Evidence Profile: Melatonin for behavioural and psychological symptoms of dementia (BPSD)

Quality assessment							Effect[6]	Quality[4]
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
BPSD – Global (follow-up 4-7 weeks)								
3	randomised trials	no serious risk of bias[1]	Serious[2]	no serious indirectness	serious[3]	none	Significant improvement in BPSD by pooled NPI and ADAS-non cog (WMD -3.48, 95% CI - 4.89 to - 2.07; 2 studies, n = 121; 2.5 to 3 mg). [341 342] In 1 cluster RCT, NPI-Q severity score not significantly different at 6 weeks (n = 94), 1 year (n = 49) or 2 years (n = 19); no significant difference in Multi Observation Scale for Elderly Subjects at same time points [343]. 1 RCT no significant difference in NPI at 7 weeks for 10 mg melatonin (n=97)[342].	⊕⊕OO LOW
BPSD – Agitation (follow-up 6 weeks to 2 years)								
1	Cluster randomised trial	no serious risk of bias[1]	Serious[2]	no serious indirectness	serious[4]	none	CMAI not significantly different between 2.5mg melatonin and placebo at 6 weeks (n =86), 1 year (n = 49) or 2 years (n = 19). [343]	⊕⊕OO LOW
BPSD – Depression (follow-up 6 weeks to 2 years)								
1	Cluster randomised trial	no serious risk of bias[1]	Serious[2]	no serious indirectness	serious[4]	none	Cornell Depression Rating Scale Score not significantly different between 2.5mg melatonin and placebo at 6 weeks (n=86), 1 year (n = 49) or 2 years (n = 19). [343]	⊕⊕OO LOW
BPSD – Mood (follow-up 6 weeks to 2 years)								
1	Cluster randomised trial	no serious risk of bias[1]	Serious[2]	no serious indirectness	serious[4]	none	Longitudinal data from Cochrane review: A worsening of mood was seen in 1 trial at 1 year (PGCARS positive). There was no significant effect on the PGCARS positive at 6 weeks and 2 years, nor was there a significant effect on the negative PGCARS negative or the overall Philadelphia Geriatric Center Morale Scale at 6 weeks, 1 year or 2 years. [343] Original analysis: A longitudinal mixed effect regression analysis in the original paper found a significant decrease in positive mood ratings (-0.55, 95%CI -1.00 to -0.10) and significant increase in negative mood ratings (0.8, 95%CI 0.20 to 1.44).	⊕⊕OO LOW
Quality of Life								
0 RCTs	No evidence available							

Quality assessment							Effect[6]	Quality[4]
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Adverse events (follow-up 7weeks & 3.5 years)								
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	No significant difference in mean number of adverse events per person or rates of individual adverse events. [342 343]	⊕⊕⊕O MODERATE

[1]The Cochrane reviewers rate as no serious risk of bias, although there is a high attrition rate as the attrition rate was equal between groups and a post-hoc sensitivity analysis demonstrated that treatment effects were not affected by the dropout pattern.

[2] There are inconsistencies in data interpretation between the modelled analysis, raw data and original and Cochrane review authors

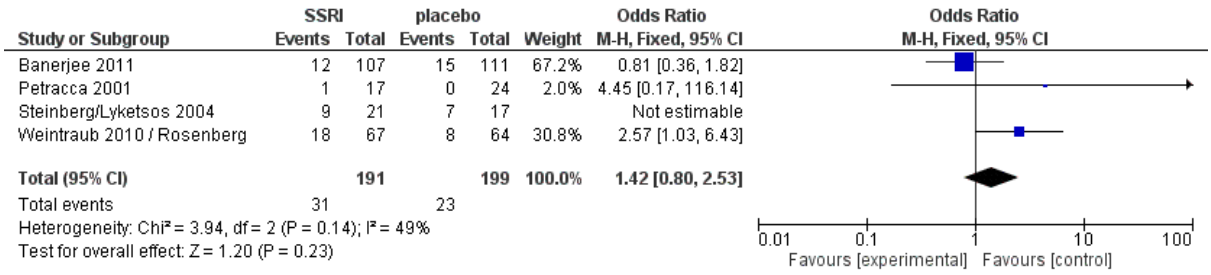
[3] Total N = 215, <400

[4] N = 86 at 6 weeks, 49 at 1 year, 19 at 2 years

[5] Total N = 191

[6] Results from systematic review by Jansen et al (2011) [316].

Forest plot of serious adverse events for SSRIs vs placebo for depression



SRQ 17: Support for carers

Clinical question

The research question as defined in the protocol and the associated PICO criteria are listed below.

Table 168 PICO for SRQ 17: Support for carers

Clinical question: Does assessment and/or intervention for the carer(s) and families produce benefits when compared to usual care?			
Population	**Intervention**	**Comparator**	**Outcome**
The carers of people with all forms of dementia	Assessment and/or intervention to support the carer	"Standard care", no support or intervention	Behavioural and psychological symptoms of dementia Carer quality of life Quality of life (person with dementia) Institutionalisation Carer impact

Literature review search strategies:

Searches for existing HTAs and Systematic reviews

Searches to identify existing Health Technology Assessment reports (HTAs) and systematic reviews were conducted in the databases specified in Table 169, using the search terms listed in the Guideline Technical Report Volume 2.

Table 169 Searches for existing HTAs and systematic reviews for SRQ 17: Support for carers

Database	Date searched	Period covered	Citations retrieved
HTA	6 May 2014	2005 to 2014	3
Cochrane (Cochrane reviews, Cochrane protocols, DARE)	6 May 2014	2005 to 2014	142
MEDLINE	6 May 2014	2005 to 2014	270
PsycInfo	6 May 2014	2005 to 2014	273
EMBASE	6 May 2014	2005 to 2014	32
PubMed	6 May 2014	2005 to 2014	9

The most recent, comprehensive and highest quality systematic review/HTA identified was conducted by Olazaran and colleagues [140] which included a search to September 2008.

Searches for additional primary studies

Searches were conducted in the databases listed in Table 170 to identify additional primary studies published since the search period of the included review. The search terms used are listed in the Guideline Technical Report Volume 2.

Table 170 Searches for primary studies/randomised controlled trials for SRQ 17: Support for carers

Database	Dates searched	Period covered	Citations retrieved
MEDLINE	9 May 2014	2008 to 2014	422
PsycInfo	9 May 2014	2008 to 2014	292
EMBASE	9 May 2014	2008 to 2014	55
PubMed	9 May 2014	2008 to 2014	10

Criteria for selecting studies for review:

Table 171 Inclusion and exclusion criteria for SRQ 17: Support for carers

Characteristic	Criteria
Study design	Inclusion: Randomised controlled trials Exclusion: Studies of other designs
Population	Inclusion: Carers of people with a diagnosis of dementia Exclusion: Other
Index test /Intervention	Inclusion: Assessment of carer needs, family/carer support in the form of counselling, education interventions, psychoeducational interventions, cognitive behavioural therapy, respite, multicomponent interventions, employment/financial/welfare/benefits/legal advice, carer support to maintain own health and participation (education, self mgt strategies, relaxation training)
Comparator	Inclusion: 'standard care' or no support or intervention
Outcomes	Behavioural and psychological symptoms of dementia Carer quality of life Quality of life (person with dementia) Institutionalisation Carer impact
Publication type	English language

Search results:

Existing HTAs and systematic reviews

The most recent, comprehensive and highest quality systematic review identified and included in the current update was published by Olazaran and colleagues [140] (Table 172). The review included 71 randomised controlled trials published in English.

Primary studies

A total of 779 citations were retrieved in the electronic database searches. 112 were reviewed in full text and 32 were included in the evidence update (Table 173).

Evidence summary:

The additional 32 RCTs were categorised by interventions, using the same approach as the Olazaran et al systematic review [140]: carer education; carer support, case management; respite care; multicomponent for the carers; multicomponent for the person with dementia and their carers.

Many of the studies were of high methodological quality and involved large sample sizes. However, when considered as a body of evidence, there was significant risk of bias present as indicated within the Evidence Profiles.

Although carer interventions were grouped into categories, the nature of the interventions within each category differed. The content of the intervention, type of health professional providing the intervention and amount of intervention varied. Study results were mixed, with some studies reporting no benefits, although there were studies that reported positive results for most of the outcomes of interest.

