National Institute for Health and Care Excellence

Final

# Dementia

## Assessment, management and support for people living with dementia and their carers

*NICE Guideline 97*

*Methods, evidence and recommendations*

*June 2018*

*Final*

*Commissioned by the National Institute for Health and Care Excellence*

**Disclaimer**
Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.



**Update information**
**October 2018:** Links have been added to patient decision aids from some recommendations. These changes can be seen in the short version of the guideline at http://www.nice.org.uk/guidance/ng97

**ISBN:** 978-1-4731-2978-8

# Contents

# Context

Dementia is a term used to describe a range of cognitive and behavioural symptoms that can include memory loss, problems with reasoning and communication and change in personality, and a reduction in a person's ability to carry out daily activities, such as shopping, washing, dressing and cooking. The most common types of dementia are: Alzheimer's disease, vascular dementia, mixed dementia, dementia with Lewy bodies and frontotemporal dementia. Dementia is a progressive condition, which means that the symptoms will gradually get worse. This progression will vary from person to person and each will experience dementia in a different way – people may often have some of the same general symptoms, but the degree to which these affect each person will vary (Dementia Gateway, Social Care Institute for Excellence).

A report published by the Alzheimer's Society found that in 2013 there were approximately 815,000 people living with dementia in the UK. If current trends continue, this number is expected to increase to 1,143,000 by 2025. In England, the National Dementia and Antipsychotic Prescribing Audit found that approximately 31,000 people were newly diagnosed with dementia in 2011. This is an increase of 8% between 2006 and 2011. Finally, in December 2017, there were 456,739 people on GP registers with a formal diagnosis of dementia, up from approximately 290,000 people in 2009/10, with the majority of this difference accounted for by an increase in diagnosis rates.

The Alzheimer's Society report found that in 2013 the total cost of dementia in the UK was estimated to be £26.3 billion. Of this, approximately £4.3 billion consists of health care, and approximately £10.3 billion consists of social care. The remaining £11.6 billion accounts for estimated unpaid care contributions.

## Why is it needed?

Providing care and support is very complex, because of the number of people living with dementia and the variation in the symptoms each person faces. This has led to considerable variation in practice. Areas that pose particular challenges for services and practitioners may include:

- coordinating care and support between different services
- what support carers need, and how this should be provided
- staff training.

This guideline makes evidence-based recommendations aiming to support these areas of practice.

Dementia also has significant costs for health and social care services. Because of this, it is important to ensure that people living with dementia can get the care and support they need, and that services provide this in an efficient and cost-effective way.

In addition, new methods for diagnosing and assessing dementia have been developed. Amyloid imaging techniques have been licensed for use in the UK, and new evidence is available for cerebrospinal fluid examination. There is also evidence on different approaches to assess and diagnose dementia subtypes. The guideline makes new recommendations on dementia diagnosis, based on a review of the latest evidence.

## What does it cover?

This guideline addresses how dementia should be assessed and diagnosed. It covers person-centred care and support, tailored to the specific needs of each person living with dementia. As part of this, it can help professionals involve people living with dementia and their carers in decision-making, so they can get the care and support they need. It also addresses care coordination and staff training, and how dementia may impact on the care offered for other conditions.

The guideline does not cover every aspect of dementia care or support, or areas where recommendations would be the same for people with or without dementia. It focuses on areas where:

- there is variation in practice, and enough evidence is available to identify what works best
- people living with dementia need different care and support to people in the same situation who do not have dementia.

## How has it been developed?

This guideline has been developed by a multidisciplinary guideline committee, using an extensive review of research evidence. To ensure that the committee had the necessary social care expertise, a subgroup of social care practitioners was recruited to develop recommendations in this area.

Given the costs of dementia and the financial pressures facing health and social care services, the committee focused on making recommendations in areas where there is good evidence available. This will help services make the most of limited resources. For areas with a lack of evidence, the committee has made recommendations for future research (on health and social care topics) to address gaps in the evidence base. Future updates of the guideline will look at any relevant new research that has been published.

Some recommendations are made with more certainty than others. We word our recommendations to reflect this. In the sections on interventions we use 'offer' to reflect a strong recommendation, usually where there is clear evidence of benefit. We use 'consider' to reflect a recommendation for which the evidence of benefit is less certain. For more information see making decisions using NICE guidelines.

## How does it relate to statutory and non-statutory guidance?

The guideline complements existing legislation and guidance. It describes how services and professionals can provide high-quality care and support.

The Prime Minister's Challenge on Dementia 2020 sets out the UK Government's strategy for transforming dementia care within the UK. The aims of the strategy include:

- improving diagnosis, assessment and care for people living with dementia
- ensuring that all people living with dementia have equal access to diagnosis
- providing all NHS staff with training on dementia appropriate to their role
- ensuring that every person diagnosed with dementia receives meaningful care.

Since the 2006 NICE guideline on dementia was developed, key new legislation has been implemented. The Care Act 2014 created a new legislative framework for adult social care, and also gives carers a legal right to assessment and support.

## Relevant legislation and statutory guidance

- NHS England (2015) Accessible Information Standard
- Care Act 2014
- Health and Social Care Act 2008 (Regulated Activities) Regulations 2014
- Department of Health (2014) Care Act 2014: Statutory Guidance for Implementation
- Department of Health (2014) Positive and Proactive Care: Reducing the need for restrictive interventions
- Health and Social Care Act 2012
- Equality Act 2010
- Mental Capacity Act 2005
- Human Rights Act 1998

## Relevant policies and non-statutory guidance

- Information Commissioner's Office (2017) Guide to the General Data Protection Regulation
- NHS England (2017) Dementia: Good Care Planning
- NHS England (2015) Implementation guide and resource pack for dementia care
- Skills for Health, Health Education England and Skills for Care (2015) Dementia Core Skills Education and Training Framework. This framework was commissioned and funded by the Department of Health and developed in collaboration by Skills for Health and Health Education England in partnership with Skills for Care
- Department of Health (2014) NHS Outcomes Framework 2015 to 2016
- Department of Health (2014) Adult Social Care Outcomes Framework 2015 to 2016

# 1 Guideline committee membership and NICE technical team

## 1.1 Guideline committee

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**Louise Allan**

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For a full list of guideline development group and declarations of interest, see Appendix A.

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**Jane Silvester**

Associate Director - Guidance and Quality Assurance management, Implementation

For social care recommendations

# 2 Strength of recommendation

Some recommendations can be made with more certainty than others. The Guideline committee makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the Guideline committee is confident that, given the information it has looked at, most patients would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

For all recommendations, NICE expects that there is discussion with the patient about the risks and benefits of the interventions, and their values and preferences. This discussion aims to help them to reach a fully informed decision (see also 'Patient-centred care').

## Interventions that must (or must not) be used

We usually use 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally we use 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

## Interventions that should (or should not) be used – a 'strong' recommendation

We use 'offer' (and similar words such as 'refer' or 'advise') when we are confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective. We use similar forms of words (for example, 'Do not offer…') when we are confident that an intervention will not be of benefit for most patients.

## Interventions that could be used

We use 'consider' when we are confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

# 3 Methods

This guideline was developed in accordance with the process set out in 'Developing NICE guidelines: the manual (2014)'. There is more information about how NICE clinical guidelines are developed on the NICE website. A booklet, 'How NICE clinical guidelines are developed: an overview for stakeholders, the public and the NHS' is available. In instances where the guidelines manual does not provide advice, additional methods are used as described below, organised by study type.

## 3.1 Evidence synthesis and meta-analyses

Where possible, meta-analyses were conducted to combine the results of quantitative studies for each outcome. For continuous outcomes analysed as mean differences, where change from baseline data were reported in the trials and were accompanied by a measure of spread (for example standard deviation), these were extracted and used in the meta-analysis. Where measures of spread for change from baseline values were not reported, the corresponding values at study end were used and were combined with change from baseline values to produce summary estimates of effect. These studies were assessed to ensure that baseline values were balanced across the treatment groups; if there were significant differences at baseline these studies were not included in any meta-analysis and were reported separately. For continuous outcomes analysed as standardised mean differences, where only baseline and final time point values were available, change from baseline standard deviations were estimated, assuming a correlation coefficient of 0.5.

## 3.2 Evidence of effectiveness of interventions

### 3.2.1 Quality assessment

GRADE was used to assess the quality of evidence for the selected outcomes as specified in 'The guidelines manual (2014)'. Where RCTs are available, these are initially rated as high quality and the quality of the evidence for each outcome was downgraded or not from this initial point. If non-RCT evidence was included for intervention-type systematic reviews then these are initially rated as low quality and the quality of the evidence for each outcome was downgraded or not from this point.

Individual RCTs, cohort studies and case-control studies were quality assessed using the CASP RCT, cohort study and case-control checklists, respectively. Each individual study was classified as being either at low, moderate or high risk of bias based on that assessment.

### 3.2.2 Methods for combining intervention evidence

Meta-analysis of interventional data was conducted with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011).

Where different studies presented continuous data measuring the same outcome but using different numerical scales (e.g. a 0-10 and a 0-100 visual analogue scale), these outcomes were all converted to the same scale before meta-analysis was conducted on the mean differences. Where outcomes measured the same underlying construct but used different instruments/metrics, data were analysed using standardised mean differences (Hedges' g).

A pooled relative risk was calculated for dichotomous outcomes (using the Mantel–Haenszel method).

Fixed- and random-effects models (der Simonian and Laird) were fitted for all syntheses, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models were the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model were clearly not met, even after appropriate pre-specified subgroup analyses were conducted, random-effects results are presented. Fixed-effects models were deemed to be inappropriate if one or both of the following conditions was met:

- Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. This decision was made and recorded before any data analysis was undertaken.
- The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 40\%$.

Meta-analyses were performed in Cochrane Review Manager v5.3.

### 3.2.3 Minimal clinically important differences (MIDs)

The Core Outcome Measures in Effectiveness Trials (COMET) database was searched to identify published minimal clinically important difference thresholds relevant to this guideline, and this list was supplemented by any additional MIDs found through studies included in the guideline. Identified MIDs were assessed to ensure they had been developed and validated in a methodologically rigorous way, and were applicable to the populations, interventions and outcomes specified in this guideline. In addition, the Guideline committee were asked to prospectively specify any outcomes where they felt a consensus MID could be defined from their experience. In particular, any questions looking to evaluate non-inferiority (that one treatment is not meaningfully worse than another) required an MID to be defined to act as a non-inferiority margin.

MIDs found through this process are given in Table 1. For other continuous outcomes not specified in the table below, no MID was defined.

**Table 1: Identified MIDs**

| Outcome | MID | Source |
|---|---|---|
| BADLS | 3.5 | Howard R, Phillips P, Johnson T, et al. Determining the minimum clinically important differences for outcomes in the DOMINO trial. Int J Geriatr Psychiatry 2011; 26: 812–817. |
| IDDD | 5 | Meeuwsen EJ, Melis RJF, van der Aa GCHM. Effectiveness of dementia follow-up care by memory clinics or general practitioners: randomised controlled trial. BMJ 2012;344:e3086. |
| MMSE | 1.4 | Howard R, Phillips P, Johnson T, et al. Determining the minimum clinically important differences for outcomes in the DOMINO trial. Int J Geriatr Psychiatry 2011; 26: 812–817. |
| NPI total score | 8 | Howard R, Phillips P, Johnson T, et al. Determining the minimum clinically important differences for outcomes in the DOMINO trial. Int J Geriatr Psychiatry 2011; 26: 812–817. |
| QoL-15D | 0.03 | Koivisto AM, Hallikainen I, Vlimki T, et al. Early psychosocial intervention does not delay institutionalization in persons with mild Alzheimer disease and has impact on neither disease progression nor caregivers' well-being: ALSOVA 3-year follow-up. Int J Geriatr Psychiatry 2016; 31: 273–283. |
| QoL-AD | 3 | Meeuwsen EJ, Melis RJF, van der Aa GCHM, et al. Effectiveness of dementia follow-up care by memory clinics or general practitioners: randomised controlled trial. BMJ 2012;344:e3086. |

| Outcome | MID | Source |
|---|---|---|
| BADLS: Bristol Activities of Daily Living Scale<br>IDDD: Interview for deterioration in daily living activities in dementia<br>MMSE: Mini-mental State Examination<br>NPI: Neuropsychiatric Inventory<br>QoL-15D: 15D health related quality of life instrument<br>QoL-AD: Quality of life in Alzheimer's disease instrument | | |

For standardised mean differences where no other MID was available, an MID of 0.2 was specified by the committee, corresponding to the threshold for a small effect size initially suggested by Cohen et al. (1988). For dichotomous outcome measures, the committee agreed that any changes in mortality, entry to long stay care and the proportions of people achieving a clinically meaningful improvement would themselves be clinically meaningful, whilst for other measures an MID interval of 0.8 to 1.25 was used.

The committee noted that the MIDs identified for specific outcome scales were all based on the level of short-term change needed to make a meaningful difference to an individual with an established diagnosis of dementia, and this made interpretation difficult when applied to mean differences between groups, particularly because dementia is a highly heterogeneous condition and therefore it would be expected there would be considerable variability between individuals in the level of response to an intervention. Additionally, it would be likely that smaller MIDs would be found for these outcomes in cases where the effects of interventions persist in the longer-term. The committee also noted that since these MIDs were derived from RCT data with clearly defined populations, it was unclear whether they would be applicable for people with different subtypes of dementia, or at different stages of severity. Therefore, it was agreed the above MIDs would not be used to downgrade for imprecision, with the line of no effect being used instead, but they would be taken in to account by the committee as parts of their discussions as to whether the findings of a review were clinically meaningful.

When decisions were made in situations where MIDs were not available, the 'Evidence to Recommendations' section of that review should make explicit the committee's view of the expected clinical importance and relevance of the findings. In particular, this includes consideration of whether the whole effect of a treatment (which may be felt across multiple independent outcome domains) would be likely to be clinically meaningful, rather than simply whether each individual sub outcome might be meaningful in isolation.

### 3.2.4 GRADE for pairwise meta-analyses of interventional evidence

The quality of the evidence for each outcome was downgraded where appropriate for the reasons outlined in Table 2

**Table 2: Rationale for downgrading evidence for intervention studies**

| GRADE criteria | Reasons for downgrading quality |
|---|---|
| Risk of bias | The quality of the evidence was downgraded if there were concerns about the design or execution of the study, including concealment of allocation, masking, loss to follow up using intervention checklists in the NICE guidelines manual (2014) |
| Inconsistency | The quality of the evidence was downgraded if, after appropriate pre-specified sensitivity analyses were conducted, there were remaining concerns about inconsistency of effects across studies: occurring when there is variability in the treatment effect demonstrated across studies (heterogeneity).<br>This was downgraded either if important differences were found between populations, interventions and/or comparators across studies included in a meta-analysis, or if there was significant unexplained statistical heterogeneity, |

| GRADE criteria | Reasons for downgrading quality |
|---|---|
| | assessed using the $I^2$ statistic, where $I^2 \geq 40\%$ was categorised as serious inconsistency. |
| Indirectness | The quality of the evidence was downgraded if there were concerns about the population, interventions and outcomes in the included studies and how directly these variables could address the specific review question. |
| Imprecision | If MIDs other than the line of no effect (1 corresponding to meaningful benefit; 1 corresponding to meaningful harm) were defined for the outcome, the outcome was downgraded once if the 95% confidence interval for the effect size crossed 1 MID, and twice if it crossed both the upper and lower MIDs.<br>If an MID was not defined for the outcome, or the line of no effect was specified as an MID, it was downgraded once if the 95% confidence interval for the effect size crossed the line of no effect (i.e. the outcome was not statistically significant), and twice if additionally the sample size of the study was sufficiently small that it is not plausible any realistic effect size could have been detected.<br>In situations where data was included, but only p values were available and not confidence intervals, the data were downgraded once for imprecision if the sample size of the study was less than 100. |

## 3.3 Methods for combining direct and indirect evidence (network meta-analysis) for interventions

Conventional pairwise meta-analysis involves the statistical combination of direct evidence about pairs of interventions that originate from 2 or more separate studies (for example, where there are two or more studies comparing A vs B).

In situations where there are more than 2 interventions, pairwise meta-analysis of the direct evidence alone is of limited use. This is because multiple pairwise comparisons need to be performed to analyse each pair of interventions in the evidence, and these results can be difficult to interpret. Furthermore, direct evidence about interventions of interest may not be available. For example studies may compare A vs B and B vs C, but there may be no direct evidence comparing A vs C. Network meta-analysis (NMA) overcomes these problems by combining all evidence into a single, internally consistent model, synthesising data from direct and indirect comparisons, and providing estimates of relative effectiveness for all comparators and the ranking of different interventions.

### 3.3.1 Synthesis

Frequentist NMAs were undertaken using the `netmeta` package in R v3.4.1. This uses a graph-theoretical method which is mathematically equivalent to frequentist network meta-analysis (Rücker 2012). Inconsistency was assessed using the overall $I^2$ value for the whole network, which is a weighted average of the $I^2$ value for all comparisons where there are multiple trials (both direct and indirect), and random-effects models were used if the $I^2$ value was above 50% (this was interpreted as showing the assumption of consistent, shared underlying means was not met, and therefore a fixed-effects model was inappropriate).

### 3.3.2 Modified GRADE for network meta-analyses

A modified version of the standard GRADE approach for pairwise interventions was used to assess the quality of evidence across the network meta-analyses undertaken. While most criteria for pairwise meta-analyses still apply, it is important to adapt some of the criteria to take into consideration additional factors, such as how each 'link' or pairwise comparison within the network applies to the others. As a result, the following was used when modifying

the GRADE framework to a network meta-analysis. It is designed to provide a single overall quality rating for an NMA, which can then be combined with pairwise quality ratings for individual comparisons (if appropriate), to judge the overall strength of evidence for each comparison.

**Table 3: Rationale for downgrading quality of evidence for intervention studies**

| GRADE criteria | Reasons for downgrading quality |
|---|---|
| Risk of bias | Not serious: If fewer than 33.3% of the studies in the network meta-analysis were at moderate or high risk of bias, the overall network was not downgraded.<br>Serious: If greater than 33.3% of the studies in the network meta-analysis were at moderate or high risk of bias, the network was downgraded one level.<br>Very serious: If greater than 33.3% of the studies in the network meta-analysis were at high risk of bias, the network was downgraded two levels. |
| Indirectness | Not serious: If fewer than 33.3% of the studies in the network meta-analysis were partially indirect or indirect, the overall network was not downgraded.<br>Serious: If greater than 33.3% of the studies in the network meta-analysis were partially indirect or indirect, the network was downgraded one level.<br>Very serious: If greater than 33.3% of the studies in the network meta-analysis were indirect, the network was downgraded two levels. |
| Inconsistency | N/A: Inconsistency was marked as not applicable if there were no links in the network where data from multiple studies (either direct or indirect) were synthesised.<br>For network meta-analyses conducted under a frequentist framework, the network was downgraded one level if the $I^2$ was greater than 50%.<br>In addition, the direct and indirect treatment estimates were compared as a check on the consistency of the network. |
| Imprecision | The overall network was downgraded for imprecision if it was not possible to differentiate between any meaningfully distinct treatments options in the network (based on 95% confidence/credible intervals). Whether two options were meaningfully distinct was judged using the MIDs defined above for pairwise meta-analysis of the outcomes, if available; or the line of no effect if MIDs were not available. |

## 3.4 Diagnostic test accuracy evidence

In this guideline, diagnostic test accuracy (DTA) data are classified as any data in which a feature – be it a symptom, a risk factor, a test result or the output of some algorithm that combines many such features – is observed in some people who have the condition of interest at the time of the test and some people who do not. Such data either explicitly provide, or can be manipulated to generate, a 2x2 classification of true positives and false negatives (in people who, according to the reference standard, truly have the condition) and false positives and true negatives (in people who, according to the reference standard, do not).

The 'raw' 2x2 data can be summarised in a variety of ways. Those that were used for decision making in this guideline are as follows:

- **Positive likelihood ratios** describe how many times more likely positive features are in people with the condition compared with people without the condition. Values greater than 1 indicate that a positive result makes the condition more likely.
  - $LR^+$ = (TP/[TP+FN])/(FP/[FP+TN])
- **Negative likelihood ratios** describe how many times less likely negative features are in people with the condition compared with people without the condition. Values less than 1 indicate that a negative result makes the condition less likely.
  - $LR^-$ = (FN/[TP+FN])/(TN/[FP+TN])

- **Sensitivity** is the probability that the feature will be positive in a person with the condition.
  - sensitivity = TP/(TP+FN)
- **Specificity** is the probability that the feature will be negative in a person without the condition.
  - specificity = TN/(FP+TN)

The following schema, adapted from the suggestions of Jaeschke et al. (1994), was used to interpret the likelihood ratio findings from diagnostic test accuracy reviews.

**Table 4: Interpretation of likelihood ratios**

| Value of likelihood ratio | Interpretation |
|---|---|
| LR ≤ 0.1 | **Very large** decrease in probability of disease |
| 0.1 < LR ≤ 0.2 | **Large** decrease in probability of disease |
| 0.2 < LR ≤ 0.5 | **Moderate** decrease in probability of disease |
| 0.5 < LR ≤ 1.0 | **Slight** decrease in probability of disease |
| 1.0 < LR < 2.0 | **Slight** increase in probability of disease |
| 2.0 ≤ LR < 5.0 | **Moderate** increase in probability of disease |
| 5.0 ≤ LR < 10.0 | **Large** increase in probability of disease |
| LR ≥ 10.0 | **Very large** increase in probability of disease |

The schema above has the effect of setting a minimal important difference for positive likelihoods ratio at 2, and a corresponding minimal important difference for negative likelihood ratios at 0.5. Likelihood ratios (whether positive or negative) falling between these thresholds were judged to indicate no meaningful change in the probability of disease.

### 3.4.1 Quality assessment

Individual studies were quality assessed using the QUADAS-2 tool, which contains four domains: patient selection, index test, reference standard, and flow and timing. Each individual study was classified as being either at low, moderate or high risk of bias based on that assessment.

### 3.4.2 Methods for combining diagnostic test accuracy evidence

Meta-analysis of diagnostic test accuracy data was conducted with reference to the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (Deeks et al. 2010).

Where applicable, diagnostic syntheses were stratified by:

- Presenting symptomatology (features shared by all participants in the study, but not all people who could be considered for a diagnosis in clinical practice).
- The reference standard used for true diagnosis.

Where five or more studies were available for all included strata, a bivariate model was fitted using the `mada` package in R v3.4.1, which accounts for the correlations between positive and negative likelihood ratios, and between sensitivities and specificities. This model requires five parameters to be fitted and is therefore not appropriate when only a small number of studies are available (Reitsma et al. 2005). Where sufficient data were not available (2-4 studies), separate independent pooling was performed for positive likelihood ratios, negative likelihood ratios, sensitivity and specificity, using Microsoft Excel. This approach is conservative as it is likely to somewhat underestimate test accuracy, due to

failing to account for the correlation and trade-off between sensitivity and specificity (see Deeks 2010), but these errors in the majority of cases will not be large enough to systematically affect decision making, and therefore an analysis was not marked down for risk of bias solely due to being based on a univariate model.

Random-effects models (der Simonian and Laird) were fitted for all syntheses, as recommended in the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (Deeks et al. 2010).

### 3.4.3 Modified GRADE for diagnostic test accuracy evidence

GRADE has not been developed for use with diagnostic studies; therefore a modified approach was applied using the GRADE framework. GRADE assessments were only undertaken for positive and negative likelihood ratios, as the MIDs used to assess imprecision were based on these outcomes, but results for sensitivity and specificity are also presented alongside those data.

Cross-sectional and cohort studies were initially rated as high-quality evidence if well conducted, and then downgraded according to the standard GRADE criteria (risk of bias, inconsistency, imprecision and indirectness) as detailed in Table 5 below.

**Table 5: Rationale for downgrading quality of evidence for diagnostic questions**

| GRADE criteria | Reasons for downgrading quality |
|---|---|
| Risk of bias | Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded.<br>Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level.<br>Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels.<br>Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies at high and low risk of bias. |
| Indirectness | Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded.<br>Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level.<br>Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels.<br>Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between direct and indirect studies. |
| Inconsistency | Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the test accuracy demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the $I^2$ statistic.<br>N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study.<br>Not serious: If the $I^2$ was less than 33.3%, the outcome was not downgraded.<br>Serious: If the $I^2$ was between 33.3% and 66.7%, the outcome was downgraded one level.<br>Very serious: If the $I^2$ was greater than 66.7%, the outcome was downgraded two levels. |

| GRADE criteria | Reasons for downgrading quality |
|---|---|
| | Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies with the smallest and largest effect sizes. |
| Imprecision | If the 95% confidence interval for a positive likelihood ratio spanned 2, the outcome was downgraded one level, as the data were deemed to be consistent with a meaningful increase in risk and no meaningful predictive value. Similarly, negative likelihood ratios that spanned 0.5 led to downgrading for serious imprecision. Any likelihood ratios that spanned both 0.5 and 2 were downgraded twice, as suffering from very serious imprecision.<br>Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios. |

## 3.5 Qualitative evidence

### 3.5.1 Quality assessment

Individual qualitative studies were quality assessed using the CASP qualitative checklist. Each individual study was classified as being either at low, moderate or high risk of bias based on that assessment.

### 3.5.2 Methods for combining qualitative evidence

Where multiple qualitative studies were identified for a single question, information from the studies was combined using a thematic synthesis. By examining the findings of each included study, descriptive themes were independently identified and coded. Once all of the included studies had been examined and coded, the resulting themes and sub-themes were evaluated to examine their relevance to the review question, the importance given to each theme, and the extent to which each theme recurred across the different studies. The qualitative synthesis then proceeded by using these 'descriptive themes' to develop 'analytical themes', which were interpreted by the reviewer in light of the overarching review questions.

### 3.5.3 CERQual for qualitative studies

CERQual was used to assess the confidence we have in the summary findings of each of the identified themes. Evidence from all qualitative study designs (interviews, focus groups etc.) was initially rated as high confidence and the confidence in the evidence for each theme was then downgraded from this initial point as detailed in Table 6 below.

**Table 6: Rationale for downgrading confidence in evidence for qualitative questions**

| CERQual criteria | Reasons for downgrading confidence |
|---|---|
| Methodological limitations | Not serious: If the theme was identified in studies at low risk of bias, the outcome was not downgraded<br>Serious: If the theme was identified only in studies at moderate or high risk of bias, the outcome was downgraded one level.<br>Very serious: If the theme was identified only in studies at high risk of bias, the outcome was downgraded two levels. |
| Relevance | High: If the theme was identified in highly relevant studies, the outcome was not downgraded<br>Moderate: If the theme was identified only in relevant and partially relevant studies, the outcome was downgraded one level. |

| CERQual criteria | Reasons for downgrading confidence |
|---|---|
| | Low: If the theme was identified only in partially relevant studies, the outcome was downgraded two levels. |
| Coherence | Coherence was addressed based on two factors:<br>• Between study – does the theme consistently emerge from all relevant studies<br>• Theoretical – does the theme provide a convincing theoretical explanation for the patterns found in the data<br>The outcome was downgraded once if there were concerns about one of these elements of coherence, and twice if there were concerns about both elements. |
| Adequacy of data | The outcome was downgraded if there was insufficient data to develop an understanding of the phenomenon of interest, either due to insufficient studies, participants or observations. |

## 3.6 Health economics

Literature reviews seeking to identify published cost–utility analyses of relevance to the issues under consideration were conducted for all questions. In each case, the search undertaken for the clinical review was modified, retaining population and intervention descriptors, but removing any study-design filter and adding a filter designed to identify relevant health economic analyses. In assessing studies for inclusion, population, intervention and comparator, criteria were always identical to those used in the parallel clinical search; only cost–utility analyses were included. Economic evidence profiles, including critical appraisal according to the Guidelines manual, were completed for included studies.

Economic studies identified through a systematic search of the literature are appraised using a methodology checklist designed for economic evaluations (NICE guidelines manual; 2014). This checklist is not intended to judge the quality of a study per se, but to determine whether an existing economic evaluation is useful to inform the decision-making of the committee for a specific topic within the guideline.

There are 2 parts of the appraisal process. The first step is to assess applicability (that is, the relevance of the study to the specific guideline topic and the NICE reference case); evaluations are categorised according to the criteria in Table 7.

**Table 7: Applicability criteria**

| Level | Explanation |
|---|---|
| Directly applicable | The study meets all applicability criteria, or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness |
| Partially applicable | The study fails to meet one or more applicability criteria, and this could change the conclusions about cost effectiveness |
| Not applicable | The study fails to meet one or more applicability criteria, and this is likely to change the conclusions about cost effectiveness. These studies are excluded from further consideration |

In the second step, only those studies deemed directly or partially applicable are further assessed for limitations (that is, methodological quality); see categorisation criteria in Table 8.

**Table 8: Methodological criteria**

| Level | Explanation |
|---|---|
| Minor limitations | Meets all quality criteria, or fails to meet one or more quality criteria but this is unlikely to change the conclusions about cost effectiveness |
| Potentially serious limitations | Fails to meet one or more quality criteria and this could change the conclusions about cost effectiveness |
| Very serious limitations | Fails to meet one or more quality criteria and this is highly likely to change the conclusions about cost effectiveness. Such studies should usually be excluded from further consideration |

Where relevant, a summary of the main findings from the systematic search, review and appraisal of economic evidence is presented in an economic evidence profile alongside the clinical evidence.

# 4 Summary of recommendations

## 4.1 Recommendations summary

Initial assessment in non-specialist settings

1. At the initial assessment take a history (including cognitive, behavioural and psychological symptoms, and the impact symptoms have on their daily life):
    - from the person with suspected dementia **and**
    - if possible, from someone who knows the person well (such as a family member).
2. If dementia is still suspected after initial assessment:
    - conduct a physical examination **and**
    - undertake appropriate blood and urine tests to exclude reversible causes of cognitive decline **and**
    - use cognitive testing.
3. When using cognitive testing, use a validated brief structured cognitive instrument such as:
    - the 10-point cognitive screener (10-CS)
    - the 6-item cognitive impairment test (6CIT)
    - the 6-item screener
    - the Memory Impairment Screen (MIS)
    - the Mini-Cog
    - Test Your Memory (TYM).
4. Do not rule out dementia solely because the person has a normal score on a cognitive instrument.
5. When taking a history from someone who knows the person with suspected dementia, consider supplementing this with a structured instrument such as the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) or the Functional Activities Questionnaire (FAQ)
6. Refer the person to a specialist dementia diagnostic service (such as a memory clinic or community old age psychiatry service) if:
    - reversible causes of cognitive decline (including delirium, depression, sensory impairment [such as sight or hearing loss] or cognitive impairment from medicines associated with increased anticholinergic burden) have been investigated **and**
    - dementia is still suspected.
7. If the person has suspected rapidly-progressive dementia, refer them to a neurological service with access to tests (including cerebrospinal fluid examination) for Creutzfeldt-Jakob disease and similar conditions.
8. For more guidance on assessing for dementia in people with learning disabilities, see the NICE guideline on mental health problems in people with learning disabilities.

Dementia diagnosis in specialist settings

9. Diagnose a dementia subtype (if possible) if initial specialist assessment (including an appropriate neurological examination and cognitive testing) confirms cognitive decline and reversible causes have been ruled out.
10. If Alzheimer's disease is suspected, include a test of verbal episodic memory in the assessment.
11. Consider neuropsychological testing if it is unclear:
    - whether or not the person has cognitive impairment **or**
    - whether or not their cognitive impairment is caused by dementia **or**
    - what the correct subtype diagnosis is.
12. Use validated criteria to guide clinical judgement when diagnosing dementia subtypes, such as:
    - International consensus criteria for dementia with Lewy bodies
    - International FTD criteria for frontotemporal dementia (primary non-fluent aphasia and semantic dementia)
    - International Frontotemporal Dementia Consortium criteria for behavioural variant frontotemporal dementia
    - NINDS-AIREN criteria (National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences) for vascular dementia
    - NIA criteria (National Institute on Aging) for Alzheimer's disease
    - Movement disorders Society criteria for Parkinson's disease dementia
    - International criteria for Creutzfeldt-Jakob disease.
13. Offer structural imaging to rule out reversible causes of cognitive decline and to assist with subtype diagnosis, unless dementia is well established and the subtype diagnosis is clear.
14. Only consider further diagnostic tests (recommendations 15-28) if:
    - it would help to diagnose a dementia subtype **and**
    - knowing more about the dementia subtype would change management.

Further tests for Alzheimer's disease

15. If the diagnosis is uncertain (see recommendation 14) and Alzheimer's disease is suspected, consider either:
    - FDG-PET (fluorodeoxyglucose−positron emission tomography−CT), or perfusion SPECT (single-photon emission CT) if FDG-PET is unavailable.

    **or**

    - examining cerebrospinal fluid for:
    - either total tau or total tau and phosphorylated-tau 181 **and**
    - either amyloid beta 1–42 or amyloid beta 1–42 and amyloid beta 1–40

If a diagnosis cannot be made after one of these tests, consider using the other one.

16. Be aware that the older a person is, more likely they are to get a false positive with cerebrospinal fluid examination.
17. Do not rule out Alzheimer's disease based solely on the results of CT or MRI scans.
18. Do not use Apolipoprotein E genotyping or electroencephalography to diagnose Alzheimer's disease.
19. Be aware that young-onset Alzheimer's disease has a genetic cause in some people.

Further tests for dementia with Lewy bodies

20. If the diagnosis is uncertain (see recommendation 14) and dementia with Lewy bodies is suspected, use $^{123}$I-FP-CIT SPECT.
21. If $^{123}$I-FP-CIT SPECT is unavailable, consider $^{123}$I-MIBG cardiac scintigraphy.
22. Do not rule out dementia with Lewy bodies based solely on normal results on $^{123}$I-FP-CIT SPECT or $^{123}$I-MIBG cardiac scintigraphy.

Further tests for frontotemporal dementia

23. If the diagnosis is uncertain (see recommendation 14) and frontotemporal dementia is suspected, use either:
    - FDG-PET **or**
    - perfusion SPECT.
24. Do not rule out frontotemporal dementia based solely on the results of structural, perfusion or metabolic imaging tests.
25. Be aware that frontotemporal dementia has a genetic cause in some people.

Further tests for vascular dementia

26. If the dementia subtype is uncertain (see recommendation 14) and vascular dementia is suspected, use MRI. If MRI is unavailable or contraindicated, use CT.
27. Do not diagnose vascular dementia based solely on vascular lesion burden.
28. Be aware that young-onset vascular dementia has a genetic cause in some people.

Telling the difference between delirium and dementia in people without a diagnosis of either

29. For people who are in hospital and have cognitive impairment with an unknown cause, consider using one of the following to find out whether they have delirium or delirium superimposed on dementia, compared with dementia alone:
    - the long confusion assessment method (CAM)
    - the Observational Scale of Level of Arousal (OSLA).
30. Do not use standardised instruments (including cognitive instruments) alone to distinguish delirium from delirium superimposed on dementia.
31. If it is not possible to tell whether a person has delirium, dementia, or delirium superimposed on dementia, treat for delirium first. For guidance on treating delirium, see treating delirium in the NICE guideline on delirium.

32. Only conduct case finding for suspected dementia as part of a clinical trial that also provides an intervention to people diagnosed with dementia.

Information provision

33. Provide people living with dementia and their family members or carers (as appropriate) with information that is relevant to their circumstances and the stage of their condition.

34. Be aware of the obligation to provide accessible information as detailed in the NHS Accessible Information Standard. For more guidance on providing information and discussing people's preferences with them, see the NICE guideline on patient experience in adult NHS services and people's experience in adult social care services.

35. At diagnosis, offer the person and their family members or carers (as appropriate) oral and written information that explains:

    - what their dementia subtype is and the changes to expect as the condition progresses
    - which healthcare professionals and social care teams will be involved in their care and how to contact them
    - if appropriate, how dementia affects driving, and that they need to tell the Driver and Vehicle Licensing Agency (DVLA) and their car insurer about their dementia diagnosis
    - their legal rights and responsibilities
    - their right to reasonable adjustments (in line with the Equality Act 2010) if they are working or looking for work
    - how the following groups can help and how to contact them:
    - local support groups, online forums and national charities
    - financial and legal advice services
    - advocacy services.

36. If it has not been documented earlier, ask the person at diagnosis:

    - for their consent for services to share information
    - which people they would like services to share information with (for example family members or carers)
    - what information they would like services to share.

Document these decisions in the person's records.

37. After diagnosis, direct people and their family members or carers (as appropriate) to relevant services for information and support (see recommendations 47 and 48 on care coordination).

38. For people who do not want follow-up appointments and who are not using other services, ask if they would like to be contacted again at a specified future date.

39. Ensure that people living with dementia and their carers know how to get more information and who from if their needs change.

40. Tell people living with dementia (at all stages of the condition) about research studies they could participate in.

Advance care planning

41. Offer early and ongoing opportunities for people living with dementia and people involved in their care (see recommendation 36) to discuss:

- the benefits of planning ahead
- lasting power of attorney (for health and welfare decisions and property and financial affairs decisions)
- an advance statement about their wishes, preferences, beliefs and values regarding their future care
- advance decisions to refuse treatment
- their preferences for place of care and place of death.

Explain that they will be given chances to review and change any advance statements and decisions they have made.

42. At each care review, offer people the chance to review and change any advance statements and decisions they have made.

Involving people in decision-making

43. Encourage and enable people living with dementia to give their own views and opinions about their care.
44. If needed, use additional or modified ways of communicating (for example visual aids or simplified text).

Staff training

45. Ensure that all health and social care staff are aware of:
    - The extent of their responsibility to protect confidentiality under data protection legislation **and**
    - any rights that family members, carers and others have to information about the person's care (see recommendation 48 on information sharing between different care settings).
46. Health and social care professionals advising people living with dementia (including professionals involved in diagnosis) should be trained in starting and holding difficult and emotionally challenging conversations.

Care coordination

47. Provide people living with dementia with a single named health or social care professional who is responsible for coordinating their care.
48. Named professionals should:
    - arrange an initial assessment of the person's needs, which should be face to face if possible.
    - provide information about available services and how to access them.
    - involve the person's family members or carers (as appropriate) in support and decision-making.
    - give special consideration to the views of people who do not have capacity to make decisions about their care, in line with the principles of the Mental Capacity Act 2005
    - ensure that people are aware of their rights to and the availability of local advocacy services, and if appropriate to the immediate situation an independent mental capacity advocate
    - develop a care and support plan, and:
        - agree and review it with the involvement of the person, their family members or carers (as appropriate) and relevant professionals

- specify in the plan when and how often it will be reviewed
- evaluate and record progress towards the objectives at each review
- ensure it covers the management of any comorbidities
- provide a copy of the plan to the person and their family members or carers (as appropriate).

49. When developing care and support plans and advance care and support plans, request consent to transfer these to different care settings as needed.
50. Service providers should ensure that information (such as care and support plans and advance care and support plans) can be easily transferred between different care settings (for example home, inpatient, community and residential care).
51. Staff delivering care and support should maximise continuity and consistency of care. Ensure that relevant information is shared and recorded in the person's care and support plan.
52. Service providers should design services to be accessible to as many people living with dementia as possible, including:
    - people who do not have a carer or whose carer cannot support them on their own
    - people who do not have access to affordable transport, or find transport difficult to use
    - people who have responsibilities (such as work, children or being a carer themselves)
    - people with learning disabilities, sensory impairment (such as sight or hearing loss) or physical disabilities
    - people who may be less likely to access health and social care services, such as people from black, Asian and minority ethnic groups.
53. After a person is diagnosed with dementia, ensure they and their family members or carers (as appropriate) have access to a memory service or equivalent hospital- or primary-care-based multidisciplinary dementia service.
54. Memory services and equivalent hospital- and primary-care-based multidisciplinary dementia services should offer a choice of flexible access or prescheduled monitoring appointments.
55. When people living with dementia or their carers have a primary care appointment, assess for any emerging dementia-related needs and ask them if they need any more support.
56. Be aware of the increased risk of delirium in people living with dementia who are admitted to hospital. See the NICE guideline on delirium for interventions to prevent and treat delirium.
57. For guidance on managing transition between care settings for people living with dementia, see:
    - the NICE guideline on transition between inpatient hospital settings and community or care home settings for adults with social care needs

- the NICE guideline on transition between inpatient mental health settings and community or care home settings
- section 1.2 of the NICE guideline on medicines optimisation.

Follow the principles in these guidelines for transitions between other settings (for example from home to a care home or respite care).

58. Review the person's needs and wishes (including any care and support plans and advance care and support plans) after every transition.

59. Do not offer the following specifically to slow the progress of Alzheimer's disease, except as part of a randomised controlled trial:

- diabetes medicines
- hypertension medicines
- statins
- non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin.

60. The three acetylcholinesterase (AChE) inhibitors donepezil, galantamine and rivastigmine as monotherapies are recommended as options for managing mild to moderate Alzheimer's disease under all of the conditions specified in 62 and 63.

61. Memantine monotherapy is recommended as an option for managing Alzheimer's disease for people with:

- moderate Alzheimer's disease who are intolerant of or have a contraindication to AChE inhibitors **or**
- severe Alzheimer's disease.

Treatment should be under the conditions specified in recommendation 6.

62. Treatment should be under the following conditions:

- For people who are not taking an AChE inhibitor or memantine, prescribers should only start treatment with these on the advice of a clinician who has the necessary knowledge and skills. This could include:
  - secondary care medical specialists such as psychiatrists, geriatricians and neurologists
  - other healthcare professionals (such as GPs, nurse consultants and advanced nurse practitioners), if they have specialist expertise in diagnosing and treating Alzheimer's disease.
- Once a decision has been made to start cholinesterase inhibitors or memantine, the first prescription may be made in primary care.
- Ensure that local arrangements for prescribing, supply and treatment review follow the NICE guideline on medicines optimisation.

63. If prescribing an AChE inhibitor (donepezil, galantamine or rivastigmine), treatment should normally be started with the drug with the lowest acquisition cost (taking into account required daily dose and the price per dose once shared care has started). However, an alternative AChE inhibitor could be prescribed if it is considered appropriate when taking into account adverse event profile, expectations about adherence, medical comorbidity, possibility of drug interactions and dosing profiles.

64. When using assessment scales to determine the severity of Alzheimer's disease, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect the results and make any adjustments they consider appropriate. Healthcare professionals should also be mindful of the need to secure equality of access to treatment for patients from different ethnic groups, in particular those from different cultural backgrounds.

65. When assessing the severity of Alzheimer's disease and the need for treatment, healthcare professionals should not rely solely on cognition scores in circumstances in which it would be inappropriate to do so. These include:

    - if the cognition score is not, or is not by itself, a clinically appropriate tool for assessing the severity of that patient's dementia because of the patient's learning difficulties or other disabilities (for example, sensory impairments), linguistic or other communication difficulties or level of education or
    - if it is not possible to apply the tool in a language in which the patient is sufficiently fluent for it to be appropriate for assessing the severity of dementia or
    - if there are other similar reasons why using a cognition score, or the score alone, would be inappropriate for assessing the severity of dementia.

In such cases healthcare professionals should determine the need for initiation or continuation of treatment by using another appropriate method of assessment.

66. For guidance on managing medicines (including covert administration), see the NICE guidelines on managing medicines for adults receiving social care in the community and managing medicines in care homes.

67. Do not stop AChE inhibitors in people with Alzheimer’s disease because of disease severity alone.

68. For people with an established diagnosis of Alzheimer’s disease who are already taking an AChE inhibitor:

    - consider memantine in addition to an AChE inhibitor if they have moderate disease
    - offer memantine in addition to an AChE inhibitor if they have severe disease.

69. For people with an established diagnosis of Alzheimer’s disease who are already taking an AChE inhibitor, primary care prescribers may start treatment with memantine (see recommendation 68) without taking advice from a specialist clinician.

70. Offer donepezil or rivastigmine to people with mild to moderate dementia with Lewy bodies.

71. Only consider galantamine for people with mild to moderate dementia with Lewy bodies if donepezil and rivastigmine are not tolerated.

72. Consider donepezil or rivastigmine for people with severe dementia with Lewy bodies.

73. Consider memantine for people with dementia with Lewy bodies if AChE inhibitors are not tolerated or are contraindicated.

74. For guidance on pharmacological management of Parkinson's disease dementia, see Parkinson's disease dementia in the NICE guideline on Parkinson's disease.
75. Only consider AChE inhibitors or memantine to people with vascular dementia if they have suspected comorbid Alzheimer's disease, Parkinson's disease dementia or dementia with Lewy bodies.
76. Do not offer AChE inhibitors or memantine for people with frontotemporal dementia.
77. Do not offer AChE inhibitors or memantine to people with cognitive impairment caused by multiple sclerosis.
78. Be aware that some commonly prescribed medicines are associated with increased anticholinergic burden, and therefore cognitive impairment.
79. Consider minimising the use of medicines associated with increased anticholinergic burden, and if possible look for alternatives:
    - when assessing whether to refer a person with suspected dementia for diagnosis
    - during medication reviews with people living with dementia.
80. Be aware that there are validated tools for assessing anticholinergic burden (for example, the Anticholinergic Cognitive Burden Scale), but there is insufficient evidence to recommend one over the others.
81. For guidance on carrying out medication reviews, see medication review in the NICE guideline on medicines optimisation.
82. Offer a range of activities to promote wellbeing that are tailored to the person's individual preferences.
83. Offer group cognitive stimulation therapy to people living with mild to moderate dementia.
84. Consider group reminiscence therapy for people living with mild to moderate dementia.
85. Consider cognitive rehabilitation or occupational therapy to support functional ability in people living with mild to moderate dementia.
86. Do not offer acupuncture to treat dementia.
87. Do not offer ginseng, vitamin E supplements or herbal formulations to treat dementia.
88. Do not offer cognitive training to treat mild to moderate Alzheimer's disease.
89. Do not offer interpersonal therapy to treat the cognitive symptoms of mild to moderate Alzheimer's disease.
90. Do not offer non-invasive brain stimulation (including transcranial magnetic stimulation) to treat mild to moderate Alzheimer's disease, except as part of a randomised controlled trial.

Agitation, aggression, distress and psychosis

91. Before starting non-pharmacological or pharmacological treatment for distress in people living with dementia, conduct a structured assessment to:
    - explore possible reasons for the person's distress **and**
    - check for and address clinical or environmental causes (for example pain, delirium or inappropriate care).

92. As initial and ongoing management, offer psychosocial and environmental interventions to reduce distress in people living with dementia.

93. Only offer antipsychotics, for people living with dementia who are either:

    - at risk of harming themselves or others **or**
    - experiencing agitation, hallucinations or delusions that are causing them severe distress.

94. Be aware that for people with dementia with Lewy bodies or Parkinson's disease dementia, antipsychotics can worsen the motor features of the condition, and in some cases cause severe antipsychotic sensitivity reactions. For more guidance, see the advice on managing delusions and hallucinations in the NICE guideline on Parkinson's disease. Be aware that interventions may need to be modified for people living with dementia

95. Before starting antipsychotics, discuss the benefits and harms with the person and their family members or carers (as appropriate). Consider using a decision aid to support this discussion.

96. When using antipsychotics:

    - use the lowest effective dose and use them for the shortest possible time
    - reassess the person at least every 6 weeks, to check whether they still need medication.

97. Stop treatment with antipsychotics:

    - the person is not getting a clear ongoing benefit from taking them **and**
    - after discussion with the person taking them and their family members or carers (as appropriate).

98. Ensure that people living with dementia can continue to access psychosocial and environmental interventions for distress while they are taking antipsychotics and after they have stopped taking them.

99. For people living with dementia who experience agitation or aggression, offer personalised activities to promote engagement, pleasure and interest.

100. Do not offer valproate to manage agitation or aggression in people living with dementia, unless it is indicated for another condition.

Depression and anxiety

101. For people living with mild to moderate dementia who have mild to moderate depression and/or anxiety, consider psychological treatments.

102. Do not routinely offer antidepressants to manage mild to moderate depression in people living with mild to moderate dementia, unless they are indicated for a pre-existing severe mental health condition.

Sleep problems

103. Do not offer melatonin to manage insomnia in people living with Alzheimer's disease.

104. For people living with dementia who have sleep problems, consider a personalised multicomponent sleep management approach that includes sleep hygiene education, exposure to daylight, exercise and personalised activities.

Parkinson's disease dementia and dementia with Lewy bodies

105. For guidance on the management of Parkinson's disease symptoms in people with Parkinson's disease dementia and Dementia with Lewy bodies, see the NICE guideline on Parkinson's disease. Be aware these interventions may need to be modified for people living with dementia.
106. Offer carers of people living with dementia a psychoeducation and skills training intervention that includes:
    - education about dementia, its symptoms and the changes to expect as the condition progresses
    - developing personalised strategies and building carer skills
    - training to help them provide care, including how to understand and respond to changes in behaviour
    - training to help them adapt their communication styles to improve interactions with the person living with dementia
    - advice on how to look after their own physical and mental health, and their emotional and spiritual wellbeing
    - advice on planning enjoyable and meaningful activities to do with the person they care for
    - information about relevant services (including support services and psychological therapies for carers) and how to access them
    - advice on planning for the future.
107. Ensure that the support offered to carers is:
    - tailored to their needs and preferences and to what they want it to achieve (for example, providing information on carer's employment rights for carers who work or want to work)
    - designed to help them support people living with dementia
    - available at a location they can get to easily
    - provided in a format suitable for them (for example individual or group sessions, or online training and support)
    - available from diagnosis and as needed after this.
108. Be aware that carer interventions are likely to be most effective when provided as group sessions.
109. Advise carers about their right to the following and how to get them:
    - a formal assessment of their own needs (known as a 'Carer's Assessment'), including their physical and mental health
    - an assessment of their need for short breaks and other respite care .
110. Be aware that carers of people living with dementia are at an increased risk of depression. For guidance on identifying and managing depression, see the NICE guideline on depression in adults.
111. Care and support providers should provide all staff with training in person-centred and outcome-focused care for people living with dementia, which should include:
    - understanding the signs and symptoms of dementia, and the changes to expect as the condition progresses
    - understanding the person as an individual, and their life story

- respecting the person's individual identity, sexuality and culture
- understanding the needs of the person and their family members or carers
- the principles of the Mental Capacity Act 2005 and the Care Act 2014.