The body of evidence supports:

- Carer education programs for increasing carer quality of life, reducing carer impact and increasing carer knowledge.
- Tailored multicomponent interventions for the carer for reducing behavioural and psychological symptoms in the person with dementia and delaying time until institutionalisation.
- Tailored multicomponent interventions for the carer and person with dementia in improving the quality of life for both the carer and the person with dementia and reducing carer impact.

NOTE: Many studies evaluating carer interventions were published pre 2000 and reporting of study design and results was not consistent with current standards (ie as described in the CONSORT statement). Thus even though original studies were obtained in full text (using the Olazaran systematic review as a source) it was rarely possible to pool study results to determine an estimate of overall effect.

Evidence statements	*GRADE Quality*	*Related recommendations*
There were no RCTs that looked at the impact of respite on outcomes for the person with dementia. One RCT failed to show a significant reduction in carer impact associated with respite use [140]. (Table 177)	Very low	CBR 101
Two RCTs of six studies identified in an existing systematic review[140] plus two [349 350] of five additional studies [351-353]investigating carer education programs reported a significant improvement on carer quality of life (low). Two (of four) RCTs reported a significant improvement in the quality of life of the person with dementia (low).[128 140 352 353] (Table 174)	Low	EBR 102
Pooling of three RCTs investigating carer support programs found a significant improvement in carer quality of life.[354-356] An additional two studies within an existing systematic review [140]	Low	EBR 102

could not be pooled but reported no effect (low). One RCT reported a significant reduction in carer impact (low)[355]. (Table 175)		
One RCT reported a significant reduction in BPSD following provision of a multicomponent intervention for carers (low).[357] One of three RCTs in a systematic review [140] reported improved quality of life for the carer; an additional study also reported a treatment effect. [358] One RCT (included in a systematic review [140]) reported a reduction in carer impact. An additional one [357] of three ([357 359 360] studies also found a reduction in carer impact (very low). (Table 178)	Very low-low	EBR 102, 85
Four RCTs included within a systematic review [140] and an additional study [188] investigating multicomponent interventions involving the person with dementia and their carer found significant reductions in BPSD whereas eight studies found no effect [140 187 350 361 362](low). Three (RCTs included in a systematic review [140] of seven total studies found an improvement in carer quality of life (low).[140] Three RCTs included in a systematic review [140] of six total studies found improved quality of life for the person with dementia (moderate).[140] (Table 179)	Low-Moderate	EBR 102, 85

Table 172 Evidence summary of included systematic reviews for SRQ 17: Support for carers

Reference	Study Design/Level of Evidence	Types of studies included	Types of participants included	Intervention	Comparison	Results	Quality appraisal[1]
Olazaran 2010 [140]	Systematic Review	Randomised controlled trials published in a peer-reviewed journal	All participants had cognitive impairment or dementia with at least 80% due to Alzheimer's disease and related disorders	The review included all non-pharmacological interventions for the person with dementia and/or the families and carer. We extracted non-pharmacological interventions that were directed at the families and carer.	Alternative intervention or no intervention	The review included 71 RCTs that evaluated interventions involving the family and carer. <u>Authors conclusions:</u> Multicomponent interventions based on family and carer education and support delayed institutionalisation	1. CA 2. N 3. Y 4. N 5. Y 6. N 7. Y 8. Y 9. Y 10. N 11. N

Abbreviations: Y=yes, N=no, CA=can't answer

1. Appraisal criteria: (1) 'a priori' design provided, (2) Duplicate study selection and data extraction, (3) Comprehensive literature search, (4) Grey literature search, (5) List of included and excluded studies provided, (6) Characteristics of included studies provided, (7) Scientific quality of the included studies assessed and documented, (8) Scientific quality of included studies used to formulate conclusions, (9) Methods to combine findings appropriate, (10) Publication bias assessed, (11) Conflict of interest included for review and each of the included studies.

Table 173 Evidence summary of randomised controlled trials published since the included systematic review for SRQ 17: Support for carers

Reference Country	Type	N(n) carers	Participants	Intervention §	Comparison	Main Outcomes	Measure/s	Length of follow up	Results/ Effect size	Risk of bias[1]
Family and carer education										
Stern 2008 [363] United States	RCT	66	Mean age Intervention group 63 Control group 62 Intervention group: 90% female Control group: 82% female	CG education Program specifically related to driving involving 4 x 2 hour education sessions. Designed to provide families and carers with the knowledge and tools needed for planning, addressing and taking action regarding driving cessation for their loved one	Two control groups: one received written material only and the other received written materials following the final outcome assessment	Family and carer ability to manage the issue of driving cessation	Study specific questionnaire on self-efficacy; Brief COPE scale; stages of change scale; study specific questions relating to relationship with person with dementia and communication re driving	Month 2	The intervention group had significantly better scores on the self-efficacy scale (p<.05) and two subscales of the coping scale (venting and acceptance (p<.05)).	1. High 2. Unclear 3. High 4. Low 5. Unclear 6. Unclear
Kwok 2013 [350] Hong Kong	RCT	42	Majority of participants aged 40-50 years. Gender intervention group 72% female, control group 70% female	CG education Education delivered in 12 sessions over the phone. Families and carers were educated and given advice on topics related to dementia caregiving, including knowledge of dementia, skills of communicating with the patient, management of behavioural and psychological symptoms of dementia, families and carers' own emotional issues, resources available in the community, and long-term care plan	Educational DVD	Family and carer impact and self-efficacy	Families and carers: Zarit Burden Interview; Revised Scale for Caregiving Self-efficacy Scale. Care recipient: Global Deterioration Scale; Abbreviated Mental Test; Cohen–Mansfield Agitation Inventory	Post-intervent.	Families and carers in the intervention group reported significantly reduced burden (median change -2.5, p=.002).	1.Low 2.Unclear 3.High 4.Low 5. Low 6. Unclear

Reference Country	Type	N(n) carers	Participants	Intervention §	Comparison	Main Outcomes	Measure/s	Length of follow up	Results/ Effect size	Risk of bias[1]
Liddle 2012 [351] Australia	RCT	36	Mean age 69 Gender 83% female	CG education Training in the MESSAGE communication strategies in dementia and RECAPS memory strategies in dementia approach. There were 2 training sessions, a DVD, summary booklet and reminder card.	Usual care	Family and carer knowledge	Communication and Memory Support in Dementia knowledge test; Zarit Carer Burden Interview; Positive Aspects of Caregiving questionnaire; Revised Memory and Behaviour Problems Checklist; Cornell Scale for Depression in Dementia; Faces scale for well being	Post-intervent.	Families and carers in the intervention group reported a statistically significant increase in knowledge (p<.01).	1. Unclear 2. Unclear 3. High 4. Low 5. High 6. Unclear
Klodnicka Kouri 2011 [349] Canada	RCT	50	Mean age 62 Gender 82% female	CG education Program based on a psycho-educational approach took place over 5 weekly sessions lasting 90-120 minutes	Usual care	Family and carer knowledge	Families and carers Self-efficacy Scale; Revised Memory and Behaviour Problems Checklist; study specific knowledge questionnaire and Communication Skills Questionnaire; Communication difficulties with the person with cognitive problems ; Degree of perceived families and carers disturbance	Post intervent. and 6 weeks after intervent.	Participants in the intervention group reported statistically significant benefits in regards to families and carers knowledge (p<.001), degree of disturbance related to communication difficulties (p<.001), self-efficacy and skills (p<.001).	1. Unclear 2. Unclear 3. High 4. Low 5. Unclear 6. Unclear

Reference Country	Type	N(n) carers	Participants	Intervention §	Comparison	Main Outcomes	Measure/s	Length of follow up	Results/ Effect size	Risk of bias[1]
Losada 2011 [364] Spain	RCT	170	Mean age intervention group 61, control group 59 Gender intervention group 82% female, control group 84% female	CG education 12 group-based weekly sessions conducted by psychologists and occupational therapists. Intervention involved family and carer training to acknowledge, analyse and flexibilise maladaptive thoughts. Barriers to participation in pleasant events were explored and principles of caring for a person with dementia were provided	Usual care	Family and carer outcomes	Dysfunctional Thoughts About Caregiving Questionnaire; adapted Leisure Time Satisfaction measure; Center for Epidemiological Studies Depression Scale	Post intervent.	Families and carers in the intervention group reported reduced levels of depression (mean difference 3.2, p=.03), dysfunctional thoughts (mean difference 8.9, p=.00) and increased participation in leisure activities (mean difference 1.9, p=.01).	1. Low 2. Unclear 3. High 4. Low 5. High 6. Unclear
Ducharme 2011 [365] Canada	RCT	111	Mean age intervention group 60, control group 63 Gender 79% women	CG education "Learning to become a carer" program. Includes 7 modules addressing families and carers perceptions, coping strategies, communication, engaging support awareness of services and planning for the future	Usual care	Family and carer outcomes	Self-efficacy scale for confidence in dealing with caregiving situations; Preparedness for caregiving; Revised Scale for Caregiving Self-Efficacy; Planning for Future Care Needs scale; Knowledge of Services scale; Carers' Assessment of Managing Index; Inventory of Socially Supportive Behaviours; Families and carers Conflict scale	Post-intervent. and 3 months after intervent.	The intervention group reported increased confidence in dealing with caregiving situations (p<.001), increased preparedness for caregiving (p<.001), increased self-efficacy (p<.001), better problem solving (p<.001).	1. Unclear 2. Unclear 3.High 4. Low 5. High 6. Unclear

Reference Country	Type	N(n) carers	Participants	Intervention §	Comparison	Main Outcomes	Measure/s	Length of follow up	Results/ Effect size	Risk of bias[1]
Guerra 2011 [352] Peru	RCT	58	Mean age intervention group 53, control group 48 Gender 86% female intervention group, 90% female control group	CG education 10/66 Families and carers Intervention which comprised five x 30 minute sessions and included assessment, basic education about dementia and training about specific problem behaviours. Intervention was delivered by a Multi-Purpose Health Worker	Wait list control	Family and carer impact	For the families and carers: Zarit Burden Interview; families and carers psychological distress SRQ20; WHOQOL-BREF For the person with dementia: Neuropsychiatric Inventory; DEMQOL	Month 6	Families and carers in the intervention group reported significantly decreased strain measures (mean difference -3.9, p<.001) compared to the control group. There were no other differences between groups.	1. Low 2. Low 3. High 4. Low 5. Low 6. Low
Kurz 2010 [366] Germany	RCT	292	Mean age 62 years Gender intervention group 60% female, control group 68% female	CG education Intervention consisted of 7 fortnightly group sessions followed by 6 refresher meetings over a total of 15 months. Content covered information about AD	Usual care	Family and carer and patient outcomes	Person with dementia: Neuropsychiatric Inventory; Alzheimer's Disease Cooperative Study Activities of Daily Living; Carers: Montgomery Asberg Depression Rating Scale; SF36; Resource Utilisation in Dementia (RUD-light)	Month 5	There were no significant differences between groups in families and carers depression or rates of institutionalisation. Subgroup analysis suggested that the intervention promoted the decision for nursing home placement in stressed carers.	1. Unclear 2. Unclear 3. High 4. Low 5. Unclear 6. High
Logsdon 2010 [128] United States	RCT	142	Mean age intervention group 71, control group 62 Gender 68%	CG education Alzheimer's Association Early Stage Memory Loss Program Involves 9 sessions for the person with dementia and families and carers on topics such as information about the condition, relationships, daily living skills, self-esteem, future planning, legal and financial considerations	Wait list control	Quality of life of the person with dementia	QOL-AD; SF36; Geriatric Depression Scale; Family Assessment Measure Communication subscale; Self Efficacy Scale; Revised Memory and Behaviour Problem Checklist – families and carers reaction component; Perceived Stress Scale	Post-intervent.	There were no significant differences in outcomes for families and carers between the intervention and wait list control groups. People with dementia reported improved quality of life (effect size d=0.44), reduced depression (effect size d=0.36).	1. Unclear 2. High 3. High 4. Low 5. Low 6.Unclear

Reference Country	Type	N(n) carers	Participants	Intervention §	Comparison	Main Outcomes	Measure/s	Length of follow up	Results/ Effect size	Risk of bias[1]
Au 2010 [367] Hong Kong	RCT	27	Mean age intervention group 57, control group 52 All female	CG education 'Coping with Caregiving' psycho-educational program. Incorporated skill-building psychoeducational approach for reducing distress through learning and practicing specific cognitive and behavioural skills. Involved 13 sessions over approx. 3 months	Wait list control group	Family and carer outcomes	Center for Epidemiologic Studies Depression Scale; Revised Scale for Caregiving Self Efficacy; Chinese Way of Coping Questionnaire	Month 3	The treatment effect on depression in the intervention group was positive but not statistically significant. There was a significant increase in families and carers self-efficacy in responding to disruptive behaviours and controlling upsetting thoughts.	1. Unclear 2. Unclear 3. High 4. Unclear 5. High 6. Unclear
Martin Carrasco 2009 [368] Spain	RCT	115	Mean age intervention group 55, control group 51 Gender intervention group 72%, control group 65%	CG education Psychoeducational Intervention Program which consisted of 8 x individual 90 min sessions over 4 months. Focus was on (a) helping the families and carers control tension and stress, (b) teaching strategies for handling behavioural problems and (c) increasing their satisfaction with life	Usual care	Family and carer impact	Zarit Burden Interview; quality of life SF36; General Health Questionnaire GHQ-28	Months 4 and 10	Families and carers in the intervention group reported reduced levels of burden. Recipients of the intervention also reported significantly higher levels of wellbeing and significantly reduced levels on the General Health Questionnaire (improved outcomes).	1. Unclear 2. Unclear 3. High 4. Unclear 5. High 6. Unclear
Gavrilova 2009 [353] Russia	RCT	60	Mean age intervention group 80, control group 79 Gender intervention group 70% female, control group 77% female	CG education 10/66 Families and carers Intervention which comprised five x 30 minute sessions and included assessment, basic education about dementia and training about specific problem behaviours. Intervention was delivered by a Multi-Purpose Health Worker	Usual care	Family and carer impact	Zarit Carer Burden Interview; carer psychological distress (SRQ 20), carer quality of life (WHOQOL-BREF). Person with dementia: Neuropsychiatric Inventory; Quality of life (DEMQOL)	Month 6	Families and carers in the intervention group reported significantly reduced burden compared to controls (adjusted effect size 0.64). No other differences found.	1. Unclear 2. Low 3. High 4. Low 5. Low 6. Unclear
Gallagher-Thompson 2007 [369] United States	RCT	184	Age: non-Hispanic completers mean 63.4, Hispanic/Latina completers 51 Gender: 100% female	CG education 'Coping with Caregiving'. Small groups of family carers met weekly for 2 hr sessions over 13-16 wks. Intervention based on cognitive behavioural principles; skills based learning approach. Involved discussion, group problem solving, strategy use and relaxation.	Empathic support provided via telephone calls of approx. 15-20 minutes fortnightly for 13-16 weeks	Family and carer outcomes	Family carer: Center for Epidemiologic Studies Depression Scale; Perceived Stress Scale; conditional bother, skill utilisation (based on questionnaire)	Month 6	Scores were significantly lower in the intervention group for depression (mean 12.8 vs mean 10.3 at follow up) perceived stress (mean 16.1 vs mean 15.2) and conditional bother.	1. Low 2. Unclear 3. High 4. Low 5. Low 6. Unclear

Reference Country	Type	N(n) carers	Participants	Intervention §	Comparison	Main Outcomes	Measure/s	Length of follow up	Results/ Effect size	Risk of bias[1]
CG support										
Charlesworth 2008 [354] UK	RCT	236	Mean age 69 Intervention group: 66% female Control group: 63% female	CG support Offer of contact with a befriending scheme. Volunteers were matched to families and carers and provided conversation, companionship and being a 'listening ear'. Weekly visits for six months	Usual care Handout provided on local services for carers	Family and carer mood and quality of life	Hospital Anxiety and Depression Scale; QALYs and EQVAS; positive and negative affectivity scale, loneliness, perceived social support, institutionalisation of the person with dementia	Months 6, 15 and 24	There were no significant differences between groups for any of the outcomes measured. The intervention was thought to be 'unlikely' to be a cost effective intervention from the point of view of society (ICER= £105,954 per incremental QALY gained).	1. Unclear 2. Low 3. High 4. Low 5. Low 6. Low
Wang 2012 [356] Hong Kong	RCT	78	Majority of families and carers were aged between 18 and 50 Gender intervention group 59% female, control group 64% female	CG support Support groups which were help fortnightly for a total of 12 sessions. The "mutual support groups" which involved recognition of carers' own psychological needs, dealing with the needs of self and family members, adopting a positive role and challenges for caregiving	Usual care	Family and carer outcomes	Neuropsychiatric Inventory Families and carers Distress Scale; WHOQOL; Family Support Services Index	Post-intervent.	Families and carers in the intervention group reported increased quality of life (mean 97 to 114, p=.001) and reduced distress (mean 47 to mean 37, p=.005).	1. Unclear 2. Unclear 3. High 4.Low 5. High 6. Unclear
Gaugler 2013 [370] United States	RCT	107	Mean age 50 Gender 94%	CG support Modified version of the NYU Families and carers Interventions. The intervention included three components: individual and family counselling, support group participation, and ad hoc counselling. Took place in 6 sessions over 4 months	Newsletter and three-monthly "check-in" calls	Institutionalisation	For the person with dementia: Institutionalisation; Global Deterioration Scale; Revised Memory and Behaviours Problem Checklist For the families and carers: Families and carers stress; Perceived Stress Scale; Geriatric Depression Scale; families and carers health; Stokes Social Network List	Months 3,6,9,12,18 and 24	Families and carers in the intervention group were significantly less likely to admit their parents to a residential care setting (66% vs 37%) and delayed their parents' time to admission significantly longer (228.36 days longer on average) than those in the control group.	1. Low 2. Low 3. High 4. Low 5. Low 6. High