112. Care providers should provide additional face-to-face training and mentoring to staff who deliver care and support to people living with dementia. This should include:
    - understanding the organisation's model of dementia care and how it provides care
    - how to monitor and respond to the lived experience of people living with dementia, including adapting communication styles
    - initial training on understanding, reacting to and helping people living with dementia who experience agitation, aggression, pain, or other behaviours indicating distress
    - follow-up sessions where staff can receive additional feedback and discuss particular situations
    - advice on interventions that reduce the need for antipsychotics and allow doses to be safely reduced
    - promoting freedom of movement and minimising the use of restraint
    - if relevant to staff, the specific needs of younger people living with dementia and people who are working or looking for work.
113. Consider giving carers and/or family members the opportunity to attend and take part in staff dementia training sessions.
114. Consider training staff to provide multi-sensory stimulation for people with moderate to severe dementia and communication difficulties.

Pain

115. Consider using a structured observational pain assessment tool:
    - alongside self-reported pain and standard clinical assessment for people living with moderate to severe dementia
    - alongside standard clinical assessment for people living with dementia who are unable to self-report pain.
116. For people living with dementia who are in pain, consider using a stepwise treatment protocol that balances pain management and potential adverse events.
117. Repeat pain assessments for people living with dementia:
    - who seem to be in pain
    - who show signs of behavioural changes that may be caused by pain
    - after any pain management intervention.

Falls

118. For guidance on managing the risk of falling for people living with dementia (in community and inpatient settings), see the NICE guideline on falls in older people. When using this guideline:

- take account of the additional support people living with dementia may need to participate effectively
- be aware that multifactorial falls interventions may not be suitable for a person living with severe dementia.

119. Ensure that people living with dementia have equivalent access to diagnosis, treatment and care services for comorbidities to people who do not have dementia. For more guidance on assessing and managing multimorbidity, see the NICE guidelines on multimorbidity and older people with social care needs and multiple long-term conditions.
120. For more guidance on providing support for older adults with learning disabilities, see the NICE guideline on care and support of people growing older with learning disabilities.
121. For guidance on setting HbA1c targets for people living with severe dementia who have type 2 diabetes, see recommendation 1.6.9 in the NICE guideline on type 2 diabetes in adults.
122. For guidance on pharmacological treatment of overactive bladder, see the NICE technology appraisal on mirabegron for treating symptoms of overactive bladder.
123. For guidance on treating faecal incontinence, see recommendations 1.7.2 and 1.7.8 in the NICE guideline on faecal incontinence.

Sensory impairment (such as sight loss, hearing loss, or both)

124. For guidance on hearing assessments for people with suspected or diagnosed dementia, see adults with suspected dementia in the NICE guideline on hearing loss
125. Encourage people living with dementia to have eye tests every 2 years. Consider referring people who cannot organise appointments themselves.
126. From diagnosis, offer people living with dementia flexible, needs-based palliative care that takes into account how unpredictable dementia progression can be.
127. For people living with dementia who are approaching the end of life, use an anticipatory healthcare planning process (see recommendation 41 on advance care planning). Involve the person and their family members or carers (as appropriate) as far as possible, and use the principles of best-interest decision-making if the person cannot make decisions about their own care.
128. For standards and measures on palliative care, see the NICE quality standard on end of life care for adults.
129. For guidance on care for people in the last days of life, see the NICE guideline on care of dying adults.
130. For guidance, on best interests decision-making, see the NICE guideline on decision-making and mental capacity.
131. Encourage and support people living with dementia to eat and drink, taking into account their nutritional needs.
132. Consider involving a speech and language therapist if there are concerns about a person's safety when eating and drinking.
133. Do not routinely use enteral feeding in people living with severe dementia, unless indicated for a potentially reversible comorbidity.

134. When thinking about admission to hospital for a person living with severe dementia, carry out an assessment that balances their current medical needs with the additional harms they may face in hospital, for example:
    - disorientation
    - a longer length of stay
    - increased mortality
    - increased morbidity on discharge
    - delirium
    - the effects of being in an impersonal or institutional environment.
135. When thinking about admission to hospital for a person living with dementia, take into account:
    - any advance care and support plans
    - the value of keeping them in a familiar environment.
136. Consider using a structured tool to assess the likes and dislikes, routines and personal history of a person living with dementia..

## 4.2 Research recommendations summary

1. Does amyloid PET imaging provide additional diagnostic value, and is it cost effective, for the diagnosis of Alzheimer's disease and other dementias when compared with standard diagnostic procedures and other imaging or biomarker tests?
2. In people with treated delirium who no longer meet the DSM-5 criteria for delirium, but who have persistent cognitive deficits, when is the most appropriate time to carry out an assessment for dementia?
3. What is the effectiveness of structured case finding (including a subsequent intervention for people identified as having dementia) in people at high risk of dementia, following up both people identified as having or not having dementia?
4. What is the effectiveness and cost effectiveness of high-intensity case management compared with usual care on quality of life (for the person living with dementia and for their carer) and the timing of entry to long-term care?
5. What are the most effective methods of care planning for people in residential care settings?
6. What are the most effective methods of care planning for people who do not have regular contact with an informal carer?
7. What is the effectiveness of structured transfer plans to ease the transition between different environments for people living with dementia and their carers?
8. What is the effectiveness of combination treatment with a cholinesterase inhibitor and memantine for people with dementia with Lewy bodies if treatment with a cholinesterase inhibitor alone is not effective or no longer effective?
9. Does actively reducing anticholinergic burden in people living with dementia improve cognitive outcomes compared with usual care?
10. What are the most effective psychosocial interventions for improving cognition, independence, activities of daily living and wellbeing in people living with dementia?
11. What is the effectiveness of unstructured community activities on wellbeing for people living with dementia?
12. What is the effectiveness and cost-effectiveness of self-management training for people living with dementia and their carers?
13. What are the most effective psychological treatments for managing depression or anxiety in people living with dementia at each stage of the condition?
14. What is the effectiveness and cost-effectiveness of dextromethorphan-quinidine for managing agitation in people living with dementia?
15. What is the effectiveness and cost-effectiveness of choline alphoscerate for managing apathy in people living with dementia?
16. What is the effectiveness of pharmacological treatments for sleep problems in people who have not responded to non-pharmacological management?

17. What is the effectiveness and cost-effectiveness of group-based cognitive behavioural therapy for carers of people living with dementia who are at high risk of developing depression?
18. What is the cost effectiveness of using a dementia-specific addition to the Care Certificate for community staff, including dementia-specific elements on managing anxiety, communication, nutritional status and personal care?
19. What is the effectiveness of training acute hospital staff in managing behaviours that challenge in people living with dementia on improving outcomes for people and their carers?
20. What are the most clinically and cost-effective non-pharmacological interventions for helping the long-term recovery of people with delirium superimposed on dementia?
21. What is the effectiveness of interventions to improve faecal and urinary continence in people living with dementia?
22. What is the impact on cognition, quality of life and mortality of withdrawing treatments for the primary and secondary prevention of vascular outcomes in people with severe dementia?
23. What is the impact on cognition, quality of life and mortality of withdrawing intensive treatments for diabetic control in people with severe dementia?
24. What are the optimal management strategies for people with enduring mental health problems (including schizophrenia) who subsequently develop dementia?
25. What are the most effective models of general and specialist palliative care support to meet the needs of people with advanced dementia?
26. What are the most effective interventions to support staff to recognise advanced dementia and develop appropriate escalation/end of life plans to facilitate care to remain at home?

# 5 Dementia diagnosis

In order to access treatment and support, people living with dementia must first receive a diagnosis. Diagnosis rates in England have been rising in recent years, but current estimates suggest that 32% of people living with dementia still do not have a formal diagnosis (http://digital.nhs.uk/catalogue/PUB30051). The provision of a dementia diagnosis should be timely, personalised and accurate; certain interventions are only suitable for specific dementia subtypes, and the implications of a diagnosis e.g. in terms of prognosis or the risk of having a genetic form of the condition, can vary significantly between subtypes. It is also vitally important to rule out reversible causes of cognitive decline, and to distinguish dementia from delirium.

Population screening for dementia is outside the scope of this guideline and is not currently recommended in the UK (https://www.gov.uk/government/news/recommendation-against-national-dementia-screening). The starting point for dementia assessment is usually the presentation of an individual to a primary care practitioner with memory or other cognitive concerns. An important part of an initial assessment is an informant history, for which structured tools are available. A range of brief instruments exist to help practitioners determine the severity of cognitive decline; however cut-off scores that define "normal" versus "impaired" cognition might not be valid in individual patients, for a variety of cultural, educational and other reasons. Common dementia mimics in primary care include depression, side-effects of medicines and sensory impairments such as hearing loss. In specialist settings, there is an increasing range of diagnostic tests to determine the underlying cause of the dementia syndrome, with a recent focus on biomarker-based tests for the presence of Alzheimer's disease neuropathology. However, in many cases the diagnosis of dementia and the identification of the subtype can be made on the basis of clinical assessment, with brain imaging used simply to exclude mimics such as brain tumours or hydrocephalus.

Expert consensus suggests that in the UK approximately 62% of dementia is due to Alzheimer's disease, 17% to cerebrovascular disease, 10% to mixed aetiologies, 4% to dementia with Lewy bodies, 2% to Parkinson's disease dementia, 2% to frontotemporal dementia and 3% to other causes (Dementia UK 2nd edition). However, among people aged under 65 these proportions are different, with a lower contribution from vascular dementia and a greater relative incidence of frontotemporal dementia (Mercy 2008), while in people aged 90 and over, mixed dementias are a larger proportion of the total (James 2012).

People living with dementia are at significantly increased risk of delirium, and many older people with delirium have undiagnosed dementia. However, some older people with delirium make an excellent cognitive recovery. Therefore distinguishing delirium alone, dementia alone and delirium superimposed on dementia is important, particularly in acute hospital settings where it might influence decisions about medicines, discharge planning and follow-up arrangements.

## 5.1 Dementia diagnosis

**Review questions**

- What are the most effective methods of primary assessment to decide whether a person with suspected dementia should be referred to a dementia service?
- What are the most effective methods of diagnosing dementia and dementia subtypes in specialist dementia diagnostic services?

### 5.1.1 Introduction

This review has two aims:

- To identify which tools and tests are the most accurate for determining which people suspected of having dementia are likely to have dementia and should be referred to a specialist dementia diagnostic service for further investigation.
- To identify which tools and tests are the most accurate for making/confirming a diagnosis of dementia and for diagnosing dementia subtypes in specialist dementia diagnostic services.

The review focused on identifying studies that fulfilled the conditions specified in Table 9 and Table 10. For full details of the review protocols, see Appendix C.

**Table 9: Review summary: primary care assessment**

| | |
|---|---|
| **Population** | People (aged 40 years and over) with a suspected diagnosis of dementia |
| **Diagnostic variables** | Potential diagnostic variables include:<br>• Clinical history<br>• Clinical cognitive assessment (e.g. Mini-Mental State Examination, (MMSE))<br>• Neuropsychological testing<br>• Physical examination<br>• Medication review |
| **Outcomes** | • Incidence of accurately identified dementia<br>• Diagnostic accuracy measures<br>• Resource use and costs |

**Table 10: Review summary: specialist care diagnosis**

| | |
|---|---|
| **Population** | People (aged 40 years and over) with a suspected diagnosis of dementia |
| **Diagnostic variables** | Potential diagnostic variables include:<br>• Specified diagnostic criteria<br>• Structural imaging (Magnetic Resonance Imaging (MRI) and Computed Tomography (CT))<br>• Single-photon emission computed tomography (SPECT) (e.g. blood flow, dopamine)<br>• Positron emission tomography (PET) (e.g. fluorodeoxyglucose (FDG), amyloid)<br>• Cerebrospinal fluid (CSF) examination<br>• Electroencephalography (EEG)<br>• Brain biopsy<br>• Neuropsychological assessment<br>• Functional assessment |

| | |
|---|---|
| | • Genetic testing<br>• Neurological examination |
| **Outcomes** | • Incidence of accurately identified dementia<br>• Diagnostic accuracy measures<br>• Resource use and costs |

### 5.1.2 Evidence review

The search strategy for this review question consisted of several separate searches for different types of evidence that were combined to identify relevant primary dementia DTA (diagnostic test accuracy) studies. They are summarised in Appendix D.

Systematic searches were initially carried out for dementia DTA systematic reviews (SR) and these reviews were mined for primary studies that matched our review protocol. The search identified 3,698 references; and 114 of these matched the review protocol at title and abstract level. These were screened as full texts and if they still met the review protocol then the individual studies included in the SRs were also screened as title and abstracts to identify potentially relevant primary DTA studies. If multiple SRs were found on the same topic then the latest and highest quality reviews were prioritised as sources of papers. In addition, we also identified 2 Cochrane reviews that were published after the search date, and 2 at the time unpublished Cochrane reviews were shared with us by the Cochrane Dementia and Cognitive Improvement Group (Seitz 2017; Chan, 2017).

Of the 118 SR references screened at full text, 37 SRs were included as sources of primary DTA studies, plus 1 primary study which was incidentally identified through this search. Systematic reviews were excluded if they did not match the review protocol, or if no primary studies were extracted from them.

Using the 37 included SRs, we identified 156 primary studies that matched our review protocol at title and abstract screening. This made 157 primary studies in total, including the additional primary study identified directly by the SR search. These potentially relevant references were ordered for full text review and 68 were included for data extraction based on their relevance to the review protocol and the presentation of data in a format suitable for analysis. We excluded studies that were not written in English or that were conference abstracts, unless data for these studies could be obtained from a Cochrane review (see analyses section below for details).

A second systematic literature search was carried out to cover the time between the searches in the SRs and the current date. In the cases where SRs were not identified for specific tests, settings (e.g. primary care) or dementia subtypes that were considered important by the committee, additional searches were carried out to bridge the evidence gaps. This search identified 8,047 references, of which 216 were screened as full texts and 56 additional primary studies were identified.

Seventy-six references from the original dementia guideline were also screened, with 7 being included for full text screening. Several of these references were already included from other searches and were excluded as duplicates on this basis (leaving 5 references to be included). One additional reference was identified from an included primary study and another 2 were provided by committee members.

In total, there were 380 primary studies included after title and abstract screening, with 124 meeting the review protocol as full texts and being used for data extraction. Prior to consultation, the searches were re-run and an additional 1,524 references were identified. Following de-duplication to remove references already identified by the previous search,

1,048 remained for title and abstract screening. Of these references, 10 were screened at full text with 5 additional studies added to the evidence review.

The included primary studies are summarised below (Section 1.4) with full references in Appendix I. The excluded studies are listed, with reasons for their exclusion, in Appendix F. Evidence tables for the included studies are presented in Appendix P.

#### 5.1.2.1 Analyses

Calculations of diagnostic test sensitivity, specificity, positive likelihood and negative likelihood ratios (LR) were carried out and are presented in the GRADE tables in Appendix G. The 2x2 tables for each individual test and the results of the QUADAS-2 assessments of risk of bias and applicability are presented in the evidence tables in Appendix P.

Data extraction and analysis was carried out using standard methods (see section 3.4) with the additional following decision rules:

1. The SRs were used as a source of primary studies rather than data itself with the exception of the Cochrane reviews stated above. If the Cochrane review used unpublished data or data from studies published in languages other than English the data was extracted from the review directly as the Cochrane reviews were judged to be of sufficiently high quality to be a reliable source of evidence. If the data was available in the original paper in an accessible format then this was used instead of the Cochrane review.
2. Studies involving screening people with Parkinson's disease (PD) or stroke for dementia were excluded unless the participants had suspected dementia at baseline, as specified in the review protocols above.
3. Studies that used the index test as part of the recruitment criteria for the trial were excluded or that index was excluded if several index tests were reported.
4. Risk of bias and indirectness/applicability was assessed at the study and index test level so that a single study could be at low risk of bias for one index test and high for another depending on how the tests were carried out and analysed.
5. Studies that were judged to be at high risk of reporting bias due to the selective reporting of only the most accurate test outcomes were excluded from the analysis or, if they contained multiple groups of tests such as neuroimaging, biomarkers and neuropsychological tests, the group of tests at risk of reporting bias was excluded but the other tests were analysed.
6. Study settings were divided into primary care, secondary care (general) and secondary care (specialist dementia) to facilitate meta-analysis.
7. The reference standard was divided into 3 categories of increasing accuracy: clinical criteria alone (applied by researchers without clinician involvement), clinician diagnosis (whether using or not using clinical criteria) and neuropathology (including autopsy and/or biopsy results).
8. Studies using unspecified criteria for diagnosis were downgraded for risk of bias as we were unable to determine whether the reference standard could accurately diagnose dementia/subtype of dementia, but studies that did not use criteria (but just listed tests) were not downgraded automatically.
9. For the evaluation of clinical criteria, autopsy was considered the most accurate reference standard, although delayed diagnosis until further symptoms emerge and diagnosis is confirmed was considered to be acceptable.
10. Diagnostic comparisons examining subgroups of participants (e.g. Alzheimer's disease (AD) versus frontotemporal dementia, [FTD]) that excluded > 10% study population were downgraded for risk of bias. This applied to analyses performed by the study authors and by NICE.
11. Data for all possible diagnostic comparisons was extracted and grouped into the following categories to simplify analysis:

a. Dementia versus no dementia. Subjective memory complaints (SMC), mild cognitive impairment (MCI) and other non-dementia diagnoses are included in no dementia group.
b. Dementia subtype versus non-dementia subtype (e.g. AD versus non-AD). Non-dementia subtype group includes SMC, MCI, other dementias and other non-dementia diagnoses.
c. Dementia subtype versus non-dementia subtype plus unclassifiable cases (as b. but with unclassifiable cases included with the non-dementia grouping for comparison)
d. Dementia subtype versus no dementia (e.g. AD versus no dementia). The no dementia subtype group includes SMC, MCI and other non-dementia diagnoses. Other dementias are excluded.
e. Dementia subtype versus other dementias (e.g. AD versus other dementias). The other dementias group includes all other dementias diagnosed, and excludes SMC, MCI and other non-dementia diagnoses.
f. Dementia subtype versus another specific dementia subtype (e.g. AD versus FTD). All other groups are excluded.

12. If study participants were diagnosed with MCI they were analysed with the no dementia group where possible. If this was not possible based on the original data provided or they were excluded from analysis by the study authors then this fact was noted and the study downgraded if >10% study population was excluded.
13. Where possible during analysis probable Alzheimer's disease was separated from possible Alzheimer's disease for comparison against non-Alzheimer's disease groups.
14. Where possible, all relevant subgroup comparisons were carried out by the NICE reviewers. In the case of most tests AD versus FTD is equivalent to FTD versus AD so both options are not presented. However, with certain neuroimaging tests a particular pattern may indicate a particular dementia subtype and thus AD versus FTD (using the AD image pattern as an index test positive outcome) is not equivalent to FTD versus AD (using the FTD image pattern as an index test positive outcome) and both comparisons are included.
15. Single-photon emission computed tomography (SPECT) studies were analysed in subgroups based on their camera types (single- or multiple-headed) as the two were not considered to be comparable by the committee. If the camera type could not be determined from information in the study then a cut-off date of 2010 was applied and all studies with data collected after this date were deemed to have used a multiple-headed camera.
16. SPECT studies using single-headed cameras were not downgraded for indirectness even though modern SPECT machines use multiple-headed cameras.
17. Pittsburgh compound B (PIB) positron emission tomography (PET) studies were excluded based on committee comments as this ligand is only used in research.
18. If a study presented multiple test cut-offs then the standard/index paper cut-offs were extracted along with the best 3 based on sensitivity and specificity. If the standard cut-off was not used/unclear then the 4 best results were extracted.
19. Studies using optimised cut-offs or presenting multiple cut-offs were downgraded for a risk of bias for that test and cut-off, although any standard cut-off result was not downgraded.
20. If the researchers carrying out the reference test were not blind/blinding was unclear to the results of the index test then this was considered a high risk of bias only if the index test was likely to influence the reference test outcome. For example, knowledge of Mini-Mental State Examination (MMSE) results was considered unlikely to alter a final reference diagnosis of dementia, but knowledge of the results of a SPECT test could influence the diagnosis of dementia and dementia subtype.
21. A study was not downgraded for risk of bias and applicability/indirectness for the same issue (e.g. exclusions at recruitment stage). In these instances the study was downgraded for risk of bias only.

22. If the index test was part of the reference test this was not considered an additional source of bias. The study was not downgraded for risk of bias as long as the researchers were blind to the other test result.
23. Studies examining diagnostic criteria were only included if they referred to the current version of the criteria (to the best of our knowledge) at the time of the evidence review. Although a new version of the DLB criteria was published during this review (McKeith et al 2017), Skogseth et al 2017 was included in the evidence review as it related to the current criteria at the start of the review.

#### 5.1.2.2 Description of included studies

A total of 124 cohort studies containing relevant diagnostic tests (Table 11, Table 12 and Table 13), and clinical criteria (Table 14) were identified. These included: cognitive screening and neuropsychological tests; informant questionnaires; clinician rating scales (Table 11); structural and other imaging tests (Table 12); and biomarker and other related tests (Table 13). Some studies looked at multiple tests using the same cohort of people and many studies presented data for several test cut-offs.

**Table 11: Summary of cognitive screening and neuropsychological tests, informant questionnaires and clinician rating scales**

| Test | Number of Studies | References (short title) | Diagnosis category |
|---|---|---|---|
| **Cognitive screening tests** | | | |
| 10- point Cognitive screener (10-CS) | 1 | Apolinario 2015 | Dementia versus no dementia |
| Total weighted, free and total recall scores of the 5-word test | 1 | Mormont 2012 | Dementia versus no dementia<br>AD versus no dementia |
| 6-item screener | 1 | Callahan 2002 | Dementia versus no dementia |
| 6-item Cognitive Impairment Test (6-CIT) | 1 | Abdel-Aziz 2015 | Dementia versus no dementia |
| 7 minute screen | 1 | Skjerve 2008 | Dementia versus no dementia |
| Abbreviated Mental Test (AMT) | 1 | Flicker 1997 | Dementia versus no dementia |
| Addenbrooke's Cognitive Exam (ACE) | 2 | Larner 2007<br>Mathuranath 2000 | Dementia versus no dementia |
| Addenbrooke's Cognitive Exam-Revised (ACE-R) | 3 | Bastide 2012<br>Hancock 2011<br>Terpening 2011 | Dementia versus no dementia |
| Addenbrooke's Cognitive Exam-III (ACE- III) | 1 | Jubb 2015 | Dementia versus no dementia |
| Clock drawing test (CDT) | 4 | Beinhoff 2005<br>Berger 2008<br>Milian 2012<br>Sager 2006 | Dementia versus no dementia |
| HIV Dementia Scale (HDS) | 1 | Skinner 2009 | HAND (HIV-associated neurocognitive disorder) versus other neurological disorders in HIV+ people |
| International HIV Dementia Scale (IHDS) | 1 | Skinner 2009 | HAND (HIV-associated neurocognitive disorder) versus |

| Test | Number of Studies | References (short title) | Diagnosis category |
|---|---|---|---|
| | | | other neurological disorders in HIV+ people |
| Letter sorting Test (LST) | 1 | Beinhoff 2005 | Dementia versus no dementia |
| Memory impairment screen (MIS) | 2 | Carnero-Pardo 2011<br>Beinhoff 2005 | Dementia versus no dementia |
| Mini-Addenbrooke's Cognitive Exam (Mini-ACE) | 1 | Larner 2017 | Dementia versus no dementia |
| Mini-Cog | 2 | Carnero-Pardo 2013<br>Milian 2012 | Dementia versus no dementia |
| Mini-Mental State Examination (MMSE) | 18 | Abdel-Aziz 2015<br>Bastide 2012<br>Callahan 2002<br>Carnero-Pardo 2013<br>Cruz-Orduna 2012<br>Flicker 1997<br>Goncalves 2011<br>Hancock 2011<br>Knaefelc 2003,<br>Kukull 1994<br>Larner 2015<br>Mathuranath 2000<br>Milian 2012<br>Mormont 2012<br>Nielsen 2013<br>Postel-Vinay 2014<br>Sager 2006<br>Yeung 2014 | Dementia versus no dementia<br>AD versus no dementia |
| Montreal Cognitive Assessment (MoCA) | 4 | Chen 2011<br>Goldstein 2014<br>Larner 2017<br>Yeung 2014 | Dementia versus no dementia |
| Orientation (OR) | 1 | Beinhoff 2005 | Dementia versus no dementia |
| Phototest | 1 | Carnero-Pardo 2011 | Dementia versus no dementia |
| Rowland Universal Dementia Assessment Scale (RUDAS) | 2 | Goncalves 2011<br>Nielsen 2013 | Dementia versus no dementia |
| Short Portable Mental Status Questionnaire (SPMSQ) | 1 | Malhotra 2013 | Dementia versus no dementia |
| Syndrom Kurztest | 1 | Skjerve 2008 | Dementia versus no dementia |
| Test your Memory (TYM) | 2 | Hancock 2011<br>Postel-Vinay 2014 | Dementia versus no dementia |
| **Clinician rating scales** | | | |
| Alzheimer's disease (AD) scale | 1 | Gustafson 2010 | AD versus other dementias |
| Frontotemporal dementia (FTD) scale | 1 | Gustafson 2010 | FTD versus other dementias |
| Hachinski Ischemic Scale (HIS) | 2 | Bachetta 2007<br>Gustafson 2010 | VaD versus AD and mixed dementias (AD with VaD)<br>VaD versus other dementias |

| Test | Number of Studies | References (short title) | Diagnosis category |
|---|---|---|---|
| Lewy Body Composite Risk score (LBCR) | 1 | Galvin 2015 | DLB versus AD<br>DLB versus other dementias |
| **Neurological tests** | | | |
| Applause sign | 1 | Bonello 2016 | Dementia versus no dementia |
| Palmo Mental Reflex | 1 | Streit 2015 | Dementia versus no dementia |
| Olfactory Test | 1 | Christensen 2017 | AD versus non-AD |
| Short smell test | 1 | Streit 2015 | Dementia versus no dementia |
| Neuropsychological tests | | | |
| Boston Naming Test (BNT) | 1 | Beinhoff 2005 | Dementia versus no dementia |
| Brief Neuropsychological Test Battery | 1 | Coutinho 2013 | Dementia versus no dementia |
| Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery | 1 | Hentschel 2005 | Dementia versus no dementia |
| Verbal Category Fluency (Animal Naming) | 1 | Beinhoff 2005, Sager 2006 | Dementia versus no dementia |
| Questionnaires completed by informant | | | |
| AD8 | 1 | Larner 2015 | Dementia versus no dementia |
| Functional Activities Questionnaire (FAQ) | 1 | Cruz-Orduna 2012 | Dementia versus no dementia |
| Informant Questionnaire on Cognitive Decline (IQCODE, 16 and 26 item versions) | 7 | Cruz-Orduna 2012<br>Flicker 1997<br>Hancock 2009<br>Garcia 2002<br>Goncalves 2003<br>Knaefelc 2003<br>Sikkes 2010 | Dementia versus no dementia<br>AD versus no dementia |
| The diagnosis category refers to the comparisons where data was available. This does not necessarily mean that the test would be used for this diagnosis in practice. Abbreviations for dementia subtypes are as follows: Alzheimer's disease (AD), Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL), corticobasal degeneration (CBD), Creutzfeldt-Jakob disease (CJD), dementia with Lewy bodies (DLB), frontotemporal dementia (FTD), HIV-associated neurocognitive disorder (HAND), Parkinson's disease dementia (PDD), primary progressive aphasia (PPA), vascular dementia (VaD). | | | |

**Table 12: Imaging and other related tests.**

| Test | Number of Studies | References (short title) | Diagnosis category |
|---|---|---|---|
| 123 I-metaiodobenzylguanidine cardiac scintigraphy (123I MIBG cardiac scintigraphy) | 7 | Estorch 2008<br>Hanyu 2006<br>Manabe 2017<br>Treglia 2012<br>Sakamoto 2014<br>Sakamoto 2017<br>Slaets 2015 | DLB versus non-DLB<br>DLB versus other dementias<br>PDD and DLB versus other dementias |
| Dopaminergic iodine−123−radiolabelled 2β− carbomethoxy−3β−(4−i | 6 | Kemp 2011<br>Treglia 2012<br>O'Brien 2009 | DLB versus non-DLB<br>DLB versus other dementias |

| Test | Number of Studies | References (short title) | Diagnosis category |
|---|---|---|---|
| odophenyl)−N−(3−fluoropropyl) nortropane single-photon emission computed tomography (123I-FP-CIT SPECT) | | Walker 2007<br>Walker 2009<br>Thomas 2017 | |
| N-isopropyl-p-[123I]iodoamphetamine single-photon emission computed tomography (123I-IMP SPECT) | 1 | Sakamoto 2014 | DLB versus non-DLB |
| 123I-IMP SPECT and 123I-MIBG cardiac scintigraphy | 1 | Sakamoto 2014 | DLB versus non-DLB |
| Technetium-99m ethyl cysteinate dimer single-photon emission computed tomography (99mTc ECD SPECT) | 2 | Kaneta 2016<br>Tripathi 2010 | AD versus non-AD<br>FTD versus non-FTD |
| Technetium-99m hexamethylpropyleneamine oxime single-photon emission computed tomography (99mTc HMPAO SPECT) | 11 | Bergman 1997<br>Boutoleu- Bretonniere 2012<br>Dobert 2005<br>Holman 1992<br>Launes 1991<br>Masterman 1997<br>McMurdo 1994<br>Read 1995<br>Rollin- Sillaire 2012<br>Talbot 1998<br>Velakoulis 1007 | Dementia versus no dementia<br>AD versus non-AD dementia plus unclassifiable<br>AD versus non-AD<br>AD versus other dementias<br>AD versus FTD<br>AD versus VaD<br>FTD versus non- FTD dementia plus unclassifiable<br>FTD versus non- FTD<br>FTD versus AD<br>FTD versus other dementias<br>FTD versus VaD<br>VaD versus AD<br>VaD versus FTD<br>VaD versus non-VaD |
| Computed tomography (CT) | 1 | O'Brien 2000 | Dementia versus no dementia<br>AD versus other dementias<br>AD versus VaD |
| Electroencephalogram (EEG) | 3 | Engedal 2015<br>Tagliapietra 2013<br>Tschampa 2005 | AD versus non-AD<br>CJD versus non-CJD<br>DLB versus non-DLB |
| (2−[18F]fluoro−2−deoxy−d−glucose positron emission tomography (FDG-PET) | 11 | Arslan 2015<br>Dobert 2005<br>Frisoni 2009<br>Hoffman 2000<br>Jagust 2007<br>Kerklaan 2014<br>Motara 2017<br>Ossenkoppele 2013<br>Panegyres 2009<br>Silverman 2001<br>Yakushev 2010 | Dementia versus no dementia<br>AD versus no dementia<br>AD versus non-AD<br>AD versus other dementias<br>AD versus DLB<br>AD versus FTD<br>DLB versus non-DLB<br>DLB versus other dementias<br>bv-FTD versus non-bv-FTD<br>bv-FTD/fd+ versus non-bv-FTD/fd+<br>FTD versus DLB |

| Test | Number of Studies | References (short title) | Diagnosis category |
|---|---|---|---|
| | | | FTD versus non- FTD<br>FTD versus other dementias |
| [18F]flutemetamol PET | 1 | Zwan 2017 | AD versus non-AD |
| MRI (Magnetic resonance imaging) | 10 | Boutoleau-Bretonniere 2012<br>Frisoni 2009<br>Hentschel 2005<br>Koikkalainen 2016<br>Schroter 2000<br>Suppa 2015<br>Tagliapietra 2013<br>Tschampa 2005<br>Van Everbroeck 2004<br>Vijverberg 2016b | Dementia versus no dementia<br>AD versus non-AD dementia plus unclassifiable<br>AD versus non-AD<br>AD versus other dementias<br>AD versus DLB<br>AD versus FTD<br>AD versus VaD<br>bv-FTD versus non-bv-FTD<br>CJD versus non-CJD<br>DLB versus AD<br>DLB versus FTD<br>DLB versus non-DLB<br>DLB versus other dementias<br>DLB versus VaD<br>FTD versus AD<br>FTD versus DLB<br>FTD versus non- FTD dementia plus unclassifiable<br>FTD versus other dementias<br>FTD versus VaD<br>VaD versus AD<br>VaD versus DLB<br>VaD versus FTD<br>VaD versus non-VaD plus unclassifiable<br>VaD versus non-VaD<br>VaD versus other dementias |
| The diagnosis category refers to the comparisons where data was available. This does not necessarily mean that the test would be used for this diagnosis in practice. Abbreviations for dementia subtypes are as follows: Alzheimer's disease (AD), Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL), corticobasal degeneration (CBD), Creutzfeldt-Jakob disease (CJD), dementia with Lewy bodies (DLB), frontotemporal dementia (FTD), behavioural variant FTD (bv-FTD), behavioural variant FTD with functional decline (bv-FTD/fd+), HIV-associated neurocognitive disorder (HAND), Parkinson's disease dementia (PDD), primary progressive aphasia (PPA), vascular dementia (VaD). | | | |

**Table 13: Biomarkers and other related tests.**

| Test | Number of Studies | References (short title) | Diagnosis category |
|---|---|---|---|
| 14-3-3 (ELISA, immunoblotting, Automated Capillary Western Assay ) | 17 | Bahl 2008<br>Beudry 1998<br>Burkhard 2001<br>Chohan 2011<br>Cuadro-Corrales 2006<br>Fourier 2017<br>Foutz 2017 | CJD versus non-CJD |

| Test | Number of Studies | References (short title) | Diagnosis category |
|---|---|---|---|
| | | Hamlin 2012<br>Kenney 2000<br>Lattanzio 2017<br>Lemstra 2000<br>Leitao 2016<br>Rohan 2015<br>Tagliapetra 2013<br>Tschampa 2005<br>Van Everbroeck 2003<br>Zerr 2000 | |
| 14-3-3 and Amyloid Beta | 1 | Van Everbroeck 2003 | CJD versus non-CJD |
| 14-3-3 and S100B | 1 | Chohan 2010 | CJD versus non-CJD |
| 14-3-3 and total tau | 1 | Chohan 2010 | CJD versus non-CJD |
| 14-3-3, total tau and S100B | 1 | Chohan 2010 | CJD versus non-CJD |
| Amyloid Beta 1-42 | 11 | Andreasen 2001<br>Boutoleu-Bretonniere 2012<br>Brandt 2008<br>Duits 2014<br>Dumurgier 2015<br>Gabelle 2012<br>Ibach 2006<br>Knapskgog 2016<br>Maddalena 2003<br>Mulder 2010<br>Van Everbroeck 2003 | AD versus other dementias<br>AD versus no dementia<br>AD versus non-AD<br>AD versus other dementias<br>AD versus DLB<br>AD versus VaD<br>CJD versus non-CJD |
| Amyloid Beta 1-42 and Total Tau | 3 | Frisoni 2009<br>Toledo 2012<br>Van Everbroeck 2003 | Dementia versus no dementia<br>AD versus non-AD<br>AD versus FTD<br>CJD versus not CJD |
| Amyloid Beta 1-42/phosphorylated tau 181 (p-tau 181) | 1 | Gabelle 2012 | AD versus non-AD |
| Amyloid Beta 1-42/Total tau | 1 | Gabelle 2012 | AD versus non-AD |
| Amyloid Beta 1-42/1-40 | | Dumurgier 2015 | AD versus non-AD |
| Apolipoprotein E (Apo E) | 1 | Mayeux 1998 | AD versus non-AD |
| Combinations of Amyloid Beta 1-42, total tau and p-tau 181 abnormal | 5 | Boutoleau-Bretonniere 2012<br>Duits 2014<br>Brandt 2008<br>Dumurgier 2015<br>Jahn 2011 | AD versus non-AD |
| Mass Spectrometry | 1 | Jahn 2011 | AD versus non-AD |
| Neuron-specific enolase | 2 | Bahl 2008, | CJD versus non-CJD |

| Test | Number of Studies | References (short title) | Diagnosis category |
|---|---|---|---|
| | | Beudry 1998 | |
| Polymerase chain Reaction (PCR) for T. pallidum genes polA, Tpp47, and bmp | 1 | Dumaresq 2013 | Neurosyphilis versus not neurosyphilis |
| Real-time quaking-induced prion conversion (RT-QuIC) | 2 | Foutz 2017<br>Lattanzio 2017 | CJD versus non-CJD |
| S100B | 3 | Chohan 2010<br>Beudry 1998<br>Coulthart 2011 | CJD versus non-CJD |
| Skin biopsy | 1 | Ampuero 2009 | CADASIL versus CADASIL-like syndromes |
| Phosphorylated -tau 181 (p-tau 181) | 10 | Boutoleau-Bretonniere 2012<br>Brandt 2008<br>Duits 2014<br>Dumurgier 2015<br>Gabelle 2012<br>Knapskgog 2010<br>Ibach 2006<br>Maddalena 2003<br>Mulder 2010<br>Toledo 2012 | AD versus no dementia<br>AD versus non-AD<br>AD versus other dementias<br>AD versus FTD |
| p-tau 181/Amyloid Beta 1-42 | 3 | Maddalena 2003<br>Duits 2014<br>Dumurgier 2015 | AD versus no dementia<br>AD versus non-AD |
| p-tau 181/ total tau | 1 | Bahl 2008, Leitao 2016 | CJD versus non-CJD |
| p-tau 181 and Amyloid Beta 1-42/1-40 | 1 | Dumurgier 2015 | AD versus non-AD |
| Total tau | 18 | Bahl 2008<br>Brandt 2008<br>Chohan 2010<br>Coulthart 2011<br>Duits 2014<br>Dumurgier 2015<br>Foutz 2017<br>Gabelle 2012<br>Hamlin 2010<br>Knapskgog 2016,<br>Lattanzio 2017<br>Leitao 2016<br>Mulder 2010<br>Rohan 2015<br>Tagliapietra 2013<br>Van Everbroeck 2003 and 2004<br>Yakushev 2010 | AD versus no dementia<br>CJD versus non-CJD |
| Total Tau and S100B | 1 | Chohan 2010 | CJD versus non-CJD |

| Test | Number of Studies | References (short title) | Diagnosis category |
|---|---|---|---|
| Total tau/Amyloid Beta 1-42 | 1 | Duits 2014 | AD versus non-AD |
| Urinary AD7c-NTP | 1 | Goodman 2007 | AD versus non-AD |
| The diagnosis category refers to the comparisons where data was available. This does not necessarily mean that the test would be used for this diagnosis in practice. Abbreviations for dementia subtypes are as follows: Alzheimer's disease (AD), Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL), corticobasal degeneration (CBD), Creutzfeldt-Jakob disease (CJD), dementia with Lewy bodies (DLB), frontotemporal dementia (FTD), HIV-associated neurocognitive disorder (HAND), Parkinson's disease dementia (PDD), primary progressive aphasia (PPA), vascular dementia (VaD). | | | |

**Table 14: Clinical criteria**

| Test | Number of Studies | References (short title) | Diagnosis category |
|---|---|---|---|
| ADDTC | 1 | Gold 2002 | VaD versus AD and mixed dementia (AD with VaD) |
| CBD consensus criteria | 1 | Alexander 2014 | CBD versus non-CBD |
| DLB consensus criteria | 1 | Skogseth 2017 | DLB versus other dementias |
| FTD consensus criteria | 1 | Mendez 2007 | FTD versus non-FTD |
| Criteria for CJD:<br>WHO CJD criteria<br>French and European criteria for CJD<br>Master's criteria for CJD | 3 | Brandel 2000<br>Heath 2010<br>Zerr 2009 | CJD versus non-CJD |
| FTDC criteria for bv-FTD | 1 | Harris 2013 | bv-FTD versus non-bv-FTD |
| Movement disorders criteria for PDD | 1 | Kiesman 2013 | PDD versus non-PDD |
| NINDS-AIREN | 2 | Gold 2002<br>Bachetta 2002 | VaD versus AD and mixed dementias (AD with VaD) |
| The diagnosis category refers to the comparisons where data was available. This does not necessarily mean that the criteria would be used for this diagnosis in practice. Abbreviations for dementia subtypes are as follows: Alzheimer's disease (AD), Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL), corticobasal degeneration (CBD), Creutzfeldt-Jakob disease (CJD), dementia with Lewy bodies (DLB), frontotemporal dementia (FTD), behavioural variant FTD (bv-FTD), HIV-associated neurocognitive disorder (HAND), Parkinson's disease dementia (PDD), primary progressive aphasia (PPA), vascular dementia (VaD). | | | |

### 5.1.3 Health economic evidence

A systematic literature search was undertaken to identify existing cost–utility analyses (CUAs) evaluating diagnostic strategies that have been published since the literature reviews in CG42. In total, 2,347 articles were returned, of which 6 were selected as potentially relevant and retrieved for full text review. Additionally, 1 study included in CG42 was deemed to be suitable for full text review against the current protocol. Of the 7 potentially suitable publications, 6 were judged to be at least partially applicable to the review question and were therefore included.

Details of the literature search are provided in Appendix D.

#### 5.1.3.1 GP-administered diagnostics

**Tong et al. (2016)** conducted a model-based cost–utility analysis, comparing 3 diagnostic strategies to diagnose Alzheimer's disease, that could be administered by a GP (MMSE, 6CIT, and GPCOG) compared with unassisted GP judgement. The patient-level model simulated a population aged over 65 years, who are assessed for cognitive impairment by their GPs in England. The primary outcome measures were costs and QALYs over the patient's life time horizon. For further details, please see the economic evidence profile in Appendix M.

The authors' base case adopted a NHS and PPS perspective that is consistent with the NICE reference case. An additional analysis was presented that took broader perspective that valued private social care costs (both in the community and patients who were in full-time care) along with informal care costs.

Diagnostic outcomes for each strategy were estimated from a range of observational literature. Transition probabilities were calculated from five pooled studies from the Ward et al. (2012) systematic review. Sources for resource-use and cost inputs included a NICE QOF cost impact statement and estimates in an Alzheimer's Society report. The price year used was 2016 and costs were expressed in UK pounds. Health utilities for patients were calculated using an equation reported in a cost–utility analysis of drug treatment for Alzheimer's disease; carer utility was not included in any analysis.

Results presented by the authors allowed the incremental analysis of each treatment option and the removal of the cost of the MMSE diagnostic test (in case a version of the MMSE diagnostic test is available as a royalty free for use by general practitioners in the UK).

Base-case results (Table 15) suggested that compared with GPCOP, both GP unassisted judgement and the MMSE are dominated strategies. The 6CIT produces more QALYs than GPCOG, but also costs an additional £186.54 per patient, resulting in an ICER of £58,689/QALY.

**Table 15: Cost–utility results from Tong et al. (2016) adjusted to show per-patient incremental cost and effects, along with the removal of the cost of MMSE licence fee**

| | Absolute | | Incremental | | |
|---|---|---|---|---|---|
| Diagnostic test | Cost | Effect | Cost | Effect | ICER |
| GPCOG | NR | NR | | | |
| GP unassisted judgement | NR | NR | £185.85 | -0.0003 QALYs | Dominated |
| MMSE | NR | NR | £119.13 | -0.0002 QALYs | Dominated |
| 6CIT | NR | NR | £186.54 | 0.0032 QALYs | £58,689 /QALY |

In probabilistic sensitivity analysis compared with, the probability of the GPCOG being the best option at a threshold of £30,000 per QALY was 75%. The probability of the 6CIT being the best option became higher than the GPCOG's when the threshold was above £50,000 per QALY.

The authors concluded that using any of the 3 cognitive screening tests was more cost-effective than the GP unassisted judgement. Among the 3 cognitive tests, the GPCOG was considered the most cost-effective option for the NHS given the referenced threshold of

£30,000 per QALY. The authors also noted that the results are sensitive to assumptions about the effectiveness of dementia medicines, and that the model results should be treated with caution.

**Wolfs et al. (2009)** conducted a cost–utility analysis alongside a 12-month cluster RCT (n=230) in the Netherlands. 33 GP practices were randomised to a multidisciplinary diagnostic strategy (DOC-PG) whilst 37 were randomised to usual care. The primary outcome measures were QALYs and costs over 12 months (no extrapolation was undertaken beyond the RCT results). For further details, please see the economic evidence profile in Appendix M.

DOC-PG consisted of a home visit by the community mental health team (CMHT) and 2 visits to university hospital departments of geriatric medicine and geriatric psychiatry. In addition, a CT scan and various blood tests were performed. The results were then discussed at a weekly interdisciplinary meeting in which a definitive diagnosis was made and a treatment plan was formulated. Usual care meant that either the diagnosis was made by the GP, or the GP referred the patient to one of the existing separate regional services.

The authors' base case adopted a broad societal perspective, including an attempt to value informal care costs; however, disaggregated results are reported, enabling the recalculation of results with a perspective that is consistent with the NICE reference case (that is, NHS and PSS costs only). Information about resources used was derived from a case report form provided by the carer. All cost prices were adopted from a standard Dutch source. The price year used was 2005 and costs were expressed in Euros.

Utilities were measured only for the patient, using the EQ-5D, administered by the patients' proxy at baseline, 6 and 12 months, with weights derived from a UK population.

Base-case results with costs not consistent with the NICE reference case removed (Table 16) suggest that DOC-GP is both more effective and more expensive than usual care, with an ICER of €11,510 per QALY gained.

**Table 16: Adjusted analysis from Wolfs et al. (2009), where costs not relevant to the NICE reference case were removed**

| | Absolute | | Incremental | | |
|---|---|---|---|---|---|
| Treatment | Cost | Effect (95% CI) | Cost | Effect (95% CI) | ICER |
| Usual care | €26,171 | 0.452 QALYs (0.432 to 0.472) | – | – | – |
| DOC-PG | €26,758 | 0.503 QALYs (0.487 to 0.519) | €587 | 0.051 QALYs (−0.01 to 0.13) | €11,510 /QALY |

The authors' analysis, which included productivity loss and informal care in the costs, resulted in a smaller additional cost of €65 for DOC-GP compared with usual care, resulting in an ICER of €1,267 per additional QALY produced.

It is not possible to remove costs excluded from the NICE reference case from the authors' probabilistic analysis. The incremental costs in the bootstrap simulation ranged over a 95% confidence interval of −€7,435 to €6,750; the equivalent range for incremental effectiveness was from −0.01 to 0.13. The probability that the DOC-PG is cost effective was 72% when QALYs are valued at €45,000 each.

The authors concluded that an integrated approach to dementia diagnosis is not demonstrably more expensive and has a high probability of being more effective than usual care in terms of QALYs.

#### 5.1.3.2 Imaging diagnostics

**Biasttu et al. (2012)** conducted a model-based cost–utility analysis, comparing 3 diagnostic strategies (standard diagnosis, standard MRI, and MRI + contrastophore-linker-pharmacophore [MRI+CLP]) for a cohort of 70 year-olds consulting for the first time following mild cognitive impairment symptoms in a French context. The diagnostic target was early Alzheimer's disease, and where this was detected, the effects of a hypothetical treatment efficient in early Alzheimer's disease were tested. The primary outcome measures were costs and QALYs over 3 years. For further details, please see the economic evidence profile in Appendix M.

The authors' base case adopted a societal perspective, including several indirect costs. It was not possible to disaggregate these costs to conduct an analysis that is consistent with the NICE reference case (that is, NHS and PSS costs only). Information about accuracy of the diagnostic strategies was derived from a range of separate observational studies. Information about resource use and costs was derived from a published economic evaluation of drugs for Alzheimer's disease. The cost of MRI was obtained from the ''Classification Commune des Actes Médicaux'', a fixed-costs scale of medical procedures based on practitioners' fees, fixed costs for the medical procedures themselves, and fixed costs for operating the equipment. All prices were converted to the year 2009 and expressed in Euros.

The authors estimated population mean quality-of-life weights people without Alzheimer's disease and published utilities for people with Alzheimer's disease at each disease stage and care setting (institution or community).

In the primary analysis, standard diagnosis compared with standard MRI costs more and produced fewer QALYs and was therefore a dominated treatment strategy. The MRI+CLP treatment strategy compared with Standard MRI cost more but also produced additional QALYS, resulting in an ICER of €88,439/QALY.

The "Screen and treat analysis", which looked at targeted screening of individuals carrying the e4 allele of the apolipoprotein E gene (ApoE4), found that the Standard Diagnosis compared with Standard MRI costs more and produced fewer QALYs and was therefore a dominated treatment strategy. The MRI+CLP treatment strategy compared with Standard MRI cost more but also produced additional QALYS, resulting in an ICER of €641,326/QALY.

The mean costs, effects and ICERs are presented in Table 17.

**Table 17: Analysis from Biasttu et al. (2012)**

| | Absolute | | Incremental | | |
|---|---|---|---|---|---|
| **Strategy** | **Cost** | **Effect** | **Cost** | **Effect** | **ICER** |
| MRI | €36,161 | 1.7710 QALYs | – | – | – |
| Standard | €36,294 | 1.7663 QALYs | €133 | -0.00470 QALYs | Dominated |
| MRI+CLP | €36,313 | 1.7731 QALYs | €152 | 0.00210 QALYs | €88,439 /QALYs |

Standard diagnosis was dominated by standard MRI compared within all scenarios. MRI+CLP was found to produce a small increase in QALYs, but was also associated with additional costs, leading to an ICER compared with standard MRI of €88,439 per QALY gained.

In a scenario involving a hypothetical new treatment, which would decrease progression from mild to moderate stage AD, the ICER for MRI+CLP compared with standard MRI decreased, but only to €60,923/QALY.

In probabilistic sensitivity analyses, the probability of MRI+CLP being cost-effective compared with standard MRI remained lower than 4% when QALYs were valued at €200,000 each.

**Homberger et al. (2015)** conducted a decision-tree analysis, comparing Florbetapir-PET with standard clinical examination alone for the diagnosis of Alzheimer's disease. In the base case, the target population were 70-year-old patients with an MMSE score of 20, who were undergoing initial assessment for cognitive impairment in Spain. The primary outcome measures were costs and QALYs over a 10-year time horizon. The authors' base case adopted a Spanish societal perspective that is broadly consistent with the NHS and PPS perspective. For further details, please see the economic evidence profile in Appendix M.

Test characteristics for the comparators were derived from disparate sources, including a cohort study for Florbetapir-PET and a review of registry data. Healthcare costs included diagnostic testing costs, medicine costs, carer time and residence in a public nursing home. All costs were adjusted to 2013 and were expressed in Euros. Health utility scores were taken from observational sources.