Reference Country	Type	N(n) carers	Participants	Intervention §	Comparison	Main Outcomes	Measure/s	Length of follow up	Results/ Effect size	Risk of bias[1]
Wang 2011 [355] Hong Kong	RCT	80	Mean age 41 Gender 65% female	CG support "Family Mutual Support Programme in Dementia Care" Program consisted of 8 fortnightly 2 hour group sessions over 6 months. Content included information about the condition, social relationships, emotional impacts of caregiving and improvement in problem solving skills in family care	Usual care	Family and carer quality of life	Family Caregiving Burden Inventory; WHOQOL-BREF; Six item Social Support Questionnaire; MMSE for the person with dementia; institutionalisation	Post intervent.	Families and carers in the intervention group reported reduced burden (mean 68 to mean 55, p<.001), increased quality of life (mean 66 to mean 79, p<.001) and a reduced number of people with dementia admitted to institutional care (mean 5 to mean 4, p<.01).	1. Unclear 2. Unclear 3. High 4. Low 5. Low 6. Unclear
Carbonneau 2011 [371] Canada	RCT	49	Age: the majority of families and carers were between 40 and 70 Gender intervention group 81%, control group 83%	CG support Adapted leisure education program scheduled over approx. 8 sessions. Included presentation of pleasant events concept, experiencing adapted activities with the care receiver, identification of activities and overcoming difficulties	Usual care	Family and carer wellbeing	General Well Being Schedule; relationships in elder care scale	Post-intervent.	There were no significant differences between groups on the outcome measures.	1. Unclear 2. High 3. High 4. Unclear 5. High 6. Unclear
Case management										
Jansen 2011 [141] Netherlands	RCT	99	Mean age intervention group 64, control group 62 Gender 64% female	Case management Case management provided by district nurses over 1 year. Case managers undertook assessment, gave advice and information, coordinated and monitored care	Usual care	Family and carer outcome	Sense of Competence Questionnaire; SF36; Center for Epidemiologic Studies Depression Scale; Self Perceived Pressure by Informal Care. The person with dementia was assessed using the Dementia Quality of Life Instrument	Month 6 and 12	There were no statistically significant differences between groups on any of the outcomes.	1. Low 2. Unclear 3. High 4. Low 5. High 6. Low
Respite care										
No new studies identified										

Reference Country	Type	N(n) carers	Participants	Intervention §	Comparison	Main Outcomes	Measure/s	Length of follow up	Results/ Effect size	Risk of bias[1]
Multicomponent families and carers										
Tremont 2008 [357] United States	RCT	33	Mean age Intervention group 66 Control group 61 Gender not reported	Multicomponent CG Telephone based psychosocial intervention (called FITT-D). 23 phone calls over one year. Involved emotional support, direction to resources, encouraging families and carers health and teaching families and carers strategies	Usual care	Family and carer impact	Zarit Burden Interview; Revised Memory and Behaviour Problem Checklist; Geriatric Depression Scale; Alzheimer's Disease Knowledge Test; SF36; Self Efficacy Scale; Family Assessment Device; Multidimensional Scale of Perceived Social Support	1 year	Carers in the intervention group reported lower levels of burden and reduced reaction to symptoms in the person with dementia.	1. Unclear 2. Unclear 3. High 4. Low 5. High 6. High
Livingstone 2013 [372] Knapp 2013 [373]	RCT	260	Mean age intervention group 62, control group 56 Gender intervention group 67% female, control group 71% female	Multicomponent CG A manual based coping intervention comprising eight sessions. The programme consisted of psychoeducation about dementia, carers' stress, and where to get emotional support; understanding behaviours of the family member being cared for, and behavioural management techniques; changing unhelpful thoughts; promoting acceptance; assertive communication; relaxation; planning for the future; increasing pleasant activities; and maintaining skills learnt. Carers practised these techniques at home, using the manual and relaxation CDs.	Usual care	Family and carer outcomes	Hospital Anxiety and Depression Scale; Zarit Burden Interview; modified Conflict Tactics Scale; Health Status Questionnaire; brief COPE. Care recipient: Neuropsychiatric Inventory; clinical dementia rating; Quality of life Alzheimer's disease Cost effectiveness analysis	Months 4, 8	Mean total scores on hospital anxiety & depression scale lower for intervention vs treatment a usual group over 8 month evaluation period (adjusted difference in means −1.80 points, p=0.02). Carers in the intervention group were less likely to have depression (odds ratio 0.24). Carers' quality of life was higher in the intervention group (difference in means 4.09) but not for the recipient of care (difference in means 0.59). The cost effectiveness calculations suggested that the intervention had a greater than 99% chance of being cost effective compared with usual treatment alone at a willingness to pay threshold of £30 000 per QALY gained, and a high probability of cost effectiveness on the HADS-T measure.	1. Low 2. Low 3. High 4. Low 5. High 6. High

Reference Country	Type	N(n) carers	Participants	Intervention §	Comparison	Main Outcomes	Measure/s	Length of follow up	Results/ Effect size	Risk of bias[1]
Kuo 2012 [358] Taiwan	RCT	129	Mean age 80, 54% female	Multicomponent CG Intervention comprised 2-session, in-home training program, each session 1 wk apart. Sessions 2-3 hrs. Behaviours of concern were identified and plan formulated to minimise stimuli, modify daily schedule and environment. Second session involved education and confirming the action plan. 1 wk after the second visit then once a month for up to 6 months, the research nurse made follow-up phone calls.	Educational materials and social phone calls	Family and carer outcomes	SF36; Center for Epidemiological Studies – Depression Scale; Families and carers Preparedness Scale; Families and carers Competence of Behavioral Problem Management Scale	2 weeks, 3 months and 6 months post intervent.	Families and carers who received the individualised home-based training program had better health outcomes in bodily pain (p<0.013), role disability due to emotional problems (p<0.013), vitality (p<0.001), better mental summary score (p<0.003), and decreased risk for depression (odds ratio = 0.15, p<0.013) than those in the control group during the 6 months following the training program.	1. Unclear 2. Unclear 3. High 4. Unclear 5. High 6. Unclear
Martindale-Adams 2013 [360] United States	RCT	154	Mean age intervention group 66, control group 65 Gender intervention group 82% female, control group 86%	Multicomponent CG Families and carers telephone support groups involving 5-6 families and carers and a group leader. The group met for 14 sessions over 1 year. Families and carers were provided with written materials on managing behaviours of concern and coping with stress. The intervention focussed on education, skills-building and support.	Pamphlets on dementia and safety	Family and carer outcomes	Families and carers: Families and carers health questionnaire; SF36 item; Zarit Burden Interview; Center for Epidemiological Studies Depression scale; General Well Being Scale; Revised Memory and Behaviour Problems Checklist Person with dementia: MMSE; SF36 item; Katz ADL Scale; Lawton and Brody IADL scale	Months 6 and 12	There were no significant differences between groups for any of the outcomes assessed.	1. Unclear 2. Unclear 3. High 4. Unclear 5. Low 6. High