In the base case (Table 18), Florbetapir-PET was associated with small additional costs and QALY gains, compared with standard examination, resulting in an ICER of €4,769 per QALY. In a scenario analysis, in which initial assessment was assumed to take place at an MMSE score of 22 compared with Florbetapir-PET produced a saving of €1,534 and produced an additional 0.019 QALYs, compared with standard examination, making it a dominant strategy.

**Table 18: Analysis from Homberger et al. (2015)**

| | Absolute | | Incremental | | |
|---|---|---|---|---|---|
| **Strategy** | **Cost** | **Effect** | **Cost** | **Effect** | **ICER** |
| Standard examination | €155,686 | 3.022 QALYs | | | |
| Florbetapir-PET | €155,722 | 3.030 QALYs | €36 | 0.008 QALYs | €4,769 /QALYs |

Over 82% of the PSA simulations showed Florbetapir-PET to be associated with an ICER of €30,000 per QALY or better. One-way sensitivity analysis showed that the model was most sensitive to the hazard ratio of institutionalisation per unit increase in MMSE.

The authors concluded that the addition for Florbetapir-PET to standard clinical examination could facilitate the diagnostic decision-making, thereby improving the treatment of patients under evaluation for cognitive impairment.

In **Hornberger et al. (2017)**, the same authors updated their analysis to assess Amyloid-β PET (Aβ-PET) imaging as an adjunct to standard diagnostic assessment with or without CSF testing for the diagnosis of Alzheimer's disease in France. The base case assumes an MMSE score of 22 at the time of evaluation and treatment initiation. The primary outcome measures were costs and QALYs over a 10-year time horizon.

Test characteristics for Aβ-PET and standard assessment were derived from separate studies. All costs were from French sources; resource use estimates were extracted from multiple sources, including government websites. Currency was standardised to 2016 Euros

(€). Both the base-case scenario and the alternative scenario included caregiver costs that were likely to be informal caregiver costs; the analyses presented here remove these costs where possible.

In the base case (Table 19), the addition of CSF to standard assessment alone made a negligible difference to costs and QALYs. Aβ-PET was associated with additional costs but also conferred greater benefits, with an ICER of 43,000/QALY.

**Table 19: Analysis from Hornberger et al. (2017).**

| | Absolute | | Incremental | | |
|---|---|---|---|---|---|
| **Strategy** | **Cost** | **Effect** | **Cost** | **Effect** | **ICER** |
| Standard assessment + CSF | €89,408 | 3.175 QALYs | | | |
| Standard assessment alone | €89,445 | 3.175 QALYs | €37 | 0.000 QALYs | Dominated |
| Standard assessment + Aβ-PET | €90,354 | 3.197 QALYs | €946 | 0.022 QALYs | €43,000/QALY |

The authors also conducted 2 additional scenario analyses, in which earlier testing and treatment initiation was assumed (at an MMSE score of 25) and additional diagnostic tests were simulated. Both scenarios suggested improved cost effectiveness for Aβ-PET; however, it is not possible to disaggregate costs that are inconsistent with the NICE reference case from these analyses.

Probabilistic sensitivity analysis, including costs that are inconsistent with the NICE reference case, suggested that there was a 95% probability that the ICER for Aβ-PET compared with standard assessment was €40,000 per QALY or better.

**McMahon et al. (2000)** conducted a model-based cost–utility analysis, comparing 4 diagnostic strategies (standard examination, visual SPECT, computed SPECT and contrast-enhanced MRI) for patients who present to an Alzheimer's disease centre in the United States. The model classified patients by disease severity and healthcare setting (community or nursing home). The primary outcome measures were costs and QALYs over an 18-month time horizon. For further details, please see the economic evidence profile in Appendix M.

The authors' base case included costs that are not consistent to the NICE reference case (patient time and self-funded travel costs). However, an additional analysis was conducted by the authors that excluded these.

The diagnostic accuracy of the tests, were derived from a single observational study, and the accuracy of standard examination was based on authors' assumption.

Resource use for the initial diagnostic work-up was based on published literature and assessment of resource use at Massachusetts General Hospital. Costs were mostly based on Medicare reimbursement rates. All costs were adjusted to the price year 1998 and were expressed in US dollars ($).

Quality of life weights for patients without Alzheimer's disease were based on a large general population cohort; utilities for people with Alzheimer's disease came from commonly cited sources. Carer utility was not included in any analysis.

In the base case analysis (Table 20), compared with standard examination, both visual and computed SPECT cost more money and produced fewer QALYs, and were therefore

considered dominated strategies. Compared with contrast-enhanced MRI produced a small QALY benefit, but the additional costs that were also associated with the approach led to an ICER of almost $500,000 per QALY gained.

**Table 20: Original analysis from McMahon et al. (2000).**

| | Absolute | | Incremental | | |
|---|---|---|---|---|---|
| **Strategy** | **Cost** | **Effect** | **Cost** | **Effect** | **ICER** |
| Standard examination | $54,762 | 0.9889 QALYs | | | |
| Visual SPECT | $55,362 | 0.9581 QALYs | $600 | -0.0308 QALYs | Dominated |
| Computed SPECT | $55,549 | 0.9888 QALYs | $787 | -0.0001 QALYs | Dominated |
| Contrast-enhanced MRI | $55,769 | 0.9910 QALYs | $1,007 | 0.0021 QALYs | $479,500 /QALY |

The sensitivity analysis conducted by the author, where patient time and travel costs (neither of which are relevant to the NICE reference case) were removed, shows a similar pattern to the authors' base case in that Visual SPECT and Computed SPECT both remained dominated treatment strategies, whilst contrast-enhanced MRI had an ICER of $328,830 per QALY.

The authors concluded that the base-case analysis suggest that it is not cost-effective to add functional imaging to the standard diagnostic work-up for Alzheimer disease.

The same authors produced an updated analysis (**McMahon et al., 2003)**, comparing standard examination, contrast-enhanced MRI, FDG PET and computed SPECT.
The authors' base case adopted a societal perspective, incorporating costs 'regardless of who incurred them'. This is likely to include items that are not consistent with the NICE reference case; however, details are not specified.

Diagnostic accuracy parameters were updated to use a wider range of observational data. No information about resource use was provided, and is therefore assumed to be the same as McMahon (2000). All costs were adjusted to the price year 1999 by using the medical component of the consumer price index and were expressed in US dollars ($). Health related quality-of-life weights were updated to Health Utilities Index Mark 3 (HUI3) values.

In the base case (Table 21), MRI was once again associated with an ICER in the order of £0.5m/QALY. Compared with MRI, both SPECT and PET were dominated.

**Table 21: Analysis from McMahon et al. (2003).**

| | Absolute | | Incremental | | |
|---|---|---|---|---|---|
| **Strategy** | **Cost** | **Effect** | **Cost** | **Effect** | **ICER** |
| Standard examination | $56,859 | 0.7092 QALYs | | | |
| Contrast-enhanced MRI | $57,877 | 0.7109 QALYs | $1,018 | 0.0017 QALYs | $598,824 /QALY |
| FDG PET | $58,590 | 0.7063 QALYs | $713 | -0.0046 QALYs | Dominated |
| Computed SPECT | $58,872 | 0.7093 QALYs | $995 | -0.0016 QALYs | Dominated |

The authors concluded that the results of this analysis suggest that a combined structural and functional examination, such as dynamic susceptibility weighted contrast-enhanced MR imaging, may be preferable to PET for the diagnosis of AD. With improvements in therapies or with negative consequences of inappropriate treatment, the incremental cost-effectiveness ratio of dynamic susceptibility weighted contrast-enhanced MR imaging becomes more favourable. Improved non-pharmacologic strategies for AD management could also make functional imaging more useful.

### 5.1.4 Evidence statements

The evidence statements in this review for diagnosing dementia are written with reference to the size of the likelihood ratios in the GRADE tables in appendix P, using the interpretation detailed in the methods section on diagnostic test accuracy (Table 4) for both point estimates and confidence intervals. Positive likelihood ratios, and their associated 95% confidence intervals, were used to determine which tests increase the probability of diagnosing dementia and negative likelihood ratios, and their associated 95% confidence intervals, were used to determine which tests decrease the probability of diagnosing dementia.

#### 5.1.4.1 Dementia versus no dementia

##### *5.1.4.1.1 Results which increase the probability of diagnosing dementia*

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **very large**:

- 10-CS (≤5) (low quality, 95% confidence interval ranged from large to very large)
- 6 item screener (≥4) (moderate quality, 95% confidence interval ranged from large to very large)
- 6 item screener (≥5) (moderate quality, 95% confidence interval ranged from very large to very large)
- 6 item screener (≥6) (moderate quality, 95% confidence interval ranged from very large to very large)
- ACE-III (<81) (low quality, 95% confidence interval ranged from moderate to very large)
- ACE-R (<74) (moderate quality, 95% confidence interval ranged from large to very large)
- CERAD battery positive (low quality, 95% confidence interval ranged from large to very large)
- CDT, Shulman scoring method (>2) (moderate quality, 95% confidence interval ranged from large to very large)
- LST (<1) (moderate quality, 95% confidence interval ranged from moderate to very large)
- Mini-Cog (Scanlan and Borson algorithm positive) (moderate quality, 95% confidence interval ranged from large to very large)
- OR (<7) (moderate quality, 95% confidence interval ranged from large to very large)
- Total Weighted Score of the 5 word Test (≤15) (low quality, 95% confidence interval ranged from moderate to very large)

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **large**:

- 10-CS (≤6) (low quality, 95% confidence interval ranged from moderate to large)
- 6 item screener (≥3) (moderate quality, 95% confidence interval ranged from large to very large)
- BNT (<13) (moderate quality, 95% confidence interval ranged from moderate to very large)

- Brief Neuropsychological Test Battery (high quality, 95% confidence interval ranged from moderate to very large)
- CDT, Shulman scoring method (>1) (moderate quality, 95% confidence interval ranged from moderate to large)
- Free recall score of the 5 word test (≤6) (low quality, 95% confidence interval ranged from moderate to very large)
- LST (<2) (moderate quality, 95% confidence interval ranged from moderate to very large)
- MMSE (<17) (moderate quality, 95% confidence interval ranged from large to very large)
- MMSE (<18 or <22 or <23 or <24) (very low to low quality, 95% confidence interval ranged from moderate to very large)
- MMSE (<19) (moderate quality, 95% confidence interval ranged from moderate to large)
- MoCA (<19) (very low quality, 95% confidence interval ranged from slight to very large)
- OR (<8) (moderate quality, 95% confidence interval ranged from moderate to very large)
- Phototest (<27) (high quality, 95% confidence interval ranged from moderate to very large)
- RUDAS (<21 or <22) (low to moderate quality, 95% confidence interval ranged from moderate to very large)
- TYM (≤30) (moderate quality, 95% confidence interval ranged from moderate to large)
- Total Recall Score of 5 word test (≤9) (low quality, 95% confidence interval ranged from moderate to very large)

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **moderate**:

- 10-CS (≤7) (very low quality, 95% confidence interval ranged from slight to moderate)
- 6 item screener (≥1) (low quality, 95% confidence interval ranged from slight to moderate)
- 6 item screener (≥1) (low quality, 95% confidence interval ranged from slight to moderate)
- 6 item screener (≥2) (moderate quality, 95% confidence interval ranged from moderate to large)
- 6 CIT (>9) (high quality, 95% confidence interval ranged from moderate to large)
- ACE (<75) (high quality, 95% confidence interval ranged from moderate to large)
- ACE (<88) (very low quality, 95% confidence interval ranged from slight to moderate)
- ACE-III (<82) (low quality, 95% confidence interval ranged from slight to moderate)
- ACE-III (<84) (very low quality, 95% confidence interval ranged from slight to moderate)
- ACE-R (<83) (moderate quality, 95% confidence interval ranged from moderate to moderate)
- ACE-R (<85) (moderate quality, 95% confidence interval ranged from slight to moderate)
- ACE-R (<89) (low quality, 95% confidence interval ranged from slight to moderate)
- AMT (<7) (low quality, 95% confidence interval ranged from moderate to large)
- AMT (<8) (very low quality, 95% confidence interval ranged from slight to moderate)
- Applause sign (<3) (high quality, 95% confidence interval ranged from moderate to large)
- BNT (<14) (moderate quality, 95% confidence interval ranged from moderate to large)
- CDT, Shulman scoring method (>3) (low quality, 95% confidence interval ranged from slight to moderate)
- CDT, Watson scoring method (>4) (low quality, 95% confidence interval ranged from slight to moderate)
- CDT, Wolf-Klein scoring method (<7) (moderate quality, 95% confidence interval ranged from moderate to moderate)

- CDT, scoring method unclear (<8) (high quality, 95% confidence interval ranged from moderate to large)
- CDT, Manos and Wu scoring method (<8) (low quality, 95% confidence interval ranged from slight to moderate)
- CT positive (moderate quality, 95% confidence interval ranged from slight to large)
- FAQ (<9) moderate quality, 95% confidence interval ranged from moderate to large)
- FDG-PET positive (high quality, 95% confidence interval ranged from moderate to large)
- IQCODE 16 item (>4.1) (low quality, 95% confidence interval ranged from slight to moderate)
- IQCODE 26 item (>3.6 or > 3.7 or >3.8 or >3.9) (very low quality, 95% confidence interval ranged from slight decrease to moderate)
- IQCODE 26 item (>4.0) (very low quality, 95% confidence interval ranged from moderate to moderate)
- IQCODE 26 item (>4.1) (low quality, 95% confidence interval ranged from moderate to large)
- LST (<3) (low quality, 95% confidence interval ranged from slight to moderate)
- MIS (<4) (high quality, 95% confidence interval ranged from moderate to large)
- MIS (<5 or <6) (moderate quality, 95% confidence interval ranged from moderate to moderate)
- MMSE (<20 or <25) (very low to moderate quality, 95% confidence interval ranged from moderate to large)
- MMSE (<21 or <27 or < 28) (low to moderate quality, 95% confidence interval ranged from moderate to moderate)
- MMSE (<26) (very low quality, 95% confidence interval ranged from slight to large)
- Palmo-Mental Reflex positive (low quality, 95% confidence interval ranged from slight to moderate)
- Palmo-Mental Reflex and short smell test (both positive) (low quality, 95% confidence interval ranged from slight to very large)
- RUDAS (<23 or <24) (low quality, 95% confidence interval ranged from moderate to large)
- RUDAS (<25 or <26) (very low quality, 95% confidence interval ranged from slight to moderate)
- 7 minute screen (P>0.6 or P>0.7) (low to moderate quality, 95% confidence interval ranged from slight to moderate)
- 7 minute screen (P>0.8) (low quality, 95% confidence interval ranged from slight to large)
- Short Smell Test positive (very low quality, 95% confidence interval ranged from slight to moderate)
- SPMSQ (≥4 or ≥ 5) (very low quality, 95% confidence interval ranged from slight to large)
- Test your memory, TYM (≤39) (moderate quality, 95% confidence interval ranged from moderate to moderate)
- Verbal category fluency (animal naming) (<14) (moderate quality, 95% confidence interval ranged from slight to moderate)
- Verbal category fluency (animal naming) (<19 or <20) (low quality, 95% confidence interval ranged from slight to moderate)

The following results **did not provide any meaningful diagnostic value** that could be differentiated from random chance:

- 10-CS (≤8) (low quality, 95% confidence interval ranged from slight increase in probability to slight increase)

- 6 item screener (≥0) (moderate quality, 95% confidence interval ranged from slight decrease in probability to slight increase)
- 99mTc-HMPAO SPECT positive (low quality, 95% confidence interval ranged from moderate decrease in probability to moderate increase)
- ACE (<83) (very low quality, 95% confidence interval ranged from slight decrease in probability to very large increase)
- AD8 (≥2) (high quality, 95% confidence interval ranged from slight increase in probability to slight increase)
- Amyloid Beta and Total Tau (low quality, 95% confidence interval ranged from slight decrease in probability to moderate increase)
- ACE-III (<88) (low quality, 95% confidence interval ranged from slight increase in probability to moderate increase)
- AMT (<10) (low quality, 95% confidence interval ranged from slight increase in probability to slight increase)
- AMT (<9) (very low quality, 95% confidence interval ranged from slight increase in probability to moderate increase)
- BNT (<15) (low quality, 95% confidence interval ranged from slight increase in probability to moderate increase)
- CDT, Shulman scoring method (>0) (low quality, 95% confidence interval ranged from slight increase in probability to moderate increase)
- CDT, Manos and Wu scoring method (<9) (low quality, 95% confidence interval ranged from slight increase in probability to slight increase)
- CDT, Lin scoring method (<3) (low quality, 95% confidence interval ranged from slight increase in probability to moderate increase)
- IQCODE 16 item (>3.5) (very low quality, 95% confidence interval ranged from slight decrease in probability to large increase)
- IQCODE 26 item (>3.5) (very low quality, 95% confidence interval ranged from slight increase in probability to moderate increase)
- Mini-ACE (<26) (high quality, 95% confidence interval ranged from slight increase in probability to slight increase)
- Mini-Cog (≤2) (moderate quality, 95% confidence interval ranged from slight increase in probability to slight increase)
- MIS (<7) (low quality, 95% confidence interval ranged from slight increase in probability to moderate increase)
- MIS (<8) (moderate quality, 95% confidence interval ranged from slight increase in probability to slight increase)
- MoCA (<22 or <24 or <25 or <26) (moderate to high quality, 95% confidence interval ranged from slight increase in probability to slight increase)
- MRI positive (very low quality, 95% confidence interval ranged from slight increase in probability to moderate increase)
- Palmo-Mental Reflex and short smell test (one positive) (low quality, 95% confidence interval ranged from slight increase in probability to moderate increase)
- SPMSQ (≥ 6) (very low quality, 95% confidence interval ranged from slight decrease in probability to slight increase)
- Syndrom Kurztest (low to moderate quality, 95% confidence interval ranged from slight increase in probability to moderate increase)
- TYM (≤42) (moderate quality, 95% confidence interval ranged from slight increase in probability to moderate increase)

- Verbal category fluency (animal naming) (<21 or <22) (low quality, 95% confidence interval ranged from slight increase in probability to moderate increase)
- Verbal category fluency (animal naming) (<23 or <24) (moderate quality, 95% confidence interval ranged from slight increase in probability to slight increase)

#### *5.1.4.1.2 Results which decrease the probability of diagnosing dementia*

The following test results **decrease** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **very large:**

- 10-CS (>7) (low quality, 95% confidence interval ranged from moderate to very large)
- 10-CS (>8) (low quality, 95% confidence interval ranged from moderate to very large)
- 6 item screener (<1) (moderate quality, 95% confidence interval ranged from large to very large)
- ACE (≥88) (low quality, 95% confidence interval ranged from moderate to very large)
- ACE-III (≥88) (low quality, 95% confidence interval ranged from slight to very large)
- AMT (≥10) (low quality, 95% confidence interval ranged from moderate to very large)
- Mini-ACE (≥26) (high quality, 95% confidence interval ranged moderate to very large)
- Mini-Cog (>2 ) (moderate quality, 95% confidence interval ranged moderate to very large)
- MIS (≥4) (high quality, 95% confidence interval ranged moderate to very large)
- MIS (≥8) (moderate quality, 95% confidence interval ranged moderate to very large)
- MMSE (≥28) (very low quality, 95% confidence interval ranged from large to very large)
- MOCA (≥19 or ≥22) (low to moderate quality, 95% confidence interval ranged from large to very large)
- MOCA (≥26) (moderate quality, 95% confidence interval ranged from moderate to very large)
- TYM (>39 or >42) (moderate to high quality, 95% confidence interval ranged from moderate to very large)
- Verbal category fluency (animal naming) (≥20 or ≥ 22 or ≥23 or ≥24 ) (moderate quality, 95% confidence interval ranged from moderate to very large)

The following test results **decrease** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **large**:

- 6 item screener (<2) (moderate quality, 95% confidence interval ranged from large to very large)
- 6CIT (≥9) (high quality, 95% confidence interval ranged from moderate to large)
- ACE (≥75) (high quality, 95% confidence interval ranged from moderate to large)
- ACE (≥83) (low quality, 95% confidence interval ranged from moderate to very large)
- ACE-III (≥81) (low quality, 95% confidence interval ranged from moderate to very large)
- ACE-III (≥84) (low quality, 95% confidence interval ranged from moderate to very large)
- ACE-R (≥74) (moderate quality, 95% confidence interval ranged from moderate to very large)
- ACE-R (≥83) (low quality, 95% confidence interval ranged from moderate to very large)
- ACE-R (≥85) (moderate quality, 95% confidence interval ranged from moderate to very large)
- ACE-R (≥89) (moderate quality, 95% confidence interval ranged from moderate to very large)
- Brief Neuropsychological Test Battery (high quality, 95% confidence interval ranged from moderate to large)

- CDT, Shulman scoring method (≤3) (moderate quality, 95% confidence interval ranged from moderate to large)
- CDT, Shulman scoring method (≤4) (moderate quality, 95% confidence interval ranged from moderate to large)
- CDT, Manos and Wu scoring method (≥9) (low quality, 95% confidence interval ranged from moderate to large)
- FAQ (≥9) (low quality, 95% confidence interval ranged from slight to very large)
- FDG-PET negative (very low quality, 95% confidence interval ranged from slight to very large)
- IQCODE 16 item (≤3.5) (moderate quality, 95% confidence interval ranged from large to very large)
- Mini-Cog (Scanlan and Borson algorithm negative) (moderate quality, 95% confidence interval ranged from large to large)
- MIS (≥5) (very low quality, 95% confidence interval ranged slight to very large)
- MIS (≥6 or ≥7) (moderate quality, 95% confidence interval ranged moderate to very large)
- MMSE (≥25 or ≥26 ) (very low quality, 95% confidence interval ranged from moderate to large)
- MMSE (≥27) (low quality, 95% confidence interval ranged from moderate to very large)
- MOCA (≥24) (low quality, 95% confidence interval ranged from slight to very large)
- TYM (>30) (moderate quality, 95% confidence interval ranged from large to large)
- Verbal category fluency (animal naming) (≥21 ) (moderate quality, 95% confidence interval ranged from moderate to very large)

The following test results **decrease** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **moderate:**

- 10-CS (>5) (low quality, 95% confidence interval ranged from moderate to moderate)
- 10-CS (>6) (low quality, 95% confidence interval ranged from moderate to large).
- 6 item screener (<3) (moderate quality, 95% confidence interval ranged from moderate to large)
- 6 item screener (<4) (moderate quality, 95% confidence interval ranged from moderate to moderate)
- ACE-III (≥82) (low quality, 95% confidence interval ranged from slight to large)
- AMT (≥7) (very low quality, 95% confidence interval ranged from slight to moderate)
- AMT (≥8) (low quality, 95% confidence interval ranged from slight to moderate)
- AMT (≥9) (low quality, 95% confidence interval ranged from moderate to large)
- BNT (≥15) (low quality, 95% confidence interval ranged from slight to moderate)
- CDT, Shulman scoring method (≤0) (moderate quality, 95% confidence interval ranged from moderate to large)
- CDT, Shulman scoring method (≤1) (moderate quality, 95% confidence interval ranged from moderate to large)
- CDT, Watson scoring method (≤4) (low quality, 95% confidence interval ranged from slight to moderate)
- CDT, scoring method unclear (≥8) (high quality, 95% confidence interval ranged from moderate to moderate)
- CDT, Manos and Wu scoring method (≥8) (moderate quality, 95% confidence interval ranged from moderate to moderate)

- CDT, Lin scoring method (≥3) (moderate quality, 95% confidence interval ranged from moderate to large)
- CERAD Battery (low quality, 95% confidence interval ranged moderate to large)
- Free recall score of the 5 word test (>6) (low quality, 95% confidence interval ranged from moderate to large)
- IQCODE 16 item (≤4.1) (moderate quality, 95% confidence interval ranged from slight to moderate)
- IQCODE 26 item (≤3.5) (low quality, 95% confidence interval ranged from moderate to large)
- IQCODE 26 item (≤3.6 or ≤3.7 or ≤3.8 or ≤3.9) (very low to low quality, 95% confidence interval ranged from moderate to moderate)
- IQCODE 26 item (≤4.0 or ≤4.1 ) (very low quality, 95% confidence interval ranged from slight to moderate)
- LST (≥3) (moderate quality, 95% confidence interval ranged from moderate to large)
- MMSE (≥17 or ≥22 or ≥24) (low to moderate quality, 95% confidence interval ranged from moderate to moderate)
- MMSE (≥18 or ≥19 or ≥23) (very low quality, 95% confidence interval ranged from slight to large)
- OR (≤7) (low quality, 95% confidence interval ranged from slight to moderate)
- Palmo-Mental Reflex and short smell test (both negative) (moderate quality, 95% confidence interval ranged from slight to moderate)
- Phototest (≥27) (high quality, 95% confidence interval ranged from moderate to large)
- RUDAS (≥21) (moderate quality, 95% confidence interval ranged from moderate to moderate)
- RUDAS (≥22 or ≥23 or≥24 or ≥25) (very low quality, 95% confidence interval ranged from slight to moderate)
- RUDAS (≥26) (low quality, 95% confidence interval ranged from moderate to large)
- 7 minute screen (P≤0.6 or ≤0.7 or ≤0.8) (low quality, 95% confidence interval ranged from slight to moderate)
- SPMSQ (<4 or <5) (low quality, 95% confidence interval ranged from moderate to large)
- Total Recall Score of 5 word test (>9) (low quality, 95% confidence interval ranged from moderate to large)
- Total Weighted Score of the 5 word Test (>15) (low quality, 95% confidence interval ranged from moderate to large)
- Verbal category fluency (animal naming) (≥14) (high quality, 95% confidence interval ranged from moderate to large)
- Verbal category fluency (animal naming) (≥19 ) (moderate quality, 95% confidence interval ranged from moderate to large)

The following results **did not provide any meaningful diagnostic value** that could be differentiated from random chance:

- 6 item screener (<0) (very low quality, 95% confidence interval ranged from very large decrease in probability to very large increase)
- 99mTc-HMPAO SPECT negative (low quality, 95% confidence interval ranged from very large decrease in probability to slight increase)
- AD8 (<2) (moderate quality, 95% confidence interval ranged from very large decrease in probability to slight increase)

- 6 item screener (<5) (low quality, 95% confidence interval ranged from slight decrease in probability to moderate decrease)
- 6 item screener (<6) (low quality, 95% confidence interval ranged from slight decrease in probability to slight decrease)
- Applause sign (≥3) (moderate quality, 95% confidence interval ranged from slight decrease in probability to moderate decrease)
- BNT (≥13) (moderate quality, 95% confidence interval ranged from slight decrease in probability to slight decrease)
- BNT (≥14) (low quality, 95% confidence interval ranged from slight decrease in probability to moderate decrease)
- CDT, Shulman scoring method (≤2) (very low quality, 95% confidence interval ranged from large decrease in probability to slight increase)
- CDT, Wolf-Klein scoring method (≥7) (low quality, 95% confidence interval ranged from slight decrease in probability to moderate decrease)
- CT negative (moderate quality, 95% confidence interval ranged from slight decrease in probability to moderate decrease)
- LST (≥1 or ≥2) (low to moderate quality, 95% confidence interval ranged from slight decrease in probability to slight decrease)
- MMSE (≥20 or ≥21) (very low quality, 95% confidence interval ranged from very large decrease in probability to slight increase)
- MOCA (≥25) (low quality, 95% confidence interval ranged from very large decrease in probability to slight increase)
- MRI negative (very low quality, 95% confidence interval ranged from very large decrease in probability to slight increase)
- OR (≤7) (moderate quality, 95% confidence interval ranged from slight decrease in probability to slight decrease)
- Palmo-Mental Reflex negative (low quality, 95% confidence interval ranged from moderate decrease in probability to slight increase)
- Palmo-Mental Reflex and short smell test (one negative) (low quality, 95% confidence interval ranged from slight decrease in probability to slight increase)
- RUDAS (≥22) (very low quality, 95% confidence interval ranged from slight decrease in probability to moderate decrease)
- Short Smell Test negative (very low quality, 95% confidence interval ranged from moderate decrease in probability to slight increase)
- SPMSQ (<6) (low quality, 95% confidence interval ranged from moderate decrease in probability to slight increase)
- Syndrom Kurztest (low to moderate quality, 95% confidence interval ranged from slight decrease in probability to moderate decrease)

#### 5.1.4.2 AD versus DLB

##### *5.1.4.2.1 Results which increase the probability of diagnosing dementia*

The following results **did not provide any meaningful diagnostic value** that could be differentiated from random chance:

- Amyloid Beta 1-42 positive (moderate quality, 95% confidence interval ranged from slight decrease in probability to moderate increase)
- FDG-PET positive (very low quality, 95% confidence interval ranged from moderate decrease in probability to slight increase)

- MRI positive (moderate quality, 95% confidence interval ranged from slight decrease in probability to slight increase)

#### *5.1.4.2.2 Results which decrease the probability of diagnosing dementia*

The following results **did not provide any meaningful diagnostic value** that could be differentiated from random chance:

- Amyloid Beta 1-42 negative (moderate quality, 95% confidence interval ranged from slight decrease in probability to moderate decrease)
- FDG-PET negative (very low quality, 95% confidence interval ranged from moderate decrease in probability to very large increase)
- MRI positive (moderate quality, 95% confidence interval ranged from slight decrease in probability to slight increase)

### 5.1.4.3 AD versus FTD

#### *5.1.4.3.1 Results which increase the probability of diagnosing dementia*

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **large**:

- Amyloid Beta 1-42 and total tau positive (moderate quality, 95% confidence interval ranged from moderate to very large)
- p-tau 181 positive (moderate quality, 95% confidence interval ranged from moderate to very large)

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **moderate**:

- 99mTc-HMPAO SPECT positive (very low quality, 95% confidence interval ranged from slight to large)
- FDG-PET positive (very low quality, 95% confidence interval ranged from slight to very large)

The following results **did not provide any meaningful diagnostic value** that could be differentiated from random chance:

- MRI positive (moderate quality, 95% confidence interval ranged from slight decrease in probability to slight increase)

#### *5.1.4.3.2 Results which decrease the probability of diagnosing dementia*

The following test results **decrease** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **very large:**

- p-tau 181 negative (moderate quality, 95% confidence interval ranged from large to very large)

The following test results **decrease** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **large**:

- Amyloid Beta 1-42 and total tau negative (moderate quality, 95% confidence interval ranged from moderate to very large)

The following test results **decrease** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **moderate:**

- 99mTc-HMPAO SPECT negative (very low quality, 95% confidence interval ranged from slight to moderate)

The following results **did not provide any meaningful diagnostic value** that could be differentiated from random chance:

- FDG-PET negative (very low quality, 95% confidence interval ranged from slight decrease in probability to moderate decrease)
- MRI negative (moderate quality, 95% confidence interval ranged from slight decrease in probability to slight increase)

#### 5.1.4.4 AD versus no dementia

##### *5.1.4.4.1 Results which increase the probability of diagnosing dementia*

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **very large**:

- Free recall score of the five word test (≤5) (low quality, 95% confidence interval ranged from large to very large)
- Total tau positive (very low quality, 95% confidence interval ranged from slight to very large)
- Total weighted score of 5-word test (≤15) (low quality, 95% confidence interval ranged from large to very large)

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **large**:

- Amyloid Beta 1-42 positive (low quality, 95% confidence interval ranged from slight to very large)
- FDG-PET positive (moderate quality, 95% confidence interval ranged from moderate to very large)
- p-tau 181/Amyloid beta 1-42 positive (moderate quality, 95% confidence interval ranged from moderate to very large)
- Total recall score of 5-word test (≤9) (low quality, 95% confidence interval ranged from moderate to very large)

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **moderate**:

- IQCODE (16 item, >3.4) (very low quality, 95% confidence interval ranged from slight to moderate)
- IQCODE (16 item, >3.5 or >3.6) (low quality, 95% confidence interval ranged from moderate to moderate)
- MMSE (16 item, <28) (low quality, 95% confidence interval ranged from moderate to large)

The following results **did not provide any meaningful diagnostic value** that could be differentiated from random chance:

- IQCODE (16 item, >3.2) (low quality, 95% confidence interval ranged from slight increase in probability to slight increase)
- IQCODE (16 item, >3.3) (very low quality, 95% confidence interval ranged from slight increase in probability to moderate increase)
- p-tau 181 positive (low quality, 95% confidence interval ranged from slight decrease in probability to moderate increase)

#### *5.1.4.4.2 Results which decrease the probability of diagnosing dementia*

The following test results **decrease** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **very large:**

- IQCODE (16 item, ≤3.2 or ≤3.3) (low quality, 95% confidence interval ranged from large to very large)
- MMSE (16 item, ≥28) (low quality, 95% confidence interval ranged from large to very large)
- Total recall score of 5-word test (>9) (low quality, 95% confidence interval ranged from moderate to very large)

The following test results **decrease** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **large**:

- Amyloid Beta 1-42 negative (moderate quality, 95% confidence interval ranged from moderate to large)
- Free recall score of the five word test (>5) (low quality, 95% confidence interval ranged from large to very large)
- IQCODE (16 item, ≤3.4 or ≤3.5) (low quality, 95% confidence interval ranged from moderate to very large)
- IQCODE (16 item, ≤3.6) (low quality, 95% confidence interval ranged from moderate to large)
- Total weighted score of 5-word test (>15) (low quality, 95% confidence interval ranged from moderate to very large)

The following test results **decrease** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **moderate:**

- FDG-PET positive (low quality, 95% confidence interval ranged from slight to large)
- p-tau 181 negative (low quality, 95% confidence interval ranged from slight to moderate)
- p-tau 181/Amyloid beta 1-42 negative (moderate quality, 95% confidence interval ranged from moderate to large)

The following results **did not provide any meaningful diagnostic value** that could be differentiated from random chance:

- Total tau negative (very low quality, 95% confidence interval ranged from slight decrease in probability to moderate decrease)

### 5.1.4.5 AD versus non-AD dementia plus unclassifiable

#### *5.1.4.5.1 Results which increase the probability of diagnosing dementia*

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **moderate**:

- 99mTc-HMPAO SPECT positive (low quality, 95% confidence interval ranged from slight to moderate)

The following results **did not provide any meaningful diagnostic value** that could be differentiated from random chance:

- MRI positive (very low quality, 95% confidence interval ranged from slight decrease in probability to moderate increase)

#### *5.1.4.5.2 Results which decrease the probability of diagnosing dementia*

The following test results **decrease** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **moderate:**

- 99mTc-HMPAO SPECT negative (low quality, 95% confidence interval ranged from slight to large)

The following results **did not provide any meaningful diagnostic value** that could be differentiated from random chance:

- MRI positive (moderate quality, 95% confidence interval ranged from slight decrease in probability to slight increase)

### 5.1.4.6 AD versus non-AD

#### *5.1.4.6.1 Results which increase the probability of diagnosing dementia*

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **very large**:

- FDG-PET/CT positive (low quality, 95% confidence interval ranged from large to very large)
- p-tau 181 and Amyloid Beta 1-42 positive (discrepancies resolved by Amyloid Beta 1-42/1-40) (low quality, 95% confidence interval ranged from large to very large)

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **large**:

- Amyloid Beta 1-42 and total tau positive (moderate quality, 95% confidence interval ranged from moderate to very large)
- Amyloid Beta 1-42 and total tau/p-tau positive (high quality, 95% confidence interval ranged from moderate to large)
- Formula Mattson (biomarkers) positive (high quality, 95% confidence interval ranged from moderate to large)
- p-tau 181 and Amyloid Beta 1-42/1-40 positive (low quality, 95% confidence interval ranged from large to very large)
- p-tau 181/Amyloid Beta 1-42 positive (very low quality, 95% confidence interval ranged from moderate to very large)
- Mass spectrometry positive (moderate quality, 95% confidence interval ranged from moderate to very large)

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **moderate**:

- Amyloid Beta 1-42 and total tau and p-tau (≥2 positive) (high quality, 95% confidence interval ranged from moderate to moderate)
- Amyloid Beta 1-42 and total tau and p-tau (2 positive) (high quality, 95% confidence interval ranged from moderate to large)
- 99mTc-ECD SPECT, all information method positive (low quality, 95% confidence interval ranged from slight to moderate)
- 99mTc-ECD SPECT, automated method positive (moderate quality, 95% confidence interval ranged from slight to moderate)
- 99mTc-HMPAO SPECT positive (low quality, 95% confidence interval ranged from slight to moderate)

- Amyloid Beta 1-42 positive (low quality, 95% confidence interval ranged from moderate to moderate)
- Amyloid Beta 1-42/p-tau positive (moderate quality, 95% confidence interval ranged from moderate to large)
- Amyloid Beta 1-42/total tau positive (moderate quality, 95% confidence interval ranged from moderate to moderate)
- Amyloid Beta 1-42/1-40 positive (low quality, 95% confidence interval ranged from moderate to moderate)
- FDG-PET positive (very low quality, 95% confidence interval ranged from slight to large)
- Flutemetamol PET positive (moderate quality, 95% confidence interval ranged from slight to moderate)
- Formula Hulstaert (biomarkers) positive (high quality, 95% confidence interval ranged from moderate to moderate)
- Formula Mulder (biomarkers) positive (high quality, 95% confidence interval ranged from moderate to moderate)
- Formula Schoonenboom (biomarkers) positive (high quality, 95% confidence interval ranged from moderate to moderate)
- p-tau 181 positive (very low quality, 95% confidence interval ranged from moderate to large)
- Total tau positive (low quality, 95% confidence interval ranged from moderate to moderate)
- Total tau/Amyloid Beta 1-42 positive (high quality, 95% confidence interval ranged from moderate to large)
- Urinary AD7c-NTP (22 micrograms/ml) positive (moderate quality, 95% confidence interval ranged from slight to moderate)

The following results **did not provide any meaningful diagnostic value** that could be differentiated from random chance:

- Amyloid Beta 1-42 and total tau and p-tau abnormal (3 positive) (very low quality, 95% confidence interval ranged from slight decrease in probability to very large increase)
- 99mTc-ECD SPECT, visual assessment alone method positive (very low quality, 95% confidence interval ranged from moderate decrease in probability to very large increase)
- EEG positive (high quality, 95% confidence interval ranged from slight increase in probability to slight increase)
- MRI positive (moderate quality, 95% confidence interval ranged from slight increase in probability to moderate increase)
- Olfactory Test ≥ 3 errors (moderate quality, 95% confidence interval ranged from large decrease in probability to moderate increase)
- Olfactory Test ≥ 4 errors (moderate quality, 95% confidence interval ranged from slight decrease in probability to moderate increase)
- Olfactory Test ≥ 5 errors (low quality, 95% confidence interval ranged from moderate decrease in probability to moderate increase)

#### *5.1.4.6.2 Results which decrease the probability of diagnosing dementia*

The following test results decrease the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **very large**:

- Formula Hulstaert (biomarkers) negative (high quality, 95% confidence interval ranged from large to very large)

The following test results **decrease** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **large**:

- Amyloid Beta 1-42 and total tau and p-tau (<2 positive) (high quality, 95% confidence interval ranged from large to large)
- Amyloid Beta 1-42/total tau positive (moderate quality, 95% confidence interval ranged from moderate to large)
- FDG-PET/CT negative (low quality, 95% confidence interval ranged from moderate to very large)
- Formula Mulder (biomarkers) negative (high quality, 95% confidence interval ranged from large to very large)
- Formula Schoonenboom (biomarkers) negative (high quality, 95% confidence interval ranged from large to very large)
- Mass spectrometry negative (moderate quality, 95% confidence interval ranged from moderate to very large)
- p-tau 181 and Amyloid Beta 1-42 negative (discrepancies resolved by Amyloid Beta 1-42/1-40) (low quality, 95% confidence interval ranged from large to very large)
- p-tau 181 and Amyloid Beta 1-42/1-40 positive (low quality, 95% confidence interval ranged from moderate to very large)
- Total tau/Amyloid Beta 1-42 negative (high quality, 95% confidence interval ranged from large to very large)
- p-tau 181/Amyloid Beta 1-42 negative (very low quality, 95% confidence interval ranged from moderate to very large)

The following test results **decrease** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **moderate:**

- Amyloid Beta 1-42 negative (low quality, 95% confidence interval ranged from moderate to moderate)
- Amyloid Beta 1-42 and total tau negative (low quality, 95% confidence interval ranged from slight to large)
- Amyloid Beta 1-42 and total tau/p-tau negative (high quality, 95% confidence interval ranged from moderate to large)
- Amyloid Beta 1-42/p-tau negative (low quality, 95% confidence interval ranged from moderate to large)
- Amyloid Beta 1-42/1-40 negative (very low quality, 95% confidence interval ranged from slight to very large)
- 99mTc-ECD SPECT, all information method negative (low quality, 95% confidence interval ranged from slight to moderate)
- FDG-PET negative (very low quality, 95% confidence interval ranged from slight to large)
- Flutemetamol PET negative (moderate quality, 95% confidence interval ranged from slight to moderate
- Formula Mattson (biomarkers) negative (high quality, 95% confidence interval ranged from moderate to moderate)
- MRI positive (low quality, 95% confidence interval ranged from large decrease to slight increase)
- p-tau 181 negative (very low quality, 95% confidence interval ranged from moderate to moderate)
- Total tau negative (very low quality, 95% confidence interval ranged from moderate to moderate)

The following results **did not provide any meaningful diagnostic value** that could be differentiated from random chance:

- Amyloid Beta 1-42 and total tau and p-tau (not 2 positive) (high quality, 95% confidence interval ranged from slight decrease in probability to slight decrease)
- Amyloid Beta 1-42 and total tau and p-tau (<3 positive) (very low quality, 95% confidence interval ranged from large decrease in probability to slight increase)
- 99mTc-ECD SPECT, automated method negative (high quality, 95% confidence interval ranged from slight decrease in probability to slight decrease)
- 99mTc-ECD SPECT, visual assessment alone method negative (very low quality, 95% confidence interval ranged from very large decrease in probability to moderate increase)
- 99mTc-HMPAO SPECT negative (moderate quality, 95% confidence interval ranged from slight decrease in probability to moderate decrease)
- EEG negative (high quality, 95% confidence interval ranged from slight decrease in probability to slight decrease)
- Olfactory Test <3 errors (moderate quality, 95% confidence interval ranged from large decrease in probability to slight increase)
- Olfactory Test <4 errors (moderate quality, 95% confidence interval ranged from moderate decrease in probability to slight increase)
- Olfactory Test <5 errors (high quality, 95% confidence interval ranged from slight decrease in probability to slight increase)
- Urinary AD7c-NTP (22 micrograms/ml) negative (moderate quality, 95% confidence interval ranged from slight decrease in probability to moderate decrease)

#### 5.1.4.7 AD versus other dementias

##### *5.1.4.7.1 Results which increase the probability of diagnosing dementia*

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **very large**:

- Amyloid Beta 1-42 and total tau positive (low quality, 95% confidence interval ranged from moderate to very large)

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **large**:

- AD scale (≥6) (high quality, 95% confidence interval ranged from moderate to very large)

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **moderate**:

- 99mTc-HMPAO SPECT positive (very low quality, 95% confidence interval ranged from slight to large)
- 14-3-3, total tau and p-tau positive (very low quality, 95% confidence interval ranged from slight to large)
- FDG-PET positive (low quality, 95% confidence interval ranged from slight to moderate)
- p-tau 181 positive (very low quality, 95% confidence interval ranged from moderate to large)
- p-tau 181/Amyloid Beta 1-42 positive (low quality, 95% confidence interval ranged from moderate to moderate)
- Total tau positive (very low quality, 95% confidence interval ranged from slight to large)
- Total tau/Amyloid Beta 1-42 positive (very low quality, 95% confidence interval ranged from slight to moderate)

The following results **did not provide any meaningful diagnostic value** that could be differentiated from random chance:

- Amyloid Beta 1-42 positive (very low quality, 95% confidence interval ranged from slight increase in probability to moderate increase)
- Apo E (≥1 allele) (moderate quality, 95% confidence interval ranged from slight increase in probability to moderate increase)
- CT positive (moderate quality, 95% confidence interval ranged from slight decrease in probability to slight increase)
- MRI positive (very low quality, 95% confidence interval ranged from slight increase in probability to moderate increase)

#### *5.1.4.7.2 Results which decrease the probability of diagnosing dementia*

The following test results **decrease** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **very large:**

- 14-3-3, total tau and p-tau negative (low quality, 95% confidence interval ranged from slight to very large)

The following test results **decrease** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **large:**

- 99mTc-HMPAO SPECT negative (low quality, 95% confidence interval ranged from large to very large)

The following test results **decrease** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **moderate:**

- AD scale (<6) (high quality, 95% confidence interval ranged from moderate to large)
- Amyloid Beta 1-42 negative (very low quality, 95% confidence interval ranged from slight to moderate)
- Amyloid Beta 1-42 and total tau negative (low quality, 95% confidence interval ranged from slight to large)
- Apo E (0 alleles) (moderate quality, 95% confidence interval ranged from slight to moderate)
- FDG-PET negative (low quality, 95% confidence interval ranged from slight to moderate)
- p-tau 181 negative (very low quality, 95% confidence interval ranged from slight to large)
- p-tau 181/Amyloid Beta 1-42 negative (low quality, 95% confidence interval ranged from moderate to large)
- Total tau negative (very low quality, 95% confidence interval ranged from slight to large)
- Total tau/Amyloid Beta 1-42 negative (very low quality, 95% confidence interval ranged from slight to moderate)

The following results **did not provide any meaningful diagnostic value** that could be differentiated from random chance:

- CT negative (low quality, 95% confidence interval ranged from slight decrease in probability to moderate increase)
- MRI negative (very low quality, 95% confidence interval ranged from large decrease in probability to slight increase)

#### 5.1.4.8 AD versus VaD

##### *5.1.4.8.1 Results which increase the probability of diagnosing dementia*

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **moderate**:

- 99mTc-HMPAO SPECT positive (very low quality, 95% confidence interval ranged from slight to large)

The following results **did not provide any meaningful diagnostic value** that could be differentiated from random chance:

- Amyloid Beta 1-42 positive (high quality, 95% confidence interval ranged from slight decrease to slight increase)
- CT positive (moderate quality, 95% confidence interval ranged from slight decrease to slight increase)
- MRI positive (low quality, 95% confidence interval ranged from slight decrease to large increase)

##### *5.1.4.8.2 Results which decrease the probability of diagnosing dementia*

The following test results **decrease** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **moderate:**

- 99mTc-HMPAO SPECT negative (low quality, 95% confidence interval ranged from slight to moderate)

The following results **did not provide any meaningful diagnostic value** that could be differentiated from random chance:

- Amyloid Beta 1-42 negative (moderate quality, 95% confidence interval ranged from moderate decrease in probability to slight increase)
- CT negative (low quality, 95% confidence interval ranged from slight decrease in probability to moderate increase)
- MRI negative (moderate quality, 95% confidence interval ranged from slight decrease in probability to slight decrease)

#### 5.1.4.9 bvFTD versus non-bvFTD

##### *5.1.4.9.1 Results which increase the probability of diagnosing dementia*

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **very large**:

- FTDC criteria positive (moderate quality, 95% confidence interval ranged from large to very large)

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **large**:

- MRI positive (moderate quality, 95% confidence interval ranged from moderate to very large)

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **moderate**:

- FDG-PET positive (low quality, 95% confidence interval ranged from slight to moderate)

- FDG-PET and MRI positive (moderate quality, 95% confidence interval ranged from moderate to large)
- FTDC criteria (probable) positive (moderate quality, 95% confidence interval ranged from moderate to large)

The following results **did not provide any meaningful diagnostic value** that could be differentiated from random chance:

- FTDC criteria (possible) positive (moderate quality, 95% confidence interval ranged from slight decrease in probability to slight increase)

#### *5.1.4.9.2 Results which decrease the probability of diagnosing dementia*

The following test results **decrease** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **very large:**

- FDG-PET and MRI positive (moderate quality, 95% confidence interval ranged from moderate to very large)

The following test results **decrease** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **large:**

- FDG-PET negative (moderate quality, 95% confidence interval ranged from moderate to very large)
- FTDC criteria (probable) negative (moderate quality, 95% confidence interval ranged from moderate to very large)

The following test results **decrease** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **moderate:**

- FTDC criteria negative (moderate quality, 95% confidence interval ranged from moderate to large)
- MRI positive (low quality, 95% confidence interval ranged from slight to large)

The following results **did not provide any meaningful diagnostic value** that could be differentiated from random chance:

- FTDC criteria (possible) negative (low quality, 95% confidence interval ranged from moderate decrease in probability to slight increase)

### 5.1.4.10 bvFTD/FD+ versus non-bvFTD/FD+

#### *5.1.4.10.1 Results which increase the probability of diagnosing dementia*

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **large**:

- FDG-PET positive (moderate quality, 95% confidence interval ranged from slight to very large)

#### *5.1.4.10.2 Results which decrease the probability of diagnosing dementia*

The following results **did not provide any meaningful diagnostic value** that could be differentiated from random chance:

- FDG-PET negative (moderate quality, 95% confidence interval ranged from slight decrease in probability to moderate decrease)

#### 5.1.4.11 CADASIL versus CADASIL-like syndromes

##### *5.1.4.11.1 Results which increase the probability of diagnosing dementia*

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **moderate**:

- Skin biopsy positive (high quality, 95% confidence interval ranged from moderate to moderate)

##### *5.1.4.11.2 Results which decrease the probability of diagnosing dementia*

The following test results **decrease** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **very large:**

- Skin biopsy negative (high quality, 95% confidence interval ranged from moderate to very large)

#### 5.1.4.12 CBD versus non-CBD

##### *5.1.4.12.1 Results which increase the probability of diagnosing dementia*

The following results **did not provide any meaningful diagnostic value** that could be differentiated from random chance:

- CBD consensus criteria positive (high quality, 95% confidence interval ranged from slight decrease in probability to slight increase)

##### *5.1.4.12.2 Results which decrease the probability of diagnosing dementia*

The following results **did not provide any meaningful diagnostic value** that could be differentiated from random chance:

- CBD consensus criteria negative (low quality, 95% confidence interval ranged from large decrease in probability to very large increase)

#### 5.1.4.13 CJD versus non-CJD

##### *5.1.4.13.1 Results which increase the probability of diagnosing dementia*

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **very large**:

- Amyloid Beta 1-42 and total tau positive (high quality, 95% confidence interval ranged from very large to very large)
- 14-3-3 and S100B (>1.0ng/ml) positive (moderate quality, 95% confidence interval ranged from large to very large)
- 14-3-3 and Amyloid Beta 1-42 positive (high quality, 95% confidence interval ranged from very large to very large)
- 14-3-3 (ELISA) positive (moderate quality, 95% confidence interval ranged from very large to very large)
- 14-3-3 Automated Capillary Western Assay positive (high quality, 95% confidence interval ranged from very large to very large)
- 14-3-3, total tau and S100B positive (moderate quality, 95% confidence interval ranged from large to very large)
- MRI (DWI) positive (high quality, 95% confidence interval ranged from moderate to very large)

- RT-QuIC positive (high quality, 95% confidence interval ranged from very large to very large)
- S100B (>4.2ng/ml) positive (high quality, 95% confidence interval ranged from very large to very large)
- Total tau and S100B positive (moderate quality, 95% confidence interval ranged from large to very large)

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **large**:

- 14-3-3 and total tau positive (moderate quality, 95% confidence interval ranged from moderate to very large)
- 14-3-3 (immunoblotting) positive (low quality, 95% confidence interval ranged from moderate to large)
- MRI positive (moderate quality, 95% confidence interval ranged from moderate to very large)
- Neuron-specific enolase positive (moderate quality, 95% confidence interval ranged from large to very large)
- p-tau 181/total tau positive (low quality, 95% confidence interval ranged from large to very large)
- S100B (>1.0ng/ml) positive (moderate quality, 95% confidence interval ranged from moderate to very large)
- S100B (>2.5ng/ml) positive (moderate quality, 95% confidence interval ranged from large to large)
- Total tau positive (low quality, 95% confidence interval ranged from moderate to very large)

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **moderate**:

- New criteria for sporadic CJD positive (very low quality, 95% confidence interval ranged from slight to large)
- WHO CJD criteria positive (very low quality, 95% confidence interval ranged from moderate to moderate)

The following results **did not provide any meaningful diagnostic value** that could be differentiated from random chance:

- 14-3-3 (multiple methods) positive (moderate quality, 95% confidence interval ranged from slight increase in probability to moderate increase)
- EEG positive (very low quality, 95% confidence interval ranged from moderate decrease in probability to large increase)
- European criteria for CJD positive (high quality, 95% confidence interval ranged from slight decrease in probability to slight increase)
- French criteria for CJD positive (moderate quality, 95% confidence interval ranged from slight increase in probability to moderate increase)
- Masters criteria for CJD positive (high quality, 95% confidence interval ranged from slight decrease in probability to slight increase)

#### *5.1.4.13.2 Results which decrease the probability of diagnosing dementia*

The following test results **decrease** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **very large:**

- 14-3-3 and Amyloid Beta 1-42 negative (high quality, 95% confidence interval ranged from large to very large)
- 14-3-3 (ELISA) negative (low quality, 95% confidence interval ranged from moderate to very large)
- 14-3-3 Automated Capillary Western Assay negative (high quality, 95% confidence interval ranged from large to very large)
- New criteria for sporadic CJD negative (low quality, 95% confidence interval ranged from moderate to very large)
- p-tau 181/total tau negative (very low quality, 95% confidence interval ranged from moderate to very large)

The following test results **decrease** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **large:**

- Amyloid Beta 1-42 and total tau negative (high quality, 95% confidence interval ranged from moderate to very large)
- 14-3-3 (multiple methods) negative (high quality, 95% confidence interval ranged from moderate to large)
- 14-3-3 (immunoblotting) positive (moderate quality, 95% confidence interval ranged from large to large)
- Masters criteria for CJD negative (moderate quality, 95% confidence interval ranged from slight to very large)
- RT-QuIC negative (moderate quality, 95% confidence interval ranged from moderate to very large)
- S100B (>2.5ng/ml) positive (moderate quality, 95% confidence interval ranged from moderate to large)
- Total tau negative (low quality, 95% confidence interval ranged from large to large)
- WHO CJD criteria negative (very low quality, 95% confidence interval ranged from large to very large)

The following test results **decrease** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **moderate:**

- 14-3-3 and S100B (>1.0ng/ml) negative (moderate quality, 95% confidence interval ranged from moderate to moderate)
- 14-3-3 and total tau negative (moderate quality, 95% confidence interval ranged from moderate to moderate)
- 14-3-3, total tau and S100B positive (low quality, 95% confidence interval ranged from slight to moderate)
- European criteria for CJD negative (moderate quality, 95% confidence interval ranged from slight to large)
- French criteria for CJD negative (high quality, 95% confidence interval ranged from moderate to large)
- MRI (DWI) negative (moderate quality, 95% confidence interval ranged from slight to large)
- Neuron-specific enolase negative (moderate quality, 95% confidence interval ranged from moderate to moderate)
- S100B (>1.0ng/ml) negative (moderate quality, 95% confidence interval ranged from moderate to moderate)
- Total tau and S100B positive (low quality, 95% confidence interval ranged from slight to moderate)

The following results **did not provide any meaningful diagnostic value** that could be differentiated from random chance:

- EEG negative (high quality, 95% confidence interval ranged from slight decrease in probability to slight decrease)
- MRI negative (low quality, 95% confidence interval ranged from slight decrease in probability to moderate decrease)
- S100B (>4.2ng/ml) negative (moderate quality, 95% confidence interval ranged from slight decrease in probability to moderate decrease)

#### 5.1.4.14 DLB versus AD

##### *5.1.4.14.1 Results which increase the probability of diagnosing dementia*

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **moderate**:

- LBCRS (≥3) (moderate quality, 95% confidence interval ranged from moderate to large)

The following results **did not provide any meaningful diagnostic value** that could be differentiated from random chance:

- MRI positive (low quality, 95% confidence interval ranged from slight increase in probability to moderate increase)

##### *5.1.4.14.2 Results which decrease the probability of diagnosing dementia*

The following test results **decrease** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **very large:**

- LBCRS (<3) (moderate quality, 95% confidence interval ranged from moderate to very large)

The following results **did not provide any meaningful diagnostic value** that could be differentiated from random chance:

- MRI negative (moderate quality, 95% confidence interval ranged from slight decrease in probability to slight increase)

#### 5.1.4.15 DLB versus FTD

##### *5.1.4.15.1 Results which increase the probability of diagnosing dementia*

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **moderate**:

- MRI positive (low quality, 95% confidence interval ranged from slight to large)

##### *5.1.4.15.2 Results which decrease the probability of diagnosing dementia*

The following results **did not provide any meaningful diagnostic value** that could be differentiated from random chance:

- MRI negative (moderate quality, 95% confidence interval ranged from slight decrease in probability to slight decrease)

### 5.1.4.16 DLB versus non-DLB

#### *5.1.4.16.1 Results which increase the probability of diagnosing dementia*

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **very large**:

- 123I-FP-CIT SPECT positive (moderate quality, 95% confidence interval ranged from large to very large)
- 123I-MIBG scintigraphy positive (low quality, 95% confidence interval ranged from moderate to very large)
- FDG-PET positive (very low quality, 95% confidence interval ranged from slight to very large)

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **large**:

- 123I-IMP SPECT and 123I-MIBG scintigraphy positive (moderate quality, 95% confidence interval ranged from moderate to very large)
- EEG positive (high quality, 95% confidence interval ranged from large to large)
- 2 or more of visual hallucinations, Parkinsonism, and RBD (high quality, 95% confidence interval ranged from moderate to large)

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **moderate**:

- 123I-IMP SPECT positive (low quality, 95% confidence interval ranged from slight to moderate)
- RBD or 2 or more of visual hallucinations, Parkinsonism, and fluctuating attention/concentration (high quality, 95% confidence interval ranged from moderate to moderate)
- 2 or more of visual hallucinations, Parkinsonism, and fluctuating attention/concentration (high quality, 95% confidence interval ranged from moderate to moderate)
- 2 or more of visual hallucinations, Parkinsonism, and fluctuating attention/concentration, or RBD (high quality, 95% confidence interval ranged from moderate to moderate)

The following results **did not provide any meaningful diagnostic value** that could be differentiated from random chance:

- MRI positive (moderate quality, 95% confidence interval ranged from slight increase in probability to moderate increase)

#### *5.1.4.16.2 Results which decrease the probability of diagnosing dementia*

The following test results **decrease** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **large:**

- 123I-IMP SPECT and 123I-MIBG scintigraphy negative (moderate quality, 95% confidence interval ranged from moderate to very large)
- 123I-MIBG scintigraphy negative (low quality, 95% confidence interval ranged from moderate to very large)
- EEG negative (moderate quality, 95% confidence interval ranged from moderate to very large)
- No RBD or less than 2 of visual hallucinations, Parkinsonism, and fluctuating attention/concentration (high quality, 95% confidence interval ranged from moderate to very large)

- Less than 2 of visual hallucinations, Parkinsonism, and fluctuating attention/concentration, or RBD (high quality, 95% confidence interval ranged from moderate to large)

The following test results **decrease** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **moderate:**

- 123I-FP-CIT SPECT negative (high quality, 95% confidence interval ranged from moderate to large)
- Less than 2 of visual hallucinations, Parkinsonism, and fluctuating attention/concentration (high quality, 95% confidence interval ranged from moderate to large)
- Less than 2 of visual hallucinations, Parkinsonism, and RBD (high quality, 95% confidence interval ranged from moderate to large)

The following results **did not provide any meaningful diagnostic value** that could be differentiated from random chance:

- 123I-IMP SPECT negative (low quality, 95% confidence interval ranged from slight decrease in probability to moderate decrease)
- FDG-PET negative (very low quality, 95% confidence interval ranged from large decrease in probability to moderate increase)
- MRI negative (high quality, 95% confidence interval ranged from slight decrease in probability to slight decrease)

#### 5.1.4.17 DLB versus other dementias

##### *5.1.4.17.1 Results which increase the probability of diagnosing dementia*

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **large**:

- 123I-FP-CIT SPECT positive (very low quality, 95% confidence interval ranged from slight to very large)
- 123I-MIBG scintigraphy positive (moderate quality, 95% confidence interval ranged from slight to very large)
- DLB consensus criteria positive (moderate quality, 95% confidence interval ranged from moderate to very large)
- LBCRS (≥3) positive (moderate quality, 95% confidence interval ranged from moderate to very large)

The following results **did not provide any meaningful diagnostic value** that could be differentiated from random chance:

- FDG-PET positive (very low quality, 95% confidence interval ranged from slight decrease in probability to very large increase)
- MRI positive (low quality, 95% confidence interval ranged from slight increase in probability to moderate increase)

##### *5.1.4.17.2 Results which decrease the probability of diagnosing dementia*

The following test results **decrease** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **very large:**

- LBCRS (≥3) negative (moderate quality, 95% confidence interval ranged from large to very large)

The following test results **decrease** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **large:**

- 123I-FP-CIT SPECT negative (high quality, 95% confidence interval ranged from moderate to very large)
- 123I-MIBG scintigraphy negative (high quality, 95% confidence interval ranged from moderate to very large)

The following test results **decrease** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **moderate:**

- DLB consensus criteria negative (low quality, 95% confidence interval ranged from slight to very large)

The following results **did not provide any meaningful diagnostic value** that could be differentiated from random chance:

- FDG-PET negative (very low quality, 95% confidence interval ranged from slight decrease in probability to slight increase)
- MRI negative (moderate quality, 95% confidence interval ranged from slight decrease in probability to slight decrease)

#### 5.1.4.18 DLB versus VaD

##### *5.1.4.18.1 Results which increase the probability of diagnosing dementia*

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **moderate**:

- MRI positive (low quality, 95% confidence interval ranged from slight to very large)

##### *5.1.4.18.2 Results which decrease the probability of diagnosing dementia*

The following results **did not provide any meaningful diagnostic value** that could be differentiated from random chance:

- MRI negative (low quality, 95% confidence interval ranged from slight decrease in probability to moderate decrease)

#### FTD versus AD

##### *5.1.4.18.3 Results which increase the probability of diagnosing dementia*

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **very large**:

- 99mTc-HMPAO SPECT positive (low quality, 95% confidence interval ranged from large to very large)

The following results **did not provide any meaningful diagnostic value** that could be differentiated from random chance:

- MRI positive (low quality, 95% confidence interval ranged from slight increase in probability to moderate increase)

##### *5.1.4.18.4 Results which decrease the probability of diagnosing dementia*

The following test results **decrease** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **moderate:**

- 99mTc-HMPAO SPECT negative (very low quality, 95% confidence interval ranged from slight to moderate)

The following results **did not provide any meaningful diagnostic value** that could be differentiated from random chance:

- MRI negative (moderate quality, 95% confidence interval ranged from slight decrease in probability to slight decrease)

#### 5.1.4.19 FTD versus DLB

##### *5.1.4.19.1 Results which increase the probability of diagnosing dementia*

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **large**:

- MRI positive (moderate quality, 95% confidence interval ranged from moderate to very large)

The following results **did not provide any meaningful diagnostic value** that could be differentiated from random chance:

- FDG-PET positive (very low quality, 95% confidence interval ranged from moderate decrease in probability to very large increase)

##### *5.1.4.19.2 Results which decrease the probability of diagnosing dementia*

The following results **did not provide any meaningful diagnostic value** that could be differentiated from random chance:

- FDG-PET negative (very low quality, 95% confidence interval ranged from moderate decrease in probability to slight increase)
- MRI negative (low quality, 95% confidence interval ranged from slight decrease in probability to moderate decrease)

#### 5.1.4.20 FTD versus non-FTD dementia versus unclassifiable

##### *5.1.4.20.1 Results which increase the probability of diagnosing dementia*

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **moderate**:

- 99mTc-HMPAO SPECT positive (low quality, 95% confidence interval ranged from slight to large)

The following results **did not provide any meaningful diagnostic value** that could be differentiated from random chance:

- MRI positive (low quality, 95% confidence interval ranged from large decrease in probability to slight increase)

##### *5.1.4.20.2 Results which decrease the probability of diagnosing dementia*

The following test results **decrease** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **moderate:**

- 99mTc-HMPAO SPECT negative (low quality, 95% confidence interval ranged from slight to large)

The following results **did not provide any meaningful diagnostic value** that could be differentiated from random chance:

- MRI negative (moderate quality, 95% confidence interval ranged from slight decrease in probability to slight increase)

#### 5.1.4.21 FTD versus non-FTD

##### *5.1.4.21.1 Results which increase the probability of diagnosing dementia*

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **very large**:

- 99mTc-ECT SPECT positive (moderate quality, 95% confidence interval ranged from very large to very large)
- FTD consensus criteria positive (high quality, 95% confidence interval ranged from moderate to very large)

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **large**:

- 99mTc-HMPAO SPECT positive (low quality, 95% confidence interval ranged from moderate to very large)
- FDG-PET positive (very low quality, 95% confidence interval ranged from moderate to very large)

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **moderate**:

- MRI positive (low quality, 95% confidence interval ranged from slight to moderate)
- SPECT/PET positive (high quality, 95% confidence interval ranged from moderate to large)

##### *5.1.4.21.2 Results which decrease the probability of diagnosing dementia*

The following test results **decrease** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **very large:**

- 99mTc-ECT SPECT negative (moderate quality, 95% confidence interval ranged from moderate to very large)

The following test results **decrease** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **large:**

- SPECT/PET negative (high quality, 95% confidence interval ranged from moderate to very large)

The following test results **decrease** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **moderate:**

- 99mTc-HMPAO SPECT negative (very low quality, 95% confidence interval ranged from slight to moderate)

The following results **did not provide any meaningful diagnostic value** that could be differentiated from random chance:

- FDG-PET negative (very low quality, 95% confidence interval ranged from slight decrease in probability to moderate decrease)

- FTD consensus criteria negative (high quality, 95% confidence interval ranged from slight decrease in probability to slight decrease)
- MRI negative (moderate quality, 95% confidence interval ranged from slight decrease in probability to moderate decrease)

#### 5.1.4.22 FTD versus other dementias

##### *5.1.4.22.1 Results which increase the probability of diagnosing dementia*

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **very large**:

- 99mTc-HMPAO SPECT positive (very low quality, 95% confidence interval ranged from slight to very large)
- FTD scale (≥6) (high quality, 95% confidence interval ranged from large to very large)

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **moderate**:

- MRI positive (low quality, 95% confidence interval ranged from moderate to moderate)

The following results **did not provide any meaningful diagnostic value** that could be differentiated from random chance:

- FDG-PET positive (very low quality, 95% confidence interval ranged from slight increase in probability to moderate increase)

##### *5.1.4.22.2 Results which decrease the probability of diagnosing dementia*

The following test results **decrease** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **very large:**

- FTD scale (<6) (high quality, 95% confidence interval ranged from moderate to very large)

The following test results **decrease** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **moderate:**

- 99mTc-HMPAO SPECT negative (very low quality, 95% confidence interval ranged from slight to moderate)

The following results **did not provide any meaningful diagnostic value** that could be differentiated from random chance:

- FDG-PET negative (very low quality, 95% confidence interval ranged from slight decrease in probability to slight increase)
- MRI negative (moderate quality, 95% confidence interval ranged from slight decrease in probability to slight decrease)

#### 5.1.4.23 FTD versus VaD

##### *5.1.4.23.1 Results which increase the probability of diagnosing dementia*

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **very large**:

- MRI positive (low quality, 95% confidence interval ranged from slight to very large increase)

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **moderate**:

- 99mTc-HMPAO SPECT positive (very low quality, 95% confidence interval ranged from slight to moderate increase)

#### *5.1.4.23.2 Results which decrease the probability of diagnosing dementia*

The following results **did not provide any meaningful diagnostic value** that could be differentiated from random chance:

- 99mTc-HMPAO SPECT negative (low quality, 95% confidence interval ranged from slight decrease in probability to slight decrease)
- MRI negative (low quality, 95% confidence interval ranged from slight decrease in probability to slight decrease)

### 5.1.4.24 HAND versus other neurological disorders in HIV+ people

#### *5.1.4.24.1 Results which increase the probability of diagnosing dementia*

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **moderate**:

- HIV dementia scale (<11) (low quality, 95% confidence interval ranged from slight to large)
- International HIV dementia scale (<10) (moderate quality, 95% confidence interval ranged from slight to moderate)
- Modified HIV dementia scale (<7.5) (very low quality, 95% confidence interval ranged from slight to moderate)

The following results **did not provide any meaningful diagnostic value** that could be differentiated from random chance:

- HIV dementia scale (<10) (moderate quality, 95% confidence interval ranged from slight decrease in probability to large increase)
- Grooved pegboard test positive (low quality, 95% confidence interval ranged from slight increase in probability to slight increase)
- Modified HIV dementia scale and grooved pegboard test, one positive (low quality, 95% confidence interval ranged from slight increase in probability to slight increase))

#### *5.1.4.24.2 Results which decrease the probability of diagnosing dementia*

The following test results **decrease** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **moderate:**

- HIV dementia scale (≥11) (low quality, 95% confidence interval ranged from slight to moderate)
- Modified HIV dementia scale (≥7.5) (very low quality, 95% confidence interval ranged from slight to moderate)

The following results **did not provide any meaningful diagnostic value** that could be differentiated from random chance:

- HIV dementia scale (≥10) (moderate quality, 95% confidence interval ranged from slight decrease in probability to slight increase)

- International HIV dementia scale (≥10) (moderate quality, 95% confidence interval ranged from large decrease in probability to slight increase)
- Modified HIV dementia scale and grooved pegboard test, both negative (very low quality, 95% confidence interval ranged from slight decrease in probability to slight decrease)
- Grooved pegboard test negative (very low quality, 95% confidence interval ranged from slight decrease in probability to moderate decrease)

#### 5.1.4.25 Neurosyphilis versus not neurosyphilis

##### *5.1.4.25.1 Results which increase the probability of diagnosing dementia*

The following results **did not provide any meaningful diagnostic value** that could be differentiated from random chance:

- CSF EIA positive (moderate quality, 95% confidence interval ranged from slight increase in probability to moderate increase )
- FTA-ABS positive (moderate quality, 95% confidence interval ranged from slight decrease in probability to slight increase)
- INNO-LIA positive (moderate quality, 95% confidence interval ranged from slight decrease in probability to slight increase)
- PCR for T. pallidum genes positive (low quality, 95% confidence interval ranged from slight increase in probability to moderate increase)
- TPPA positive (moderate quality, 95% confidence interval ranged from slight decrease in probability to slight increase)

##### *5.1.4.25.2 Results which decrease the probability of diagnosing dementia*

The following test results **decrease** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **very large:**

- CSF EIA negative (moderate quality, 95% confidence interval ranged from slight to very large)

The following results **did not provide any meaningful diagnostic value** that could be differentiated from random chance:

- FTA-ABS negative (very low quality, 95% confidence interval ranged from very large decrease in probability to moderate increase)
- INNO-LIA negative (very low quality, 95% confidence interval ranged from very large decrease in probability to large increase)
- PCR for T. pallidum genes negative (moderate quality, 95% confidence interval ranged from slight decrease in probability to slight increase)
- TPPA negative (low quality, 95% confidence interval ranged from moderate decrease in probability to slight increase)

#### 5.1.4.26 PDD/DLB versus other dementias

##### *5.1.4.26.1 Results which increase the probability of diagnosing dementia*

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **large**:

- 123I-MIBG scintigraphy positive (moderate quality, 95% confidence interval ranged from moderate to very large)

#### *5.1.4.26.2 Results which decrease the probability of diagnosing dementia*

The following test results **decrease** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **very large:**

- 123I-MIBG scintigraphy negative (moderate quality, 95% confidence interval ranged from moderate to very large)

### 5.1.4.27 PDD versus non-PDD

#### *5.1.4.27.1 Results which increase the probability of diagnosing dementia*

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **very large**:

- Movement disorders criteria for PDD (≤120) (low quality, 95% confidence interval ranged from slight to very large)

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **moderate**:

- FCSRT-IR 3-FR (≤22) (low quality, 95% confidence interval ranged from slight to very large)
- Movement disorders criteria for PDD (≤123) (low quality, 95% confidence interval ranged from slight to very large)
- ROCF (≤22) (low quality, 95% confidence interval ranged from slight to very large)

The following results **did not provide any meaningful diagnostic value** that could be differentiated from random chance:

- Movement disorders criteria for PDD (≤132) (low quality, 95% confidence interval ranged from slight increase in probability to moderate increase)

#### *5.1.4.27.2 Results which decrease the probability of diagnosing dementia*

The following test results **decrease** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **very large:**

- Movement disorders criteria for PDD (>123) (moderate quality, 95% confidence interval ranged from moderate to very large)
- Movement disorders criteria for PDD (>132) (low quality, 95% confidence interval ranged from slight to very large)

The following test results **decrease** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **large:**

- ROCF (>22) (moderate quality, 95% confidence interval ranged from moderate to very large)

The following test results **decrease** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **moderate:**

- FCSRT-IR 3-FR (>22) (moderate quality, 95% confidence interval ranged from moderate to very large)
- Movement disorders criteria for PDD (>120) (low quality, 95% confidence interval ranged from moderate to large)

#### 5.1.4.28 PPA versus non-PPA

##### *5.1.4.28.1 Results which increase the probability of diagnosing dementia*

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **very large**:

- FDG-PET positive (moderate quality, 95% confidence interval ranged from large to very large)

##### *5.1.4.28.2 Results which decrease the probability of diagnosing dementia*

The following results **did not provide any meaningful diagnostic value** that could be differentiated from random chance:

- FDG-PET negative (low quality, 95% confidence interval ranged from moderate decrease in probability to slight increase)

#### 5.1.4.29 VaD and mixed dementias versus AD

##### *5.1.4.29.1 Results which increase the probability of diagnosing dementia*

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **moderate**:

- HIS (≥5) (low quality, 95% confidence interval ranged from moderate to moderate)

##### *5.1.4.29.2 Results which decrease the probability of diagnosing dementia*

The following test results **decrease** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **large:**

- HIS (<5) (low quality, 95% confidence interval ranged from moderate to large)

#### 5.1.4.30 VaD versus AD and mixed dementia

##### *5.1.4.30.1 Results which increase the probability of diagnosing dementia*

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **moderate**:

- ADDTC (possible) positive (moderate quality, 95% confidence interval ranged from slight to large)
- ADDTC (possible and probable) positive (low quality, 95% confidence interval ranged from slight to moderate)
- NINDS-AIREN (possible) positive (moderate quality, 95% confidence interval ranged from slight to large)
- NINDS-AIREN (possible and probable) positive (low quality, 95% confidence interval ranged from slight to moderate)

The following results **did not provide any meaningful diagnostic value** that could be differentiated from random chance:

- ADDTC (probable) positive (moderate quality, 95% confidence interval ranged from slight decrease in probability to large increase)
- HIS (≥7) (low quality, 95% confidence interval ranged from slight increase in probability to moderate increase)

- NINDS-AIREN (probable) positive (moderate quality, 95% confidence interval ranged from slight decrease in probability to large increase)

#### *5.1.4.30.2 Results which decrease the probability of diagnosing dementia*

The following test results **decrease** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **moderate:**

- ADDTC (possible) negative (moderate quality, 95% confidence interval ranged from slight to large)

The following results **did not provide any meaningful diagnostic value** that could be differentiated from random chance:

- ADDTC (probable) negative (high quality, 95% confidence interval ranged from slight decrease in probability to slight increase)
- ADDTC (possible and probable) negative (low quality, 95% confidence interval ranged from slight decrease in probability to moderate decrease)
- HIS (<7) (low quality, 95% confidence interval ranged from moderate decrease in probability to slight increase)
- NINDS-AIREN (possible) negative (moderate quality, 95% confidence interval ranged from slight decrease in probability to moderate decrease)
- NINDS-AIREN (probable) negative (high quality, 95% confidence interval ranged from slight decrease in probability to slight increase)
- NINDS-AIREN (possible and probable) negative (low quality, 95% confidence interval ranged from slight decrease in probability to moderate decrease)

### 5.1.4.31 VaD versus AD

#### *5.1.4.31.1 Results which increase the probability of diagnosing dementia*

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **very large**:

- MRI positive (moderate quality, 95% confidence interval ranged from very large to very large)

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **moderate**:

- 99mTc-HMPAO SPECT positive (low quality, 95% confidence interval ranged from slight to large)

#### *5.1.4.31.2 Results which decrease the probability of diagnosing dementia*

The following test results **decrease** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **moderate:**

- 99mTc-HMPAO SPECT negative (low quality, 95% confidence interval ranged from moderate to large)
- MRI negative (low quality, 95% confidence interval ranged from slight to large)

#### 5.1.4.32 VaD versus DLB

##### *5.1.4.32.1 Results which increase the probability of diagnosing dementia*

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **very large**:

- MRI positive (moderate quality, 95% confidence interval ranged from moderate to very large)

##### *5.1.4.32.2 Results which decrease the probability of diagnosing dementia*

The following test results **decrease** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **moderate:**

- MRI negative (low quality, 95% confidence interval ranged from slight to large)

#### 5.1.4.33 VaD versus FTD

##### *5.1.4.33.1 Results which increase the probability of diagnosing dementia*

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **very large**:

- MRI positive (moderate quality, 95% confidence interval ranged from large to very large)

The following results **did not provide any meaningful diagnostic value** that could be differentiated from random chance:

- 99mTc-HMPAO SPECT positive (low quality, 95% confidence interval ranged from slight decrease in probability to large increase)

##### *5.1.4.33.2 Results which decrease the probability of diagnosing dementia*

The following test results **decrease** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **moderate:**

- MRI negative (low quality, 95% confidence interval ranged from slight to large)

The following results **did not provide any meaningful diagnostic value** that could be differentiated from random chance:

- 99mTc-HMPAO SPECT negative (low quality, 95% confidence interval ranged from large decrease in probability to slight increase)

#### 5.1.4.34 VaD versus non-VaD dementia plus unclassifiable

##### *5.1.4.34.1 Results which increase the probability of diagnosing dementia*

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **moderate**:

- MRI positive (moderate quality, 95% confidence interval ranged from moderate to large)

##### *5.1.4.34.2 Results which decrease the probability of diagnosing dementia*

The following results **did not provide any meaningful diagnostic value** that could be differentiated from random chance:

- MRI negative (low quality, 95% confidence interval ranged from very large decrease in probability to slight increase)

#### 5.1.4.35 VaD versus non-VaD

##### *5.1.4.35.1 Results which increase the probability of diagnosing dementia*

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **very large**:

- MRI positive (high quality, 95% confidence interval ranged from very large to very large)

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **moderate**:

- 99mTc-HMPAO SPECT positive (low quality, 95% confidence interval ranged from slight to moderate)

##### *5.1.4.35.2 Results which decrease the probability of diagnosing dementia*

The following test results **decrease** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **moderate:**

- 99mTc-HMPAO SPECT negative (moderate quality, 95% confidence interval ranged from slight to moderate)
- MRI negative (moderate quality, 95% confidence interval ranged from slight to large)

#### 5.1.4.36 VaD versus other dementias

##### *5.1.4.36.1 Results which increase the probability of diagnosing dementia*

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **very large**:

- MRI positive (moderate quality, 95% confidence interval ranged from very large to very large)

The following test results **increase** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **large**:

- HIS (≥7) (high quality, 95% confidence interval ranged from moderate to very large)

##### *5.1.4.36.2 Results which decrease the probability of diagnosing dementia*

The following test results **decrease** the probability of diagnosing dementia in a person with suspected dementia to a degree that is likely to be **moderate:**

- HIS (<7) (moderate quality, 95% confidence interval ranged from slight to moderate)
- MRI negative (low quality, 95% confidence interval ranged from slight to large)

#### 5.1.4.37 Health economics

##### *5.1.4.37.1 GP administered diagnostics*

One directly applicable UK cost–utility model with potentially serious limitations explored 3 GP-administered diagnostic strategies for over 65 year-olds, concluding that MMSE, 6CIT, and GPCOG are all more cost effective than a GP's unassisted judgement. Among the 3 tests, the GPCOG was considered the most cost-effective option for the NHS, unless QALYs are valued at £60,000 each, in which case the small additional QALY gain associated with 6CIT would be worth its additional costs. Assuming a threshold of £30,000 per QALY, the probability of the GPCOG being the best option was 75%.

One partially applicable Dutch trial-based cost–utility analysis with potentially serious limitations compared multidisciplinary diagnosis with usual care in suspected dementia. Once costs outside the NICE reference case were removed, the multidisciplinary approach cost an additional €587, and produced an additional 0.051 QALYs, resulting in an ICER of €11,510 per QALY compared with usual care. Probabilistic sensitivity analysis (from which non-reference-case costs could not be disaggregated) suggested that the probability that multidisciplinary diagnosis is cost effective was 72% when QALYs are valued at €45,000 each.

#### *5.1.4.37.2 Imaging diagnostics*

One partially applicable French cost–utility model with potentially serious limitations compared MRI, contrast-enhanced MRI and usual diagnosis. Standard diagnosis was dominated by standard MRI in all scenarios. Contrast enhancement was found to produce a small increase in QALYs, but was also associated with additional costs. The probability of contrast-enhanced MRI being optimal remained lower than 4% at all thresholds up to €200,000/QALY.

One partially applicable Spanish cost–utility model with potentially serious limitations compared Florbetapir-PET with standard clinical examination, finding additional costs of €36 and benefits of 0.008 QALYs, resulting in an ICER of €4,769/QALY. In a scenario where patients underwent initial assessment with an MMSE of 22, Florbetapir-PET was found to be dominant. Over 82% of the PSA simulations showed Florbetapir-PET to be cost effective if QALYs are valued at €30,000 each. A closely related, partially applicable model with potentially serious limitations compared Aβ-PET compared with standard diagnostic assessment in France. It found costs and QALYs were both higher with Aβ-PET, with an ICER of €43,000/per QALY. Probabilistic sensitivity analysis suggested that ICERs were below €40,000 per QALY in more than 95% of simulations; however, it was not possible to remove costs that are inconsistent with the NICE reference case from this analysis.

One partially applicable cost–utility model with potentially serious limitations found that SPECT (visual and computed) cost more money and produced fewer QALYs than standard examination. Contrast-enhanced MRI produced a small QALY benefit, but the additional costs that were also associated with the approach led to an ICER of over $300,000 per QALY gained. In an updated version of the same model (this time with limitations assessed as minor) MRI was associated with an ICER in the order of £0.5m/QALY. Both SPECT and PET were dominated by MRI.

### 5.1.5 Evidence to recommendations

#### 5.1.5.1 Primary assessment

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| **Relative value of different outcomes** | The committee noted that the outcomes of interest varied during the diagnosis process. During the initial assessment in primary care, the committee looked for cognitive tests with high positive likelihood ratios/high sensitivity to ensure that the majority of people with possible dementia would be referred for further assessment. The negative likelihood ratios/specificity were thought to be less important at this stage, but there was a balance as the committee chose not to recommend tests with specificity below 70% to prevent too many false positives being referred to specialist care. In addition, there were sufficient tests with higher positive likelihood ratios/sensitivities and negative likelihood ratios/specificities to render the use of less specific tests unnecessary. The committee also noted that the four metrics reported (positive and negative likelihood ratios, sensitivity and specificity), despite being based on the same underlying data, covered slightly different aspects of diagnostic accuracy, and |

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| | therefore it was important to consider all of them as part of decision making. |
| **Trade-off between benefits and harms** | **General issues**<br>Being diagnosed with dementia can be a stressful and traumatic experience. The committee recognised this and noted the importance of guiding people with suspected dementia through the assessment process carefully. In particular, it is essential that information is provided throughout the diagnostic process and continued informed consent is obtained for investigations that may be particularly stressful (e.g. imaging and lumbar puncture for cerebrospinal fluid (CSF) biomarker tests).<br>The committee commented that it was also important to consider situations where a patient may not want a referral for an assessment/diagnosis, and the potential disadvantageous outcomes that might result from this choice (e.g. problems with obtaining support, care and treatment).<br>**Decision making in primary care**<br>The committee discussed the importance of the initial assessment of a person presenting with suspected dementia. In particular, they stressed the value of taking a good history from the person, focusing not just on cognitive, behavioural and psychological symptoms, but on the impact of these symptoms on a person's daily life. They noted that appointment times in primary care are short compared with those in secondary care and that, as a result, physicians need to use a brief validated cognitive test with a high sensitivity and specificity to rapidly determine whether there is a possibility of dementia. They also noted that an initial assessment should include a physical examination and tests (such as blood and urine tests) to exclude reversible causes of cognitive decline.<br>The committee reviewed the evidence and noted that a number of cognitive tests met the high sensitivity and specificity criteria (including ACE, ACE-III, ACE-R, MoCA, MMSE, CERAD battery), but that these tests were too long or complex for routine use in primary care.<br>The committee noted that although the MoCA had a high sensitivity and specificity at certain thresholds, in practice the test was not liked by memory clinic staff due to the large number of false positives seen. This was reflected in the evidence by the wide confidence interval for specificity at the optimal test threshold of <19 and by the much lower specificity point estimates at other test cut-offs. In addition, based on their experience, the test was not well tolerated by people with suspected dementia. Taking these issues into account, the committee decided not to recommend MoCA for the initial assessment of people with suspected dementia in primary or secondary care settings.<br>The committee recommended a choice of brief cognitive tests that they considered suitable for a primary care setting that had high sensitivity (≥ 80%) and good specificity (≥ 70%). The committee agreed that the evidence presented did not favour a single test, leading them to recommend a selection of possible tests. It was also noted that selecting a choice of tests using a different method (e.g. picking those with the largest +ve and –ve likelihood ratios) would lead to a slightly different list of favoured tests. However, because there were a considerable number of tests found to have very similar levels of diagnostic accuracy, the committee were confident the choice of metric used for analysis would not lead to a recommendation that was more or less clinically appropriate.<br>Certain tests (such as the 5 word recall test and verbal fluency tests) are weighted towards verbal recall memory, which is an important domain affected in Alzheimer's disease. The committee agreed that |

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| | other forms of dementia, such as dementia with Lewy bodies and vascular dementia, often do not show such pronounced memory defects at initial presentation and may not be detected using these tests. The committee noted that, although in the UK about two thirds of the population living with dementia have Alzheimer's disease, it is very important for the physician to select the test appropriately based on whether the person with suspected dementia presented with memory impairment.<br>The committee also made an accompanying 'do not' recommendation to stress the importance of the physician not basing the decision not to refer a person for further assessment solely on the basis of a normal cognitive test result.<br>The committee agreed that the person considering referral should carry out routine investigations and tests to rule out reversible causes of cognitive impairment. No data was found to support these investigations or the usefulness of history taking in the diagnosis of dementia, but the committee considered this to be general good practice based on their experience and made a recommendation to reflect this, and agreed that failing to rule out reversible causes of cognitive decline may lead to over referrals, both wasting resources and causing unnecessary stress to individuals.<br>The committee discussed the importance of taking an informant history. The committee recommended a structured tool, such as the as the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) or the Functional Activities Questionnaire (FAQ), to help with this process, noting that this also demonstrated a good balance between sensitivity and specificity. They stressed that this should be in addition to and not instead of a conversation with the informant. The committee also noted that the IQCODE could be completed by an informant alone and at a later date as needed.<br>**Rapidly progressive dementia**<br>The committee noted there was clear evidence that CSF tests had both high sensitivity and specificity for detecting CJD. They also noted that in the UK, standard practice for all people with suspected rapidly progressive dementia would be to refer them to a specialist centre for both testing and management, and it is in this specialist setting that CSF testing would be conducted. The committee therefore agreed it was appropriate to make a recommendation reflecting this practice, which was justified by the strong evidence for the appropriateness of CSF testing in this population. |
| **Consideration of health benefits and resource use** | Although there was a substantial amount of economic evidence for these review questions, of the 6 economic studies, only 1 study (Wolfs et al. 2009) was conducted alongside a clinical trial. This meant that the remaining 5 studies were based on modelling, and incorporated a substantial amount of uncertainty in the large number of model input parameters. Furthermore, the benefits of early diagnosis were understood to be speculative as the committee accepts that there are no disease modifying treatments available for dementia. Many of the included studies modelled hypothetical treatments that may be efficient in early dementia.<br>The committee considered the study by Biasttu et al. (2012) but did not consider the paper to present reliable estimates of cost effectiveness of the diagnostic strategies considered, as costs not relevant to the NICE reference case could not be removed from the analysis. Furthermore, Biasttu et al. (2012) lacked any sensitivity analyses.<br>The committee considered the study by Tong et al. (2016) made a strong case for 6CIT as it was free and had the highest sensitivity for dementia and mild cognitive impairment from all tests examined that are used in a UK setting. However, this study made use of old data |

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| | for the unassisted GP strategy, and data on the GPCOG was from a screening study rather than a study in people with suspected dementia, and this reduced the committee's confidence in the evidence.<br>The committee considered the study by Wolfs et al. (2009) which compared DOC-PG with usual care and were uncertain of the study's findings applicability to a UK setting, as it was not possible to remove costs not relevant to the NICE reference case.<br>The committee considered two studies by McMahon (McMahon et al. 2000 and McMahon et al. 2003) which examined standard examination, visual SPECT, computed SPECT and contrast-enhanced MRI and considered them to be unreliable to form recommendations as ICERs for all examined treatments were either dominant or excessive to commonly accepted cost-effectiveness thresholds, no information was provided as to what was required before people with dementia were able to present to the specialist diagnostic centres and the authors had competing interests that the committee considered of potential importance.<br>The committee considered two studies by Hornberger (Hornberger et al. 2015 and Hornberger et al. 2017) and found both studies, which examined the use of florbetapir positron emission tomography, to be of limited value to form a positive recommendation, as there was a very small non-significant increase in QALYs gained and the authors had competing interests that the committee considered of potential importance.<br>The committee agreed that, since the MMSE is under copyright and attracts a fee, it should not be used where another similar test with comparable sensitivity and specificity is available for free (e.g. 10-CS, MIS, TYM for initial assessment in primary care). ACE and ACE-R also include an MMSE score and should be avoided for the same reason. Although the MMSE has been used extensively in the past and is relatively inexpensive, the money saved by using a comparable, free test can be spent elsewhere where there is greater need. The committee also noted that more complex (and therefore time-consuming) tests did not appear to be more effective at detecting dementia than shorter and simpler tests, and it was therefore a more efficient use of resources to use these briefer tests within a time-constrained primary care setting.<br>The committee commented that the IQCODE (Informant Questionnaire on Cognitive Decline in the Elderly) and FAQ had the advantage of being self-administered tests. It could therefore be completed in the waiting room by the informant. This could free up time in the appointment for the GP to listen to the patient and informant, potentially reducing the number of appointments needed to reach an initial diagnosis and saving money for the NHS. The TYM (Test Your Memory) test has a similar advantage. |
| **Quality of evidence** | Positive and negative likelihood ratios were used to determine the diagnostic accuracy of the tests and the level of confidence/degree of uncertainty surrounding this estimate. Large positive likelihood ratios were associated with large increases in the probability that a person with a positive test had dementia, while large negative likelihood ratios were associated with large decreases in the probability of having dementia given a negative test result. The confidence intervals for these measures, and the minimally important differences specified for them in section 3.4, were used to determine the level of precision in the evidence, which together with consideration of the risk of bias, heterogeneity and applicability made up the overall quality rating for the studies.<br>The committee noted that the quality of the evidence was low in the case of many tests due to serious or very serious risk of bias issues. |

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| | This was largely due to poor reporting of blinding procedures and that it was likely that index and reference tests were assessed without knowledge of each other, but that this could not be assumed in the absence of a statement to such effect. Other common issues that led to downgrading for risk of bias included the use of optimised test thresholds and subgroup analyses that excluded large segments of the study population (for example, people with mild cognitive impairment). The committee agreed that it was appropriate to downgrade for risk of bias if > 10% study population was excluded from an analysis. However, they also noted that these subgroup analyses were useful in providing data on test performance in diagnosing between dementia subtypes, especially as case-control data was excluded from the evidence review.<br>The committee noted that a large body of case-control evidence was omitted from this review on the basis that the comparison of patient groups of interest to control groups could inflate test sensitivity and specificity. However, case-control studies often detailed the development and validation of the diagnostic tests and the committee was able to use its knowledge of the literature to provide additional support for its decisions. This was particularly important where the evidence from cohort studies was of low or very low quality. However, they acknowledged that the use of cohort studies examining the diagnosis of people with suspected dementia provided evidence for test accuracy under circumstances closer to real-life.<br>There was a shortage of diagnostic test accuracy studies involving people with suspected dementia in a primary care setting. As a result the committee were forced to extrapolate from the results obtained using appropriate tests in a specialist secondary care setting. Based on the committee's experience, certain tests (including MRI, CT, SPECT, PET and biomarkers) were not considered to be useful to determine whether to refer a person with suspected dementia for further investigation. These tests would not be available in a primary care setting and their value lies later in the diagnostic pathway to help with dementia subtype classification.<br>It was noticeable that some tests were missing from the evidence base. The committee commented that there was a lack of data on the GPCOG test, which is routinely used in GP surgeries in the UK. However, this test is used to screen for dementia and no published evidence was found in a population with suspected dementia (the available studies were all on dementia screening, which is not within the scope of this guideline). A similar problem was found with the CAMCOG test, as the studies identified were excluded for using the test to screen for dementia and/or being case-control studies. Primary studies using Cantab mobile and Cantab insight were also missing. In addition, there was a shortage of evidence for diagnosing dementia in people with Parkinson's disease or stroke as the evidence found was focused on screening for dementia in these people and was inadmissible as a result. |
| **Other considerations** | The committee agreed that physicians should be aware of the additional challenges of diagnosing dementia in certain vulnerable groups, such as people with learning difficulties and Down's syndrome, and those people with language and sensory impairment, lower educational levels and a low standard of literacy. Whilst the evidence base did not allow them to make specific recommendations for how the diagnostic pathway should be different for these groups of individuals, they agreed that it was important that people from these more difficult to diagnose groups should be assessed by a clinician with specialist skills in those areas, who would be familiar with the difficulties and able to make appropriate adaptations to the process used. A cross-reference to the NICE guideline on mental health problems in people with learning disabilities was also added, |

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| | which provides advice on some specific instruments to use when assessing for dementia in people with learning disabilities.<br>The committee agreed that some tests (e.g. MoCA) are less robust in certain population groups due to cultural differences (educational levels, language issues), and this can skew the resulting diagnosis of dementia/ continued suspicion of dementia. They stressed the need to take these issues into account when choosing cognitive tests and to select test cut-offs appropriately based on the characteristic of the person with suspected dementia. For this reason, the committee agreed it would not be appropriate to specify cut-offs that should be used for tests, as these would need to be adjusted for particular individuals.<br>The committee noted that neuropsychological tests are not designed to be used to diagnose dementia. Rather they either assess performance in one single aspect of cognition (e.g. episodic memory or naming ability) or may be grouped into batteries that either cover performance in a range of aspects (e.g. RBANS) or give a detailed profile of performance across the elements of one broad construct such as memory (e.g. Wechsler Memory Scale). By providing this detailed information about cognitive functioning a thorough neuropsychological assessment can contribute useful information to the process of reaching a dementia diagnosis and distinguishing between dementia sub-types.<br>The committee commented that primary care physicians may need support and training to develop the skills to make appropriate referrals for dementia diagnosis and that the use of the IQCODE could help provide some structure to their discussions with informants. |

#### 5.1.5.2 Diagnosing dementia in specialist services

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| **Relative value of different outcomes** | The committee agreed that, once a person was being assessed for dementia in specialist diagnostic services, it was important that any test (or battery of tests) used should have a balance between positive likelihood ratios/sensitivity and negative likelihood ratios/specificity. They also noted that people who are difficult to diagnose may go through multiple sequential tests before arriving at a diagnosis, and therefore it was important to consider all test that might provide relevant diagnostic value, and not only what is the single best test for a given diagnosis.<br>The committee also noted that the four metrics reported (positive and negative likelihood ratios, sensitivity and specificity), despite being based on the same underlying data, covered slightly different aspects of diagnostic accuracy, and therefore it was important to consider all of them as part of decision making. |
| **Trade-off between benefits and harms** | **General issues**<br>The committee discussed the potentially stressful and unpleasant diagnostic tests that could be used in a specialist setting. These include lumbar puncture to obtain cerebrospinal fluid (CSF) for biomarker tests, MRI and other imaging tests. These tests may not be well tolerated by all patients, particularly those with claustrophobia (MRI) or people with more severe dementia. The committee noted that it was important to use these tests only if they are required to reduce diagnostic uncertainty, if the person with suspected dementia/with dementia requiring subtype diagnosis agrees and if they can comply with test requirements. The committee agreed that to avoid unnecessary tests being undertaken, it was important to include a specific recommendation stating these tests only be undertaken if they would reduce diagnostic uncertainty and reducing that uncertainty would change management. |

In addition, the committee discussed the advantage to the person with an uncertain diagnosis of dementia, and for the NHS (see below), of carrying out certain tests (e.g. SPECT, PET imaging and biomarker tests) in series rather than parallel. Carrying out these tests in parallel may result in a faster diagnosis, but this may also mean that unnecessary tests are performed and patients are exposed to additional stressful situations. As a result the committee recommended that these tests be performed sequentially, in either order, but that the remaining test should be 'considered' if diagnosis remained unclear.

**Initial diagnosis in a specialist care setting**

Following referral to specialist care, the committee recommended the use of validated criteria to guide the clinician during the diagnostic process. The committee noted that there was limited evidence for the diagnostic accuracy of the criteria. The quality of the data was variable with high sensitivity and specificity in some cases (DLB consensus criteria (high quality), FTDC criteria for bv-FTD (moderate quality), Movement Disorders Society for PDD (low to moderate quality) and lower sensitivity with good specificity in others (NINDS-AIREN (low to moderate quality), FTDC criteria for frontotemporal dementia (high quality). However, as clinical criteria had formed the reference standard for the assessment of diagnostic test accuracy for the majority of tests, the committee agreed it was appropriate to accept them as the current gold standard approach for diagnosis of dementia subtypes. The committee recognised that the most accurate reference standard (neuropathology) was usually unavailable for use before death.

The committee agreed it was appropriate only to consider studies that looked at the current versions of clinical criteria, although this was not always easy to determine (for example in the case of Creutzfeldt-Jakob disease). No studies were found that evaluated the current version of the NINCDS-ADRDA criteria. In addition, data for the diagnostic accuracy of the revised FTD diagnostic criteria (Rascovsky 2011) were not included in this evidence review as it was presented in such a way that specificity could not be calculated. (All of the study participants had a diagnosis of FTD at baseline and the study did not include the final diagnostic results for people who were not diagnosed with FTD initially). The committee noted that a new version of the DLB consensus criteria was due to be published, but decided to examine the evidence obtained for the existing criteria in the meantime. The committee agreed that if a new version of clinical criteria had yet to be validated, but had been developed using a robust methodology and based on the original version, it was reasonable to assume that it would be at least as accurate as the earlier version of the criteria.

The committee reviewed the evidence for the diagnosis of dementia subtypes. The committee also noted that in the UK about two thirds of people with dementia are diagnosed with Alzheimer's disease. The committee noted that people with Alzheimer's disease often have deficits in verbal recall and memory (see also discussion in table above) and as a result it recommended that a test of verbal episodic memory should be used where Alzheimer's disease is suspected.

The committee agreed there was also a subset of people with an unclear diagnosis in whom a referral for formal neuropsychological testing would be appropriate, either if it is unclear if a person has cognitive decline, or if the cause of cognitive decline or correct subtype diagnosis is unclear. The committee agreed it was appropriate to make a 'consider' recommendation around neuropsychological testing to cover these issues. They noted that there was evidence for a range of individual test instruments, but that

selecting the appropriate ones for an individual and correctly interpreting the results often needed input from a neuropsychologist.

The committee discussed the importance of making an accurate diagnosis based on the fewest tests possible to limit the number of tests a person with suspected dementia is subjected to and to reduce costs to the NHS (see above for more details). The committee recommended that only after an initial assessment has been completed should structural imaging (e.g. CT or MRI) be offered to people who still have suspected dementia or require dementia subtype diagnosis. The committee agreed that although MRI had good specificity for most dementia subtypes the sensitivity was low. However, the evidence showed that it had good sensitivity, specificity and moderate to large positive LRs for vascular dementia and behavioural variant frontotemporal dementia based on low to moderate quality evidence. The committee also noted there are a proportion of people for which dementia is well established and the subtype diagnosis is clear who would not need structural imaging, and agreed this was important to reflect in the recommendation.

The committee noted that there can be problems with the interpretation of imaging data by non-specialists and commented that where scans are requested by primary care physicians/non-specialists, specialist input should be obtained to help them interpret scan data. This will facilitate faster, more accurate diagnosis of dementia and reduce unnecessary tests and referrals.