Reference Country	Type	N(n) carers	Participants	Intervention §	Comparison	Main Outcomes	Measure/s	Length of follow up	Results/ Effect size	Risk of bias[1]
Joling 2012 [374] Netherlands	RCT	192	Mean age intervention group 68, control group 71 Gender 70% female	Multicomponent CG Six sessions were held over a year. Intervention was tailored to the needs of the families and carers and included psycho-education, problem solving techniques and engaging family networks in order to enhance support. Issues such as management of behavioural problems and coping with feelings of guilt were addressed. Ad hoc telephone counselling was available beyond the scheduled sessions.	Usual care	Family and carer mood	Mini International Neuropsychiatric Interview; Center for Epidemiologic Studies Depression Scale; Hospital Anxiety and Depression Scale for anxiety; Families and carers Reaction Assessment; SF12	Month 12 post-intervent.	There were no benefits associated with the intervention.	1. Low 2. Low 3. High 4. Low 5. High 6. Low
Davis 2011 [359] United States	RCT	46	Mean age intervention group 57, control group 61 Gender intervention group 83% female, control group 68% female	Multicomponent CG FITT-NH intervention. Delivered via 10 phone calls over 3 months for families and carers who's loved one had moved into a care home. Incorporated emotional adjustment, families and carers-staff interaction, family functioning, health behaviours and social support and role change.	Usual care	Family and carer outcomes	Families and carers Guilt Questionnaire for Nursing Home Placement; Center for Epidemiology Studies Depression Scale; Burden Interview; Nursing Home Hassles Scale; Ohio Department of Aging Family Satisfaction Instrument; SF36; data on visitation, social support and negative reactions to care recipients behaviour	Post-intervent.	Families and carers receiving the intervention reported a significant reduction in feelings of guilt related to placement (mean 50 to mean 37, p=.03) and reported more positive perceptions of interactions with staff (p=.02). There were no significant differences on the other outcome measures.	1. Unclear 2. Unclear 3. High 4. Low 5. Low 6. High

Reference Country	Type	N(n) carers	Participants	Intervention §	Comparison	Main Outcomes	Measure/s	Length of follow up	Results/ Effect size	Risk of bias[1]
Multicomponent person with dementia and families and carers										
Eloniemi-Sulkava 2009 [375] Finland	RCT	125	Mean age intervention group 78, control group 77 Gender: Approximately ¾ were female	Multicomponent PWD + CG Family care coordinator, education sessions, geriatrician, support groups for families and carers and individualised services. Program lasted for up to 24 months	Usual care	Use and costs of social and health care services	Time from enrolment to institutionalisation; use of services; Barthel Index; Neuropsychiatric Inventory; Zarit Burden Scale	Months 6, 12 and 24	At 1.6 years, a larger proportion of patients in the control group were in institutional care however, at 2 years the difference was not significant. When the costs of the intervention were considered, there were no significant cost savings in the intervention group.	1. Low 2. Low 3. High 4. High 5. Low 6. High
Gitlin 2010 [188] United States	RCT	272	Mean age 66 Gender 82% female	Multicomponent PWD +CG Intervention occurred over 24 weeks and involved up to 9 occupational therapy sessions and 2 nursing sessions plus 3 phone calls. Goal setting, home assessment, problem solving and action plans, strategies to reduce families and carers stress were used and assistive devices provided. The nurse addressed any potential causes of behavioural symptoms related to medical conditions (eg pain, dehydration)	No intervention	Frequency of behaviours of concern and family and carer upset and confidence managing	Frequency of behaviours of concern; families and carers upset; confidence managing behaviours; Zarit Burden measure; Center for Epidemiologic Studies Depression Scale; Perceived Change Index; Task Management Strategy Index	Months 4 and 6	At 4 months, significantly more intervention families and carers reported improvement in targeted problem behaviour compared with control group (67.5%vs 45.8%, p=0.02), reduced upset with the behaviour (p=.03) and enhanced confidence managing the behaviour (p=.01). Intervention families and carers also reported less burden (p=.05) and better wellbeing (p=.001) than controls. Fewer intervention families and carers had depressive symptoms than control group families and carers (53% vs 68%, p=.02).	1. Low 2. Low 3. High 4. Low 5. Low 6. Low

Reference Country	Type	N(n) carers	Participants	Intervention §	Comparison	Main Outcomes	Measure/s	Length of follow up	Results/ Effect size	Risk of bias[1]
Gitlin 2010 [187] United States	RCT	237	Mean age 82 Gender: 68% female	Multicomponent PWD +CG "COPE" intervention: Assessment (patient capability, medical testing, home environment, family carer communication, concerns), family carer education (patient capabilities, potential effects of medications, pain, constipation, dehydration) and family carer training to address concerns and help reduce stress. Training in problem solving, communication, engaging patients in activities and simplifying tasks was tailored to the needs of the dyad. Dyads received up to 10 sessions over 4 months with an occupational therapist	Up to 3 phone calls and provision of written educational materials	Functional dependence	For the person with dementia: adapted Functional Independence Measure; Qol-AD scale; activity engagement scale; Agitated Behaviour in Dementia Scale For the family carer: Perceived Change Index; family carer confidence; problem management measure; intervention benefit scale	Months 4 and 9	Patients in the intervention group had significantly less functional dependence (effect size d=0.21) and significantly less dependence in instrumental activities of daily living (effect size d=0.43). Participants in the intervention group had improved engagement (effect size d=0.26). Family carers had improved wellbeing (effect size d=0.30). At 4 months, 63% of dyads in the intervention group eliminated 1 or more carer-identified problem vs 45% of the control group.	1. Low 2. Low 3. High 4.Low 5. Low 6. Low
Chien 2011 [361] Hong Kong	RCT	92	Mean age 45 Gender 66%	Multicomponent PWD +CG Program was conducted fortnightly over 5 months. A multidisciplinary group identified intervention goals. The program included case management, education, support and problem solving, information about relationships, community resources and improvement of home care and finance skills. Peer mentors helped with problem solving.	Usual care	Family and carer impact	Family Caregiving Burden Inventory; WHOQoL-BREF; Six item Social Support Questionnaire; Family Support Services Index; Neuropsychiatric Inventory Questionnaire; Mini Mental State Examination; Institutionalisation	Week 1, Month 12 and Month 18	Over the 18 months, families and carers in the intervention group reported greater improvement in client symptoms (mean 82/144 to mean 76/144, p<.01), reduced number of people with dementia in institutional care (mean duration 13 days to 9 days, p<.001), increased families and carers quality of life mean 65/144 to mean 83/144, p<.001) and decreased burden (mean 68/96 to mean 46, p<.001).	1. Low 2. Unclear 3. High 4. Low 5. Low 6. Unclear

Reference Country	Type	N(n) carers	Participants	Intervention §	Comparison	Main Outcomes	Measure/s	Length of follow up	Results/ Effect size	Risk of bias[1]
Kwok 2012 [376] Hong Kong	RCT	102	Mean age 78 Gender intervention group 59%, control group 56%	Multicomponent PWD + CG Support from case manager via home visits and phone calls, home based cognitive stimulation activities for the person with dementia and a telephone hotline to access the case manager. An OT advised on coping strategies, skills training and behavioural management and linked the person with local services.	Usual care	Quality of life of person with dementia and family and carer stress	Person with dementia: MMSE; CSDD; NPI; Personal Wellbeing Index for Intellectually Disabled. Families and carers: Zarit Burden Interview; Personal Wellbeing Index; General Health Questionnaire	Months 4 and 12	Depression scores of the person with dementia in the intervention group were significantly reduced at 4 months (p<.005).	1. Unclear 2. Unclear 3. High 4. Unclear 5. High 6. Unclear
Waldorff 2012 [362] Phung 2013 [377] Sogaard 2014 [378] Denmark	RCT	330	Mean age 66 Gender intervention group 53% female, control group 55% female	Multifaceted PWD + CG "DAISY" intervention. Tailored program conducted over 8-12 months. Involved up to 7 counselling sessions, (4-5 with the families and carers present), a group education course about the condition building in peer support, phone call support, written information and a journal.	Usual care	Patient outcomes	Person with dementia: MMSE, Cornell Depression Scale for Dementia; EQVAS; Quality of Life Scale for AD; Neuropsychiatric Inventory; Alzheimer's Disease Cooperative Study ADL scale. Families and carers: Geriatric Depression Scale; EQVAS	12 Month	There were no significant differences in outcomes however there was a small difference in depression scores in patients in favour of the intervention group. There were no differences at 3 year follow-up.	1. Low 2. Low 3. High 4. Low 5. High 6. Low
Judge 2013 [379] United States	RCT	128	Mean age 65 Gender 74% female	Multicomponent PWD + CG Combines educational skills and cognitive rehabilitation training. Six sessions provided to the dyad covering: educational information, effective communication, managing memory, staying active, recognising emotions and behaviours	Written educational materials	Family and carer outcomes	Families and carers mastery; Emotional health strain; physical health strain; self-efficacy; role captivity; dyadic relationship strain; depression; anxiety; quality of life; self-esteem	Month 3	Intervention families & carers, vs controls, had decreased care-related strain as indicated by lower emotional health strain, dyadic relationship strain, role captivity, and higher caregiving mastery. Intervention families & carers had improved well-being as indicated by fewer symptoms of depression and anxiety.	1. Unclear 2. Unclear 3. High 4. Low 5. High 6. Low