The committee discussed which tests to perform to diagnose dementia subtypes if diagnostic uncertainty remained at this point.

**Diagnosing Alzheimer's disease**

In keeping with the committee's earlier discussion about minimising test burden for patients, they decided to recommend that the physician 'consider' the use of biomarkers **or** more specialised imaging (FDG-PET, SPECT) for people with suspected Alzheimer's disease where diagnostic uncertainty remains. The committee noted the role of imaging to help exclude other pathologies. Based on the strength of the biomarker evidence (ranging from low to high quality for different tests and combinations of tests) they used a 'consider' recommendation.

Biomarkers can be useful for the diagnosis of certain dementia subtypes, but there are a number of issues that need to be considered, including difficulty in obtaining samples from patients (see above) and the lack of reliability of some of these tests in older people. Specifically, the committee noted that it was very important to consider the age of a patient before referring them for biomarker tests. Biomarker levels are altered in certain types of dementia (such as Alzheimer's disease and Creutzfeldt-Jakob disease), but their levels change with age as well. This means that the tests will give more false positives in older people as the levels of biomarkers are also altered in cognitively normal people of this age. The committee made a 'be aware' recommendation to accompany the use of biomarkers for the diagnosis of Alzheimer's disease to highlight this issue.

The committee noted the importance of knowing the mean age and age range for the interpretation of diagnostic test accuracy evidence, in particular for biomarker data. In the case of Toledo (2012), they commented that the sensitivities and specificities of p-tau 181, and amyloid beta and total tau combined were particularly high compared with other studies (e.g. Frisoni, 2009; Dumurgier, 2015). This may be linked to the mean age (69 years) of the participants, which is about 10 years lower than the average memory clinic population in the UK.

Where there was clinical suspicion of Alzheimer's disease, the committee recommended that the use of FDG-PET be 'considered'

by the physician based on the variable quality of evidence from very low to moderate. Good sensitivities, specificities and LRs were seen when the test was used to distinguish AD from other dementias, no dementia and non-AD, but the test was less diagnostically informative for distinguishing AD from FTD and DLB.

If FDG-PET was unavailable, the committee recommended that perfusion SPECT be 'considered'. This category included HMPAO SPECT and ECD SPECT. The committee agreed that there was insufficient difference between the test accuracy and likelihood ratios for these tests to warrant recommendation of either one over the other. In both cases, evidence quality was variable (very low to moderate), sensitivity and specificity were good (around 70 -80%), with mostly moderate positive and negative LRs. They noted however, that HMPAO SPECT was the type routinely used in the UK, and this was unlikely to change.

Based on the committee's earlier discussion about the benefits to the person with suspected dementia of carrying out certain tests in series, they recommended that the other test should be 'considered' should diagnostic uncertainty remain.

The committee decided to write a 'do not use' recommendation for apolipoprotein E (ApoE) genetic testing as ApoE status is associated with an increased risk of dementia rather than being a biomarker for the occurrence of dementia. The committee also included EEG in the 'do not use' recommendation as the test provided no meaningful diagnostic information for diagnosing AD based on the positive and negative likelihood ratios from high-quality evidence. The committee noted that while there were other tests that also did not provide meaningful diagnostic information, these were not commonly used in the UK, and they agreed it was important to retain the recommendation on EEG from the old guideline so as to not give the impression that the situation has changed.

The committee noted that a proportion of people with early-onset Alzheimer's disease will have a genetic cause for their dementia, and agreed it was appropriate to include a 'be aware' recommendation on this issue.

**Diagnosing dementia with Lewy bodies**

The committee noted that DLB resulted in distinctive features on SPECT that could be used for diagnosis. The committee recommended the use of 123I-FP-CIT SPECT for the diagnosis of DLB based on low to high quality evidence from 5 studies comparing DLB to non-DLB or other dementias. The positive and negative likelihood ratios were large to very large with high sensitivity and specificity.

The committee chose not to recommend IMP-SPECT as it had lower sensitivity and specificity than 123I-FP-CIT SPECT, with a moderate positive likelihood ratio and a negative likelihood ratio that showed the test gave no meaningful diagnostic information and was based on low quality evidence.

The committee discussed the evidence for the use of MIBG cardiac scintigraphy for the diagnosis of DLB. The evidence from 5 studies looking at DLB versus non-DLB was of low quality, but had good sensitivity, specificity and large to very large likelihood ratios. Another single study looking at DLB versus other dementias provided moderate to high quality evidence with similar diagnostic accuracy. Taken together, this evidence led the committee to make a 'consider' recommendation. Importantly, they observed that this test was not useful for diagnosing PDD, as MIBG imaging results were already abnormal in PD.

The committee discussed the importance of not ruling out a diagnosis of DLB solely based on these imaging tests, as they are not

completely accurate, and it made a recommendation to reflect this issue.

The evidence presented suggested that EEG could be useful for the diagnosis of DLB (moderate-high quality evidence, large positive and negative likelihood ratios and high sensitivity and specificity). However, the committee commented that the data was from 1 study that used complex processing of results (and a convoluted algorithm) and that this would be beyond a standard clinical neurophysiology department in the UK. In practice, EEG is used qualitatively in the NHS, and no evidence was available using this method. They did not recommend EEG here as a result.

The committee also noted that the Lewy body composite risk score (LBCRS) is not actually a diagnostic test for dementia, but rather asks about symptoms to facilitate diagnosis.

People with PD do not only develop PDD, but may be diagnosed with PD then AD. The committee commented that the Rey-Osterrieth complex figure test (ROCF) and cued recall tests are not suitable to distinguish PDD from PD with AD.

**Diagnosing frontotemporal dementia**

The committee discussed the evidence regarding FDG-PET and perfusion SPECT (ECD-SPECT and HMPAO-SPECT) for the diagnosis of FTD. They agreed that the evidence for FDG-PET was of very low to moderate quality, with low sensitivity, high specificity, moderate to large positive likelihood ratios and not diagnostically meaningful to large negative likelihood ratios. In the case of diagnosing PPA versus non-PPA the evidence quality was higher (low to moderate) and the positive likelihood ratio was very large. As a result, the committee decided to recommend that physicians use this test when diagnostic uncertainty remains, in particular because of the very high specificities seen.

There were multiple studies looking at HMPAO SPECT for the diagnosis of FTD versus other types of dementia. In all cases, the evidence for multiple-headed cameras alone gave higher sensitivity (around 0.7 versus 0.5) and similar specificity (around 0.9) than when this was combined with data for single-headed cameras, which are no longer in use. Data quality was very low to moderate, with moderate to very large positive and negative likelihood ratios. In contrast, the evidence for ECD-SPECT was confined to 1 moderate quality study which found that this test was very sensitive and specific, with very large positive and negative likelihood ratios for the diagnosis of FTD. Based on the evidence and their experience that HMPAO SPECT imaging was a more established technique in the UK, the committee decided not to specify which type of SPECT be carried out, but to recommend perfusion SPECT be considered as an alternative to FDG-PET.

The committee commented that FTD may be easy to diagnose if the scan demonstrates a clear pattern of unilateral or bilateral frontal or temporal lobe atrophy, but a person can have a normal scan and still have FTD. As a result, the committee made a ‘do not’ recommendation to prevent FTD being ruled out solely based on the above recommended tests.

The committee noted that a proportion of people with frontotemporal dementia will have a genetic cause for their dementia, and agreed it was appropriate to include a ‘be aware’ recommendation on this issue.

**Diagnosing vascular dementia**

MRI was recommended by the committee for cases where diagnostic uncertainty remains, but there is suspicion of vascular dementia. This recommendation was based on moderate to high quality evidence from 2 studies associated with moderate to large positive likelihood

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| | ratios and good sensitivity (0.7-0.8) and specificity. Low to moderate quality evidence from the same studies was associated with moderate negative likelihood ratios.<br>In cases where MRI was unavailable or contraindicated, the committee recommended that computed tomography (CT) be used instead. Whilst no specific evidence was identified looking at the diagnostic accuracy of CT for vascular dementia, they agreed that the positive results found for MRI implied that other forms of structural imaging were also likely to provide diagnostic value, as similar features would be detected on CT and MRI. They also agreed that MRI should be the first choice of test, as this was the test with clear and robust evidence to support its use.<br>The committee commented that it was unclear how much vascular damage on a scan was sufficient to impair patient functioning. They noted that it was relatively straightforward to interpret effects on function from low or high levels of vascular disease, but the clinical relevance of moderate levels of vascular disease on imaging was often less clear. In these cases, the committee suggested that physicians refer to clinical criteria and seek expert advice where needed.<br>The committee noted that a proportion of people with early-onset vascular dementia will have a genetic cause for their dementia, and agreed it was appropriate to include a 'be aware' recommendation on this issue. |
| **Consideration of health benefits and resource use** | The committee agreed that in cases of diagnostic uncertainty, carrying out biomarker and imaging tests in series, rather than in parallel, may result in a clear diagnosis with reduced patient exposure to potentially traumatic tests and at a reduced cost to the NHS.<br>The committee noted that, whilst there were costs associated with many of the tests recommended (in particular, imaging and biomarkers) these tests were already routinely in use in the NHS and therefore there should not be a substantial change in resource use from the recommendations made. They also noted that, for imaging tests, the largest cost was the initial purchase of the machinery itself, and afterwards the incremental cost of each test begin carried out was much lower. |
| **Quality of evidence** | Positive and negative likelihood ratios were used to determine the diagnostic accuracy of the tests and the level of confidence/degree of uncertainty surrounding this estimate. Large positive likelihood ratios were associated with large increases in the probability that a person with a positive test had dementia, while large negative likelihood ratios were associated with large decreases in the probability of having dementia given a negative test result. The confidence intervals for these measures, and the minimally important differences specified for them in section 3.4, were used to determine the level of precision in the evidence, which together with consideration of the risk of bias, heterogeneity and applicability made up the overall quality rating for the studies.<br>The committee discussed the importance of ensuring that a study population was relevant for UK diagnostic services and agreed it was appropriate to downgrade a study for indirectness if the participants had less education than the general UK population, or if the age of the people recruited was lower than was considered to be representative of the UK memory clinic population. It noted that the variability in sensitivity and specificity observed between studies using the same tests may be due to differences in the populations tested. The committee agreed that certain tests are more vulnerable to this issue than others (e.g. certain cognitive tests, discussed in primary assessment table above). |

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| | The committee agreed that the evidence on rarer dementia subtypes (HAND, neurosyphilis, CADASIL, and corticobasal degeneration) was not sufficiently strong for any recommendations to be made. They also agreed that these people were likely to be in highly specialist care, and therefore an inability to make recommendations in the guideline was unlikely to have an impact on their care. |
| **Other considerations** | Please see the primary care table above for a discussion of the issues surrounding the diagnosis of dementia in vulnerable populations.<br>The committee noted there was only limited evidence available around the accuracy and cost-effectiveness of amyloid imaging despite there now being licensed products available for this. They agreed the evidence was not sufficient to make recommendations on its use, but that it was appropriate to make a research recommendation on this topic. They noted that amyloid imaging was likely to be used towards the end of the diagnostic pathway in individuals difficult to diagnose with more standard tests, and therefore agreed the research recommendation should focus on the additional value provided by amyloid imaging over and above standard diagnostic assessment, and the comparative value with other imaging or biomarker tests that could be used. |

### 5.1.6 Recommendations

**Initial assessment in non-specialist settings**

1. **At the initial assessment take a history (including cognitive, behavioural and psychological symptoms, and the impact symptoms have on their daily life):**
    - from the person with suspected dementia **and**
    - if possible, from someone who knows the person well (such as a family member).

2. **If dementia is still suspected after initial assessment:**
    - conduct a physical examination **and**
    - undertake appropriate blood and urine tests to exclude reversible causes of cognitive decline **and**
    - use cognitive testing.

3. **When using cognitive testing, use a validated brief structured cognitive instrument such as:**
    - the 10-point cognitive screener (10-CS)
    - the 6-item cognitive impairment test (6CIT)
    - the 6-item screener
    - the Memory Impairment Screen (MIS)
    - the Mini-Cog
    - Test Your Memory (TYM).

4. **Do not rule out dementia solely because the person has a normal score on a cognitive instrument.**

5. **When taking a history from someone who knows the person with suspected dementia, consider supplementing this with a structured instrument such as the**

**Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) or the Functional Activities Questionnaire (FAQ)**

6. **Refer the person to a specialist dementia diagnostic service (such as a memory clinic or community old age psychiatry service) if:**
    - reversible causes of cognitive decline (including delirium, depression, sensory impairment [such as sight or hearing loss] or cognitive impairment from medicines associated with increased anticholinergic burden) have been investigated **and**
    - dementia is still suspected.

7. **If the person has suspected rapidly-progressive dementia, refer them to a neurological service with access to tests (including cerebrospinal fluid examination) for Creutzfeldt-Jakob disease and similar conditions.**

8. **For more guidance on assessing for dementia in people with learning disabilities, see the NICE guideline on mental health problems in people with learning disabilities.**

**Dementia diagnosis in specialist settings**

9. **Diagnose a dementia subtype (if possible) if initial specialist assessment (including an appropriate neurological examination and cognitive testing) confirms cognitive decline and reversible causes have been ruled out.**

10. **If Alzheimer's disease is suspected, include a test of verbal episodic memory in the assessment.**

11. **Consider neuropsychological testing if it is unclear:**
    - whether or not the person has cognitive impairment **or**
    - whether or not their cognitive impairment is caused by dementia **or**
    - what the correct subtype diagnosis is.

12. **Use validated criteria to guide clinical judgement when diagnosing dementia subtypes, such as:**
    - International consensus criteria for dementia with Lewy bodies
    - International FTD criteria for frontotemporal dementia (primary non-fluent aphasia and semantic dementia)
    - International Frontotemporal Dementia Consortium criteria for behavioural variant frontotemporal dementia
    - NINDS-AIREN criteria (National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences) for vascular dementia
    - NIA criteria (National Institute on Aging) for Alzheimer's disease
    - Movement disorders Society criteria for Parkinson's disease dementia
    - International criteria for Creutzfeldt-Jakob disease.

13. **Offer structural imaging to rule out reversible causes of cognitive decline and to assist with subtype diagnosis, unless dementia is well established and the subtype diagnosis is clear.**

14. **Only consider further diagnostic tests (recommendations 15-28) if:**
    - it would help to diagnose a dementia subtype **and**
    - knowing more about the dementia subtype would change management.

**Further tests for Alzheimer's disease**

15. **If the diagnosis is uncertain (see recommendation 14) and Alzheimer's disease is suspected, consider either:**
    - FDG-PET (fluorodeoxyglucose–positron emission tomography–CT), or perfusion SPECT (single-photon emission CT) if FDG-PET is unavailable.

      **or**
    - examining cerebrospinal fluid for:
      - either total tau or total tau and phosphorylated-tau 181 **and**
      - either amyloid beta 1–42 or amyloid beta 1–42 and amyloid beta 1–40

    **If a diagnosis cannot be made after one of these tests, consider using the other one.**

16. **Be aware that the older a person is, more likely they are to get a false positive with cerebrospinal fluid examination.**

17. **Do not rule out Alzheimer's disease based solely on the results of CT or MRI scans.**

18. **Do not use Apolipoprotein E genotyping or electroencephalography to diagnose Alzheimer's disease.**

19. **Be aware that young-onset Alzheimer's disease has a genetic cause in some people.**

**Further tests for dementia with Lewy bodies**

20. **If the diagnosis is uncertain (see recommendation 14) and dementia with Lewy bodies is suspected, use $^{123}$I-FP-CIT SPECT.**

21. **If $^{123}$I-FP-CIT SPECT is unavailable, consider $^{123}$I-MIBG cardiac scintigraphy.**

22. **Do not rule out dementia with Lewy bodies based solely on normal results on $^{123}$I-FP-CIT SPECT or $^{123}$I-MIBG cardiac scintigraphy.**

**Further tests for frontotemporal dementia**

23. **If the diagnosis is uncertain (see recommendation 14) and frontotemporal dementia is suspected, use either:**
    - FDG-PET **or**
    - perfusion SPECT.

24. **Do not rule out frontotemporal dementia based solely on the results of structural, perfusion or metabolic imaging tests.**

25. **Be aware that frontotemporal dementia has a genetic cause in some people.**

**Further tests for vascular dementia**

26. **If the dementia subtype is uncertain (see recommendation 14) and vascular dementia is suspected, use MRI. If MRI is unavailable or contraindicated, use CT.**

27. **Do not diagnose vascular dementia based solely on vascular lesion burden.**

28. **Be aware that young-onset vascular dementia has a genetic cause in some people.**

### 5.1.7 Research recommendations

1. **Does amyloid PET imaging provide additional diagnostic value, and is it cost effective, for the diagnosis of Alzheimer's disease and other dementias when compared with standard diagnostic procedures and other imaging or biomarker tests?**

For more details on the research recommendation made, and the rationale behind it, see appendix L.

## 5.2 Distinguishing dementia from delirium or delirium with dementia

**Review question**

- What are the most effective methods of differentiating dementia or dementia with delirium from delirium alone?

### 5.2.1 Introduction

The aim of this review question was to determine the effectiveness of different diagnostic tests in differentiating between groups of patients with dementia, delirium with dementia or delirium alone, in people without a current diagnosis of either dementia or delirium. The review identified studies that fulfilled the conditions specified in Table 22. The full review protocol is available in Appendix C.

**Table 22: Review summary: differential diagnosis of dementia and delirium**

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| **Population** | People (aged 40 years and over) with cognitive impairment and no current diagnosis of dementia or delirium |
| **Diagnostic variables** | Relevant diagnostic variables may include:<br>• History data<br>• Duration of delirium<br>• IQCODE |
| **Outcomes** | • Incidence of accurately identified dementia<br>• Diagnostic accuracy measures<br>• Inappropriate discharge rates<br>• Inadequate care planning rates<br>• Resource use and costs |

### 5.2.2 Evidence review

A systematic literature search was carried out to identify cohort studies, cross-sectional studies or systematic reviews of diagnostic accuracy studies. Two thousand four hundred and fifty eight references were screened at the title and abstract level, with 40 potentially relevant references being ordered for full text review. Of these references, 5 were selected for inclusion based on their relevance to the review protocol and the presentation of data which was in a useful format for analysis. One additional paper was screened at full text and included from re-run searches conducted at the end of the guideline. The excluded studies are listed, with reasons for their exclusion, in Appendix F. Evidence tables for the included studies are presented in Appendix E.

#### 5.2.2.1 Analyses

Calculations of diagnostic test sensitivity, specificity, positive likelihood and negative likelihood ratios (LR) were carried out and are presented in the GRADE tables in Appendix G. Initial analyses examine the ability of the test to distinguish between delirium or delirium with dementia patients from dementia alone patients. If the 95% confidence interval for the likelihood ratios in this analysis did not cross 1 (i.e. the result was statistically significant) then the data for separating delirium alone versus delirium with dementia patients was also analysed.

#### 5.2.2.2 Description of included studies

The characteristics of the included studies are summarised in Table 23. References for the included studies are given in appendix I.

**Table 23: Summary of included studies**

| Study details | Study population | Diagnostic test(s) | Reference test | Outcome(s) |
|---|---|---|---|---|
| Cole (2002) | Patients ≥ 65 years admitted to a medical department from the emergency department | • Confusion Assessment Method (CAM)<br>• Delirium Index (DI) | Diagnostic and Statistical Manual of Mental Disorders III (DSM-III-R) for delirium and Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) for dementia | Comparison between the number of errors and prevalence of symptoms on the CAM and DI and diagnosis using DSM-III-R |
| Erkinjuntti (1987) | Patients ≥ 65 years admitted to a medical department | • Short Portable Mental Status Questionnaire (SPMSQ) | Dementia Scale | Comparison between the number of SPMSQ errors and diagnosis using the dementia scale |
| Leonard (2016) | Patients ≥ 60 years with altered mental state referred to a psychiatry for later life consultation-liaison service | • Delirium Rating Scale Revised 98 (DRS-R98)<br>• Cognitive Test for Delirium (CTD)<br>• Neuropsychiatric Inventory (NPI) | Diagnostic and Statistical Manual of Mental Disorders (DSM) IV for delirium or dementia and (IQCODE-Short form) for dementia and cognitive difficulties | Comparison between the DRS-R98 mean and item severity scores, CTD or NPI scores and the reference diagnosis |
| Meagher (2010) | Patients with altered mental state identified on daily rounds | • Delirium Rating Scale Revised 98 (DRS-R98)<br>• Cognitive Test for Delirium (CTD) | Diagnostic and Statistical Manual of Mental Disorders (DSM) IV for delirium or dementia | Comparison between the DRS-R98 mean and item severity scores or CTD scores and the reference diagnosis |
| Richardson (2017) | Patients > 70 years old who were admitted to 5 acute or rehabilitation hospitals. | • Attention test<br>• Observational Scale of Level of Arousal (OSLA) | DSM-5 for delirium with IQCODE and MMSE for dementia | The diagnostic accuracy of the index tests compared with the reference diagnosis. |
| Trzepacz (2001) | Patients with dementia or delirium, Schizophrenia, depression or other psychiatric disorders from a range of medical | • Delirium Rating Scale Revised 98 (DRS-R98)<br>• Cognitive Test for Delirium (CTD) | Diagnostic and Statistical Manual of Mental Disorders (DSM) IV for delirium or dementia | Comparison between the DRS-R98 mean scores (severity and total) or CTD scores and the reference diagnosis |

| Study details | Study population | Diagnostic test(s) | Reference test | Outcome(s) |
|---|---|---|---|---|
| | and nursing home settings | | | |

### 5.2.3 Health economic evidence

Standard health economic filters were applied to the clinical search for this question, and a total of 262 citations was returned. Following review of titles and abstracts, no full text studies were retrieved for detailed consideration. Therefore, no relevant cost–utility analyses were identified for this question.

### 5.2.4 Evidence statements

The evidence statements in this review for distinguishing delirium from dementia are written with reference to the size of the likelihood ratios in the GRADE tables in appendix G, section G1.2, using the interpretation detailed in the methods section on diagnostic test accuracy (Table 4) for both point estimates and confidence intervals. Positive likelihood ratios, and their associated 95% confidence intervals, were used to determine which tests increase the probability of having delirium or delirium with dementia and negative likelihood ratios, and their associated 95% confidence intervals, were used to determine which tests decrease the probability of having delirium or delirium with dementia. This rationale also applies to the evidence statements for the sections on distinguishing delirium from delirium with dementia, and delirium with dementia from dementia.

#### 5.2.4.1 Distinguishing delirium and delirium with dementia from dementia

##### *5.2.4.1.1 Results that increase the probability of having delirium or delirium with dementia*

The following test results **increase** the probability a person has delirium or delirium with dementia to a degree that is likely to be **very large**:

- DRS-R98 Total score, cut off >21.50 (very low quality, 95% CI goes from slight to very large)
- DRS-R98 Total score, cut off >22.50 (very low quality, 95% CI goes from slight to very large)
- DRS-R98 Severity score, cut off >17.00 (very low quality, 95% CI goes from slight to very large)
- Combination of OSLA and Attention Test, cut off >9 (low quality, 95% confidence interval goes from large to very large)

The following test results **increase** the probability a person has delirium or delirium with dementia to a degree that is likely to be **large**:

- <4 errors using the SPMSQ (low quality, 95% CI goes from slight to very large)
- DRS-R98 Item Severities- Temporal onset of symptoms, scoring ≥ 2 (moderate quality, 95% CI goes from moderate to very large)
- DRS-R98 Total score, cut off 17.75 (very low quality, 95% CI goes from slight to very large)

The following test results **increase** the probability a person has delirium or delirium with dementia to a degree that is likely to be **moderate**:

- > 5 symptoms using the CAM (low quality, 95% CI goes from slight to moderate)

- > 6 symptoms using the CAM (moderate quality, 95% CI goes from moderate to moderate)
- > 4 symptoms using the DI (moderate quality, 95% CI goes from moderate to moderate)
- <5 errors using the SPMSQ (low quality, 95% CI goes from slight to large)
- DRS-R98 Item Severities- Sleep-wake cycle disturbance, scoring ≥ 2 (low quality, 95% CI goes from slight to large)
- DRS-R98 Item Severities- Perceptual disturbances and hallucinations, scoring ≥ 2 (low quality, 95% CI goes from slight to very large)
- DRS-R98 Item Severities- Lability of affect, scoring ≥ 2 (low quality, 95% CI goes from slight to very large)
- DRS-R98 Item Severities- Language, scoring ≥ 2 (low quality, 95% CI goes from slight to large)
- DRS-R98 Item Severities- Thought process abnormalities, scoring ≥ 2 (low quality, 95% CI goes from slight to moderate)
- DRS-R98 Item Severities- Motor agitation, scoring ≥ 2 (low quality, 95% CI goes from slight to large)
- DRS-R98 Item Severities- Orientation, scoring ≥ 2 (low quality, 95% CI goes from slight to moderate)
- DRS-R98 Item Severities- Attention, scoring ≥ 2 (low quality, 95% CI goes from slight to moderate)
- DRS-R98 Item Severities- Physical disorder, scoring ≥ 2 (low quality, 95% CI goes from slight to moderate)
- DRS-R98 Severity score, cut off 15.25 (very low quality, 95% CI goes from moderate to large)
- <4 points on the SSF item of CTD (low quality, 95% CI goes from slight to very large)
- OSLA, cut off >4 (low quality, 95% confidence interval goes from moderate to large)

The following test results **increase** the probability a person has delirium or delirium with dementia to a degree that is likely to be **slight**:

- > 2 symptoms using the DI (moderate quality, 95% CI goes from slight to moderate)
- > 3 symptoms using the DI (low quality, 95% CI goes from slight to moderate)

The following results were **not significantly different** from random chance:

- <3 errors using the SPMSQ (low quality)
- DRS-R98 Item Severities- Delusions, scoring ≥ 2 (low quality)
- DRS-R98 Item Severities- Motor retardation, scoring ≥ 2 (low quality)
- DRS-R98 Item Severities- Short-term memory, scoring ≥ 2 (low quality)
- DRS-R98 Item Severities- Long-term memory, scoring ≥ 2 (low quality)
- DRS-R98 Item Severities- Visuospatial processing, scoring ≥ 2 (low quality)
- DRS-R98 Item Severities- Fluctuations in symptom severity, scoring ≥ 2 (low quality)

#### *5.2.4.1.2 Results that decrease the probability of having delirium or delirium with dementia*

The following results **decrease** the probability a person has delirium or delirium with dementia to a degree that is likely to be **very large**:

- ≤ 5 symptoms using the CAM (moderate quality, 95% CI goes from very large to very large)

- ≤ 6 symptoms using the CAM (moderate quality, 95% CI goes from very large to very large)
- DRS-R98 Total score, cut off <17.75 (low quality, 95% CI goes from very large to very large)
- DRS-R98 Total score, cut off <21.50 (low quality, 95% CI goes from very large to moderate)
- DRS-R98 Severity score, cut off <15.25 (low quality, 95% CI goes from very large to moderate)

The following results **decrease** the probability a person has delirium or delirium with dementia to a degree that is likely to be **large**:

- DRS-R98 Item Severities- Physical disorder, scoring < 2 (moderate quality, 95% CI goes from large to moderate)
- DRS-R98 Total score, cut off <22.50 (low quality, 95% CI goes from very large to moderate)
- DRS-R98 Severity score, cut off <17.00 (low quality, 95% CI goes from very large to moderate)
- Combination of OSLA and Attention Test, cut off ≤9 (low quality, 95% confidence interval goes from very large to moderate)

The following results **decrease** the probability a person has delirium or delirium with dementia to a degree that is likely to be **moderate**:

- ≤2 symptoms using the DI (low quality, 95% CI goes from moderate to slight)
- ≤3 symptoms using the DI (low quality, 95% CI goes from moderate to slight)
- ≥4 errors using the SPMSQ (low quality, 95% CI goes from moderate to slight)
- ≥5 errors using the SPMSQ (low quality, 95% CI goes from large to slight)
- DRS-R98 Item Severities- Sleep-wake cycle disturbance, scoring <2 (low quality, 95% CI goes from moderate to slight)
- DRS-R98 Item Severities- Attention, scoring <2 (low quality, 95% CI goes from moderate to slight)
- DRS-R98 Item Severities- Temporal onset of symptoms, scoring <2 (low quality, 95% CI goes from moderate to slight)
- ≥4 points on the SSF item of CTD (low quality, 95% CI goes from moderate to slight)
- OSLA, cut off ≤4 (low quality, 95% CI goes from very large to moderate)

The following results **decrease** the probability a person has delirium or delirium with dementia to a degree that is likely to be **slight**:

- ≤4 symptoms using the DI (low quality, 95% CI goes from slight to slight)
- ≥3 errors using the SPMSQ (moderate quality, 95% CI goes from slight to slight)
- DRS-R98 Item Severities- Perceptual disturbances and hallucinations, scoring <2 (moderate quality, 95% CI goes from slight to slight)
- DRS-R98 Item Severities- Lability of affect, scoring <2 (moderate quality, 95% CI goes from slight to slight)
- DRS-R98 Item Severities- Language, scoring <2 (moderate quality, 95% CI goes from slight to slight)
- DRS-R98 Item Severities- Thought process abnormalities, scoring <2 (moderate quality, 95% CI goes from slight to slight)
- DRS-R98 Item Severities- Motor agitation, scoring <2 (moderate quality, 95% CI goes from slight to slight)

- DRS-R98 Item Severities- Motor retardation, scoring <2 (moderate quality, 95% CI goes from slight to slight)
- DRS-R98 Item Severities- Orientation, scoring <2 (moderate quality, 95% CI goes from slight to slight)

The following results were **not significantly different** from random chance:

- DRS-R98 Item Severities- Delusions, scoring <2 (moderate quality)
- DRS-R98 Item Severities- Short-term memory, scoring <2 (moderate quality)
- DRS-R98 Item Severities- Long-term memory, scoring <2 (moderate quality)
- DRS-R98 Item Severities- Visuospatial processing, scoring <2 (moderate quality)
- DRS-R98 Item Severities- Fluctuations in symptom severity, scoring <2 (moderate quality)

#### 5.2.4.2 Distinguishing delirium from delirium with dementia

##### *5.2.4.2.1 Results that increase the probability of having delirium alone*

The following results **increase** the probability a person has delirium alone to a degree that is likely to be **slight**:

- ≤3 symptoms using the DI (low quality, 95% CI goes from slight to moderate)
- DRS-R98 Item Severities- Sleep-wake cycle disturbances, scoring ≥ 2 (moderate quality, 95% CI goes from slight to slight)
- DRS-R98 Item Severities- Thought process abnormalities, scoring ≥ 2 (low quality, 95% CI goes from slight to moderate)
- DRS-R98 Item Severities- Temporal onset of symptoms, scoring ≥ 2 (moderate quality, 95% CI goes from slight to slight)

The following results were **not significantly different** from random chance:

- >5 symptoms using the CAM (moderate quality)
- >6 symptoms using the CAM (moderate quality)
- >2 symptoms using the DI (moderate quality)
- >3 symptoms using the DI (moderate quality)
- >4 symptoms using the DI (low quality)
- <3 errors using the SPMSQ (low quality)
- <4 errors using the SPMSQ (low quality)
- <5 errors using the SPMSQ (low quality)
- DRS-R98 Item Severities- Perceptual disturbances and hallucinations, scoring ≥ 2 (low quality)
- DRS-R98 Item Severities- Lability of affect, scoring ≥ 2 (low quality)
- DRS-R98 Item Severities- Language, scoring ≥ 2 (low quality)
- DRS-R98 Item Severities- Motor agitation, scoring ≥ 2 (low quality)
- DRS-R98 Item Severities- Orientation, scoring ≥ 2 (low quality)
- DRS-R98 Item Severities- Attention, scoring ≥ 2 (moderate quality)
- DRS-R98 Item Severities- Physical disorder, scoring ≥ 2 (moderate quality)
- <4 points on the SSF item of CTD (moderate quality)

#### *5.2.4.2.2 Results that decrease the probability of having delirium alone*

The following results **decrease** the probability a person has delirium alone to a degree that is likely to be **moderate**:

- ≥5 errors using the SPMSQ (low quality, 95% CI goes from large to slight)
- DRS-R98 Item Severities- Thought process abnormalities, scoring <2 (low quality, 95% CI goes from moderate to slight)
- DRS-R98 Item Severities- Temporal onset of symptoms, scoring <2 (low quality, 95% CI goes from moderate to slight)

The following results **decrease** the probability a person has delirium alone to a degree that is likely to be **slight**:

- DRS-R98 Item Severities- Sleep-wake cycle disturbances, scoring <2 (low quality, 95% CI goes from moderate to slight)
- ≤4 symptoms using the DI (low quality, 95% CI goes from moderate to slight)

The following results were **not significantly different** from random chance:

- ≤2 symptoms using the DI (low quality)
- ≤5 symptoms using the CAM (moderate quality)
- ≤6 symptoms using the CAM (moderate quality)
- ≥3 errors using the SPMSQ (moderate quality)
- ≥4 errors using the SPMSQ (low quality)
- DRS-R98 Item Severities- Perceptual disturbances and hallucinations, scoring <2 (moderate quality)
- DRS-R98 Item Severities- Lability of affect, scoring <2 (moderate quality)
- DRS-R98 Item Severities- Language, scoring <2 (moderate quality)
- DRS-R98 Item Severities- Motor agitation, scoring <2 (moderate quality)
- DRS-R98 Item Severities- Orientation, scoring <2 (moderate quality)
- DRS-R98 Item Severities- Attention, scoring <2 (low quality)
- DRS-R98 Item Severities- Physical disorder, scoring <2 (low quality)
- ≥4 points on the SSF item of CTD (moderate quality)

### 5.2.4.3 Distinguishing delirium with dementia from dementia

#### *5.2.4.3.1 Results that increase the probability of having delirium with dementia*

The following test results **increase** the probability a person has delirium with dementia to a degree that is likely to be **very large**:

- OSLA, cut off >4 (low quality, 95% confidence interval goes from moderate to very large)
- Combination of OSLA and Attention Test, cut off >9 (low quality, 95% confidence interval goes from moderate to very large)

#### *5.2.4.3.2 Results that decrease the probability of having delirium with dementia*

The following test results **decrease** the probability a person has delirium with dementia to a degree that is likely to be **very large**:

- Combination of OSLA and Attention Test, cut off ≤9 (low quality, 95% confidence interval goes from very large to moderate)

The following test results **decrease** the probability a person has delirium with dementia to a degree that is likely to be **moderate**:

- OSLA, cut off ≤4 (low quality, 95% confidence interval goes from large to moderate)

#### 5.2.4.4 Health economic evidence

No health economic evidence was identified for this review question.

### 5.2.5 Evidence to recommendations

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| **Relative value of different outcomes** | The committee noted that the tests for delirium examined in this review consist of multiple domains some of which are impaired in both people with dementia and those with delirium, while other domains such as attention and concentration are important issues in delirium, but not necessarily impaired in dementia. This meant that some tests were inherently better suited to differentiate between delirium and dementia than others.<br>The committee agreed that both likelihood ratios and sensitivity and specificity were relevant outcomes for the review, and the decision as to which was most important in a given situation would depend on whether the test was being used for ruling out or ruling in potential cases. |
| **Trade-off between benefits and harms** | The committee agreed that the length of the test for delirium was very important. The DRS-R98 was considered too long to be usefully applied in a non-specialist NHS setting. The CTD was also considered problematic due to its length and the requirement for props, but most particularly as it included a number of non-specific items to detect cognitive problems that were likely to be positive in people with dementia as well as those with delirium.<br>The committee agreed that the high sensitivity, reasonable specificity (particularly using a cut-off of >6 symptoms) and positive likelihood ratio of the CAM test meant that it was a suitable choice to distinguish between delirium and delirium superimposed on dementia from dementia alone and therefore decided to recommend the use of this test for this purpose with a 'consider' level of strength due to the low-moderate quality of the evidence reviewed. The committee agreed the evidence was equally strong for the use of the Observational Scale of Level of Arousal (OSLA), and this was also added to the same recommendation. Whilst the sensitivity and specificity were somewhat different between these two measures, the committee agreed this was likely to be a result of the particular cut-offs chosen to use on the tests in the studies, and the overall diagnostic accuracy of the tests was similar between the studies. The committee noted there were other tests (such as the Short Portable Mental State Questionnaire) which also had good positive likelihood ratios, but decided not to recommend them as the negative likelihood ratios were less good than for either the long CAM or the OSLA.<br>The committee commented that the CAM test existed in both long (10 questions) and short (the first 4 questions) forms. The committee noted that the short CAM was already recommended for use in the delirium guideline section 1.5.1, but as the data provided in Cole 2002, referred to the long CAM it was only able to recommend the use of the long CAM to distinguish dementia from delirium in this guideline. They also agreed that it made logical sense that the additional information provided by the long CAM may be helpful in situations where differential diagnosis is more complex, whilst the short CAM remains appropriate in less complex cases.<br>The committee agreed that the tests presented lacked sufficient specificity to allow differentiation between people with delirium superimposed on dementia from delirium alone. Therefore it decided to |

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| | issue a 'do not use' recommendation to highlight the importance of the clinician not relying on standardised tests alone to distinguish groups here. The committee agreed that if any uncertainty regarding diagnosis remained then the person exhibiting an altered mental state should be treated for delirium first. It decided to make a similar recommendation to that in the delirium guideline at the end of part 1.5.1 where this was clearly stated.<br>The committee agreed that when people with an altered mental state screened negative for delirium it was important to determine whether they had dementia instead and this should follow the standard advice given in the section of the guideline on diagnosing dementia and dementia subtypes, which already includes reference to ruling out reversible causes of cognitive decline.<br>The committee discussed the importance of assessing people who were successfully treated for delirium for the presence of underlying dementia, but noted the uncertainty surrounding the best time interval for this assessment. The committee agreed that this issue would make a suitable research recommendation, and would best be evaluated using a cohort study that regularly assessed peoples cognitive performance following delirium (for example, at 1, 2, 3, 6, 9 and 12 months), and identified the point at which cognition scores stabilise, which would be the appropriate time to assess for dementia. |
| **Trade-off between net health benefits and resource use** | No economic evidence was identified for this review question and economic evidence was not prioritised. The committee agreed that inaccurate diagnoses of either delirium or dementia would be both expensive and harmful for the person involved, and therefore the potential additional time for using the long version of the CAM would be justified by the costs saved from not providing inappropriate treatments based on incorrect diagnoses. |
| **Quality of evidence** | The committee noted that although the DRS-R98 total and severity scores reported high sensitivity and specificity in detecting delirium versus dementia, the very low quality of the data in this study (Trzepacz, 2001) and the length of the test meant that they were unable to recommend it. The committee was unable to recommend the use of the short CAM in preference to the long CAM to diagnose delirium in the absence of evidence examining the short CAM in the population of interest (people with an altered mental state who could have dementia, delirium or delirium superimposed on dementia). |
| **Other considerations** | The committee noted that people with cognitive impairment who were diagnosed with delirium had specific social needs that remained to be determined, but considered that this fell into the category of a delirium guideline research recommendation rather than one that could be included here.<br>The committee noted that people who had previously experienced delirium were at increased risk of developing dementia. It commented that older people usually took longer to recover from delirium and that delirium was rarely diagnosed in people <35 years old. |

### 5.2.6 Recommendations

**Telling the difference between delirium and dementia in people without a diagnosis of either**

**29. For people who are in hospital and have cognitive impairment with an unknown cause, consider using one of the following to find out whether they have delirium or delirium superimposed on dementia, compared with dementia alone:**

- the long confusion assessment method (CAM)

- the Observational Scale of Level of Arousal (OSLA).

30. **Do not use standardised instruments (including cognitive instruments) alone to distinguish delirium from delirium superimposed on dementia.**

31. **If it is not possible to tell whether a person has delirium, dementia, or delirium superimposed on dementia, treat for delirium first. For guidance on treating delirium, see treating delirium in the NICE guideline on delirium.**

### 5.2.7 Research recommendations

2. **In people with treated delirium who no longer meet the DSM-5 criteria for delirium, but who have persistent cognitive deficits, when is the most appropriate time to carry out an assessment for dementia?**

For more details on the research recommendation made, and the rationale behind it, see appendix L.

## 5.3 Case finding for people at high risk of dementia

**Review question**

- What are the most effective methods of case finding for people at high risk of dementia?

### 5.3.1 Introduction

The aims of this review were to establish whether case finding alters the incidence of correct dementia diagnoses in people at high risk of dementia and what effect this has on the outcomes for these people. Studies were not considered to be relevant if they only reported the incidence of dementia identified; studies also needed to contain an intervention component for individuals identified as living with dementia. The review focused on identifying studies that fulfilled the conditions specified in Table 24. For full details of the review protocol, see Appendix C.

**Table 24: Review summary: case finding for people at high risk of dementia**

| | |
|---|---|
| **Population** | People (aged 40 years and over) who are at high risk of dementia in:<br>• Primary care<br>• Acute hospitals<br>• Care homes<br>• People over 60 at high vascular risk (prior stroke)<br>• People with learning disabilities<br>• People with other neurological disorders (MS) |
| **Intervention** | Standard cognitive tests |
| **Outcomes** | • Incidence of dementia (and other conditions) correctly identified in people classified as at risk<br>• Delay to diagnosis<br>• Sensitivity, specificity, NPV, PPV<br>• Health related quality of life<br>• Overtreatment<br>• Resource use and cost |

### 5.3.2 Evidence review

A systematic literature search was carried out to identify prospective cohort studies and RCTs of case finding approaches. Two thousand, two hundred and seventy eight references were screened at the title and abstract level, with 6 potentially relevant references being ordered for full text review, including a systematic review for the US Preventative Services Task Force (Lin, 2013). One extra study (Borson, 2007) was identified during screening for another related review. Of these references, 1 (van den Dungen, 2016) was selected for inclusion based on its relevance to the review protocol. The systematic review (Lin, 2013) was unable to find any trials that directly assessed whether case finding affected decision making and outcomes for patients, carers or society. This is in agreement with our findings as the single identified RCT was published after the systematic review. ClinicalTrials.gov was also checked to identify additional clinical trials relevant to this question. One ongoing dementia diagnosis RCT was found (Fowler, 2014), but not included. The excluded studies are listed, with reasons for their exclusion, in Appendix F. Evidence tables for the included studies are presented in Appendix E, and GRADE profiles in appendix G.

#### 5.3.2.1 Description of included studies

The characteristics of the included study are summarised in Table 25. References for the included studies are given in appendix I.

**Table 25: Included study**

| Study reference | Study design | Study population | Intervention & comparator | Relevant outcomes | Comments |
|---|---|---|---|---|---|
| Van den Dungen (2016) | Cluster RCT | In stage 1: 647 people with possible cognitive impairment across 15 primary care practices.<br>In stage 2: 145 of the patients from stage 1. | Intervention Stage 1: training of family physicians to diagnose dementia<br>Intervention Stage 2: assessment of cognition and functioning by study two practice nurses.<br>Comparator for both stages: no additional training and usual care | Primary outcome: new diagnoses of MCI and dementia<br>Secondary outcome: mental health of patients and their relatives | Location: Netherlands<br>Follow up: 12 months |

### 5.3.3 Health economic evidence

Standard health economic filters were applied to the clinical search for this question, and a total of 684 citations was returned. Following review of titles and abstracts, no full text studies were retrieved for detailed consideration. Therefore, no relevant cost–utility analyses were identified for this question.

### 5.3.4 Evidence statements

#### 5.3.4.1 Primary outcomes

Very low-quality evidence from a single cluster RCT containing 647 participants across 15 primary care practices could not detect a difference in the number of new diagnoses of dementia and MCI between control practices and those taking part in a dementia education programme for family physicians over a 12 month period.

Very low-quality evidence from a single cluster RCT containing 145 participants across 15 primary care practices could not detect a difference in the number of new diagnoses of dementia and MCI between control practices and those taking part in a dementia education programme for family physicians with practice nurse assessment for dementia over a 12 month period.

#### 5.3.4.2 Secondary outcomes

Moderate-quality evidence from a single cluster RCT containing 145 participants across 15 primary care practices could not detect a difference in the mental health or quality of life of trial participants or their relatives between people attending the control and intervention practices over a 12 month period, as measured by MH5, EQ5D and QoL-AD (outcomes for participants) and EQ-5D, GHQ12, SSCQ (outcomes for close relatives) questionnaires.

#### 5.3.4.3 Health economic evidence

No health economic evidence was identified for this review question.

### 5.3.5 Evidence to recommendations

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|---|---|
| **Relative value of different outcomes** | The committee agreed that while case finding required the targeted screening of people at high risk of dementia, it was important that this was coupled with an intervention to provide care to people after diagnosis. An intervention that merely identified people but then did not alter anything about their future care was unlikely to be beneficial, and could indeed increase anxiety in people without providing any equivalent advantages.<br>The committee noted that the secondary outcomes used to measure participant and carer outcomes in the van den Dungen trial were appropriate and likely to detect any benefit and harm associated with case finding and subsequent case management.<br>The committee commented that the use of the CAMCOG in preliminary studies by van den Dungen (2012) could have overestimated the likely yield of dementia diagnoses if normative data for this test was obtained from a more highly educated population than the sample included in this study. |
| **Trade-off between benefits and harms** | The committee noted that there was no evidence from the van den Dungen trial to suggest that participants or their carers received any benefit or sustained harm from case finding as judged by their reported quality of life outcomes. However, the committee noted that a diagnosis of dementia can be upsetting and a proportion of people may be wrongly diagnosed (false positive) due to diagnostic test inaccuracy, leading to inappropriate treatment and unnecessary stress. In addition, case finding may consume resources that could be better used elsewhere. The committee noted that a case finding programme would be particularly wasteful if a large proportion of people at high risk of dementia refused to be subsequently tested, as was the case in the van den Dungen trial. Thus the committee was unwilling to recommend case finding and proposed that it should only be used as part of an appropriately designed research study that includes an intervention for people diagnosed with dementia following identification.<br>The committee noted that in the context of the acute hospital there are already recommendations to screen for delirium. This is different from screening for dementia and should still be carried out in accordance with the NICE delirium guideline<br>The committee agreed that the lack of evidence regarding the effectiveness of case finding in dementia necessitated a research recommendation for studies that include an intervention component for the people identified as having dementia. The committee agreed that this recommendation should be for structured case finding with defined criteria for the selection of high risk patients. |
| **Consideration of health benefits and resource use** | The committee agreed that case finding was not resource neutral, and that in the absence of subsequent treatment strategies with proven benefits for people who have been identified through case finding, it is not a good use of resources. |
| **Quality of evidence** | The committee noted the shortage of evidence to address the effectiveness of case finding for dementia.<br>The committee discussed whether the van den Dungen trial met the study selection criteria sufficiently. In particular the committee commented that the RCT used clinician recollection and medical records to identify people with possible cognitive impairment to form their high risk group. The committee noted that while case finding required the targeted screening of people at high risk of dementia, a more scientific basis would be needed to define these groups for testing in practice.<br>The committee commented that the control arm of this trial also involved participants identified as having possible dementia by their |

| | |
|---|---|
| | primary care physicians and that as a result of this identification process there may have been an increase in the diagnosis of dementia and MCI in this group as well. This could account for the lack of difference in the new diagnoses of dementia between the control and intervention groups.<br>The committee noted that diagnosis of MCI, but not dementia, was increased in the intervention group compared with the control group. The committee commented that that the dementia management intervention was likely to have had less impact on the people diagnosed with MCI, and this may have contributed to the similarity in participant and carer outcomes between the control and intervention groups.<br>The committee noted that the RCT had several additional limitations: the low incidence of dementia and MCI in the intervention arm despite selecting people with possible cognitive impairment, the problems of nurses and physicians failing to comply with the study protocol in the intervention arm and the low level of consent for stage 2 of the trial by people with possible dementia. This lack of compliance by the medical staff and people with possible dementia would also be expected in real life, and therefore this trial may be accurately replicating the difficulties that could be encountered in introducing case finding interventions to general practice. |
| **Other considerations** | The committee agreed that it was particularly important to ensure that people with learning disabilities were included in the research recommendation as a group of people at high risk of dementia.<br>The committee noted that case finding for dementia was introduced in acute hospitals as part of the Commissioning for Quality and Innovation (CQUIN) 2013/14 guidance; the committee's recommendations should be interpreted as applying to situations outside this existing guidance. |

### 5.3.6 Recommendations

**32. Only conduct case finding for suspected dementia as part of a clinical trial that also provides an intervention to people diagnosed with dementia.**

### 5.3.7 Research recommendations

**3. What is the effectiveness of structured case finding (including a subsequent intervention for people identified as having dementia) in people at high risk of dementia, following up both people identified as having or not having dementia?**

For more details on the research recommendation made, and the rationale behind it, see appendix L.

# 6 Involving people living with dementia in decisions about care

When faced with a progressive medical condition most people will be interested in how that condition will be managed in the future. To be successful, advanced care planning must have the person and their wishes at its centre. Professionals may face challenges as they offer support and guidance throughout this process.

Each person's situation is unique, and therefore some people living with dementia will want as much practical support and information as is available in their location; others may deny they have problems and reject help; and again others may prefer to defer all decisions to the authority of the health or social care professional. Professionals will also need to adapt their approach when supporting and communicating as the dementia progresses, and this can become increasingly problematic if a person's mental capacity fluctuates. Many people living with dementia and their carers or families would prefer the health or social care professional to initiate the conversation about advance planning and discuss how to get access to advice.

Providing good quality, timely information for the person living with dementia can help increase their involvement in key decisions and help them to have a share in the decision making process. We should not assume that a person living with dementia will lack mental capacity, and even if a person living with dementia does lack the mental capacity to make a certain decision, this does not mean that they will lack it with regards to other decisions they face. The Mental Capacity Act 2005 Code of Practice provides clear instruction as to how people without the capacity can be supported to make a decision or when others have to make decisions for the person, such as during a best interest meeting.

Each person's family dynamic is unique. During discussions about advanced care planning various family members, and especially the primary carer, can feel conflicted; attempting to balance the needs of the person they are caring for, their own needs, and those of the rest of the family. At times families can become divided as to the best way forward, which can lead to disagreements, or there may be specific cultural needs which for each member of the family carry their own set of values and considerations. With all this in mind, professionals will need to ensure they are working to maintain the person living with dementia's own social network, as well as provide support that helps to maintain family cohesion.