§ categories: Carer education, Case management, Respite care, Multicomponent, Multicomponent PWD +Carer

Abbreviations: AD=Alzheimer's disease; CG=caregiver education; CSDD= Cornell Scale for Depression in Dementia; hr=hour(s); NPI=Neuropsychiatric inventory; OT= occupational therapist; PWD=person with dementia; RCT=randomised controlled trial; wk=week(s)

1. Risk of bias: (1) Random sequence generation, (2) Allocation concealment, (3) Blinding of participants and personnel, (4) Blinding of outcome assessment, (5) Incomplete outcome data, (6) Selective reporting

Table 174 GRADE Evidence Profile: Education programs for the families and carers versus usual care

Quality assessment							Effect	Quality
No of studies[1]	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Behavioural and psychological symptoms								
11 randomised trials		serious[3]	serious[4]	no serious indirectness	no serious imprecision	none	Olazaran includied 6 RCTs and found that 2 of the RCTs reported a positive result[2] [140] 2 RCTs (Klodnicka Kouri [349]and Kwok[350]) were pooled: SMD 0.27 lower (0.69 lower to 0.16 higher).Neither study found significant results but trend towards effectiveness. 3 RCTs (Liddle[351], Guerra[352], Gavrilova[353]) found no significant differences between groups Overall: 2 out of 11 RCTs have found a positive effect and an additional 2 studies showed a trend towards effectiveness.	⊕⊕OO LOW
Families and carers quality of life								
9 randomised trials		serious[3]	serious[4]	no serious indirectness	no serious imprecision	none	Olazaran [140] included 5 RCTsand found that 3 of the RCTs assessing this outcome reported a positive result[2] 2 RCTs reported statistically significant improvements in some or most domains (Kurz[366], Martin Carrasco[368]) 2 RCTs reported no significant changes (Gavrilova[353], Guerra[352]) although the RCT by Guerra suggested a trend towards improved physical QOL in the intervention group Overall: 5 out of 9 RCTs have found a positive effect with an additional study showing a trend towards effectiveness	⊕⊕OO LOW
Quality of life								
4 randomised trials		serious[3]	serious[4]	no serious indirectness	no serious imprecision	none	Olazaran[140] included 1 RCT that reported a positive result[2] 1 RCT (Logsdon[380]) reported significant improvement 2 RCTs reported no significant changes (Gavrilova[353], Guerra[352]) although Gavrilova showed a trend towards effectiveness of intervention Overall: 2 out of 4 RCTs have found a positive effect with an additional study showing a trend towards effect	⊕⊕OO LOW

Quality assessment							Effect	Quality
No of studies[1]	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**		
Institutionalisation								
4 randomised trials		serious[3]	serious[4]	no serious indirectness	no serious imprecision	None	Olazaran [140]included 3 RCTs and found that none of the studies assessing this outcome reported a positive result[2] 1 RCT (Kurz[366]) reported no significant difference between groups Overall: 0 out of 4 RCTs have found a reduction in institutionalisation.	⊕⊕OO LOW
Carer impact								
8 randomised trials		serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	None	Olazaran [140] included 3 RCTs and found that 1 trial assessing this outcome found a positive result[2] 4 RCTs (Guerra[352], Gavrilova[353], Kwok[350], Martin-Carrasco[368]) found that families and carers receiving intervention reported significantly reduced burden relative to the control group 1 RCT (Liddle[351]) found no significant difference between groups Overall: 5 out of 8 RCTs have found a positive effect	⊕⊕⊕O MODERATE
Knowledge regarding dementia and services								
3 randomised trials		serious[3]	no serious inconsistency	serious[5]	serious[6]	None	2 RCTs (Ducharme[365], Klodnicka Kouri[349]) pooled: SMD 0.42 higher (0.1 to 0.73 higher) 1 RCT (Liddle[351]) reported significantly greater knowledge regarding communication and memory support in dementia Overall: 3 out of 3 RCTs have found a positive effect	⊕OOO VERY LOW

[1]Number of studies reporting outcome data. Some studies reported that they measured an outcome but have not provided the results for the outcome.
[2]A positive outcome was defined as 95% confidence interval excluding zero effect
[3]Limited detail regarding methodology published for most studies
[4]Downgraded due to inconsistency – likely attributed to differences in intervention
[5]Surrogate outcome
[6]Small total sample

Table 175 GRADE Evidence Profile: Carer support programs for the families and carers versus usual care

Quality assessment							Effect	Quality
No of studies[1]	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Behavioural and psychological symptoms								
1 randomised trial		serious[3]	no serious inconsistency	no serious indirectness	serious[6]	None	Olazaran [140] found that 0/1 RCTs found a positive result [140]	⊕⊕OO LOW
Families and carers quality of life								
5 randomised trials		serious[3]	serious[4]	no serious indirectness	no serious imprecision	None	Olazaran [140]found 0 out of 2 RCTs measuring this reported an increased quality of life associated with intervention [140] 3 RCTs (Charlesworth[381], Wang 11[355], Wang 12[356]) were pooled: SMD 0.55 higher (0.33 to 0.76 higher) Overall: Pooling of 3 studies showed an overall increase in QOL. An additional two studies found no significant effect	⊕⊕OO LOW
Quality of life (person with dementia)								
1 randomised trial		serious[3]	no serious inconsistency	no serious indirectness	serious[6]	None	1 RCT (Charlesworth[381]) found no sig difference between groups	⊕⊕OO LOW
Institutionalisation								
4 randomised trials		serious[3]	serious[4]	no serious indirectness	no serious imprecision	None	Olazaran[140]: 0/1 RCTs assessing this found a positive result [140] 2 RCTs (Gaugler[370], Wang 2011[355]) found a reduction in institutionalisation (Gaugler: person with dementia less likely to be admitted to residential care and delayed time til admission; Wang 2011: reduced number of people admitted to institutional care (mean 5 versus mean 4)) 1 RCT (Charlesworth[381]) found no significant differences between groups Overall: 2 out of 4 RCTs have reported reduced institutionalisation	⊕⊕OO LOW
Carer impact								
1 randomised trial		serious[3]	no serious inconsistency	no serious indirectness	serious[6]	None	1 RCT (Wang 2011[355]) reported a significant reduction in carer impact in the intervention group	⊕⊕OO LOW

[1]Number of studies reporting outcome data. Some studies reported that they measured an outcome but have not provided the results for the outcome.
[2]A positive outcome was defined as 95% confidence interval excluding zero effect
[3]Limited detail regarding methodology published for most studies
[4]Downgraded due to inconsistency – likely attributed to differences in intervention
[5]Surrogate outcome
[6]Small total sample

Table 176 GRADE Evidence Profile: Case management intervention versus usual care

Quality assessment							Effect	Quality
No of studies[1]	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Behavioural and psychological symptoms								
No evidence available								
Families and carers quality of life								
2 randomised trials		serious[3]	no serious inconsistency	no serious indirectness	serious[6]	none	Olazaran[140] including 1 RCT found that there was no positive result[2] 1 RCT (Jansen[141]) reported no significant improvement [140] Overall: 0 of 2 RCTs have reported a positive result	⊕⊕OO LOW
Quality of life (person with dementia)								
2 randomised trials		serious[3]	serious[4]	no serious indirectness	serious[6]	none	Olazaran [140]including 1 RCT found that the study reported a positive result[2] 1 RCT (Jansen[141]) reported no significant improvement [140] Overall: 1 of 2 RCTs reported a positive result	⊕OOO VERY LOW
Institutionalisation								
1 randomised trial		serious[3]	no serious inconsistency	no serious indirectness	serious[6]	none	Olazaran[140] including 1 RCT found that there was no positive result[2] [140] Overall: 0 of 1 RCTs have reported a positive result	⊕⊕OO LOW
Carer impact								
2 randomised trials		serious[3]	serious[4]	no serious indirectness	serious[6]	none	Olazaran [140]including 2 RCTs found that 1 of the 2 RCTs assessing this outcome reported a positive result[2] [140] Overall: 1 of 2 RCTs have reported a positive result	⊕OOO VERY LOW