Each organisation will have its own set of policies and protocols and there are a number of legal requirements that professionals must adhere to. We must ensure that these regulations are used to work for the person living with dementia, not against them. This will often require working closely with other agencies in partnership to ensure the person living with dementia, their families and carers receive high quality support.

## 6.1 Barriers and facilitators to involvement in decision making for people living with dementia

**Review questions**

- What barriers and facilitators have an impact on involving people living with dementia in decisions about their present and future care?
- What barriers and facilitators have an impact on how people living with dementia can make use of advance planning?

### 6.1.1 Introduction

**Table 26: Review summary: Barriers and facilitators to accessing care**

| | |
|---|---|
| **Population** | • People (aged 40 years and over) living with dementia<br>• Carers of people (aged 40 years and over) living with dementia |
| **Phenomena of interest** | • Equity of access (financial, physical or geographic restrictions)<br>• Behaviours and attitudes of professionals<br>• Communication<br>• Loss of autonomy<br>• Information needs |
| **Outcomes** | • Experiences and satisfaction of people living with dementia<br>• Experiences and satisfaction of carers of people living with dementia |

Qualitative studies and qualitative evidence syntheses were included if they explored the barriers and facilitators to involving people living with dementia in decisions about their present and future care, and making use of advance planning. Studies needed to contain participants from the UK, report the views of either people living with dementia or their carers, and match the criteria given in Table 26. For full details of the review protocol, see Appendix C.

. Papers were excluded if they:

- did not report the views people living with dementia or their carers in the UK
- included only quantitative analysis of the collected information
- were not in English language
- were abstracts, conference proceedings and other unpublished studies.

### 6.1.2 Evidence review

A single search was conducted for all the qualitative questions included in this guideline, which returned a total of 10,085 references. References were screened based on their titles and abstracts, and the full texts of 61 references that were potentially relevant to these review questions were requested. Ten qualitative studies exploring the barriers and facilitators to involving people living with dementia in decisions about their care were included in the review. The included studies are summarised in Table 27. The 51 excluded papers, with reasons for exclusion, are presented in Appendix F.

#### 6.1.2.1 Description of included studies

A summary of the included primary studies for this review question is given in Table 27. In addition, one systematic review of qualitative studies exploring barriers and facilitators for carers making decisions for people with dementia (Lord 2011) was also included. For the full

evidence tables and full CERQual profiles please see Appendix E and Appendix G. References for the included studies are given in appendix I.

**Table 27: Summary of included primary studies**

| Study details | Study population | Methods | Outcome |
|---|---|---|---|
| Bisson (2009) | People with symptoms of Huntington's disease, carers, asymptomatic people who had the altered Huntington's disease gene, clinicians, a medical ethicist, two advisors and a lawyer | In-depth interviews | Development of a care pathway for advanced decisions for people with Huntington's disease. |
| Dening (2017) | 6 people living with dementia and 7 carers | Intervention: Asking dyads questions about their past, present and future healthcare decision making<br>Method of data collection: semi-structured interviews | The opinions of people living with dementia and their carers |
| Goodman (2013) | People with dementia or people considered to have dementia by the care home manager | Guided conversations | An exploration of the preferences and priorities of care for people with dementia. |
| Livingston (2010) | Carers of people living with dementia | Focus groups and individual interviews | An identification of the common difficult decisions made by family carers on behalf of people with dementia, and facilitators of and barriers to such decisions. |
| Mackenzie (2006) | Carers of people with dementia | Semi-structured interviews | An investigation of East European and South Asian family carers with regards to how they negotiate the stigma of dementia. |
| Murphy (2013) | People with dementia and their carers | A cross-over trial involving narrative interviews and a questionnaire | A study of how useful Talking Mats were for people with dementia and their carers with regards to making decisions together. |
| Parveen (2017) | 20 family carers of South Asian people living with dementia. There were an additional 22 people who were not carers but were family members. | Intervention: Information Programme for South Asian families (IPSAF)<br>Method of data collection: focus group interviews | The opinions of familial carers of South Asian people living with dementia |
| Poppe (2013) | People with mild dementia, carers and members of staff | In-depth interviews | Evaluation of the Advanced Care Planning in Early Dementia tool. |
| Samsi (2013) | People with dementia and their carers | Longitudinal interview study | A study of how people with dementia and their carers make decisions. |

### 6.1.3 Health economic evidence

As this review question was qualitative in nature, it was not appropriate to conduct a search for economic literature.

### 6.1.4 Evidence statements

#### 6.1.4.1 Barriers to decision making

The following barriers were identified to involving people living with dementia in decision about their current and future care:

- Individuals denying they have problems – a barrier to advance planning on the part of the people with dementia and carers was difficulty for some people with dementia or carers to accept the diagnosis (high confidence)
- Individuals rejecting help - people will often reject help, either because they feel they do not need it or because accepting help would involve psychologically acknowledging the severity of their problems (high confidence)
- Individuals having a deference towards the authority of healthcare professionals - knowing that they had dementia affected confidence in expressing opinions, self-esteem and whether they thought their views were worth listening to (very low confidence)
- Individuals having a poor relationship with their formal or informal carers (very low confidence)
- Healthcare professional not recognising the problems people have and their need for support - healthcare professionals may not recognise people need additional assistance to be involved in decision-making particularly when people are not open about difficulties they are having (high confidence)
- Late diagnoses of dementia - if the diagnosis of dementia is delayed, this can make it difficult for all the necessary advance discussions to be had before capacity issues start to occur (high confidence)
- Lack of quality information given in a timely fashion, and available whenever best suits the individual (high confidence)
- Confidentiality issues preventing carers having the information they feel they need to support decision-making (high confidence)
- Staff sticking to protocols and policies, rather than having individualised discussions (high confidence)
- Carers feeling conflict between the different roles they have to fulfil (high confidence)
- Friend carers felt less able to support decision-making than family carers (low confidence)
- Carer guilt about decisions made - feelings of anguish and guilt over decisions made. Journey towards a decision was directed by a mixture of fatigue and a lack of obvious or available alternatives. Feelings of guilt and failure were particularly strong for people obliged to cope alone (high confidence)
- Conflict within families - when the person living with dementia was involved in decision-making, they usually expressed reluctance to move to a care home. This often led the carer either to delay the decision or exclude the person living with dementia from decision-making (high confidence)
- Rigidity of healthcare system, and difficulty in changing decisions made - people felt that once a decision was reached, it was then difficult to change this decision if circumstances changed, and this led to a reluctance to make initial decisions (high confidence)
- An inability to plan due to unpredictability of condition and waiting lists for interventions – people struggle with knowing when to seek care home placement due to dementia being

unpredictable and wait lists of institutions. Some patients find discussing the future difficult without knowing what the future will bring (high confidence)

- Often there was one partner more dominant in decision-making. (low confidence)
- Fear of stigma prevented carers and people living with dementia from seeking help. (low confidence)
- Becoming the main decision-maker for some carers was wearisome and felt like a burden (medium confidence)
- Limited knowledge of the legal system to support decision-making when capacity was lost, including advance care planning and Lasting Powers of Attorney (low confidence)

#### 6.1.4.2 Facilitators for decision making

The following facilitators were identified to involving people living with dementia in decision about their current and future care:

- Reconceptualisation and adjustment to altered circumstances, and presentation of decision-making as trying to maximise independence - allowing services to develop slowly (high confidence)
- Practical support and information provided by healthcare professionals - suggesting interventions to facilitate agreement, or structured approaches to decision making. Collaboration with staff helped carers with decision-making, and this was facilitated by a trusted healthcare professional who consulted them and advocated effectively (high confidence)
- Healthcare professionals initiating conversation about advance planning - people felt that clinician's raising these discussions helped them with decision-making (high confidence)
- Access to legal and financial advice (high confidence)
- Structured decision support and discussion tools - open-ended, structured tools may be useful to guide discussions around advance planning. Staff who had not yet conducted any advance care planning discussions themselves were unsure how to initiate the discussion with those people with dementia who had not raised the issue themselves, but saw the tool as a potential way of facilitating this (low confidence)
- Carers accompanying patients on visits to healthcare professionals (high confidence)
- Shared decision-making approaches - carers found it helpful to hear the perspectives of other members of the family or professionals when making decision on behalf of the person living with dementia – they felt it "gave permission" to make decisions (high confidence)
- Family cohesion and support (high confidence)
- Social support networks - extended family, voluntary and community networks (high confidence)
- Alternative communication strategies - discussing care was facilitated by using Talking Mats. Talking Mats helped the participants living with dementia to be aware of what their family members were doing for them, and were seen an enjoyable activity which improved communication between the person living with dementia and his/her family (low confidence)

#### 6.1.4.3 Issues identified in Huntington's disease

The following facilitators were identified in a study specifically in people with Huntington's disease

- Importance of information provision - easy-to-follow, consistent verbal and written information was desired, which should be Huntington's disease specific (low confidence)

- Importance of therapeutic relationship between individual and an expert in Huntington's disease - an established therapeutic relationship with an expert in Huntington's disease. Personal qualities such as being approachable, caring and sensitive with good communication skills were felt to be important (low confidence)
- Early introduction to advance decisions - opinions of patients with Huntington's disease were different to professionals. Professionals were reluctant to approach service users too early, particularly asymptomatic individuals with the altered Huntington's disease gene, for fear of causing distress (low confidence)
- Importance of advance decision forms (low confidence)
- Importance of discussions on power of attorney (low confidence)

#### 6.1.4.4 Health economic evidence

As this review question was qualitative in nature, it was not appropriate to conduct a search for economic literature.

### 6.1.5 Evidence to recommendations

| | |
|---|---|
| **Relative value of different outcomes** | The committee agreed that it was useful to have evidence of both barriers and facilitators to decision making for people living with dementia. However, evidence involving facilitators was of greater value because it translated more easily to recommendations, whilst where a barrier was identified without an accompanying facilitator, it was not always easy to think of a practical solution to overcome that barrier. |
| **Trade-off between benefits and harms** | The committee noted that the evidence demonstrated that most people living with dementia expressed a clear preference for being offered information early, usually soon after diagnosis. However where people living with dementia or their carers did not want to receive the information soon after diagnosis the committee agreed that the person's wishes should be respected but it is important that the information is offered on an ongoing basis or when requested by the person. The committee also noted that people diagnosed with dementia may need more than 1 appointment to be able to process and understand the information. Therefore a recommendation was made that people living with dementia be offered information and opportunities for discussion on an ongoing basis.<br>The committee agreed with the finding in the evidence that some people, following a diagnosis, may not initially want follow-up appointments or referral to other services, but that these people may change their minds later. Therefore, the committee agreed that professionals should consider providing these people the opportunity to be contacted at a specified future time, when they decide they do want to access more information and support. If this is not available, there is a risk that people may live without appropriate support for a considerable period of time before things become sufficiently bad that services once again become involved.<br>The committee agreed with the finding in the evidence that that how some professionals currently interpret patient confidentiality guidance may have the unintended consequence of reducing standards of care. If appropriate information is not shared with informal carers this can make it difficult for carers to provide the necessary support for people living with dementia. Therefore, the committee recommended that when dementia is diagnosed, the person's consent should be sought for information sharing with their carers and/or family members. The reason that this conversation should happen at diagnosis is because the person living with dementia is more likely at that time to have capacity to decide who they would like their |

information to be shared with. The committee noted that if consent for information sharing has been obtained, this information should be recorded in the person's records. This should help to enable carers and/or family members to provide a better standard of appropriate care.

The committee agreed that the data protection training offered to staff who work with people who have dementia should specifically cover the benefits of sharing information where permission has been given. Sharing information enables other health and social care professionals to step in and work effectively with the person.

The committee agreed with the finding in the evidence that advocacy and voluntary support services are important for people living with dementia and the committee agreed that the advocacy and voluntary support service recommendations from the previous guideline should be retained (informing people about the services that are available). However the evidence presented identified that people living with dementia and their carers benefit from access to financial and legal services and these services were added to the list of services to inform people about.

The committee agreed it was important to discuss both advance statements and advance directives with people living with dementia for as long as they have the ability to be involved in decision making. It was noted that some people living with dementia feel discouraged from making advance decisions because they are concerned they would not be able to change these decisions in the future. Therefore, it was agreed that a recommendation be made that people living with dementia are offered regular opportunities to make changes to their advance statements and advance directives. To further support this, the committee noted that people living with dementia should be advised upfront that they will be able to change their advance statements and advance directives in the future, to ensure that fears that advanced statements and advanced directives cannot be changed do not act as a barrier to advance planning.

The committee agreed that advance planning forms should be standardised as far as possible, to maximise their level of transferability. This is to ensure that the wishes of the person living with dementia can be understood by everyone who needs to read them. Whilst it was noted that it was not possible to ensure national standardisation, it was agreed that at a local level this should be a more achievable goal. The recommendation made by the committee on this subject is reported in section 7.1.6 on coordinating care for people living with dementia.

The committee agreed that training staff in managing difficult and emotional conversations should enable them to have the confidence to initiate and support discussions on advance planning. The evidence presented to the committee suggests that many people living with dementia and their carers would prefer staff to initiate such conversations. However, the evidence also demonstrates that it is common for staff to lack confidence in their ability to discuss advance planning because staff feel that advance planning involves difficult and emotional conversations. The committee noted this training would also be important for people involved in the diagnosis of dementia, as this was another time where emotionally challenging conversations would take place.

The evidence suggests that people living with dementia can have a lack of confidence in the value of their own opinions. This is a significant barrier for people with dementia to make decisions about their care, as healthcare professionals may not be able to recognise the problems people have and their need for support. Therefore, the committee agreed that it was important that carers and staff were

| | |
|---|---|
| | aware of possible low self-esteem or confidence in people living with dementia so they can try to overcome this barrier. The committee agreed that people living with dementia should be encouraged and enabled to give their own views and opinions. The word 'enable' was included in the recommendations because it is proactive.<br>The evidence presented further suggests that alternative communications strategies (such as pictorial communication tools) are a facilitator to involving people living with dementia in decision making. Therefore, the committee recommended that their use should be considered by carers and healthcare professionals. |
| **Consideration of health benefits and resource use** | The committee agreed that for the majority of the recommendations made, any changes in resource use were likely to come from potentially needing more time to complete appointments. However, because the recommendations provide advice on potential approaches rather than prescribe specific actions, the committee agreed they were not likely to lead to a significant increase in resource use.<br>The only recommendations the committee agreed would have a specific cost attached to them were the 2 recommendations made around staff training. However, the committee were confident that the costs are justified by the long-term benefits of better-trained staff. |
| **Quality of evidence** | The committee agreed that overall the evidence was of good quality and the issues identified agreed with their practical experience. It was, however, noted that the reliance on qualitative evidence meant it was not possible to offer prescriptive recommendations in many areas, but rather more general guidance.<br>For the purposes of developing dementia guidelines, the study in Huntington's disease was agreed to be of lower value. This is because some people in the study had the Huntington's disease gene and had not yet developed symptoms at the time the research was conducted. Nevertheless, it was agreed this study was still valuable because it provided a different perspective; that of a younger population. |
| **Other considerations** | The committee noted that there are many subgroups of people living with dementia who may have very different information needs (e.g. younger people, those with comorbidities, people with rarer dementia subtypes). They agreed it was important that the information provided be tailored to these different circumstances, rather than only general information about dementia being provided.<br>The committee also agreed it was appropriate to cross-refer in this section to both the NHS Accessible Information Standard (which it is a requirement for people to follow) and the NICE guidelines on patient experience in adult NHS services and people's experience in adult social care services, which provides more advice on providing appropriate information, and making that information accessible.<br>Sections of recommendations referring to people in or looking for work were also informed by the evidence review on the specific needs of younger people living with dementia (section 17).<br>The committee noted that there was considerable interest from many people living with dementia in being involved in research, but people were often unaware of opportunities to do so. The committee therefore agreed it was appropriate to make a recommendation that people living with dementia be informed about opportunities to participate in research. |

### 6.1.6 Recommendations

#### Information provision

33. **Provide people living with dementia and their family members or carers (as appropriate) with information that is relevant to their circumstances and the stage of their condition.**

34. **Be aware of the obligation to provide accessible information as detailed in the NHS Accessible Information Standard. For more guidance on providing information and discussing people's preferences with them, see the NICE guideline on patient experience in adult NHS services and people's experience in adult social care services.**

35. **At diagnosis, offer the person and their family members or carers (as appropriate) oral and written information that explains:**
    - what their dementia subtype is and the changes to expect as the condition progresses
    - which healthcare professionals and social care teams will be involved in their care and how to contact them
    - if appropriate, how dementia affects driving, and that they need to tell the Driver and Vehicle Licensing Agency (DVLA) and their car insurer about their dementia diagnosis
    - their legal rights and responsibilities
    - their right to reasonable adjustments (in line with the Equality Act 2010) if they are working or looking for work
    - how the following groups can help and how to contact them:
        - local support groups, online forums and national charities
        - financial and legal advice services
        - advocacy services.

36. **If it has not been documented earlier, ask the person at diagnosis:**
    - for their consent for services to share information
    - which people they would like services to share information with (for example family members or carers)
    - what information they would like services to share.

    **Document these decisions in the person's records.**

37. **After diagnosis, direct people and their family members or carers (as appropriate) to relevant services for information and support (see recommendations 47 and 48 on care coordination).**

38. **For people who do not want follow-up appointments and who are not using other services, ask if they would like to be contacted again at a specified future date.**

39. **Ensure that people living with dementia and their carers know how to get more information and who from if their needs change.**

40. **Tell people living with dementia (at all stages of the condition) about research studies they could participate in.**

**Advance care planning**

41. **Offer early and ongoing opportunities for people living with dementia and people involved in their care (see recommendation 36) to discuss:**
    - the benefits of planning ahead
    - lasting power of attorney (for health and welfare decisions and property and financial affairs decisions)
    - an advance statement about their wishes, preferences, beliefs and values regarding their future care
    - advance decisions to refuse treatment
    - their preferences for place of care and place of death.

    **Explain that they will be given chances to review and change any advance statements and decisions they have made.**

42. **At each care review, offer people the chance to review and change any advance statements and decisions they have made.**

**Involving people in decision-making**

43. **Encourage and enable people living with dementia to give their own views and opinions about their care.**

44. **If needed, use additional or modified ways of communicating (for example visual aids or simplified text).**

**Staff training**

45. **Ensure that all health and social care staff are aware of:**
    - The extent of their responsibility to protect confidentiality under data protection legislation **and**
    - any rights that family members, carers and others have to information about the person's care (see recommendation 48 on information sharing between different care settings).

46. **Health and social care professionals advising people living with dementia (including professionals involved in diagnosis) should be trained in starting and holding difficult and emotionally challenging conversations.**

# 7 Care planning, review and co-ordination

In order to deliver outcome focused person centred care it is essential that a comprehensive care and support plan is in place which is co-ordinated and reviewed regularly. For this reason, it should be easily identified and accessible.

Person centred care is a broad term and involves a wide range of elements. It can range from life story work with people living with dementia to an organisational framework that values all people within an organisation, both those providing care and those being cared for. Brooker and Latham (2016) in Person Centred Dementia Care discuss these elements within their influential book. They state that person centred care should be a constant thread throughout the whole cycle of dementia services from memory clinics and initial diagnosis to end of life care for people living with dementia.

It is important that there is a person who is responsible for co-ordinating all aspects of health and social care. Whilst this person isn't necessarily responsible for the delivery of all aspects of the care and support plan, someone needs an overview to ensure that services and care are delivered in a co-ordinated and timely manner, without duplication. This ensures that the person living with dementia or the person's family have the security of knowing who to contact, and stops people having to constantly repeat their history and care needs.

The time after diagnosis can be a very difficult and emotional time for people newly diagnosed with dementia and responses vary across the spectrum from denial to a desire to know and understand everything about dementia. Therefore, people working in services need to understand that people respond to diagnosis in varied ways and post diagnostic support must be person centred to each individual as opposed to a standard pathway. This means accessing post-diagnosis support in a timely way, which fits the individual needs of the person with dementia and their carer.

Post-diagnosis reviews should also be undertaken in ways and at intervals which reflect the individual needs of the patient. To ensure the maximisation of benefits for the person with dementia and their carer, the review should be meaningful, holistic in approach with actions and outcomes being clearly recorded in the care and support plan.

## 7.1 Health and social care co-ordination

**Review questions**

- What are the most effective methods of care planning, focussing upon improving outcomes for people with dementia and their carers?
- How should health and social care be co-ordinated for people living with dementia?

### 7.1.1 Introduction

These questions considered randomised controlled trials and qualitative evidence on effective models of care planning and co-ordination for improving the care and experiences of people living with dementia and their carers. Full details of the review protocol are available in appendix C.

**Table 28: Review summary: qualitative evidence**

| | |
|---|---|
| **Population** | • People (aged 40 years and over) living with dementia<br>• Carers of people (aged 40 years and over) living with dementia |
| **Phenomena of interest** | • Methods and models of care planning for people living with dementia<br>• Models of health and social care co-ordination, which may include features such as:<br>• Configuration and integration of services<br>• Timing and delivery of services (e.g. transfers, referral pathways)<br>• Staff communication<br>• Location of services |
| **Outcomes** | • Experiences and satisfaction of people living with dementia<br>• Experiences and satisfaction of carers of people living with dementia |

**Table 29: Review summary: quantitative evidence**

| | |
|---|---|
| **Population** | • People (aged 40 years and over) living with dementia<br>• Carers of people (aged 40 years and over) living with dementia |
| **Interventions** | • Methods and models of care planning for people living with dementia |
| **Comparator** | • Each other<br>• Standard care |
| **Outcomes** | • Clinical outcomes including cognitive, functional and behavioural ability<br>• Access to health and social care support<br>• Patient and carer wellbeing, experience and satisfaction<br>• Patient and carer health-related quality of life<br>• Resource use and costs |

Randomised controlled trials, qualitative studies and systematic reviews of randomised controlled trials or qualitative studies were included if they explored how health and social care should be co-ordinated or explored the most effective methods of care planning and focussed upon improving outcomes for people with dementia and their carers. Studies needed to report the views of either people living with dementia or their carers, and match the criteria given in either Table 28 or Table 29. Papers were excluded if they:

- were not in English language
- were abstracts, conference proceedings and other unpublished studies.

### 7.1.2 Evidence review

#### 7.1.2.1 Qualitative evidence

A single search was conducted for all the qualitative questions included in this guideline, which returned a total of 10,085 references. References were screened based on their titles and abstracts, and the full texts of 90 references that were potentially relevant to these review questions were requested. Eighteen qualitative studies exploring care coordination were included in the review. The included studies are summarised in Table 30. For the full evidence tables and full CERQual profiles please see Appendix E and Appendix G. The 73 excluded papers, with reasons for exclusion, are presented in Appendix F. References for the included studies are given in appendix I.

##### *7.1.2.1.1 Description of included studies*

**Table 30: Summary of included studies**

| Study details | Study population | Methods | Outcomes |
|---|---|---|---|
| Brooker (2017) | 9 people living with dementia and 6 carers | Intervention: post-diagnostic psychosocial interventions<br>Method of data collection: focus groups. | The opinions of people living with dementia and their carers |
| Bunn (2017) | 28 people living with dementia | Intervention: management of comorbidities alongside dementia<br>Method of data collection: semi-structured interviews and focus groups. | The opinions of people living with dementia and their carers |
| Dayson (2016) | 9 carers of people living with dementia | Intervention: resilience service<br>Method of data collection: interviews | The opinions of carers of people living with dementia |
| Faith 2015 | 6 people living with mild dementia | Intervention: self-management course for people living with dementia.<br>Method of data collection: Interviews | The opinions of people living with dementia |
| Gethin-Jones 2014 | 20 familial carers of people living with dementia who were living alone | Intervention: outcome-focused care for people with dementia who are living alone.<br>Method of data collection: Semi-structured interviews | The opinions familial carers of people living with dementia who are living alone |
| Gibson 2007 | 10 people living with dementia and their carers | Interventions: community-based vs clinic-based memory service | The opinions of people living with dementia and their carers |

| Study details | Study population | Methods | Outcomes |
|---|---|---|---|
| | | Method of data collection: in-depth qualitative interviews | |
| Gladman 2007 | 15 carers of people living with dementia | Intervention: Daisy Chain: a commercial person-centred dementia service that seems to have some elements of case management<br>Methods of data collection: semi-structured interviews, observation and focus groups | The opinions of carers of people living with dementia |
| Górska 2013 | 12 people living with dementia and 19 carers | Intervention: a dementia service in Scotland.<br>Method of data collection: semi-structured interviews | The opinions of people living with dementia and their carers |
| Hean 2011 | An unspecified number of people living with dementia and their carers. | Intervention: an integrated memory assessment and support service.<br>Method of data collection: interviews | The opinions of people living with dementia and their carers |
| Iliffe 2014 | 6 people living with dementia and 10 carers | Intervention: case management<br>Method of data collection: interviews | The opinions of people living with dementia and their carers |
| Innes 2014 | 6 people living with dementia and 12 family carers | Intervention: post-diagnostic support in a remote and rural region in Scotland.<br>Method of data collection: Semi-structured interviews | Participant experiences of post-diagnostic support |
| Kelly 2016 | 8 people living with dementia and 8 family carers | Intervention: post-diagnostic support.<br>Method of data collection: Semi-structured interviews | Participant experiences of post-diagnostic support |
| Moore 2011 | An unspecified number of carers of people living with dementia | Intervention: self-directed support.<br>Method of data collection: Interviews | The opinions of carers of people living with dementia |
| Popham 2012 | 25 people living with dementia in residential care homes and 11 carers | Intervention: residential care home, which includes aspects of case coordination/management<br>Method of data collection: Interviews using open questions. | The opinions of people living with dementia and residential care home managers with regards to what extent the care home environment met the requirements of residents. Sheffield Care Environment Assessment Matrix (SCEAM) |
| Rothera 2008 | 27 people living with dementia and 18 family carers | Intervention: a specialist multiagency home support service. | The opinions of carers of people living with dementia |

| Study details | Study population | Methods | Outcomes |
|---|---|---|---|
| | | Method of data collection: semi-structured interviews | |
| Sonola 2013 | 9 people living with dementia and 9 carers | Intervention: case coordination service<br>Method of data collection: interviews | The opinions of carers of people living with dementia |
| Toms 2015 | 13 people living with early stage dementia and 11 carers | Intervention: self-management<br>Method of data collection: semi-structured interviews | The opinions of people living with dementia and their carers |
| Willis 2011 | 16 people living with dementia and 15 carers | Intervention: memory service that was also a one-stop shop for case coordination/management.<br>Method of data collection: interviews | The opinions of people living with dementia and carers |

#### 7.1.2.2 Quantitative evidence

A single search was conducted that returned a total of 5,735 references. These references were screened for RCTs that evaluated case management/planning/coordination interventions. A key feature of the references identified was that they involved a single specified individual being responsible for managing/planning/coordinating care. References were screened based on their titles and abstracts, and the full texts of 79 references that were potentially relevant to the review question were requested. Of these, 53 were excluded on full text review, with reasons for exclusion presented in Appendix F. Twenty six studies were analysed individually and in the following groups: by country, the profession of the individual case managing/planning/coordinating, frequency of follow-up, and the contact method when following-up. For the full evidence tables and full GRADE profiles please see Appendix E and Appendix G. References for the included studies are given in appendix I.

##### *7.1.2.2.1 Description of included studies*

**Table 31: Summary of included studies – RCT evidence**

| Study details | Study population | Methods | Outcomes |
|---|---|---|---|
| Bass (2015) | 114 people living with dementia and their carers. | Intervention: care-coordination program<br>Control: usual care. | Cognitive impairment, behavioural symptoms, hospital admissions |
| Bass (2014) | 194 people living with dementia and their carers. | Intervention: care-coordination program<br>Control: usual care. | Unmet need, embarrassment about memory problems, isolation, relationship strain, depression. |

| Study details | Study population | Methods | Outcomes |
|---|---|---|---|
| Bass (2013) | 718 people living with dementia and their carers. | Intervention: care-coordination program<br>Control: usual care. | Unmet needs, carer strains, depression, support resources. |
| Bass (2003) | 157 family carers of people living with dementia. | Intervention: integrating Alzheimer's Association care consultation service with health care services offered by a large managed care system.<br>Control: usual care. | Health service usage, carer satisfaction, carer depression and strain. |
| Callahan (2006) | 114 people living with dementia and their carers. | Intervention: Interdisciplinary team led by an advanced practice nurse working with the patient's family carer and integrated within primary care.<br>Control: usual care. | Patient Neuropsychiatric inventory, Cornell Scale for Depression, Telephone interview for cognition, ADLs, carer Neuropsychiatric Inventory, carer patient health questionnaire. |
| Chien (2008) | 88 people living with dementia and their carers. | Intervention: Case manager who together with another nurse, prioritised problem areas and formulated a multidisciplinary education program for each family on effective dementia care.<br>Control: usual care. | Family Caregiving Burden Inventory, World Health Organization Quality of<br>Life Scale, 6-item Social Support Questionnaire, MMSE, 12-item Neuro-psychiatric Inventory, Institutionalization over the past 6 months, Family Support Services Index. |
| Chien (2011) | 92 people living with dementia and their carers. | Intervention: Case manager who together with another nurse, prioritized the problems and formulated an individualized education and support programme for each family.<br>Control: usual care. | Family Caregiving Burden Inventory, World Health Organisation Quality of Life Scale, Six item<br>Social Support Questionnaire, MMSE, Neuropsychiatric Inventory, Family Support<br>Services Index. |
| Chodosh (2015) | 43 people living with dementia and their carers. | Intervention: Care management delivered in person and by telephone.<br>Control: Care management delivered by telephone only. | ZARIT Caregiver Burden: 22-question scale, Revised Memory and Behaviour Problem Checklist, carer depression, Carer Quality of Life, Advance directive discussed or completed and documented, Carer involved in care plan development, received services or information, Safe return program (for wandering) discussed or recommended, aware of identification items, enrolled in safety programs, receipt of caregiving assistance or respite/support services |

| Study details | Study population | Methods | Outcomes |
|---|---|---|---|
| Chu (2000) | 75 people living with dementia and their carers. | Intervention: Comprehensive home care program<br>Control: usual care. | Geriatric Depression Scale-Short Form, functional performance, The Burden Interview, Memory and Behaviour Checklist, level of depressive symptoms of the carers. |
| Dias (2008) | 59 people living with dementia and their carers. | Intervention: a trained Community Team that focused on supporting the carer through information on dementia, guidance on behaviour management, a single psychiatric assessment and psychotropic medication if needed.<br>Control: usual care. | Carer mental health, Zarit Burden Score, distress due to behavioural disturbances, behavioural problems in the subject and activities of daily living. |
| Eloniemi-Sulkava (2001) | 100 people living with dementia and their carers. | Intervention: systematic, comprehensive support by a dementia family care coordinator<br>Control: usual care. | Time to institutionalization (period in community care) from enrolment of patients in the study to their placement in long-term institutional care. |
| Eloniemi-Sulkava (2009) | 125 people living with dementia and their carers. | Intervention: a multicomponent intervention program with a family care coordinator, a geriatrician, support groups for carers, and individualized services.<br>Control: usual care. | Time from enrolment to institutionalization of spouses with dementia and use of services and service expenditure of couples. |
| Fortinsky (2009) | 84 people living with dementia and their carers. | Intervention: standardised assessment tool and a care consultant who had monthly contact with each family carer. A monthly care plan was organised.<br>Control: educational and community resource information but no care consultation. | Nursing home admission rate, self-efficacy for symptom management, self-efficacy for accessing support services, depressive symptoms, carer burden, and physical symptoms. |
| Jansen (2011) | 99 people living with dementia and their carers. | Intervention: case management by district nurses.<br>Control: usual care. | Carer's sense of competence, carer's quality of life, physical component summary, carer's depressive symptoms, carer's burden, care recipient's Quality of life, care received. |
| Kwak (2011) | 94 people living with dementia and their carers. | Intervention: Tailored Caregiver Assessment and Referral (TCARE®) protocol, a care management process designed to help family carers, on care planning and carer outcomes.<br>Control: usual care. | Service recommendation, compliance, and use. Carer identity discrepancy, carer burden, depressive symptoms. |

| Study details | Study population | Methods | Outcomes |
|---|---|---|---|
| Lam (2010) | 92 people living with mild dementia and their carers. | Intervention: case management by occupational therapist.<br>Control: usual care. | MMSE, Cornell Scale for Depression in Dementia score, Neuropsychiatric Inventory score, Personal Wellbeing Index for Intellectually Disabled, Zarit Burden Interview score, Personal Wellbeing Index for Adult, General Health Questionnaire score. |
| Meeuwsen (2012) | 153 people living with dementia and their carers. | Intervention: Coordination of care by memory clinic.<br>Control: Coordination of care by GP. | Quality of life, caregiving burden, geriatric depression scale, neuropsychiatric inventory, carer's personality, carer depression and anxiety, carer's mastery, carer's neuropsychiatric inventory, social support. |
| Miller (1999) | 8095 people living with dementia and their carers. | Intervention: case management and for an 80% discount on community care benefits, up to about $600 per month.<br>Control: usual care. | Nursing home entry rates. |
| Newcomer (1999) | 1906 people living with dementia and their carers. | Intervention: case management and for up to $699 per month in community care benefits.<br>Control: usual care. | Carer burden, carer depression. |
| Samus (2014) | 188 people living with dementia and their carers. | Intervention: 18-month care coordination intervention to systematically identify and address dementia-related care needs through individualized care planning; referral and linkage to services; provision of dementia education and skill-building strategies; and care monitoring by an interdisciplinary team.<br>Control: usual care. | Time to transfer from home and total percent of unmet care needs. |
| Schoenmakers (2010) | 46 people living with dementia and their carers. | Intervention: a care counsellor, coordinating care in quasi-unstructured way.<br>Control: usual care. | Depression in the family carer, coping behaviour of the carer, anxiety of the carer, carer burden, activities of daily living, neuropsychiatric symptoms. |
| Shelton (2001) | 412 people living with dementia and their carers. | Intervention: registered nurses as case managers and operating within a multispecialty physician group practice and a vertically integrated healthcare system | Likelihood of hospitalization, ADL limitations. |

| Study details | Study population | Methods | Outcomes |
|---|---|---|---|
| | | Control: usual care. | |
| Tanner (2015) | 171 people living with dementia and their carers. | Intervention: MIND at Home, a community-based, multicomponent, care coordination intervention.<br>Control: usual care. | Carer unmet needs, carer burden, depression, QOL. |
| Van Mierlo (2015) | 49 informal carers of people with dementia, supported by 19 randomised case<br>Managers participated in the study | Intervention: The DEMentia Digital Interactive Social Chart (DEM-DISC) is an ICT tool to support customised disease management in dementia.<br>Control: usual care. | Camberwell Assessment of Needs for the Elderly. |
| Vickrey (2006) | 290 people living with dementia and their carers. | Intervention: Disease management program led by care managers<br>Control: usual care. | Connection of patient-carer dyad with community agencies, receipt of caregiving assistance or respite/support services, patient health-related quality of life, quality of patient's health care, carer confidence in caregiving, carer health-related quality of life, social support, received as much help as needed with behaviour problem. |
| Xiao (2016) | 61 family carers of people living with dementia. All were from 10 minority groups. | Intervention: personalised carer support<br>Control: usual care. | Sense of competence, severity of BPSD, carer distress, usage of respite care, usage of carer support group, usage of dementia helpline, satisfaction with service providers, usage of community aged care, community aged care at home. |

### 7.1.3 Health economic evidence

Standard health economic filters were applied to the clinical search for this question, and a total of 5,127 citations was returned. Details of the literature search are provided in Appendix D. Following review of titles and abstracts, no full-text studies were retrieved for detailed consideration. Therefore, no relevant cost–utility analyses were identified. However, 1 cost–utility analysis that was relevant to this review question was identified in a literature search for another review question. Therefore 1 study was included in this review.

#### 7.1.3.1 Case management

**Vroomen et al. (2016)** conducted a trial-based cost-utility analysis alongside a Dutch 2-year prospective, observational cohort study with 521 informal carers and community-dwelling persons with dementia. The study compared case management provided within 1 care organisation (intensive case management model [n=234], ICMM), case management where care was provided by different care organizations within 1 region (linkage model [n=214], LM), and a group with no access to case management (control) (n=73). For further details, please see the economic evidence profile in Appendix M.

Cost diaries were used to estimate costs from a societal perspective; where possible, costs inconsistent with the NICE reference case were excluded from the results presented here. Table 32 shows the costs that we have included in our analysis. Costs were adjusted to price year 2010 and expressed in Euros (€).

Health-related quality of life was measured using the EQ-5D-3L (carer-rated for the person living with dementia).

**Table 32: Costs from Vroomen et al. (2016) with societal costs removed**

| | ICMM | LM | Control |
|---|---|---|---|
| Person living with dementia: QALYs | 1.25 | 1.18 | 1.27 |
| Carer+person living with dementia QALYs | 2.9 | 2.9 | 3.0 |
| General practice | € 1,279 | € 1,362 | € 1,088 |
| Hospital and outpatient clinics | € 2,642 | € 3,336 | € 4,835 |
| Overnight care | € 313 | € 227 | € 318 |
| Day centre | € 6,135 | € 7,190 | € 10,506 |
| Long term institutionalization | € 6,017 | € 5,688 | € 11,227 |
| Welfare services | € 3,043 | € 4,050 | € 20,784 |
| Medications | € 2,220 | € 1,867 | € 1,766 |
| Case management costs | € 3,120 | € 2,469 | - |
| Home care | Excluded | | |
| Home-making services | | | |
| Informal care costs | | | |
| **Total costs** | **€ 24,769** | **€ 26,189** | **€ 50,524** |

The mean incremental costs and effects are presented in Table 33.

**Table 33: Costs and effects calculated for Vroomen et al. (2016)**

| | Absolute | | Incremental | | |
|---|---|---|---|---|---|
| **Strategy** | **Cost** | **Effect** | **Cost** | **Effect [a]** | **ICER** |
| ICMM | €24,769 | 2.9 QALYs | | | |
| LM | €26,189 | 2.9 QALYs | €1,420 | -0.02 QALYs | Dominated |
| Control | €50,524 | 3.0 QALYs | €25,755 | -0.0004 QALYs | Dominated |

[a] *difference adjusted for baseline utility*

Assuming QALYs are valued at £20–30,000, the QALY losses observed with both ICMM and LM are small enough to justify the large savings associated with these forms of case management.

The authors report probabilistic sensitivity analyses suggesting a 0.992 probability that ICMM has an ICER of €30,000 or better compared with control, and a 0.977 probability that ICMM has an ICER of €30,000 or better compared with LM. However, these analyses include costs outside the NICE reference case that cannot be disaggregated.

The authors concluded that their study provides preliminary evidence that the ICMM is cost effective compared with the control group and LM.

### 7.1.4 Evidence statements

#### 7.1.4.1 Qualitative evidence

##### *7.1.4.1.1 Self-management intervention*

The following themes were identified for the self-management intervention for people living with dementia and their carers:

- Although people living with dementia said that they could not recall all of the activities, they had enjoyed the training program (low confidence)
- The participants felt empowered: training programs encouraged people living with dementia to continue with their hobbies and goals. Access to a budget provided a sense of empowerment (moderate confidence)
- Peer support, such as provided by support groups, was considered valuable by participants (low confidence)
- Additional support, such as a support group, was available, but these were often time-limited, which led both carers and people with dementia to the question of what happened when such support ended (low confidence)
- Respondents thought that professional support was important for effective self-management, and valued this resource. They thought that this help was necessary because not everything could be self-managed within the family (low confidence)
- Many respondents were unsure how to access the services that were available, and reported finding them limited and poorly integrated. This made it harder to self-manage the condition (low confidence)
- The approach of normalising difficulties was evident in many interviews (low confidence)
- A sense of stoicism, often expressed when respondents gave their ideas about self-management, was evident in many interviews, and this seemed to be a form of psychological management (low confidence)

#### *7.1.4.1.2 Outcome-focused/needs-led care vs standard care*

The following themes identified for outcome-focused/needs-led care vs standard care for people living with dementia and their carers:

- Standard care: The most common concern of familial carers is the feeling of not being able to cope (non-comparative questioning) (moderate confidence)
- Standard care: The sense of isolation expressed by the participants came over very strongly. This isolation appeared to come from their sense that they were on the outside with little control because the care was planned by the other professionals. Family carers felt that they were isolated as they had all the responsibility and in their eyes and potentially all the blame when things went wrong (moderate confidence)
- Outcome-focussed care: There was an improvement in the carers' self-reported subjective well-being, after the outcome-focused homecare intervention had been implemented (high confidence)
- Outcome-focussed care: All the carers felt the subjective well-being of their relative had improved after the six month outcome-focused care intervention (moderate confidence)

#### *7.1.4.1.3 Community-based case management*

The following themes were identified for community-based case management for people living with dementia and their carers:

- Meeting health and social care professionals at home was more relaxing and less stressful compared with using the memory service (moderate confidence)
- Being at home facilitated communication with health and social care professionals (moderate confidence)
- The case manager was good at identifying needs and providing the right support (moderate confidence)
- Carers expected case managers to provide information about dementia and services (moderate confidence)
- Case managers should be proactive in asking carers and people living with dementia if they feel they need assistance. This is because participants frequently expressed a reluctance to initiate contact with the case manager, which undermines the concept that they could ask for help when needed (moderate confidence)
- A common reason why people living with dementia and their carers do not initiate contact with case managers is because they associate case managers with assisting with 'major' problems such as arranging residential care homes. They do not associate case managers with assisting with day-to-day issues (moderate confidence)
- People living with dementia and their carers preferred to have their case manager based at their GP's surgery. This is because there was the perception that their GP's surgery would then be a 'one-stop shop'. In addition, having the case manager at the GP's surgery provided an additional opportunity to talk to the case manager while visiting the GP's surgery (moderate confidence)
- For some, exposure to others at more severe stages of the illness within the clinic was a potent contributor towards anxiety, illustrating what could be expected as the disease progresses. Appointments at home removed this exposure (moderate confidence)
- Case management made access to services easier including GPs, benefit checks and links to other services (moderate confidence)
- A key aspect of case management valued by people living with dementia and their carers was the idea of background support that could easily be called on at a time of need (moderate confidence)

- For people living with dementia and their carers to feel comfortable about contacting the case manager in the event of difficulties, there needed to be time and opportunities to develop a deeper relationship (moderate confidence)
- Face-to-face and telephone contact were both considered acceptable, although face-to-face contact was often preferred as it facilitated relationship building better than telephone contact (moderate confidence)

#### *7.1.4.1.4 Memory-clinic case management*

The following themes were identified for memory clinic case management for people living with dementia and their carers:

- For memory services that do not have post-diagnostic support, many participants expressed feelings of abandonment or 'being sent away' by professionals on receipt of diagnosis (moderate confidence)
- For memory services that do have post-diagnostic support, people with dementia and their carers explained the value of having support as soon after diagnosis as possible and the importance of skilled, knowledgeable, sensitive project workers to deliver support (moderate confidence)
- Carers frequently reported positively on the help received from the project workers with claiming benefits (moderate confidence)
- Carers spoke of receiving support with arranging Power of Attorney and valued the input from project workers in negotiating the process (moderate confidence)
- The service and nature of the staff made carers and people living with dementia feel supported and reassured. (Having a named person to contact in times of crisis, and the security that they would not left to manage alone.) (high confidence)
- People living with dementia felt pressure of time because the psychiatrist was busy (very low confidence)
- There were accounts of receiving no information, or insufficient or inappropriate information following diagnosis (moderate confidence)
- Some carers expressed discomfort with some of the information they received. Some felt that it was too much to face too soon. Many participants stated that a 'one size fits all' approach was not what they wanted (moderate confidence)
- Participants valued that information was delivered by the project workers on a one-to-one basis and specifically targeted to individual needs and wishes (moderate confidence)
- People living with dementia and their carers liked seeing the same person throughout treatment (high confidence)
- People living with dementia and their carers recognised the one stop shop aspect of the memory service. Ten participants described the memory service as a central point of access to all necessary services (low confidence)
- People living with dementia and their carers valued transport that was arranged by case managers/project workers (high confidence)
- Memory service post-diagnostic support when individualised and one-to-one, causes people with dementia to re-engage socially or with old hobbies (moderate confidence)

#### *7.1.4.1.5 Daisy Chain: a commercial person-centred dementia service that seems to have some elements of case management*

The following themes were identified for Daisy Chain:

- The person-centred community-based dementia service was well received, provides a personalised service and helped carers to cope (low confidence)

- There are sometimes differences of opinion between people living with dementia, paid carers and familial carers (low confidence)

#### *7.1.4.1.6 Non-specified case management style(s) in predominantly remote and rural areas in Scotland*

The following themes were identified for non-specified case management style(s) in predominantly remote and rural areas in Scotland:

- The lack of alternative options sometimes led to provision of no support at all (very low confidence)
- Poor coordination of services. The participants particularly emphasized poor communication between existing services, which results in unsatisfactory case management and delays in service provision. The need for a single point of access to information and service coordination was expressed as a means to manage these challenges and to facilitate more efficient and effective service delivery. Participant reports also highlighted inconsistencies in care provision and suggested the need for well-defined care pathways (high confidence)
- Some experienced lack of continuity of care. This can lead to poor communication and is confusing (high confidence)
- There were high satisfaction levels with the support received from the Community Mental Health Team (moderate confidence)
- Participants discussed the importance of staff building a rapport with the person living with dementia. This facilitates communication (very low confidence)
- When it was available, a carers' group (carer support) was appreciated (very low confidence)
- Practical support was important to most carers who received help from private or voluntary services regularly. Carers perceived this type of support as an opportunity to take a respite from caregiving responsibilities. Many used the respite time to rest, run errands which required getting out, or to attend carers meetings (very low confidence)
- Information was not always in a format appropriate for the person living with dementia or their carer (moderate confidence)
- The way information was delivered was important. Participants preferred a direct approach with the opportunity to ask questions (moderate confidence)
- Care managers should be proactive in anticipating the needs of people living with dementia and their carers and provide relevant information (very low confidence)

#### *7.1.4.1.7 Case management in residential care homes*

The following theme was identified for case management in residential care homes:

- Participants spoke about having the freedom to be able to carry out normal everyday activities and domestic chores (moderate confidence)

### 7.1.4.2 Quantitative evidence

#### *7.1.4.2.1 Care coordination/management using a protocol/action plan*

Moderate-quality evidence from up to 8 RCTs containing 2,474 people living with dementia found improvements in quality of life and rates of entry in to long stay care for the person living with dementia and carer burden for people offered case management versus usual care, but could not differentiate cognition, depressive symptoms or behavioural and psychological symptoms of dementia for the person living with dementia, or carer depressive symptoms or quality of life. Across the studies, larger gains were seen in studies with more frequent follow-up, studies where the case manager was a nurse, studies where contact was

made face-to-face in the person's home, and studies conducted in Hong Kong. However, these differences were difficult to interpret as there was considerable correlation between these features across the studies.

#### *7.1.4.2.2 Care coordination/management using a specific structured protocol vs care coordination/management that is unstructured*

Moderate- to low-quality evidence from 1 RCT containing 73 people living with dementia could not differentiate outcomes for carers between people offered care coordination/management using a specific structured protocol vs care coordination/management that is unstructured.

#### *7.1.4.2.3 Care coordination by telephone vs care coordination in-person*

**Care coordination by telephone ('experimental') vs care coordination in-person ('control'). Follow-up frequency was monthly for the first 3 months and quarterly thereafter**

Moderate-quality evidence from 1 RCT containing 43 people living with dementia found that care coordination in-person improved carer quality of life (benefits of caregiving) compared with follow-up by telephone. However, this study could not differentiate quality of life of the person living with dementia, the total number of problems, carer depressive symptoms, carer quality of life (spirituality and faith) or carer burden.

#### *7.1.4.2.4 Follow-up organised by memory clinic vs GP*

**Follow-up organised by memory clinic vs GP**

High-quality evidence from 1 RCT containing 153 people living with dementia found that follow-up by GP was associated with less carer depressive symptoms and anxiety compared with follow-up by memory clinic. However, this study could not differentiate outcomes relating to the person living with dementia, carer quality of life, carer social involvement, carer neuropsychiatric index, carer personality or carer mastery.

#### *7.1.4.2.5 Medicare Alzheimer's disease demonstration*

**The Medicare Alzheimer's disease demonstration (care coordination/management with unspecified follow-up frequency) vs usual care**

Moderate-quality evidence from 1 RCT containing 412 people living with dementia found that care coordination/management with unspecified follow-up frequency reduces the likelihood of any carer hospitalisation compared with usual care. However, this study could not differentiate emergency department visits.

Low-quality evidence from 1 RCT containing 7,803 people living with dementia could not differentiate rates of entry into residential care between people offered care coordination/management with an unspecified follow-up frequency

Low-quality evidence from 1 RCT containing 1,906 people living with dementia could not differentiate carer outcomes between people offered care coordination/management with an unspecified follow-up frequency.

#### *7.1.4.2.6 DEM-DISC*

**Care coordination/management using DEM-DISC vs care coordination/management without DEM-DISC**

Very low- to low-quality evidence from 1 RCT containing 49 people living with dementia could not differentiate outcomes for people living with dementia between people offered care coordination/management using DEM-DISC compared with care coordination/management without DEM-DISC.

#### *7.1.4.2.7 Personalised carer support for minority groups*

**Personalised carer support for minority groups vs usual care for minority groups**

Moderate- to low-quality evidence from 1 RCT containing 61 people living with dementia found that personalised carer support for minority groups compared with usual care for minority groups improves carer sense of competence, carer quality of life (mental), care recipient's behavioural problems, carer distress, and carer's satisfaction with service providers. However, personalised carer support increased usage of respite care. This study could not differentiate carer quality of life (physical) nor usage of community aged care.

### 7.1.4.3 Health economics - Two forms of case management

One partially applicable cost–utility analysis with very serious limitations conducted alongside a cohort study explored the cost-effectiveness of 2 forms of case management. Both forms of case management resulted in a very small loss of QALYs compared with control, but resulted in significant cost savings. An intensive case management model was found to dominate a linkage model of case management.

## 7.1.5 Evidence to recommendations

| | |
|---|---|
| **Relative value of different outcomes** | The aim of this review question was to identify the most effective methods of care planning, focussing upon improving outcomes for people with dementia and their carers. Therefore, the committee agreed that studies with interventions and outcomes benefitting people living with dementia and their carers would be more relevant compared with studies that just looked at carers alone. |
| **Trade-off between benefits and harms** | **The importance of linking care coordination recommendations to the diagnosis recommendations**<br>The committee noted that occasionally people living with dementia are diagnosed as having dementia but are then 'forgotten' by the system. The harm of this is that by the time a care and support plan is made, that individual's control over planning their future care might be lost forever. Therefore, the committee agreed that the care coordination recommendations will be linked into the 'at diagnosis' recommendations because care management and formulating a care and support plan should start from diagnosis. However it was noted that no matter what stage of dementia a person has, they should always have a care and support plan.<br>**The importance of having recommendations that will lead to better coordination of care**<br>The committee agreed that studies that had good results (particularly Chien 2008, Chien 2011) had components of care that already exist throughout the NHS. However, these studies had relatively better coordination compared with most NHS current practice. The committee agreed that current NHS practice is more fragmented, potentially because funding comes from different places, and that |

better coordination would be likely to lead to better outcomes for people living with dementia and their carers.

**A single named individual responsible for coordinating care**

The committee agreed that the positive overall findings from the studies on case management provided robust evidence that there should be a single person responsible for coordinating care. Otherwise, it is common for health and social care professionals to assume that other members within the team are coordinating care when they are not. The majority of the studies that involved care coordination had one person as the single named individual responsible for coordinating care, and these studies showed an improvement in the quality of life of the person living with dementia, and reductions in both burden and depression for the carer.

**The initial assessment of needs should be face to face whenever possible**

The committee agreed that the initial assessment of needs should be face to face whenever possible. The studies that have particularly good results (Chien 2008, Chien 2011) involve face to face assessments of needs, and the committee agreed this was in line with their experience. They also agreed that it was important for the recommendations to be pro-active in identifying potential problems rather than reactive. In addition, it was noted that it was not always possible to identify in advance which individuals would benefit from a face to face assessment.

The committee agreed that the person conducting a face-to-face assessment does not have to be the person coordinating care. For example, in some situations the district nurse coordinates the care but the general practitioner provides much of the care.

Therefore, the committee agreed that health and social care professionals should ensure that people living with dementia who have healthcare or support needs have a single named individual responsible for co-ordinating their care, who should ensure there is an initial assessment of their needs.

**Offering information about available services**

The committee noted that studies with good results usually involve the care coordinator offering information to the informal carers on available services and how to access them, and noted this was in line with their own experience. The committee agreed that this should be incorporated into the recommendations.

**Involving carers, agreeing the care and support plan and reviewing it**

The committee noted that studies which have good results (for example, Chien 2008, Chien 2011) involve a documented and regularly reviewed care and support plan. These studies often involve the person's carers and family members in support and decision making. Therefore, the committee agreed that the person's carers and family members (if appropriate) should be involved in support and decision making. In addition, the care and support plan should be agreed with the individual and their carers and/or family members (as appropriate). A review date should also be agreed and there should be a discussion about how that plan will be reviewed, and a copy of the plan should be provided to the person living with dementia and their carers (if appropriate).

**People living with dementia who refuse assistance**

The committee noted that if the person does not have capacity to make decisions about their care, special consideration should be given to the individual's views, in line with the principles of the Mental Capacity Act. They noted that the term 'special consideration' has a specific meaning with the Act, and was therefore the correct term to

include in the guideline. Related to this, they also felt it was important to inform people about the availability of local advocate services, and in particular their rights to an independent mental capacity advocate, should they meet the criteria for needing one.

**Recording progress**

The committee agreed that when reviewing care and support plans with the person living with dementia, progress should be evaluated and recorded against the objectives in the original care and support plan, in coordination with all professionals involved in the person's care. They noted this was in line with best practice in current UK services.

**Services to ensure that the maximum number of people living with dementia can access them**

The committee noted that people who live alone who do not have regular contact with a carer are at risk of poor outcomes. In addition, carers can have comorbidities that make it more difficult for both them and the person they are caring for to access services. The committee agreed that situations like these can lead to equity of access problems. Therefore, the committee agreed that service providers should design services to ensure that the maximum number of people living with dementia can access them. This includes people who do not have an informal carer, people whose informal carer is not able to support them to access services, and people who do not have access to affordable transport or find transport difficult to use. It would also include groups with comorbidities that might limit access to services, or who are from groups who may be less likely to access health and social care services, and the committee felt it appropriate to specify learning disabilities, sensory impairment, and people from black, Asian and minority ethnic groups as examples.

**Ensuring access to information**

The committee agreed that people living with dementia and their carers should know where, who from and how to obtain information or if their needs change. Evidence for this came from Iliffe 2014, Kelly 2016, Gorska 2013, Innes 2014 and Moore 2017, and was in line with the committee's own experience.

**Transferring information**

The committee noted that the interventions in Samas 2014 and Vickrey 2006 involve using special software to assist coordination. The committee agreed that the beneficial results of these studies could be partly because of the more reliable transfer of information.

The committee noted that when people living with dementia are transferred from their home to residential care, their information is often not sent with them. As a result, when the person living with dementia is transferred to a residential care home, their care and support plan often has to be created again. In addition, when information is not sent with the person to the residential care home, established personal routines are sometimes not respected.

Therefore, the committee agreed that service providers should ensure that information about people living with dementia (including care and support plans and advanced care and support plans) can be easily transferred between different care settings (including between home, community and residential care), including requesting consent for these to be transferred when they are produced. The committee agreed that the evidence did not allow them to be more specific about how this should be ensured, and that different local areas may adopt different solutions to this problem.

**Maximising the consistency and efficiency of care**

| | |
|---|---|
| | The committee agreed that staff delivering care and support should maximise continuity and consistency of care. This statement refers to ensuring continuity of the people delivering care and consistency of approach. If this is not possible, the committee noted that it is important to ensure that relevant information is shared across services/people providing care. This information should be recorded in the person's care and support plan. This approach will reduce duplication of questions asked by professionals and increase efficiency. Evidence for this was found in Gorska 2013 and Innes 2014. |
| **Consideration of health benefits and resource use** | The economic evidence for 2 forms for case management supported the idea that case management did not make patient's dementia any worse in terms of QALYs, but could result in significant cost savings. The committee agreed that the recommendations resulting from other evidence considered by the committee should not incur extra costs as the components of care recommended already exist. To the contrary, ensuring that there is an initial assessment of needs (identifying potential problems) and ensuring that information is transferred, with consent, should result in cost savings. Transferring information should avoid duplication of effort and expense, which can be considerable – for example, saving hours of time for professionals for each person living with dementia. Furthermore, having a single named individual responsible for coordinating care for patients with dementia should improve efficiency in the use of resources. |
| **Quality of evidence** | The quality of the evidence was sufficient to recommend care coordination, the formulation of a care and support plan and transfer of information. However, the committee noted that none of the RCTs included people living with dementia who do not have an informal carer. Therefore, the committee took care to include recommendations that would help people living with dementia who do not have informal carers.<br>The committee noted that the evidence base primarily came from people living in the community, and there was a lack of evidence on people in residential care settings. They agreed on the basis of this evidence that recommendations should be made to cover the whole population of people living with dementia, as the key principles of well-coordinated care are likely to be similar across cares settings, and it was agreed that it was inappropriate to exclude people from recommendations as a result of where they live/are receiving care. |
| **Other considerations** | The committee noted that sometimes people who live with dementia do not realise they have dementia and refuse care. This can place a great deal of burden and stress on their informal carers. They committee noted it was important in these situations for the carer to continue to receive appropriate support.<br>**Research recommendations**<br>The benefits of high intensity case management for the UK are difficult to estimate on the basis of the data available because of the differences between countries with regards to primary care provision and the thresholds for entry to long-stay care. The committee agreed that UK-based RCTs should be conducted to determine the impact of higher intensity case management compared with usual care on institutionalisation and quality of life. These should measure the quality of life of both the person living with dementia and their carer(s). From a commissioning perspective, reducing entry to long-stay care is a key aim and would be a priority. Ideally, studies should also include people at various stages of dementia.<br>The committee noted that none of the RCTs involved care planning for people in residential care settings. Therefore, the committee agreed that research should be conducted to find the most effective methods of care planning for people in residential care settings. |

The committee felt that it was important to include a research question to find the most effective methods of care planning for people who do not have regular contact with an informal carer. This is because it is common for people living with dementia to not have regular contact with a carer and these people are often the ones with the greatest needs and are frequently left out. The committee agreed that whilst it may be more difficult to recruit people without carers than those with in to research studies, it was important these people are not forgotten when research is undertaken.

Sections of recommendations referring to younger people were also informed by the evidence review on the specific needs of younger people living with dementia (section 17).

### 7.1.6 Recommendations

#### Care coordination

**47. Provide people living with dementia with a single named health or social care professional who is responsible for coordinating their care.**

**48. Named professionals should:**

- arrange an initial assessment of the person's needs, which should be face to face if possible.
- provide information about available services and how to access them.
- involve the person's family members or carers (as appropriate) in support and decision-making.
- give special consideration to the views of people who do not have capacity to make decisions about their care, in line with the principles of the Mental Capacity Act 2005
- ensure that people are aware of their rights to and the availability of local advocacy services, and if appropriate to the immediate situation an independent mental capacity advocate
- develop a care and support plan, and:
  - agree and review it with the involvement of the person, their family members or carers (as appropriate) and relevant professionals
  - specify in the plan when and how often it will be reviewed
  - evaluate and record progress towards the objectives at each review
  - ensure it covers the management of any comorbidities
  - provide a copy of the plan to the person and their family members or carers (as appropriate).

**49. When developing care and support plans and advance care and support plans, request consent to transfer these to different care settings as needed.**

**50. Service providers should ensure that information (such as care and support plans and advance care and support plans) can be easily transferred between different care settings (for example home, inpatient, community and residential care).**

**51. Staff delivering care and support should maximise continuity and consistency of care. Ensure that relevant information is shared and recorded in the person's care and support plan.**

52. **Service providers should design services to be accessible to as many people living with dementia as possible, including:**
    - people who do not have a carer or whose carer cannot support them on their own
    - people who do not have access to affordable transport, or find transport difficult to use
    - people who have responsibilities (such as work, children or being a carer themselves)
    - people with learning disabilities, sensory impairment (such as sight or hearing loss) or physical disabilities
    - people who may be less likely to access health and social care services, such as people from black, Asian and minority ethnic groups.

### 7.1.7 Research recommendations

4. **What is the effectiveness and cost effectiveness of high-intensity case management compared with usual care on quality of life (for the person living with dementia and for their carer) and the timing of entry to long-term care?**

5. **What are the most effective methods of care planning for people in residential care settings?**

6. **What are the most effective methods of care planning for people who do not have regular contact with an informal carer?**

For more details on the research recommendations made, and the rationale behind them, see appendix L.

## 7.2 Post diagnosis review for people living with dementia

**Review question**

- How should people living with dementia be reviewed post diagnosis?

### 7.2.1 Introduction

The aim of this review was to identify how and where people living with dementia should be reviewed post diagnosis, and also to identify any harms caused by failures in, or inappropriate models of, post diagnosis review for people living with dementia. The review focused on identifying studies that fulfilled the conditions specified in Table 34. For full details of the review protocol, see Appendix C. This question specifically focused on studies where the intervention was a method of, location for, or individual responsible for reviewing a person living with dementia, rather than a treatment or service being provided to the individual. The specified trial intervention needed to be an element of how the person is reviewed.

**Table 34: Review summary: review post diagnosis for people living with dementia**

| | |
|---|---|
| **Population** | • People (aged 40 years and over) living with dementia and admitted to hospital |
| **Intervention** | Models of post diagnosis review for people living with dementia, which may include features such as:<br>• Review of mental health (memory, mood, challenging behaviours)<br>• Review of physical health (including co-morbidities)<br>• Review of functional ability<br>• Nutrition and hydration (swallowing)<br>• Lifestyle advice<br>• Medication review (including co-prescribing)<br>• Information needs<br>• Driving safety review<br>• Financial advice<br>• Future care planning needs<br>• Carer support and assessment |
| **Comparator** | • Each other<br>• Usual care |
| **Outcomes** | • Clinical outcomes including cognitive, functional and behavioural ability<br>• Process outcomes (e.g. adherence of staff to review protocols)<br>• Access to health and social care support<br>• Patient and carer experience and satisfaction<br>• Patient and carer health-related quality of life<br>• Equity of access to services<br>• Adverse events (medication)<br>• Resource use and costs |

### 7.2.21 Evidence review

A systematic literature search was carried out to identify any comparative quantitative study designs (RCT's, non-randomised controlled trials, before and after studies and cohort studies). A total of 8,678 references were screened at the title and abstract level, with 33 potentially relevant references being ordered for full text review. Of these references, 5 were selected for inclusion based on their relevance to the review protocol. The excluded studies are listed, with reasons for their exclusion, in Appendix F. For the full evidence tables and full GRADE profiles please see Appendix E and Appendix G.

#### 7.2.2.17 Description of included studies

The characteristics of the included studies are summarised in Table 35. References for the included studies are given in appendix I.

**Table 35: Included studies**

| Study reference | Study design | Study population | Intervention & comparator | Relevant outcomes | Comments |
|---|---|---|---|---|---|
| Bass (2003) | Randomised controlled trial | 157 people living with dementia | Intervention: Care consultations comprising use of managed health services in partnership with use of Alzheimer's associations services<br>Comparison: Usual managed care services only | • No of Emergency department visits<br>• Hospital admissions<br>• Physician visits<br>• Case management visit<br>• Use of direct care community services<br>• Use of non-Association support services | Location: USA<br>Follow up: 12 months |
| Crotty (2004) | Randomised controlled trial | 154 residents with medication problems and/or challenging behaviours | Intervention: Multidisciplinary case conferences<br>Comparison: Usual care | • Medication Appropriateness Index (MAI)<br>• Behaviour (Nursing Home Behaviour Problem Scale) | Location: Australia<br>Follow-up: 3 months |

| Study reference | Study design | Study population | Intervention & comparator | Relevant outcomes | Comments |
|---|---|---|---|---|---|
| Kohler (2014) | Randomised controlled trial | 235 community living dyads of people living with dementia/ carers | Intervention: Multidisciplinary regional dementia network<br>Comparison: Usual care | • Cognition (MMSE)<br>• Functional (NAA; IADL)<br>• Quality of life (EQ5D; QOL-AD) | Location: Germany<br>Follow-up 6-12 months |
| Meeuwsen (2012) | Randomised controlled trial | 175 community living dyads of people living with dementia/ carers | Intervention: Post-diagnosis dementia care in memory clinic<br>Comparison: Post-diagnosis dementia care by GP | • Quality of life (QoL-AD)<br>• Depression (GDS)<br>• Functional (Interview for deterioration in daily living in dementia) | Location: Netherlands<br>Follow-up:12 months |
| Nourhashemi (2010) | Randomised controlled trial | 574 people living with Alzheimer's disease | Intervention: Comprehensive standardised evaluation every six months<br>Comparison: Usual care | • Functional decline (ADCS-ADL)<br>• Mean time to admission<br>• Risk of admission to residential care<br>• Risk of mortality<br>• Reason for admission (worsening medical conditions)<br>• Reason for admission (carer related reasons) | Location: France<br>Follow-up 24 months |

1

### 7.2.3 Health economic evidence

A systematic literature search was undertaken to identify existing cost–utility analyses evaluating how people living with dementia should be reviewed post-diagnosis. In total, 3,291 articles were returned, of which 3 were selected as potentially relevant and retrieved for full text review. Of these studies, 1 study considering memory clinics compared with GP follow-up was deemed relevant and included.

#### 7.2.3.1 Memory clinic versus GP follow up

**Meeuwsen et al. (2013)** conducted a cost–utility analysis alongside the Dutch AD-Euro RCT summarised above, comparing the cost effectiveness of memory clinics with GP care for the review and coordination of care of people with mild-to-moderate dementia. The primary outcome measures were QALYs and costs over 12 months after diagnosis. For further details, please see the economic evidence profile in Appendix M.

The authors' base case adopted a broad societal perspective, including an attempt to value productivity loss and informal care costs; however, disaggregated results are reported, enabling the recalculation of results with a perspective that is consistent with the NICE reference case. Information about resources used was derived from a case report form provided by the carer. The study also used the hospital information system, GP electronic medical records and information from different healthcare workers involved to estimate resources used. Cost prices were based on standard Dutch sources. All prices were converted to the year 2009 and expressed in Euros.

Utilities were generated for both patient and carer using the EQ-5D, with Dutch utility weights.

Base-case results (Table 36) suggested memory clinics are associated with cost savings of €512 per person compared with the GP group. Aside from GP and memory clinic contacts, only 1 variable was significantly different between the 2 arms: there were 8 hospital admissions in the memory clinic group compared with 16 in the GP group – there was no discussion or further information provided as to why this was the case. A QALY benefit of 0.025 in favour of the GP group was found. Taken together, these results suggest that memory clinics save money that may be considered sufficient to justify the QALY losses with which they are associated; however, both cost and QALY differences are relative small and extremely uncertain.

**Table 36: Analysis from Meeuwsen et al. (2013) adjusted to remove productivity loss and informal care costs**

| | Absolute | | Incremental | | |
|---|---|---|---|---|---|
| Strategy | Cost | Effect | Cost | Effect (95%CI) | ICER |
| Memory clinic | €17,912 | NR | | | |
| GP | €18,424 | NR | €512 | 0.025 QALYs (−0.114 to 0.064) | €20,480 /QALY |

The authors' probabilistic sensitivity analysis (from which it was not possible to disaggregate costs not considered by the NICE reference case) showed that memory clinics were cost saving, compared with GP follow-up, in 59% of cases and the probability that they are associated with an ICER of €50,000 or better was around 50%.

The authors concluded that no evidence was found that memory clinics were cost effective compared with GPs for post-diagnosis review and coordination of care of people with dementia in the first year after diagnosis. The authors used UK utility weights in a scenario analysis; the results were deemed similar to the Dutch analyses and were therefore not presented by the authors.

### 7.2.4 Evidence statements

#### 7.2.4.1 Care reviews and consultations in partnership with Alzheimer's associations services versus usual managed care services only

Moderate- to high-quality evidence from 1 RCT of 157 people living with Alzheimer's disease found the use of case management was significantly greater at 12 months follow up for people receiving the intervention but could not differentiate number of hospital admissions, number of emergency department visits, number of physician visits, use of direct care community services or use of non- Association information and support for people who were reviewed using managed health services in partnership with Alzheimer's Association services compared with usual managed care services only.

#### 7.2.4.2 Multidisciplinary case conferences versus usual care

Low- to moderate-quality evidence from 1 RCT of 154 aged care residents with pain and dementia related problem behaviours and medication problems found significant improvements at 3 months in the appropriate use of medicines (Medicines Appropriation Index), but could not differentiate number of medicines (Medicines Appropriation Index), number of drugs, changes in the number of drugs, or behaviour (Nursing Home Behaviour Problem Checklist) for people receiving a medication advisory case conference compared with usual care.

#### 7.2.4.3 Network multidisciplinary monitoring and care versus usual care

Low-quality evidence from 1 RCT of 235 people living with dementia could not differentiate between functional outcomes (NAA; IADL), patient reported health outcomes (EQ5D-VAS), cognition (MMSE), quality of life (QOL-AD), or carers' health related quality of life (EQ5D-VAS; SF36 physical health, SF36 mental health) for people being reviewed using a network of multidisciplinary care compared with usual care.

#### 7.2.4.4 Memory clinic review and monitoring versus GP review and monitoring

Moderate- to high-quality evidence from 1 RCT of 175 people newly diagnosed with mild to moderate dementia could not differentiate between quality of life (QOL-AD, carer report; QOL-AD, patient report), neuropsychiatric symptoms (NPI), functional outcomes (Interview for deterioration in dementia) or depressive symptoms (GDS) for people being reviewed in a memory clinic compared with GP care.

Outcomes for carers found higher levels of depressive symptoms (CES-D), and anxiety (STAI trait) for people receiving care in a memory clinic compared with GP care but could not differentiate quality of life (QOL-AD); social support (ISB), sense of competence, emotional problems (NPI), mastery (PMS) or personality (EPQ).

#### 7.2.4.5 Standardised evaluation and assessment in memory clinic versus usual care in memory clinic

Very low- to moderate-quality evidence from 1 RCT of 574 people living with Alzheimer's disease found that admissions due to worsening conditions were significantly reduced and admissions due to carer reasons were significantly greater at 2 years follow up but could not differentiate between functional decline at 2 years (ADCS-ADL), mean time of admission to care at 2 years, risk of admission to care or risk of mortality at 2 years for people being reviewed by specialist care in a memory clinic compared with usual care in a memory clinic.

#### 7.2.4.6 Health economic evidence

##### *7.2.4.6.1 Memory clinic versus GP follow up*

One partially applicable trial-based cost–utility analysis with potentially serious limitations explored the cost effectiveness of memory clinics compared with general practitioner care for the review and coordination of care for people with mild-to-moderate dementia in the first year after diagnosis. When costs not relevant to the NICE reference case were excluded, memory clinics were cheaper than GP care, and associated with a decrease in QALYs, resulting in a point-estimate ICER of €20,480 saved per QALY forgone with memory clinics instead of GP care. Results were subject to substantial uncertainty: at a 95% confidence level, the data were consistent with cost savings and/or QALY gains with either approach.

### 7.2.5 Evidence to recommendations

| | |
|---|---|
| **Relative value of different outcomes** | The committee agreed that the purpose of adopting a specific strategy for reviewing people living with dementia would be to improve their clinical outcomes, and so the same patient outcome measures would be relevant here as for questions on treatment (cognition, quality of life etc.) It also agreed that these improvements would be achieved through more effective reviewing strategies better identifying individual needs, and therefore leading to a more efficient and effective use of other services. Therefore, measures like 'people given appropriate and timely access to services', or 'reductions in inappropriate service or medicine use' would also be valuable outcomes. |
| **Trade-off between benefits and harms** | The committee noted that for typical patients, only having routinely scheduled appointments and standard structured assessments may not deal with the reality of situations experienced by people living with dementia. It agreed that reviewing people living with dementia requires a flexible approach and is dependent upon individual needs, rather than reliant upon a prescriptive approach. The committee recognised that a flexible approach would have different implications at each stage of the dementia trajectory. People living with more severe dementia may also be living with multiple comorbidities, which may require more rapid reviews and more frequent follow up. The committee agreed that continuity of care is of paramount importance in considering the evolving needs of people living with dementia.<br>The committee recognised there was wide variation in the arrangement of memory service facilities in the UK and agreed it would not be appropriate to recommend a specific service model for reviewing people living with dementia. It highlighted the importance of not losing people in the system and recognised that every service contact could be used as an opportunity to provide dementia care (for example, during GP annual reviews). For this reason, the committee agreed it would be more important to allow people living with dementia to have access to a multidisciplinary service, involving both health, social care and volunteer services, in order to address issues on a more emergent basis. |

| | |
|---|---|
| **Consideration of health benefits and resource use** | The committee acknowledged that Meeuwsen (2012) did not find any significant or clinically meaningful differences in health outcomes between the intervention (memory clinics) and control group (GP care). The economic evaluation alongside the trial (Meeuwsen et al 2013) found that the memory clinics intervention compared with GP care produced a small saving in terms of costs, but also produced fewer QALYs. However, as the author's economic evaluation considered costs which were not relevant to the NICE reference case, an analysis was conducted where these costs were removed. Under these circumstances, it was found that the memory clinics intervention was showing a smaller saving in costs and an equal loss of QALYs compared with the author's economic evaluation.<br>The committee agreed that it would not be appropriate to make a recommendation based on this evidence showing insignificant savings and loss of QALYs. |
| **Quality of evidence** | The committee agreed that the evidence presented did not directly address the full complexity of the issues that relate to reviewing a person living with dementia, although there were certain aspects that could be taken from the included studies.<br>The committee noted that although the evidence they had seen was located oversees, similar practices could be observed in UK practice. For example it is not unusual to observe collaborations between care management services and volunteer services or charities in the UK, similar to that cited in Bass (2003).<br>In addition, the use of scheduled (bi-yearly) appointments had been considered in Nourhashemi (2010). That study had reported no significant benefit for clinical and functional outcomes, for people who had received scheduled appointments and who had been reviewed in a structured or prescriptive manner. The committee concluded that a more beneficial service would be likely to reflect current practice and focus more upon an emergent and flexible approach to reviewing people living with dementia and addressing person-centred need based upon a multidisciplinary co-ordination of care. |
| **Other considerations** | The committee acknowledged that a post-diagnosis review of people living with dementia impacts upon all members of the family. It therefore agreed that all recommendations would be relevant to both people living with dementia and their cares and family members. |

### 7.2.6 Recommendations

**53. After a person is diagnosed with dementia, ensure they and their family members or carers (as appropriate) have access to a memory service or equivalent hospital- or primary-care-based multidisciplinary dementia service.**

**54. Memory services and equivalent hospital- and primary-care-based multidisciplinary dementia services should offer a choice of flexible access or prescheduled monitoring appointments.**

**55. When people living with dementia or their carers have a primary care appointment, assess for any emerging dementia-related needs and ask them if they need any more support.**

# 8 Inpatient care

At any one time up to 25% of acute hospital beds are occupied by people living with dementia. People with dementia often experience longer durations of hospital admission, delays in leaving hospital and reduced levels of independent functioning (CQC 2017, DAA 2016). Over recent years there have been a range of initiatives to focus action and attention on improving the experience and outcomes of hospital care for people with dementia (DAA, Dementia Friendly Hospitals Charter & Dementia CQUIN). Acute hospital admission can be a time of distress, confusion and delirium for someone with dementia. These factors may contribute to a decline in global functioning and reduced ability to return home to independent living. The achievement of improved or at least maintained levels of independent functioning is a minimum expectation following a period of acute care. This is a key opportunity in the persons journey with dementia for holistic comprehensive care planning to be undertaken with the person and their significant others.

Acute hospital admission has been identified as a key opportunity for people with previously undiagnosed dementia to access appropriate assessment & diagnosis of dementia to; improve their care and treatment while in hospital, facilitate appropriate early discharge and enable access to a full range of post-diagnostic support and interventions.

The extent to which the needs of people with dementia experiencing an acute hospital admission are understood and effectively met remains variable across the country (CQC 2014 & 2017, RcPsych 2016). Many examples of improvements in this area of care over recent years have been identified, strengthened by local commissioning arrangements and good clinical leadership, but there remains significant local variation in how effectively people experiencing dementia in a hospital setting are diagnosed and then provided with appropriate tailored individual support and discharge planning.

# 8.1 Caring for people living with dementia who are admitted to hospital

**Review question**

- How should people living with dementia be cared for when admitted to hospital?

## 8.1.1 Introduction

The aim of this review was to identify the most appropriate ways to care for people living with dementia when they are admitted to hospital and to identify any harms that may be caused by failures in or inappropriate models of hospital care for people living with dementia. The review focused on identifying studies that fulfilled the conditions specified in Table 37. For full details of the review protocol, see Appendix C.

**Table 37: Review summary: inpatient care for people living with dementia**

| | |
|---|---|
| **Population** | • People (aged 40 years and over) living with dementia and admitted to hospital |
| **Intervention** | Models of hospital care for people living with dementia, which may include elements such as:<br>• Additional support from hospital staff/others<br>• Information needs (both information for the person living with dementia and the information needs of the hospital staff)<br>• Person-centred assessment<br>• Assessment for hospital discharge (timing of discharge)<br>• Family/carer information needs, access and involvement in care<br>• Types of ward<br>• Environmental design<br>• Comprehensive geriatric assessment<br>• Medicines reconciliation and review |
| **Comparator** | • Each other |
| **Outcomes** | • Clinical outcomes including cognitive, functional and behavioural ability<br>• Process outcomes (e.g. adherence of staff to care protocols)<br>• Staff wellbeing and job satisfaction, skill levels<br>• Access to health and social care support<br>• Patient and carer experience and satisfaction<br>• Patient and carer health-related quality of life<br>• Co-patient experience<br>• Adverse events<br>• Equity of access to services<br>• Resource use and costs |

## 8.1.2 Evidence review

A systematic literature search was carried out to identify any comparative quantitative study designs (for example RCTs, non-randomised controlled trials, before and after studies and cohort studies). A total of 8,857 references were screened at the title and abstract level, with 46 potentially relevant references being ordered for full text review. Of these references, 5 were selected for inclusion based on their relevance to the review protocol. The excluded studies are listed, with reasons for their exclusion, in Appendix F. Evidence tables for the included studies are presented in Appendix E, with GRADE profiles in appendix G.

### 8.1.2.11 Description of included studies

2 The characteristics of the included studies are summarised in Table 38. References for the included studies are given in appendix I.

3 **Table 38: Included studies**

| Study reference | Study design | Study population | Intervention & comparator | Relevant outcomes | Comments |
|---|---|---|---|---|---|
| Baldwin (2004) | RCT | 153 medically ill people with cognitive impairment and/or depression in a district general hospital | • Intervention: Multi-faceted nurse led intervention<br>• Comparator: Usual care | • Health of Nation outcome scale<br>• Geriatric Depression Scale<br>• MMSE<br>• Length of stay in hospital (days)<br>• Readmissions at 3 months<br>• Death at 3 months | Study location UK<br>General hospital |
| Boltz (2015) | Non-randomised controlled trial | 86 patient/carer dyads of hospitalised people living with dementia | • Intervention: Family centred function focused care<br>• Comparator: Usual care | • Patient outcomes:<br>○ Hospital readmission<br>○ Occurrence of delirium<br>○ Activities of daily living<br>○ Utilisation of post-acute rehabilitation<br>• Carer outcomes<br>○ Preparedness for caregiving<br>○ Anxiety<br>○ Depression<br>○ Strain | Study location: USA<br>General hospital |
| Campbell (2004) | Prospective cohort | 52 people with end-stage dementia (defined by FAS &NHO guidelines) treated in an ICU | • Intervention: Proactive case finding and collaboration between palliative care service and ICU staff<br>• Comparator: Usual care | • Hospital and ICU length of stay<br>• Use of non-beneficial resource<br>• Establishment of do not resuscitate goals | Study location USA<br>ICU |

| Study reference | Study design | Study population | Intervention & comparator | Relevant outcomes | Comments |
|---|---|---|---|---|---|
| Goldberg (2013)<br>NIHR TEAM trial | RCT | 600 people aged over 65 years with confusion (delirium/ cognitive impairment) admitted for acute medical care | • Intervention: Specialist medical and mental health unit<br>• Comparator: Standard care | • Quality of life (EQ-5D (short London handicap); DEMQOL; EuroQoL)<br>• Physical disability<br>• Cognitive Impairment<br>• Carer strain<br>• Carer psychological wellbeing | Study location<br>UK<br>Acute General hospital |
| Villars (2013) | Before and after study | 390 people with Alzheimer's disease hospitalised in a special acute care unit | • Intervention: Geriatric team unit<br>• Comparator: Usual care | • Rate of re-hospitalisations 1 month post discharge<br>• Vocally disruptive behaviours | Study location<br>France<br>Special acute care unit |

1

### 8.1.3 Health economic evidence

A systematic literature search was undertaken to identify existing cost–utility analyses (CUAs) evaluating how people living with dementia should be cared for when admitted to hospital. In total, 3,367 articles were returned, of which 1 was selected as potentially relevant and retrieved for full-text review, after which it was deemed relevant and included.

**Medical and mental health unit**

**Tanajewski et al. (2015)** compared the cost effectiveness of a dedicated medical and mental health unit (MMHU) with usual care (acute geriatric medical wards and general (internal) medical wards). The authors conducted a cost-–utility analysis alongside the trial of an elderly acute care medical and mental health unit (NIHR TEAM trial; Goldberg et al., 2013) (n=600), an RCT conducted between 2010 and 2012 in the UK, and collected health care utility data using the EQ-5D-3L with societal weights. Primary outcome measures were QALYs and costs over 90 days. For further details, please see the economic evidence profile in Appendix M.

Service-use data included health and social care costs. Rates of resource use were taken from electronic administrative records systems used to record patient care and were costed using standard reference costs. Data were collected for 3 months post-hospital admission and 1 year pre-admission. The mean results are presented in Table 39.

**Table 39: Base-case cost–utility results – Tanajewski et al., 2015**

| | Absolute | | Incremental | | |
|---|---|---|---|---|---|
| Treatment | Costs (95% CI) | Effects (95% CI) | Costs (95% CI) | Effects (95% CI) | ICER |
| **Standard care** | £7,862 (7,758, 7,965) | 0.108 QALYs (0.101, 0.114) | | | |
| **Medical and mental health unit (MMHU)** | £7,714 (7,606, 7,822) | 0.109 QALYs (0.102, 0.116) | £-149 (-298, 4) | 0.001 QALYs (-0.006, 0.008) | Dominant |

Over a period of 90 days, MMHUs resulted in monetary savings and an increased number of QALYs, making MMHUs a dominant strategy. Probabilistic analysis showed that there is a 58% probability of the MMHU being dominant, and a 94% probability of cost effectiveness, if QALYs are valued at £20,000 each. The probability of the MMHU being cost-saving with QALY loss (SW quadrant of the cost–utility plane) was 39%.

The authors concluded that the specialist unit for people with delirium and dementia did not demonstrate convincing benefits in health status over usual hospital care, as no significant effect on QALY gain was observed. However, the results did show a trend towards cost savings and a high probability of cost effectiveness from a combined health and social care perspective, when usual criteria were applied.

### 8.1.4 Evidence statements

#### 8.1.4.1 Nurse-led mental health liaison service versus usual care

Very low- to low-quality evidence from an RCT containing 153 participants could not differentiate levels of depressive symptoms (Geriatric Depression Scale), cognition (MMSE), general health (Health of Nations Outcome Scale), length of stay, the number of psychotropic medications prescribed at discharge, number readmitted to hospital and number of deaths in

hospital between hospitalised people living with dementia, cognitive impairment or depressive symptoms being cared for by a nurse-led mental health liaison service compared with usual care.

#### 8.1.4.2 Family-centred function focused care versus usual care

Very-low to low-quality evidence from 1 non-randomised controlled trial containing 86 participants found improved levels of activities of daily living (Barthel Index) and walking performance and reduced delirium incidence and delirium severity in hospitalised people living with dementia receiving family-centred function focused care compared with usual care, but could not differentiate length of stay, number of hospital readmissions, utilisation of post-acute rehabilitation at discharge, gait and balance (Tinetti Scale) or carer related outcomes.

#### 8.1.4.3 Proactive case finding with palliative care service versus usual care

Very-low to low-quality evidence from 1 cohort study conducted in the USA containing 52 participants found reduced length of stay in hospital and ICU and reduced levels of ICU workload after DNR rules were established in people in hospitalised people living with dementia who had been proactively identified in liaison between ICU staff and the palliative care service versus usual care, but could not differentiate levels of mortality, length of time from admission until do not resuscitate goals were established, length of stay from establishment of do not resuscitate goals until discharge or ICU workload before DNR rules were established.

#### 8.1.4.4 Specialist medical and mental health unit versus usual care

Very low- to moderate-quality evidence from 1 randomised controlled trial containing 600 participants could not differentiate cognition (MMSE), activities of daily living (Barthel Index), quality of life (DEMQOL self-report, DEMQOL proxy, EQ5D self-report, EQ5D proxy), general health measures (London Handicap Scale), number returning home from hospital within 90 days, overall mortality, readmissions or carer strain (Carer Strain Index) between hospitalised people living with dementia and/or delirium receiving care at a specialist medical and mental health unit versus usual care.

#### 8.1.4.5 Follow-up individualised care plan versus usual care

Very low-quality evidence from 1 observational study containing 390 participants could not differentiate early ER rehospitalisation rates at discharge and after 3 months or early rehospitalisation rates in any ward at discharge and after 3 months in hospitalised people living with dementia receiving an individualised follow-up care plan versus usual care.

#### 8.1.4.6 Health economic evidence

One directly applicable trial-based cost–utility analysis with minor limitations found that, compared with usual care, a dedicated medical and mental health unit resulted in cost savings of £149 per person and were associated with a small gain in QALYs of 0.001, rendering the strategy dominant. Probabilistic analysis showed a 58% probability of the dedicated unit being dominant and a 94% probability of cost effectiveness, when QALYs were valued at £20,000 each.

### 8.1.5 Evidence to recommendations

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| **Relative value of different outcomes** | The committee recognised the relevance of all studies included in the evidence base, although they agreed, given the inclusion of an |

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| | economic evaluation alongside the study, that the NIHR TEAM trial was the most relevant. They also agreed that the outcome measures used in this study were reasonable, and would be expected to capture any major differences found between the two groups. |
| **Trade-off between benefits and harms** | The committee agreed that none of the interventions tested showed consistent evidence of benefits for either patients or carers, and therefore it was not appropriate to make any specific recommendations based on these trials.<br>Although the committee agreed the NIHR funded TEAM trial (Goldberg, 2013) had demonstrated an appropriate model of care within a UK based hospital, they acknowledged there would be practical considerations in service delivery if this model was applied at a nationwide level. In particular, the committee recognised this model would be difficult to roll out nationally, as it would require a major reorganisation of staff in many UK hospitals. For this reason, the committee agreed there were not compelling clinical reasons to write a recommendation in support of this service delivery model.<br>The committee agreed that, despite the lack of evidence found for specific interventions to improve hospital care for people living with dementia, there were nonetheless specific issues people with dementia faced in hospital. In particular, they agreed it was often not appropriate for people living with dementia to be treated on general hospital wards, and felt that a geriatric ward was usually a more appropriate location. Whilst these wards are not dementia specific, a high enough proportion of people passing through them are likely to have dementia (simply based on the underlying prevalence in the population) and therefore the staff are likely to be better trained and more experienced with people living with dementia than those on a general hospital ward.<br>The committee also agreed that because the hospital population fluctuates, there are times when there will be a higher proportion of people living with dementia than at other times. Therefore, it would not be viable for the NHS to arrange units for older aged care into separate units specifically for people who are living with dementia and those who do not have dementia. The presence of some such units, but without the capacity to accept all people with dementia, risked creating a culture of inequity, whereby patients unable to access a specialist unit would potentially be treated as “being in the wrong place”, and therefore be likely to get sub-optimal care. The committee agreed the correct approach was rather to take elements of best care found in specialist units and apply these to all geriatric units, thereby raising the overall standard of care. |
| **Consideration of health benefits and resource use** | The committee acknowledged that TEAM trial did not find any significant or clinically meaningful differences in health outcomes between the intervention (MMHU - medical and mental health unit) and control group (acute geriatric and general medical wards) and therefore the economic evaluation (Tanajewski 2015) shifted the focus onto how savings were made with the MMHU intervention compared with control group (usual care). The committee expressed concern about the level of breakdown of costs provided in the paper as it was not clear where the cost savings for MMHU had come from, and the committee agreed it did not seem likely that such savings would be achieved in practice from what is a more staff-intensive model of care. The committee agreed the only way such savings would be possible in such a model would be either if the extra permanent staffing led to substantial reductions in spending on agency/temporary staff, or if increased staff knowledge led to a reduction in inappropriate interventions (e.g. unnecessary investigations). In the absence of sufficient detail in the paper to address these issues, the committee agreed that it would not be |

| | |
|---|---|
| | appropriate to make a recommendation solely based on evidence of cost saving that is unlikely to be achievable in practice. |
| **Quality of evidence** | The committee did not have any real concerns about the overall quality of the evidence they had seen. Although the results of the TEAM trial (Goldberg, 2013) demonstrated non-significant outcomes and were unable to differentiate outcomes when looking at care provided by a specialised service unit compared with usual care, the committee acknowledged it was a well-controlled trial, which had included a substantial sample of 600 individuals.<br>The committee recognised there were differences in care between the populations reported in the US papers and populations that are cared for in the UK. This was particularly relevant to interpretation of the service delivery model reported in Campbell (2004). The patient population described within the Intensive Care Unit would have been very different to patient populations in an ICU within a UK setting. For this reason the committee were cautious about highlighting that model of service organisation.<br>The committee acknowledged there was a mixed population of people included in two papers (Goldberg 2013; and Baldwin 2004) where people with delirium (Goldberg) and depression (Baldwin) were included alongside people living with dementia. The committee agreed these would not have had a negative influence upon interpretation of results because in practice the structural organisation of in-patient care for people living with delirium and dementia were likely to be similar. The committee did agree, however, that people living with dementia were at substantially increased risk of delirium when in hospital, and therefore it was appropriate to cross-refer to the sections of the delirium guideline on interventions to both prevent and treat delirium. |
| **Other considerations** | The committee noted there were other forms of evidence, and although these did not directly fulfil the inclusion criteria as defined in the review protocol for this question, they may provide further insight into the relevance of certain models of care. In particular, the committee highlighted the qualitative evidence that was conducted alongside the TEAM trial to provide insights into experiences of those involved in that model of care. The committee also recognised that Rapid Assessment, Interface and Discharge protocols are applied in current practice for more general older aged populations. The committee also highlighted there are other established national standards set out for healthcare practitioners to follow, in particular advice from the Royal College of Psychiatrists for managing older people in acute hospital settings. |

### 8.1.6 Recommendations

**56. Be aware of the increased risk of delirium in people living with dementia who are admitted to hospital. See the NICE guideline on delirium for interventions to prevent and treat delirium.**

# 9 Care setting transitions

Improper/poorly managed discharges from a service/environment (home, care home, hospital or respite care) can lead to increased stress and anxiety, both for people living with dementia and those caring for them. This uncertainty of transition can amplify negative feelings and cause unnecessary distress. Poor transition/planning between services can lead to increased likelihood of re-hospitalisation, delayed discharges, failed discharges, inappropriate placements and carer breakdown (Naylor 2008).

There is much documentation surrounding poor communication and planning when transitioning from one setting to another. Completing multi-disciplinary discharge meetings and ensuring all relevant parties are included in such decisions is vital in maintaining good communication and positive outcomes. Working in a collaborative manner increases positive outcomes by ensuring that everyone is aware of the support required and where this can best be achieved.

The Care Act 2014 discusses the responsibility of those working in adult care to ensure a person's wellbeing when managing and supporting their care, respecting the individual's wishes and the things that matter to them. The principal purpose is to ensure that everyone has support to meet their individual needs, rather than a one size fits all style of care.

When transitioning from one environment/setting to another the fundamental principles that apply are: planning, communication, collaboration and person centred support.

# 9.1 Managing the transition between different settings for people living with dementia

**Review question**

- What are the most effective ways of managing the transition between different settings (home, care home, hospital, and respite) for people living with dementia?

## 9.1.1 Introduction

The aims of this review were to establish the most effective ways of managing the transition between different settings for people living with dementia, and their carers. The review focused on identifying studies that fulfilled the conditions specified in Table 40. For full details of the review protocol, see Appendix C.

**Table 40: Review summary: Managing the transition between different settings**

| | |
|---|---|
| **Population** | People (aged 40 years and over) living with dementia |
| **Factors/Interventions** | Policies or systems for managing transfers between settings for people living with dementia, which may include elements such as:<br>• Assessment of person's needs and living environment (destination environment)<br>• Systems for monitoring and adjusting plans as needs change<br>• Ways of confirming required services are in place pre-transfer<br>• Involvement of family members and carers<br>• Transfer of information (continuity of care)<br>• Maintaining relationships<br>• Timing of transfer |
| **Outcomes** | • Clinical outcomes including cognitive, functional and behavioural ability<br>• Rates of delayed discharge<br>• Access to health and social care support<br>• Patient and carer experience and satisfaction<br>• Patient and carer health-related quality of life<br>• Adverse events<br>• Resource use and costs |

Randomised controlled trials and systematic review of randomised controlled trials were included if they compared different methods of managing transitions between care settings. Papers were excluded if they:

- were not in the English language
- were abstracts, conference proceedings and other unpublished studies.
- considered transitions into or out of inpatient hospital settings: these transitions are covered by another NICE guideline. (NG26: Transition between inpatient hospital settings and community or care home settings for adults with social care needs)
- considered transitions into or out of inpatient mental health settings: these transitions are covered by another NICE guideline. (NG53: Transition between inpatient mental health settings and community or care home settings)
- considered aspects of medicines-related communication systems when patients move between care settings: this is covered by another NICE guideline. (NG5: Medicines optimisation: the safe and effective use of medicines to enable the best possible outcomes)

### 9.1.2 Evidence review

A total of 3,451 unique citations were identified through a systematic search, of which 46 were retrieved for full-text appraisal. Four of these studies ultimately met the criteria for inclusion, with the remaining 42 studies excluded, with reasons for exclusion given in Appendix F. The included studies are summarised in Table 41. For the full evidence tables and full GRADE profiles please see Appendix E and Appendix G. References for the included studies are given in appendix I.

#### 9.1.2.1 Description of included studies

**Table 41: Summary of included studies**

| Study details | Study population | Interventions | Outcomes |
|---|---|---|---|
| Davies (2011) | 56 carers of people living with dementia who have recently moved to a care home | Psychosocial intervention (TIFF-NH) versus usual care | • Carer burden<br>• Carer depression<br>• Carer satisfaction with facility |
| Gaugler (2011) | 406 carers of people living with dementia who are transitioning to a care home | Psychosocial intervention (NYU carer intervention) versus usual care | • Carer burden<br>• Carer depression<br>• |
| Gaugler (2015) | 36 carers of people living with dementia who have recently moved to a care home | Psychosocial intervention (RCTM) versus usual care | • Carer burden<br>• Carer stress<br>• Carer depression<br>• Carer satisfaction with facility<br>• Carer satisfaction with role |
| McGilton (2003) | 32 people living with Alzheimer's disease who have recently changed care home | Way finding (reorientation) intervention versus usual care | • Agitation<br>• Spatial orientation |

### 9.1.3 Health economic evidence

Standard health economic filters with social care outcome terms were applied to the clinical search for this question, and a total of 2,974 citations was returned. Following review of titles and abstracts, no full text studies were retrieved for detailed consideration. Therefore, no relevant cost–utility analyses were identified for this question.

### 9.1.4 Evidence statements

#### 9.1.4.1 Intervention for people living with dementia

Low-quality evidence from 1 RCT containing 32 people could not differentiate levels of agitation or spatial disorientation between people with Alzheimer's disease relocated to a new nursing home facility intervention who were offered or not offered a reorientation intervention.

#### 9.1.4.2 Interventions for carers

Very low to low-quality evidence from 1 RCT containing 406 people found lower levels of depressive symptoms in carers of people living with dementia transitioning to nursing homes

who were offered comprehensive psychosocial support (New York University Carer Intervention) compared with those not offered support, but could not differentiate levels of carer burden.

Very low-quality evidence from 2 RCTs containing 82 people could not differentiate levels of carer burden, stress, depressive symptoms, satisfaction with the care facility or role satisfactions between carers of people living with dementia transitioning to nursing homes who were offered psychosocial interventions compared with those not offered interventions.

#### 9.1.4.3 Health economic evidence

No health economic evidence was identified for this review question.

### 9.1.5 Evidence to recommendations

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| **Relative value of different outcomes** | The committee agreed that, in order to recommend specific transfer interventions, data from quantitative studies (particularly randomised controlled trials) would be necessary. They agreed that data from qualitative studies alone would be unlikely to be sufficient to recommend potentially expensive interventions<br>The committee also discussed the existing NICE guidelines on transfers between different settings, to assess their applicability for people living with dementia. |
| **Trade-off between benefits and harms** | The committee agreed that the following NICE guidelines on transfer are relevant to this guideline: *Transition between inpatient mental health settings and community or care home settings* (NG53), *Transition between inpatient hospital settings and community or care home settings for adults with social care needs* (NG27) and the recommendations specifically on transfer in section 1.2 of *Medicines optimisation: the safe and effective use of medicines to enable the best possible outcomes* (NG5). The committee therefore agreed that it would be appropriate to cross-refer to these pieces of guidance. The reason why other sections of NG5 were not referred to in this section is because they do not relate to the transfer of people.<br>The committee agreed that all further recommendations should then focus on areas of transfer particularly relevant to people living with dementia, over and above standard transfers.<br>The main distinct feature of people who live with dementia were identified as being the difficulty in ensuring that needs and wishes (including any Do Not Attempt Resuscitation (DNAR) documentation) are reviewed. In the experience of the committee, this is very important information that is commonly missing or not understood. For example, when a person living with dementia is transferred from one environment to another, staff are often unsure as to whether a pre-existing DNAR form is still relevant because potentially the person's needs or wishes have changed.<br>The committee wanted the phrase "needs and wishes" to be included, rather than refer to further specific documents. The aim of this is to get staff to think about what the needs and wishes of people are and to enable life-story documentation to be reviewed. In addition, there are already separate recommendations on what information should be documented in the palliative care and barriers and facilitators to involvement in decision-making sections of this guideline.<br>The committee agreed it was important to include the phrase "after any transitions" because this is when information is reviewed by the new staff taking care of the person. |

| | |
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| | The committee therefore made the recommendation that after any transition, to ensure that the person's needs and wishes (including any DNAR documentation) are reviewed.<br>The committee also agreed that the same principles underlying good practice for transfers to and from inpatient settings would also be applicable for transfers within the community, and therefore agreed it would be appropriate to make recommendations that these principles also be applied in the community setting. Whilst no specific evidence was identified for community transitions, the committee agreed that the evidence identified for inpatient transfers that led to the development of recommendations for those guidelines could reasonably be extrapolated to the community setting as well. |
| **Consideration of health benefits and resource use** | The committee agreed that the following additional recommendation should incur no additional cost. This is because this recommendation should be current standard practice, and the problems caused by information not being appropriately shared are likely to have a higher resource burden than the cost of ensuring appropriate transfer of information. |
| **Quality of evidence** | The committee agreed that none of the RCTs on specific transfer interventions provided strong enough evidence to make specific additional recommendations, over and above those in the other NICE guidelines on transitions between care settings. |
| **Other considerations** | The committee agreed that future research should be done on the questions of appropriately managing transitions for people living with dementia, as it is an important issue for service providers that it not currently addressed in the research literature. The committee advised that future RCTs should involve people living with dementia and compare a structured transfer plan to standard care. Examples of useful outcomes are: quality of life measures, narrative opinions, costs and adverse events. |

### 9.1.6 Recommendations

**57. For guidance on managing transition between care settings for people living with dementia, see:**

- the NICE guideline on transition between inpatient hospital settings and community or care home settings for adults with social care needs
- the NICE guideline on transition between inpatient mental health settings and community or care home settings
- section 1.2 of the NICE guideline on medicines optimisation.