[1]Number of studies reporting outcome data. Some studies reported that they measured an outcome but have not provided the results for the outcome.
[2]A positive outcome was defined as 95% confidence interval excluding zero effect
[3]Limited detail regarding methodology published for most studies
[4]Downgraded due to inconsistency – likely attributed to differences in intervention
[5]Surrogate outcome
[6]Small total sample

Table 177 GRADE Evidence Profile: Respite intervention versus usual care

Quality assessment							Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Behavioural and psychological symptoms								
0	No evidence available					none		
Families and carers quality of life								
0	No evidence available					none		
Quality of life (person with dementia)								
0	No evidence available					none		
Institutionalisation								
0	No evidence available					none		
Carer impact								
1	Randomised trial	very serious	no serious inconsistency	no serious indirectness	serious	none	Olazaran: found 0 of 1 studies assessing this outcome found a positive result [140]	⊕OOO VERY LOW

[1]Number of studies reporting outcome data. Some studies reported that they measured an outcome but have not provided the results for the outcome.
[2]A positive outcome was defined as 95% confidence interval excluding zero effect
[3]Limited detail regarding methodology published for most studies
[4]Downgraded due to inconsistency – likely attributed to differences in intervention
[5]Surrogate outcome
[6]Small total sample

Table 178 GRADE Evidence Profile: Multicomponent intervention for the families and carers

Quality assessment							Effect	Quality
No of studies[1]	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Behavioural and psychological symptoms								
1 randomised trial		serious[3]	no serious inconsistency	no serious indirectness	serious[6]	none	1 RCT (Tremont) found a MD 11.56 lower (18.56 to 4.56 lower)[357] Overall: 1 of 1 RCT found a positive result	⊕⊕OO LOW
Families and carers quality of life								
6 randomised trials		serious[3]	serious[4]	no serious indirectness	no serious imprecision	none	Olazaran [140] included 3 RCTs and found that 1 of the studies assessing this outcome reported a positive result[2] 1 RCT reported a positive outcome on QOL for families and carers in the intervention group in some domains (Kuo[358]) 2 RCTs found no significant benefits (Livingston[372], Joling[374]) although Livingston found a trend towards effectiveness Overall: 2 of 6 RCTs have found positive results; one of these studies showed a trend towards effect	⊕⊕OO LOW
Quality of life (person with dementia)								
2 randomised trials		serious[3]	serious[4]	no serious indirectness	serious[6]	none	Olazaran [140]included 1 RCT and found that the study reported a positive result[2] 1 RCT found no significant difference (Livingston[372]) although there was a trend towards effectiveness Overall: 1 of 2 RCTs have found a positive result and the other RCT found a trend towards effectiveness	⊕OOO VERY LOW

Quality assessment							Effect	Quality
No of studies[1]	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Institutionalisation								
5 randomised trials		serious[3]	serious[4]	no serious indirectness	no serious imprecision	none	Olazaran[140] included 5 RCTs and pooled 3 high quality RCTs and found a positive effect for institutional delay (odds ratio 0.67 (95%CI 0.49 to 0.92) indicating 33% less institutionalisation after 6-12 months. An additional 2 RCTs of lower quality included in the review were unable to be pooled and showed no significant effect. Overall: Pooling of 3 RCTs (out of 5) found a positive effect	⊕⊕OO LOW
Carer impact								
4 randomised trials		serious[3]	serious[4]	no serious indirectness	serious[6]	none	Olazaran [140]included 1 RCT found that this study reported a positive result[2] 3 RCTs were pooled and found no significant benefits (Davis[359], Martindale Adams[360], Tremont[357]). The study by Tremont reported positive effects Overall: 2 out of 4 RCTs found a positive effect	⊕OOO VERY LOW

[1]Number of studies reporting outcome data. Some studies reported that they measured an outcome but have not provided the results for the outcome.
[2]A positive outcome was defined as 95% confidence interval excluding zero effect
[3]Limited detail regarding methodology published for most studies
[4]Downgraded due to inconsistency – likely attributed to differences in intervention
[5]Surrogate outcome
[6]Small total sample

Table 179 GRADE Evidence Profile: Multicomponent interventions for the families and carers and the person with dementia versus usual care

Quality assessment							Effect	Quality
No of studies[1]	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Behavioural and psychological symptoms								
13 randomised trials		serious[3]	serious[4]	no serious indirectness	no serious imprecision	None	Olazaran[140] included 8 RCTs and found 4 of 8 RCTs assessing this outcome reported a positive result[2]. Three of these RCTs were pooled which found an overall positive result (effect size 0.57 (95%CI 0.21 to 0.92) 3 RCTs were pooled – none of the studies or the overall effect was positive (Chien[361], Kwok[350], Waldorff[362]) Gitlin 2010 (COPE)[187] No significant differences between groups Gitlin 2010[188] found significant improvement in the problem behaviour Overall: 5 of 13 studies have found a positive result	⊕⊕OO LOW
Families and carers quality of life								
7 randomised trials		serious[3]	serious[4]	no serious indirectness	no serious imprecision	none	Olazaran[140] included 4 RCTs and found 3 of 4 RCTs assessing this outcome reported a positive result[2]. Two of these RCTs were pooled and showed an overall positive effect (effect size 0.68 (95%CI 0.36 to 1.00) 3 RCTs were pooled (Chien[361], Judge[379], Waldorff[362]) – neither the individual studies nor the overall effect was not significant (SMD 0.11 higher (0.07 lower to 0.28 higher)) Overall: 3 of 7 RCTs have found a positive result	⊕⊕OO LOW

Quality assessment							Effect	Quality
No of studies[1]	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Quality of life (person with dementia)								
6 randomised trials		serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Olazaran[140] included 4 RCTs and found 3 of 4 RCTs assessing this outcome reported a positive result[2]. Two of these RCTs were pooled and showed overall positive effect (effect size 0.561 (95%CI 0.09 to 1.04) 2 RCTs (Waldorff[362], Gitlin 2010 COPE[187]) found no significant effect Overall: 3 out of 6 RCTs have found a positive result	⊕⊕⊕O MODERATE
Institutionalisation								
5 randomised trials		serious[3]	serious[4]	no serious indirectness	no serious imprecision	none	Olazaran[140] included 3 RCTs and found that 0 of 3 RCTs assessing this outcome reported a positive result[2] 2 RCTs reported positive results for this outcome: Eloniemi-Sulkava[375] reported that a lower proportion of people in the intervention group were institutionalised at 1.6 years however at 2 years there was no difference. Chien[361] also reported lower use of institutional care in the intervention group Overall: 2 out of 5 RCTs have reported a positive result	⊕⊕OO LOW
Carer impact								
7 randomised trials		serious[3]	serious[4]	no serious indirectness	no serious imprecision	none	Olazaran[140] included 3 RCTs found that 1 of the 3 RCTs assessing this outcome reported a positive result[2] 3 RCTs were pooled: 2 of the studies and the overall effect was positive ((Chien[361], Gitlin[188], Judge[379]) SMD 0.32 lower (0.51 to 0.14 lower)) 1 RCT (Kwok[350]) found no significant effects on burden from intervention. Overall: 3 out of 7 RCTs have reported a positive result	⊕⊕OO LOW

Abbreviations: AD – Alzheimer's Disease; ADL - ; CG – COPE – DAISY – DEMQoL - EQVAS – FITT-D – FITT-NH – HADS –T – IADL – ICER – MESSAGE – PWD – patient with dementia; QALY – QoL – Quality of Life; RECAPS – RCT – randomised controlled trials; RUD-Light – SF12/SF36 – SRQ20 – WHOQoL-BREF –

[1]Number of studies reporting outcome data. Some studies reported that they measured an outcome but have not provided the results for the outcome.
[2]A positive outcome was defined as 95% confidence interval excluding zero effect
[3]Limited detail regarding methodology published for most studies
[4]Downgraded due to inconsistency – likely attributed to differences in intervention
[5]Surrogate outcome
[6]Small total sample

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Appendix 1: Identification and appraisal of existing guidelines

Inclusion criteria

1. Guidelines must be comprehensive (i.e. not just related to assessment or one aspect of management or one setting (eg General Practice))
2. Guidelines must be evidence based (guideline must report on systematic literature searches and explicit links between individual recommendations and their supporting evidence
3. Guidelines must be national or international
4. The search must have been run in the past 10 years (ie 2005-2014)
5. Must be published in English
6. Not funded by a pharmaceutical company
7. Guidelines will be excluded if they are written by a single person (individual)

Search for existing Guidelines

We searched the following guideline clearinghouses and websites on the 6th of February 2014: National Guideline Clearinghouse, Guidelines International Network, Ontario Guidelines Advisory Committee, Institute for Clinical Systems Improvement, NICE, New Zealand Guideline Group, SIGN, Canadian Agency for Drugs and Technology in Health, Canadian Medical Association Infobase, Google using the terms 'dementia' and 'Alzheimer's'. We also searched Medline (search terms available in the Guideline Technical Report Volume 2).

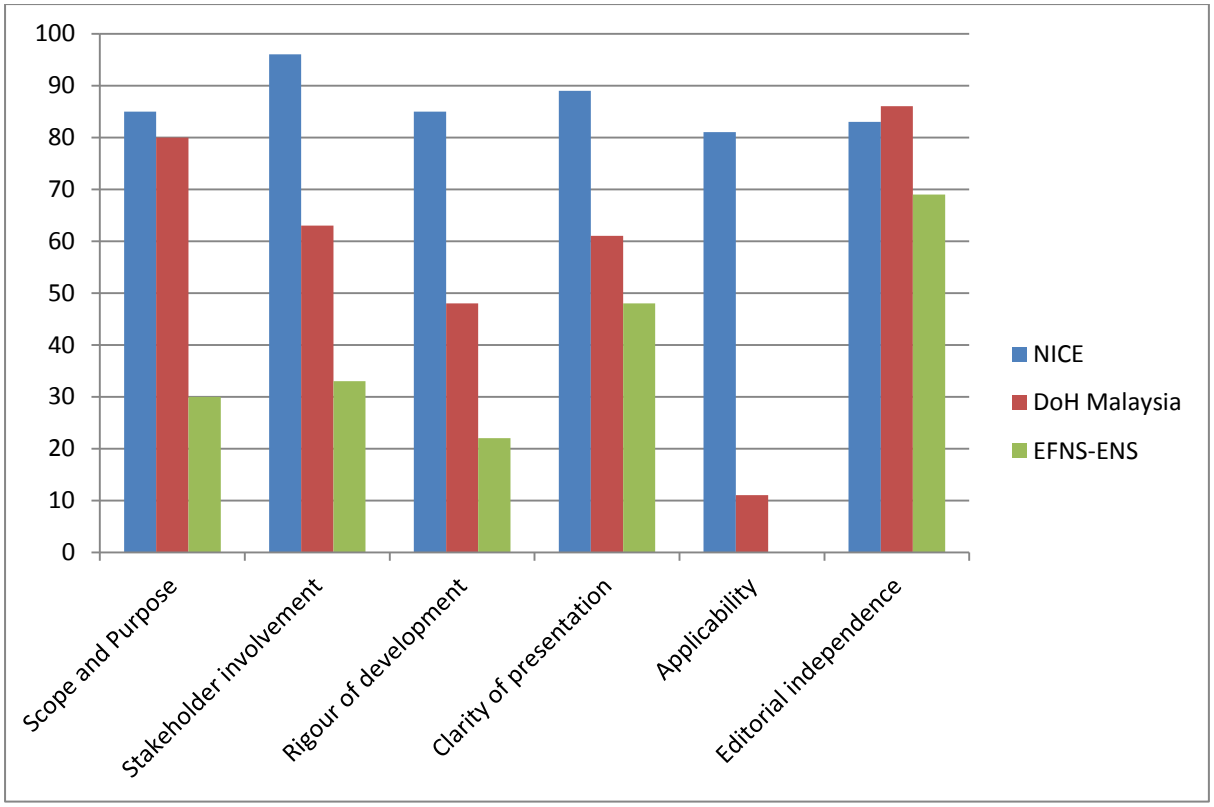
Search results

Three guidelines meeting the eligibility criteria were identified; the NICE Guidelines (2006), The European Guidelines (2010; 2012) and the Malaysian Guidelines (2009).

Title	Publisher	Country, Language	Publication date	End of search date
Dementia CG42	NICE	England, English	2006	Sept 2005
EFNS-ENS guidelines on the diagnosis and management of Alzheimer's and disorders associated with dementia	EFNS	Europe, English	2010 2012	May 2009 June 2011
Management of dementia	DoH Malaysia	Malaysia, English	2009	June 2009

Guideline appraisal

The three Guidelines were appraised by three people (Kate Laver, Robert Cumming and Rachel Milte) independently using the AGREE II checklist. Results are presented in the Figure below and demonstrate that the NICE Guideline consistently received the highest ratings and was therefore selected as being the Guideline most suitable for adaptation.


100
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Scope and Purpose
Stakeholder involvement
Rigour of development
Clarity of presentation
Applicability
Editorial independence
NICE
DoH Malaysia
EFNS-ENS

Appendix 2 Guideline Adaptation Committee

Membership and Acknowledgements

Efforts were made to invite individuals who (1) had relevant practical experience in the management of dementia in Australia, (2) were highly respected in their fields, (3) were skilled in the appraisal of scientific evidence, (4) represented the various geographical areas across Australia, and (5) were able to make the necessary time commitment. In addition the organising committee approached the Australian Association of Social Workers for representation. Consumer representatives were sought via the Consumer Dementia Research Network (within Alzheimer's Australia) who contributes to the work of the NHMRC Partnership Centre.

We wish to thank Ms Joan Jackman, Ms Christine Bryden and Ms Kate Swaffer who commented on drafts of the guideline from a consumer perspective.

We also wish to thank Dr Owen Davies (geriatrician) and Ms Heather Forbes (pharmacist) who provided valuable advice on specific clinical questions (in particular refining inclusion and exclusion criteria for some systematic review questions) during the process of guideline development. We thank Kate Smith and Melissa Lindeman for their input in developing recommendations relating to the care of Indigenous Australians.

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GUIDELINE ADAPTATION COMMITTEE	
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Prof Lindy Clemson	Occupational therapy Professor in Ageing and Occupational Therapy University of Sydney
Prof Maria Crotty	Rehabilitation Physician Professor of Rehabilitation Flinders University and Repatriation General Hospital
Margaret Dietz	Social Work Team leader, Monash Aged Persons Mental Health Service Community APAT team
Prof Brian Draper	Psychiatry Director, Academic Department for Old Age Psychiatry Prince of Wales Hospital Professor (Conjoint), School of Psychiatry University of NSW
Prof Leon Flicker	Geriatric Medicine Professor of Geriatric Medicine University of Western Australia
Meg Friel	Consumer representative Alzheimer's Australia Consumer Dementia Research Network
Louise Heuzenroeder	Consumer representative Alzheimer's Australia Consumer Dementia Research Network
A/Prof Susan Koch	Nursing Principal Research Officer, RDNS Research Institute
Prof Sue Kurrle	Geriatric Medicine Curran Professor in Health Care of Older People, University of Sydney Director, NHMRC Cognitive Decline Partnership Centre Senior Staff Specialist Geriatrician, Hornsby Ku-ring-gai Health Service
Prof Rhonda Nay	Nursing Emeritus Professor in Nursing La Trobe University
Prof Dimity Pond	General Practice Professor, Discipline of General Practice University of Newcastle
Dr Jane Thompson	Consumer representative Alzheimer's Australia Consumer Dementia Research Network
Yvonne Santalucia	Multicultural Aged Officer South Western Sydney Local Health District
A/Prof Craig Whitehead	Chair of Organising Committee Geriatric Medicine Regional Clinical Director of Rehabilitation and Aged Care, Southern Adelaide Health Service

GUIDELINE ADAPTATION COMMITTEE	
A/Prof Mark Yates	Geriatric Medicine Director of Clinical Studies, Grampians Clinical School Deakin University Ballarat Health Services

SCIENTIFIC	
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Dr Suzanne Dyer	Researcher and Systematic Reviewer Flinders University *Non-voting member of the Guideline Adaptation Committee
Dr Deborah Chen	Systematic Reviewer Flinders University
A/Prof Tracy Merlin	Methodological consultant Managing Director of Adelaide Health Technology Assessment (AHTA) University of Adelaide