**Follow the principles in these guidelines for transitions between other settings (for example from home to a care home or respite care).**

**58. Review the person's needs and wishes (including any care and support plans and advance care and support plans) after every transition.**

### 9.1.7 Research recommendations

**7. What is the effectiveness of structured transfer plans to ease the transition between different environments for people living with dementia and their carers?**

For more details on the research recommendation made, and the rationale behind it, see appendix L.

# 10 Modifying risk factors for dementia progression

Several risk factors have been described for dementia, and most also apply to the main subtype of Alzheimer's disease. These include factors such as: advancing age, female sex, low education, possession of certain genetic risk factors, such as apolipoprotein E4, family history of dementia, history of depression, history of head injury, pre-existing history of learning difficulties, especially Down's syndrome. However, in addition, there has been much recent interest in several vascular risk factors which have also emerged as risk factors for dementia and also for Alzheimer's disease. These include smoking, hypertension, hypocholesterolaemia, diabetes, ischemic heart disease, obesity, lack of exercise and atrial fibrillation. The main clinical implication of these vascular risk factors, as opposed to the other risk factors described, is that all are potentially modifiable. Epidemiological evidence has largely informed our knowledge about risk factors, but such evidence cannot indicate whether modification of any or all of these risk factors will either prevent the development of dementia or, more relevantly for the current guideline, delay the progression of cognitive or functional impairment in those with established dementia. This question concerns whether modifying risk factors may have an effect on slowing the progression of dementia in those with recognised dementia.

The mechanism by which such modification may delay the progression of dementia, if they are effective, is not entirely clear. The two broad hypotheses would be, firstly, that such modification will reduce the accumulation of additional vascular burden in such subjects, an effect which is known to accelerate the expression of dementia even in those with Alzheimer's disease, for example by reducing the occurrence of subcortical vascular disease (white matter lesions and lacunar infarcts). The second is potentially through direct modification of degenerative (Alzheimer's-type, i.e. plaque and tangle) pathology, since there is some evidence both from the animal literature and limited human studies that vascular factors such as hypertension and diabetes, as well as ischemic damage which might be secondary to vascular changes, can hasten the spread of Alzheimer-type changes.

# 10.1 Risk factors for dementia progression

**Review question**

- What effect does modifying risk factors have on slowing the progression of dementia?

## 10.1.1 Introduction

The aim of this review question is to assess whether interventions targeting underlying risk factors for progression can be used to slow progression of dementia, or its sequelae, after diagnosis. The interventions in question are based on known modifiable risk factors that have not been addressed in other sections of this guideline. The review identified studies that fulfilled the conditions specified in Table 42. For full details of the review protocol, see appendix C.

**Table 42: Review summary: modifying risk factors for dementia progression**

| | |
|---|---|
| **Population** | People (aged 40 years and over) living with dementia |
| **Interventions** | • Interventions to modify risk factors for dementia progression. Potentially modifiable risk factors may include:<br>• Alcohol consumption<br>• Smoking<br>• Obesity<br>• Diabetes<br>• Hypertension<br>• Hypercholesterolaemia<br>• Diet<br>• Non-steroidal anti-inflammatory drugs<br>• Antipsychotics |
| **Comparator** | • No intervention |
| **Outcomes** | • Rates of dementia progression<br>• Clinical outcomes including cognitive, functional and behavioural ability<br>• Patient and carer experience and satisfaction<br>• Patient and carer health-related quality of life<br>• Adverse events<br>• Resource use and costs |

## 10.1.2 Evidence review

A systematic literature search for systematic reviews and RCTs identified 3,217 references. These were screened at title and abstract level, with 43 papers (9 systematic reviews and 34 RCTs) ordered as potentially relevant. Of these studies, 6 RCTs assessing the effect of risk factor modification on dementia progression were included. Fifteen additional references were identified through assessment of the bibliographies of excluded systematic reviews and RCTs, all of which were included. In total, 20 studies (reported in 21 publications) were included, with 36 excluded at full-text review. The original protocol for this question specified that it should include studies of at least 12 months duration. However, due to the relatively low number of RCTs identified, this was expanded to include trials of at least 6 months duration. The studies excluded at full-text review, and the reasons for exclusion, are given in appendix F.

#### 10.1.2.11 Description of included studies

Randomised controlled trials assessing 4 different types of interventions were found:

- Two studies evaluated the efficacy of antidiabetic drugs for reducing cognitive decline (namely, rosiglitazone). In these studies rosiglitazone was given to people living with Alzheimer's disease who did not have diabetes.
- Ten trials were identified that assessed the safety and efficacy of non-steroidal anti-inflammatory drugs (NSAIDs) for reducing cognitive decline in people living with Alzheimer's disease. NSAIDs included naproxen, aspirin, indomethacin, tarenflurbil (an R-enantiomer of flurbiprofen), ibuprofen, diclofenac, celecoxib and rofecoxib. It was noted that rofecoxib was withdrawn from the market in 2004; however, the identified evidence was included in analyses to explore the class effect of NSAIDs.
- Four trials were identified that assessed the efficacy of statins (atorvastatin and simvastatin) for reducing cognitive decline in people living with Alzheimer's disease.
- Four trials were identified that assessed the efficacy of antihypertensive drugs for reducing cognitive decline. Three of these studies included people living with Alzheimer's disease whereas 1 study included people with subcortical vascular dementia. It was noted that some of these studies included people who did not have hypertension. Antihypertensive drugs included telmisartan, nimodipine amlodipine, perindopril, captopril, enalapril imidapril, nifedipine and nilvadipine.

For the purpose of this review, studies which assessed the efficacy of dietary supplements, exercise and antipsychotics for treating aggression or psychosis, were not included. This is because the evidence on these interventions was considered elsewhere in the guideline. For the full evidence tables and full GRADE profiles please see Appendix E and Appendix G. References for the included studies are given in appendix I.

**Table 43: Summary of included studies: antidiabetic medicines**

| Study details | Study population | Interventions | Outcomes |
|---|---|---|---|
| Gold (2010) | 581 people with probable Alzheimer's disease. Living status not specified. | Rosiglitazone 2 mg, rosiglitazone 8 mg, donepezil 10 mg or placebo. | • Cognitive outcomes (MMSE; ADAS-cog)<br>• Functional ability (Disability Assessment of Dementia test)<br>• Clinical global assessment (CIBIC+)<br>• Behavioural/Neuropsychological outcomes (NPI)<br>• Adverse events |
| Risner (2006) | 511 people with mild to moderate Alzheimer's disease. Living status not specified. | Rosiglitazone 2 mg, rosiglitazone 4 mg, rosiglitazone 8 mg or placebo. | • Cognitive outcomes (ADAS-cog)<br>• Clinical global assessment (CIBIC+, collected but not reported)<br>• Adverse events |

**Table 44: Summary of included studies: NSAIDs**

| Study details | Study population | Interventions | Outcomes |
|---|---|---|---|
| Aisen (2003) | 351 people with probable Alzheimer's disease. Living status not specified. | Naproxen 220 mg bid., rofecoxib 25 mg, or placebo. | • Cognitive outcomes (ADAS-cog)<br>• Functional ability (ADCS-ADL)<br>• Behavioural/Neuropsychological outcomes (NPI)<br>• Dementia severity (CDR-SB)<br>• Quality of life (QoL-AD)<br>• Adverse events |
| Bentham (2008) | 310 people with probable Alzheimer's disease. Living at home. | Aspirin 75 mg or aspirin avoidance. | • Cognitive outcomes (MMSE)<br>• Functional ability (BADLS)<br>• Behavioural/Neuropsychological outcomes (NPI, collected but not reported)<br>• carer outcomes (GHQ)<br>• Adverse events |
| De Jong (2008) | 51 people with probable Alzheimer's disease. Living either at home or at a nursing home. | Indomethacin 50 mg bid. or placebo. | • Cognitive outcomes (ADAS-cog; MMSE)<br>• Clinical global assessment (CIBIC+)<br>• Functional ability (IDDD)<br>• Behavioural/Neuropsychological outcomes (NPI)<br>• Carer outcomes (NPI-D)<br>• Adverse events |
| Green (2009) | 1,649 with mild to moderate Alzheimer's disease. Living in the community. | Tarenflurbil 400 mg bid., tarenflurbil 800 mg bid. or placebo. | • Cognitive outcomes (ADAS-cog; MMSE)<br>• Functional ability (ADCS-ADL)<br>• Behavioural/Neuropsychological outcomes (NPI)<br>• Dementia severity (CDR-SB); Quality of life (QOL-AD)<br>• Carer outcomes (CBI)<br>• Adverse events |
| Pasqualetti (2009) | 132 people with probable Alzheimer's disease. Living status not specified. | Ibuprofen 400 mg bid. or placebo. | • Cognitive outcomes (ADAS-Cog; MMSE)<br>• Clinical global assessment (CIBIC+)<br>• Functional ability (BADLS)<br>• Behavioural/Neuropsychological outcomes (NPI)<br>• Dementia severity (CDR-SB) |

| Study details | Study population | Interventions | Outcomes |
|---|---|---|---|
| | | | • Depression (BDI; GDS)<br>• Carer outcomes (STA1-Y1; STA1-Y2)<br>• Adverse events |
| Reines (2004) | 692 people with probable or possible Alzheimer's disease. Living status not specified | Rofecoxib 25 mg or placebo | • Cognitive outcomes (ADAS-Cog; MMSE)<br>• Clinical global assessment (CIBIC+)<br>• Functional ability (ADCS-ADL)<br>• Dementia severity (CDR-SB)<br>• Adverse events |
| Rogers (1993) | 44 people with probable Alzheimer's disease. Living status not specified. | Indomethacin (Dosage adjusted to weight) or placebo. | • Cognitive outcomes (ADAS-Cog; MMSE; BNT; Token test)<br>• Adverse events |
| Scharf (1999) | 41 people with probable Alzheimer's disease. Living status not specified. | Diclofenac plus misoprostol (Dosage not specified) or placebo. | • Cognitive outcomes (ADAS-Cog; ADAS-Noncog; MMSE)<br>• Clinical global assessment (GDS; CGIC)<br>• functional ability (IADL; PSMS)<br>• Carer outcomes (cGIC)<br>• Adverse events, collected but insufficiently reported |
| Soininen (2007) | 461 people with probable or possible Alzheimer's disease. Living status not specified. | Celecoxib 200 mg bid. or placebo. | • Cognitive outcomes (ADAS-Cog; MMSE)<br>• Clinical global assessment (CIBIC+)<br>• Nurses' Observation Scale For Geriatric Patients [NOSGER])<br>• Behavioural/Neuropsychological outcomes (Behave-AD2)<br>• Depression (MADRS)<br>• Adverse events |
| Wilcock (2008) | 189 people with probable Alzheimer's disease. Living in the community. | Tarenflurbil 400 mg bid., tarenflurbil 800 mg bid. or placebo. | • Cognitive outcomes (ADAS-Cog)<br>• Functional ability (ADCS-ADL)<br>• Dementia severity (CDR-SB)<br>• Adverse events |

**Table 45: Summary of included studies: statins**

| Study details | Study population | Interventions | Outcomes |
|---|---|---|---|
| Feldman (2010) | 640 people with probable Alzheimer's disease, most of whom were living in the community. | Atorvastatin 40 mg bid. or placebo. | • Cognitive outcomes (ADAS-Cog; MMSE)<br>• Functional ability (ADFACS)<br>• Clinical global assessment (ADCS-CGIC)<br>• Behavioural/Neuropsychological outcomes (NPI)<br>• Dementia severity (CDR-SB)<br>• Carer outcomes<br>• Healthcare resource |
| Sano (2011) | 406 people with probable Alzheimer's disease. Living status not specified. | Simvastatin (20 mg per day for 6 weeks, and simvastatin 40 mg thereafter) or placebo. | • Cognitive outcomes (ADAS-Cog; MMSE)<br>• Functional ability (ADCS-ADL)<br>• Behavioural/Neuropsychological outcomes (NPI)<br>• Caregiving hours<br>• Adverse events |
| Simons (2002) | 44 people with probable Alzheimer's disease. Living status not specified. | Simvastatin or placebo. | • Cognitive outcomes (ADAS-Cog; MMSE)<br>• Lipid concentrations |
| Sparks (2005) & Sparks (2006) | 63 people with probable or possible Alzheimer's disease. Living status not specified. | Atorvastatin 40 mg bid. or placebo. | • Cognitive outcomes (ADAS-Cog; MMSE)<br>• Functional ability (ADCS-ADL, collected but not reported)<br>• Clinical global assessment (CGIC)<br>• Behavioural/Neuropsychological outcomes (NPI)<br>• Depression (GDS) |

**Table 46: Summary of included studies: antihypertensive medicines**

| Study details | Study population | Interventions | Outcomes |
|---|---|---|---|
| Kume (2012) | 20 people with probable Alzheimer's disease. Living status not specified. | Telmisartan 40 to 80 mg or amlodipine 5 to 10 mg. | • Cognitive outcomes (MMSE; ADAS-Cog; WMS-R logical memory test)<br>• Blood pressure changes<br>• Cerebral blood flow |

| Study details | Study population | Interventions | Outcomes |
|---|---|---|---|
| Ohrui (2004) | 162 people with probable Alzheimer's disease. Living status not specified. | Brain-penetrating ACE inhibitors (perindopril 2 mg or captopril 37.5 mg), non-brain-penetrating ACE inhibitors (enalapril 5 mg or imidapril 5 mg) or a calcium-channel blocker (nifedipine 20 mg or nilvadipine 4 mg). | • Cognitive outcomes (MMSE) |
| Morich (2012) | 1,648 people with Alzheimer's disease. Living at home. | Nimodipine 90 mg, nimodipine 180 mg, or placebo. | • Cognitive outcomes (MMSE; ADAS-Cog; ADAS-total score; BSR; GERRI)<br>• Clinical global assessment (GDS; CGI-S; CGI-I)<br>• Adverse events |
| Pantoni (2005) | 242 people subcortical dementia. Living status not specified. | Nimpdodipine 30 mg tid. or placebo. | • Cognitive outcomes (MMSE; SCAG test; set test; digit span test for working memory)<br>• Clinical global assessment (NOSGER)<br>• Verbal fluency (Zahlen-Verbingdungs test; lexical production)<br>• Depression (HAM-D)<br>• Motor performance |

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### 10.1.3 Health economic evidence

Standard filters plus social care extras were applied to the clinical search for this question, and a total of 1,455 citations was returned. Following review of titles and abstracts, no full text studies were retrieved for detailed consideration. Therefore, no relevant cost-utility analyses were identified for this question.

### 10.1.4 Evidence statements

#### 10.1.4.1 Antidiabetic drugs versus placebo

Very low to low-quality evidence from up to 2 RCTs, including 882 people living with Alzheimer's disease, found no meaningful differences in cognition, global assessment, behavioural and psychological symptoms, adverse events, serious adverse events or adverse events leading to discontinuation between people offered rosiglitazone or placebo.

#### 10.1.4.2 NSAIDs versus placebo

Very low- to moderate-quality evidence from up to 8 RCTs, including 3,284 people living with Alzheimer's disease, found no meaningful differences in cognition, global assessment, behavioural and psychological symptoms, dementia severity, quality of life, serious adverse events or mortality between people offered NSAIDs or placebo.

Low-quality evidence from up to 7 RCTs, including 2,989 people living with Alzheimer's disease, found better functional ability in people offered NSAIDs compared with those who received placebo, but these differences were either not clinically significant or did not persist in a sensitivity analysis removing rofecoxib (a treatment that has been withdrawn from the market).

Low-quality evidence from up to 6 RCTs, including 3,533 people living with Alzheimer's disease, found higher levels of adverse events leading to discontinuation in people offered NSAIDs compared with those receiving a placebo.

#### 10.1.4.3 Statins versus placebo

Very low- to moderate-quality evidence from up to 4 RCTs, including 1,084 people living with Alzheimer's disease, found no meaningful differences in cognition, behavioural and psychological symptoms, adverse events, serious adverse events or mortality between people offered statins or placebo.

Moderate-quality evidence from 1 RCT, including 639 people living with Alzheimer's disease, found higher levels of adverse events leading to discontinuation in participants who were offered statins compared with those who received placebo.

#### 10.1.4.4 Antihypertensive drugs

##### *10.1.4.4.1 Calcium-channel blockers versus placebo*

Low-quality evidence from 1 RCT, including 1,442 people living with Alzheimer's disease, found no meaningful differences in cognition, measured by ADAS-cog scores, between people who received calcium-channel blockers and those who received placebo. However, moderate-quality evidence from the same trial found a smaller decline in cognition, measured

by MMSE scores, in people treated by calcium-channel blockers compared with those who received placebo.

Low-quality evidence from 1 RCT, including 1,636 people living with Alzheimer's disease, found no meaningful differences in global assessment, adverse events, or discontinuation due to adverse events between people who received calcium-channel blockers and those who received placebo. Moderate-quality evidence from the same trial found higher levels of serious adverse events in people who received calcium-channel blockers compared with those who received placebo.

#### 10.1.4.5 Angiotensin II receptor antagonist versus calcium-channel blocker

Moderate-quality evidence from 1 RCT, including 20 people living with Alzheimer's disease, found no meaningful differences in cognition between people treated by and angiotensin II receptor antagonist or a calcium-channel blocker.

#### 10.1.4.6 Brain-penetrating angiotensin converting enzyme (ACE) inhibitor versus calcium-channel blocker

Moderate-quality evidence from 1 RCT, including 108 people living with Alzheimer's disease, found smaller declines in cognition in people treated by brain-penetrating ACE inhibitors compared with those treated by calcium-channel blockers.

##### *10.1.4.6.1 Non-brain-penetrating angiotensin converting enzyme (ACE) inhibitor versus calcium-channel blocker*

Moderate-quality evidence from 1 RCT, including 108 people living with Alzheimer's disease, found smaller declines in cognition in people treated by non-brain-penetrating ACE inhibitors compared with those treated by calcium-channel blockers.

#### 10.1.4.7 Health economic evidence

No health economic evidence was identified for this review question.

### 10.1.5 Evidence to recommendations

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| **Relative value of different outcomes** | The committee agreed that, since the aim of these interventions was to modify the underlying progression of dementia, the outcome measures that would provide the most information were measures of cognition. They noted that comparatively small differences in cognition may prove to be meaningful, provided they are sustained over a long period of time.<br>The original protocol specified that only trials of at least 12 months duration would be included. However, due to the relatively low number of RCTs identified, the committee agreed it was appropriate to expand this to include trials of at least 6 months duration. |
| **Trade-off between benefits and harms** | **Antidiabetic drugs**<br>The committee agreed the included studies did not provide any evidence that antidiabetic drugs (specifically rosiglitazone) were effective in slowing the progression of Alzheimer's disease. The committee discussed whether the evidence on rosiglitazone was sufficient to make generic recommendations about all antidiabetic drugs. It was agreed that clinicians would not offer a drug to patients without robust assessments of its disease modifying effects. As a result, the committee felt that a "do not offer recommendation" would apply to all antidiabetic drugs, as there is no evidence of clinical effectiveness. |

**NSAIDs**

The committee noted there was weak evidence of a potentially small effect on some outcomes with NSAIDs for people with Alzheimer's disease. Specifically, there was a small improvement in functional ability at 12 months. However, the magnitude of this benefit was below the level defined as being clinically significant, and there was no evidence of an effect on cognition or other clinical outcomes. The committee agreed this small difference may have been a direct result of the anti-inflammatory effects of NSAIDs, and there was no evidence it was mediated through changes in disease progression.

The committee noted that although absolute rates of adverse events were similar between people who were treated with NSAIDs and those who received placebo, more adverse events leading to discontinuation were observed in people who were given NSAIDs. The committee agreed that the trend is not uncommon in trials which assess the safety of NSAIDs. This is because there are certain red-flag adverse events associated with NSAID treatment which will automatically lead to people being taken out of trials.

The committee agreed that the evidence was consistent with a class effect for NSAIDs and therefore it was appropriate that a negative recommendation be made for the entire class. The committee agreed it was appropriate to specifically mention aspirin within the recommendation, as it was included within the evidence base but is not always recognised as being an NSAID.

**Statins**

The committee agreed the included studies did not provide any evidence that statins were effective in slowing the progression of Alzheimer's disease. The committee agreed that the evidence was consistent with a class effect for statins and therefore it was appropriate that a negative recommendation be made for the entire class. As with NSAIDs, there was evidence of higher levels of adverse events leading to discontinuation with treatment, which was agreed to be consistent with what would be expected in trials of statins in people without dementia.

**Antihypertensive drugs**

The committee agreed there was no robust evidence of improvements in cognition for people living with dementia treated with antihypertensive drugs. Whilst there was a small positive benefit on the MMSE at 6 months, this effect was not replicated at 12 months, nor was the same benefit found on the other measure of cognition in the study (the ADAS-cog). Significant differences in cognition were found between ACE inhibitors and calcium-channel blockers, but this was based on a small study in which it was not clear if participants or assessors were blinded. The committee therefore agreed the balance of the evidence did not suggest a clear positive benefit with antihypertensive drugs, and therefore it was appropriate to include them within the 'do not offer' recommendation made.

**Future research**

The committee noted that there is currently ongoing research in a number of the drug classes included in this review, looking at long-term effects on cognition in people living with dementia. They therefore agreed it was appropriate to add a caveat to the recommendation, allowing for their use as part of randomised controlled trials. Since much of this research is already ongoing, the committee did not feel it was appropriate to make a specific research recommendation, as no specific intervention was found to be promising enough to justify a positive recommendation for research.

| | |
|---|---|
| **Trade-off between net health benefits and resource use** | No positive recommendations were made for this review questions, and therefore the committee was not concerned by the lack of economic evidence identified. Furthermore, they agreed that the recommendations made would not result in any increase in resource use. |
| **Quality of evidence** | The committee noted that all but one of the identified studies only included people living with Alzheimer's disease. The committee considered that it was unlikely that trial participants had mixed dementias because the diagnostic criteria for Alzheimer's disease excludes other types of dementia. Furthermore, some of the studies explicitly stated that people were excluded if they had modified Hachinski score greater than 4, ruling out people with a high likelihood of vascular dementia. As a result, it was considered there was insufficient evidence to make recommendations on other types of dementia.<br>In other areas of this guideline, in particular in areas around non-pharmacological interventions, evidence has been extrapolated from Alzheimer's disease to other forms of dementia, as the committee agreed that there are some situations where people with similar symptoms need the same kinds of support, regardless of the underlying cause of the dementia. However, since the intention of these interventions is specifically to modify disease progression, and this effect is likely to differ based on the underlying disease, it was not appropriate to extrapolate the evidence to other types of dementia in this context.<br>The committee noted the absence of studies evaluating non-pharmacological or behavioural interventions for modifying risk factors like poor diet, obesity, alcohol consumption and smoking. |
| **Other considerations** | The committee noted that studies that assessed the effect of antidiabetic drugs on dementia progression included people without diabetes at baseline. Abnormal insulin signalling has been identified as a feature of Alzheimer's disease. As a result, it was considered that these studies focused on poor insulin signalling as a risk factor, rather than diabetes. The committee also noted that studies which assessed whether statins affected cognitive decline in people with Alzheimer's disease included people without hypercholesterolaemia. Furthermore, some of the studies which assessed the efficacy of antihypertensive medicines included normotensive people (without primary hypertension).<br>The committee agreed it was important to specify in the recommendation that the negative recommendations made only considered the use of these treatments for the purposes of slowing dementia, and people who needed to be treated for a co-morbidity should continue to receive treatment as normal. To clarify this, the committee agreed it was appropriate to cross-refer to the relevant NICE guidelines for the diagnosis and management of diabetes, hypercholesterolaemia and hypertension. |

### 10.1.6 Recommendations

**59. Do not offer the following specifically to slow the progress of Alzheimer's disease, except as part of a randomised controlled trial:**

- diabetes medicines
- hypertension medicines
- statins
- non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin.

# 11 Cholinesterase inhibitors and memantine for dementia

The three cholinesterase inhibitors, donepezil, rivastigmine, galantamine, and the NMDA receptor antagonist, memantine, are currently the only effective licensed treatments for dementia (O'Brien 2017). They are thought to be largely symptomatic agents and although effects on the underlying disease process have been proposed, there is no convincing evidence that they modify the disease process in Alzheimer's or any other type of dementia.

There have been several studies demonstrating their efficacy in Alzheimer's disease, leading to their licensing and NICE HTA approval for use in mild to moderate Alzheimer's disease (for donepezil, rivastigmine, galantamine) and moderate to severe Alzheimer's disease (for memantine). There have also been some studies in other disorders, including dementia with Lewy bodies and Parkinson's disease dementia, where cholinesterase inhibitors have been shown to be effective (Stinton 2015), and frontotemporal and vascular dementia, where they have generally not (O'Brien 2015, O'Brien 2017). Memantine has been trialled in dementia with Lewy bodies and Parkinson's disease dementia, without clear evidence of efficacy as yet (Stinton 2015).

Historically, initiation of these drugs has been by specialists in dementia, usually based in secondary care. There has often been ongoing specialist review of these drugs, and often recommendations that treatment be withdrawn when a certain stage of illness is reached. However, these drugs have been licenced for over a decade and there is now substantial experience in their use. They are generally safe and side effects are well recognised. Although it is important that the drugs are only started following an appropriate, accurate, specialist diagnosis, the actual initiation and monitoring of these drugs by specialists in secondary care might no longer be needed.

This chapter includes four important and closely related review questions: 1) who should start and review the three cholinesterase inhibitors and memantine in people with Alzheimer's disease; 2) when and if treatment with these drugs should be withdrawn for those with Alzheimer's disease; 3) whether there is evidence for the efficacy of co-prescription of cholinesterase inhibitors and memantine (which do have different actions); and 4) whether there is evidence of effectiveness for cholinesterase inhibitors and memantine in Parkinson's disease and in other dementias.

# 11.1 Cholinesterase inhibitors and memantine for people living with Alzheimer's disease

**Review question**

- Who should start and review the following pharmacological interventions: (donepezil, galantamine, rivastigmine, memantine) for people with Alzheimer's disease and how should a review be carried out?

## 11.1.1 Introduction

The aim of this review question was to determine which clinicians should prescribe and review donepezil, galantamine, rivastigmine or memantine for the cognitive symptoms of dementia in people diagnosed with Alzheimer's disease. It includes a partial update of the existing NICE technology appraisal guidance TA217 (Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease).

## 11.1.2 Evidence review

A systematic evidence search was conducted (see appendix D) which identified 6344 articles. The titles and abstracts were screened and 66 full-text papers were identified for inclusion. Sixty three papers were subsequently excluded because they did not fit the inclusion criteria. Two studies described in 3 papers were presented to the committee (Aupperle et al., 2000; Aupperle et al., 2003; Watanabe et al., 2012).

A review flowchart is provided in appendix K, and the excluded studies (with reasons for exclusion) are shown in appendix F.

**Table 47: Review summary**

| | |
|---|---|
| **Population** | • People aged 40 years and over with a diagnosis of Alzheimer's disease |
| **Intervention** | • The initiation and review of donepezil, galantamine, rivastigmine, memantine by non-specialists in any setting (for example secondary care; mental health services; community mental health services, including memory clinics; GP outreach clinics; primary care)<br>• Shared-care prescribing protocols |
| **Comparator** | • The initiation and review of donepezil, galantamine, rivastigmine, memantine by psychiatrists (including old age psychiatrists and those specialising in learning disability), neurologists, and physicians specialising in the care of older people |
| **Outcome** | • Clinical outcome including cognitive functional and behavioural ability<br>• Over-prescribing/under-prescribing and potentially avoidable adverse effects (including hospital admission)<br>• Medication errors<br>• Access to health and social care support<br>• Adherence<br>• Patient and carer experience and satisfaction<br>• Resource use and cost |

For full details of the review protocol please see appendix C.

There was no restriction on study design for inclusion in the evidence review. However, it was anticipated that the most useful study types would be observational designs including prospective/ retrospective cohort studies. It was expected that the most appropriate design

would be a study that compares non-specialist prescribing of these interventions with specialist prescribing.

The committee was interested in identifying evidence relating to both the prescribing and reviewing of AChEs and memantine. This is because it was expected that the prescribing of these medications for people living with Alzheimer's disease may be carried out by a different health professional to the person undertaking the review. Evidence associated with these practices was identified independently.

#### 11.1.2.1 Description of included studies

Two observational studies were included in the evidence review. One study presented in 2 papers provided evidence on the prescribing of donepezil for people living with Alzheimer's disease and 1 paper was identified as evidence for reviewing treatment with donepezil.

The quality of evidence for each outcome was considered using the approach recommended by the Grading Recommendations, Assessment, Development and Evaluation (GRADE) working group. Due to variations in the way the outcome data were reported by each study, the evidence statements were presented by intervention/study rather than by outcome.

For a summary of included studies please see Table 48 (for the full evidence tables and full GRADE profiles please see Appendix E and Appendix G). References for the included studies are given in appendix I.

### 11.1.3 Health economic evidence

A literature review was undertaken by applying standard health economic filters to the clinical literature searches. In total, 1,049 records were returned; 0 were retained as cost–utility analyses that addressed the review question.

### 11.1.3.11 Description of included studies

**Table 48: Summary of included studies**

| Author (year) | Study type | Participant details | Comparisons | Outcomes of interest | Length of follow up | Study location |
|---|---|---|---|---|---|---|
| **Prescribing donepezil** | | | | | | |
| Aupperle et al. (2000); Aupperle et al. (2003) | Retrospective cohort | **Patient characteristics:**<br>All patients had received an initial evaluation and diagnosis of Alzheimer's disease from a university diagnostic clinic<br>Evaluable total:<br>Original population receiving diagnosis (N=80)<br>**Participants with 1-year follow up data:**<br>(N= 58)<br>mean age 78.8 years<br>MED (n=31);<br>mean age = 82.9 years<br>GERO (n=27);<br>mean age = 80.4 years<br>**Participants with 2-year follow up data:**<br>(N= 39)<br>mean age 78.4 years<br>MED (n=22);<br>mean age = not reported<br>GERO (n=17);<br>mean age = not reported | • Participants being seen by a primary care physician<br>• Compared with:<br>• Participants being seen by a member of a geriatric psychiatry facility | • Clinical outcome (including cognitive, functional, behavioural ability)<br>• Access to health care and social care support<br>• Concordance and compliance<br>• Patient and carer experience and satisfaction<br>• | • 1 year (2000)<br>• 2 years (2003) | USA |
| **Reviewing donepezil** | | | | | | |

| Author (year) | Study type | Participant details | Comparisons | Outcomes of interest | Length of follow up | Study location |
|---|---|---|---|---|---|---|
| Watanabe et al. (2012) | Observational before-and-after study | **Patient characteristics:**<br>The records of patients diagnosed with AD or mixed AD/VaD were followed up with the GP<br>Evaluable total:<br>Total sample (N=111)<br>Non DOCS (n=59);<br>mean age = 79.0 years<br>DOCS (n=52);<br>mean age = 77.2 years | • Participants enrolled into a donepezil outpatient advisory service after it was established (DOCS)<br>• Compared with:<br>• Participants enrolled before a donepezil outpatient advisory service was established (non DOCS) | • Concordance and compliance<br>• Patient and carer experience and satisfaction | • 4 weeks | Japan |

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### 11.1.4 Evidence statements

#### 11.1.4.1 Prescribing donepezil (speciality versus non-speciality prescribing)

Very low to low-quality evidence from 1 observational study conducted in the USA in the 1990s with 57 participants found at 1 year follow up the number of people receiving a prescription of donepezil was significantly lower for people being seen by a primary care physician compared with those seen by a geriatric psychiatrist.

At 1 year follow up, the study reported a mean Clinical Dementia Rating significantly higher (indicating more severe dementia) for people being seen by a primary care physician compared with those being seen by a geriatric psychiatrist. The use of health and social care support (including number of hospitalisations, use of home health aides and dementia day care programs), and the mean carer distress rating were not significantly different for people being seen by a primary care physician compared with those being seen by a geriatric psychiatrist.

In the same study, at 2 year follow up, (39 participants), the number of people receiving a prescription of donepezil and the use of health and social care support (including number of hospitalisations, use of assisted living and residence in nursing homes) were not significantly different for people being seen by a primary care physician compared with those being seen by a geriatric psychiatrist.

#### 11.1.4.2 Reviewing donepezil (advisory service versus no advisory service)

Very low-quality evidence from 1 before-and-after study conducted in Japan with 111 participants reported the number of people living with Alzheimer's disease who were continuing to use donepezil after 1 year was significantly greater for people using an advisory consultation service compared with those who had not used this service. The mean duration of donepezil treatment and mean level of understanding for patients and carers was also significantly higher for people using the advisory consultation service compared with those who had not used the service.

#### 11.1.4.3 Health economic evidence

No health economic evidence was identified for this review question.

### 11.1.5 Evidence to recommendations

| | |
|---|---|
| **Relative value of different outcomes** | The Guideline committee agreed it was important that included outcomes considered the impact of medication changes on access to health and social care support and also reflected outcomes for both people living with dementia and their carers. The committee recognised that the outcomes presented in the evidence review were limited and felt this was consistent with the very low quality of the evidence (see 'Quality of evidence' below). The committee noted that the processes for issuing and dispensing prescriptions differ across primary and secondary care settings. For example, it was perceived that the issuing of repeat prescriptions in primary care is likely to be more reactive to requests from the person living with dementia, whereas the issuing of prescriptions in specialist services is perceived to be more proactive when treatment is initiated.<br>The committee noted that the number of prescriptions dispensed may not necessarily equate to adherence with prescribed medication, as it does not indicate whether people take the medicines dispensed. |

| | |
|---|---|
| | The committee observed for the outcome concordance and compliance, that the relative risk associated with the number of prescriptions at 2 year follow up did not identify a significant effect; however the primary data indicated a large difference. The committee considered this magnitude of effect as potentially important regardless of statistical significance.<br>Although, in Aupperle et al. 2003, the authors did not report standard deviation at 2 year follow up the committee noted that, participants who were seen by a geriatric psychiatrist experienced an overall slight improvement in Clinical Dementia Rating (CDR) over 2 years. The committee thought this would be very unusual, as Alzheimer's disease is a degenerative condition.<br>The committee agreed that the outcomes reported were in line with their own clinical experience. It was noted that people with dementia in non-specialist settings may be more likely to stop medications. |
| **Quality of evidence** | The committee agreed that the evidence presented was very low quality and noted the methodological limitations of the identified studies.<br>The committee agreed that the identified research evidence would not necessarily reflect current practice in the UK for the use of AChEs. It was noted that the studies were conducted during the 1990s, when clinicians were much less familiar with AChEs. The included studies were also conducted overseas where healthcare systems and services differ to practice in the UK.<br>For Aupperle et al. (2000) and Aupperle et al. (2003) the committee noted that the observational design of the studies meant that there was a high risk of selection bias. The committee further noted that the observational design of Aupperle et al. (2003) meant there was a lack of interpretable findings on reasons for attrition, making it difficult to infer whether attrition was a consequence of adverse effects or lack of efficacy.<br>The committee acknowledged the limitations of the Watanabe et al. (2012) study. They agreed the observational design, small sample size, short follow up and selective reporting reflected that the study was very low quality. |
| **Trade-off between benefits and harms** | The committee discussed the evidence base and agreed that they would be unable to make recommendations based solely on the reported outcomes.<br>The committee raised concerns about the lack of evidence identified in relation to the initiation of AChEs and memantine but agreed that initiation is implicitly linked to diagnosis. It noted that recommendation 1.1 and 1.2 of TA217 imply that a diagnosis is needed before treatment can be initiated. The committee agreed that the purpose of memory clinics is not solely to prescribe AChEs and memantine but to provide specialist assessment in diagnosing, treating and supporting people living with dementia. The committee noted that the current guideline suggests that diagnosis should be made by a specialist (CG42 1.4.3.1), and that this will be subject to a separate evidence review as part of the ongoing update.<br>The committee acknowledged the practical issues around the mechanisms for prescribing, dispensing and monitoring medication adherence. Committee members raised concerns that people may have to wait for a diagnosis before they can start treatment but the committee agreed that there should not be an artificial barrier preventing the transfer of care between specialist and non-specialist healthcare settings. The committee was keen to ensure that AChEs and memantine were only initiated following a diagnosis and those treatment recommendations are made by a clinician with appropriate specialist expertise. However, it acknowledged the difficulties that sometimes arise where the diagnosing clinician is required to issue the first prescription for an AChE or memantine. The committee acknowledged |

| | |
|---|---|
| | that licensing for AChEs and memantine (as set out in each product's Summary of Product Characteristics; SPC) is clear about initiation and supervision of these drugs and therefore agreed that it was appropriate to reflect this in the recommendations. The committee noted that the SPCs for each of the AChEs and memantine make reference to initiation and supervision of treatment by specialist physicians. However, it noted that the wording of these SPCs pre-dates legislative changes, in the early 2000s, which authorised the use of non-medical prescribers. The committee agreed that any interpretation of the recommendations would need to take account of this different prescribing environment. For this reason, the committee thought it was not necessary to stipulate that treatment should be initiated by physicians (i.e. doctors) alone, and preferred to emphasise that the prescriber starts treatment on advice from a healthcare professional with specialist experience, regardless of professional label. The committee also agreed it was important to note that once a decision has been made to initiate therapy, then prescriptions can be made in primary care.<br>The committee discussed their concerns over communication of information between specialist and non-specialist settings and agreed that reference to NICE's Medicines Optimisation guideline (NG5) would be helpful. The committee discussed recommendation 1.2 in the NICE Medicines Optimisation guideline which considers medicines-related communication systems where patients move between care settings, which is of particular relevance. However, following further discussion, it was agreed that reference to all of NG5 would be more appropriate. When considering the monitoring and review of these drugs, the committee noted and agreed that an annual dementia review is mandated. They agreed that these drugs should be part of the annual dementia review as opposed to a standard medicines review. The committee noted again that it would be appropriate to refer to the Medicines Optimisation NICE guidance with regard to medication review, and the arrangements that should be in place between different care settings (in this instance, secondary and primary care). |
| **Trade-off between net health benefits and resource use** | No published health economic evidence was identified for this review question. The committee noted that, in the past (including when TA217 was published), the medicines under consideration all had proprietary status, but they are all now available in generic formulations. This change has been accompanied by a significant fall in the acquisition costs of the drugs. The committee felt that, if cost containment had been a motivating factor in restricting prescribing to people with specialist experience of Alzheimer's disease, this was no longer such a substantial concern. However, the committee emphasised that other reasons for involving specialists remain relevant. |
| **Other considerations** | It was noted that the current recommendations make reference to carers' views. The committee agreed that this is an important consideration. However following discussion it was agreed that it could be adequately addressed by cross-reference to NICE's Medicines Optimisation guideline (NG5), which gives detailed guidance on the need to involve carers in the diagnosis, management and treatment of individuals. It was also agreed to be appropriate to add addition cross-references to the NICE guidelines on managing medicines for adults receiving social care in the community, and managing medicines in care homes, in particular because these guidelines includes specific recommendations around covert administration, which will be relevant for some people living with dementia. This guideline will be relevant for people with all dementia subtypes, not only those with Alzheimer's disease included in this review.<br>This section also includes the recommendations directly incorporated in to this guideline from NICE technology appraisal 217. |

### 11.1.6 Recommendations

Recommendations shaded in grey are taken directly from NICE technology appraisal guidance 217 and were not updated as part of this guideline, and therefore no changes to these recommendations can be made.

**60. The three acetylcholinesterase (AChE) inhibitors donepezil, galantamine and rivastigmine as monotherapies are recommended as options for managing mild to moderate Alzheimer's disease under all of the conditions specified in 62 and 63.**

**61. Memantine monotherapy is recommended as an option for managing Alzheimer's disease for people with:**

- moderate Alzheimer's disease who are intolerant of or have a contraindication to AChE inhibitors **or**
- severe Alzheimer's disease.

**Treatment should be under the conditions specified in recommendation 6.**

**62. Treatment should be under the following conditions:**

- For people who are not taking an AChE inhibitor or memantine, prescribers should only start treatment with these on the advice of a clinician who has the necessary knowledge and skills. This could include:
  - secondary care medical specialists such as psychiatrists, geriatricians and neurologists
  - other healthcare professionals (such as GPs, nurse consultants and advanced nurse practitioners), if they have specialist expertise in diagnosing and treating Alzheimer's disease.
- Once a decision has been made to start cholinesterase inhibitors or memantine, the first prescription may be made in primary care.
- Ensure that local arrangements for prescribing, supply and treatment review follow the NICE guideline on medicines optimisation.

**63. If prescribing an AChE inhibitor (donepezil, galantamine or rivastigmine), treatment should normally be started with the drug with the lowest acquisition cost (taking into account required daily dose and the price per dose once shared care has started). However, an alternative AChE inhibitor could be prescribed if it is considered appropriate when taking into account adverse event profile, expectations about adherence, medical comorbidity, possibility of drug interactions and dosing profiles.**

**64. When using assessment scales to determine the severity of Alzheimer's disease, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect the results and make any adjustments they consider appropriate. Healthcare professionals should also be mindful of the need to secure equality of access to treatment for patients from different ethnic groups, in particular those from different cultural backgrounds.**

**65. When assessing the severity of Alzheimer's disease and the need for treatment, healthcare professionals should not rely solely on cognition scores in circumstances in which it would be inappropriate to do so. These include:**

- if the cognition score is not, or is not by itself, a clinically appropriate tool for assessing the severity of that patient's dementia because of the patient's learning difficulties or other disabilities (for example, sensory impairments), linguistic or other communication difficulties or level of education or
- if it is not possible to apply the tool in a language in which the patient is sufficiently fluent for it to be appropriate for assessing the severity of dementia or
- if there are other similar reasons why using a cognition score, or the score alone, would be inappropriate for assessing the severity of dementia.

**In such cases healthcare professionals should determine the need for initiation or continuation of treatment by using another appropriate method of assessment.**

66. **For guidance on managing medicines (including covert administration), see the NICE guidelines on managing medicines for adults receiving social care in the community and managing medicines in care homes.**

## 11.2 Co-prescription and withdrawal of cholinesterase inhibitors and memantine in Alzheimer's disease

**Review questions**

- How effective is the co-prescription of cholinesterase inhibitors and memantine for the treatment of Alzheimer's disease?
- When should treatment with donepezil, galantamine, rivastigmine, memantine be withdrawn for people with Alzheimer's disease?

### 11.2.1 Introduction

The aim of these review questions was to determine the effectiveness and cost-effectiveness of memantine plus a cholinesterase inhibitor for cognitive enhancement in Alzheimer's disease and to determine the clinically appropriate points to withdraw treatment with donepezil, galantamine, rivastigmine and memantine for people with Alzheimer's disease.

The review identified studies that fulfilled the conditions specified in Table 49 and Table 50. For full details of the review protocols, see Appendix C.

**Table 49: Review summary: co-prescription of cholinesterase inhibitors and memantine for the treatment of Alzheimer's disease**

| | |
|---|---|
| **Population** | People with a diagnosis of Alzheimer's disease |
| **Interventions** | Memantine plus a cholinesterase inhibitor |
| **Comparator** | • Memantine<br>• Cholinesterase inhibitors<br>• Placebo<br>• Dose escalation is a possible alternative to co-prescription |
| **Outcomes** | • Clinical outcomes including cognitive, functional and behavioural ability<br>• Adverse events<br>• Patient and carer experience and satisfaction<br>• Patient and carer health-related quality of life<br>• Resource use and costs |

**Table 50: Review summary: withdrawal of cholinesterase inhibitors and memantine for people living with Alzheimer's disease**

| | |
|---|---|
| **Population** | People aged (40 years and over) with a diagnosis of Alzheimer's disease and currently being treated with donepezil, galantamine, rivastigmine and/or memantine |
| **Interventions** | Withdrawal of pharmacological treatment<br>Explicit stopping rule for pharmacological treatment |
| **Comparator** | Continuation of previous treatment<br>Change of treatment drug (to another of the specified 4 drugs)<br>Change of treatment dose<br>Alternative stopping rules |
| **Outcomes** | Clinical outcomes including cognition, function, behaviour and neuropsychiatric symptoms<br>Adverse events<br>Patient and carer experience and satisfaction<br>Patient and carer health-related quality of life |

Resource use and costs

### 11.2.2 Evidence review

Two separate systematic searches were undertaken to address the 2 questions in this section.

For the co-prescription of cholinesterase inhibitors and memantine a systematic search identified 1,914 references. Fifty three references were ordered for full text review after screening upon title and abstract and 8 papers were included in the final review.

Five papers (Howard, 2012; Tariot 2004; Dysken 2014; Porsteinsson 2008 and Grossberg 2013) recruited people who were currently receiving a cholinesterase inhibitor as treatment for their Alzheimer's disease and involved randomisation to co-prescription with memantine or placebo memantine. To assist with analysis, additional data was sought from the authors of the DOMINO-AD trial (Howard, 2012; please see Appendix E for this information). Two papers (Araki 2014; Choi 2011) compared co-prescription of a cholinesterase inhibitor to monotherapy with the same cholinesterase inhibitor. One paper (Shao 2015) randomised people with mild to moderate Alzheimer's disease to different treatment arms for each cholinesterase inhibitor and compared these to placebo. For a detailed list of excluded studies and reasons for exclusion see Appendix F.

For discontinuation of cholinesterase inhibitors and memantine, the search identified 1,242 references. The references were screened on their titles and abstracts and 35 references were ordered for full text review. Thirty two papers were subsequently excluded because they did not fit the inclusion criteria (see Appendix F for a detailed list of excluded studies and reasons for their exclusion). Three papers were included in the evidence review. A further 3 papers included outcomes for people discontinued from cholinesterase inhibitors, but these did not meet the criteria for the review as they did not include a population of people taking a cholinesterase inhibitor at start of the study, but rather people were included in the study, started on treatment and then had the treatment withdrawn as part of the same study.

All 3 included papers involved randomisation to withdrawal of a cholinesterase inhibitor and replacement with placebo. One study reported in 2 papers (Howard *et al*., 2012; Howard *et al*., 2015) additionally randomised people within each arm to receive active or placebo memantine, creating a 2x2 factorial trial design. The other study (Herrmann *et al.*, 2016) recruited people on a range of cholinesterase inhibitors (rivastigmine, galantamine, donepezil) and reported outcomes without stratifying by the specific cholinesterase inhibitor which had been continued or withdrawn.

A summary of the characteristics of the included studies is provided in and Table 51 and Table 52. Data from the included studies were extracted into evidence tables. See Appendix E for the full evidence tables, and for the full GRADE profiles see Appendix G. References for the included studies are given in appendix I.

Results for co-prescription versus cholinesterase inhibitor monotherapy are presented in 2 separate ways. The first analysis uses the full dataset, and stratifies the analysis into mild-to-moderate, and moderate-to-severe populations, as each of the included trials recruits 1 of those 2 subpopulations. The second analysis subdivides the population into separate mild, moderate and severe subgroups, using additional information obtained from a Cochrane review of memantine in dementia, and from the authors of the DOMINO-AD trial. It was not possible to obtain data for all outcomes of all trials in this format, and therefore this analysis contains only a subset of the participants included in the full analysis.

### 11.2.2.11 Description of included studies

2 **Table 51: Included studies for co-prescription of cholinesterase inhibitors and memantine**

| Study reference | Study type | Study population | Intervention and comparator | Relevant outcomes | Comments |
|---|---|---|---|---|---|
| **Donepezil plus memantine versus donepezil plus placebo** | | | | | |
| Howard 2012 | Randomised controlled trial | Moderate to severe Alzheimer's disease | Combination of donepezil 10mg / day plus memantine 5mg/ day increasing to 20mg/day versus placebo | • SMMSE<br>• Bristol ADL scale<br>• NPI<br>• DEMQOL proxy<br>• GHQ-12 | Follow up 52 weeks<br>Location: UK |
| Tariot 2004 | Randomised controlled trial | Moderate to severe Alzheimer's disease | Participants currently receiving donepezil additionally received memantine 5mg/day increasing to 20mg/day versus placebo | • ADCS-ADL<br>• CIBIC plus<br>• NPI<br>• Severe impairment Battery<br>• Behaviour rating scale for Geriatric Patients | Follow up 24 weeks<br>Location: USA |
| **Any Cholinesterase inhibitor plus memantine versus placebo** | | | | | |
| Dysken 2014 | Randomised controlled trial | Mild to moderate possible or probable Alzheimer's disease | One arm of TEAM AD (trial of vitamin A and memantine in Alzheimer' disease)<br>Participants currently receiving cholinesterase inhibitors additionally received memantine (titrated to 20 mg/ day) versus placebo | • ADCS-ADL<br>• MMSE<br>• ADAS-cog<br>• NPI<br>• Caregiver Activity survey<br>• Any adverse events | Follow up ranged from 6 months to 2 years<br>Location USA<br>14 VA centres |
| Porsteinsson 2008 | Randomised controlled trial | Mild to moderate probable Alzheimer's disease | Participants currently receiving cholinesterase inhibitors additionally received memantine 20mg/ day<br>versus placebo | • ADAS-Cog<br>• ADCS-ADL<br>• NPI<br>• MMSE<br>• Adverse events | Follow up 24 weeks<br>Location: USA |

| Study reference | Study type | Study population | Intervention and comparator | Relevant outcomes | Comments |
|---|---|---|---|---|---|
| Grossberg 2013 | Randomised controlled trial | Moderate to severe probable Alzheimer's disease | MEM-MD-50 Participants currently receiving cholinesterase inhibitors additionally received once daily (28mg) extended release memantine versus placebo | • ADCS-ADL<br>• Severe Impairment Battery<br>• CIBIC plus<br>• NPI<br>• Verbal fluency test<br>• Any adverse events | Follow up 24 weeks<br>Location : multinational<br>Study dose memantine was a higher dose extended release formulation |
| **Donepezil plus memantine versus donepezil only** | | | | | |
| Araki 2014 | Randomised controlled trial | Moderate to severe Alzheimer's disease | Participants currently receiving donepezil additionally received memantine 5mg/ day increasing to 20mg/day versus donepezil only | • MMSE<br>• NPI<br>• Japanese Zarit Burden Interview<br>• Clinical Global Impression-Improvement | Follow up 24 weeks<br>Location: Japan |
| **Rivastigmine plus memantine versus rivastigmine only** | | | | | |
| Choi 2011 | Randomised open label trial | Moderate to severe probable Alzheimer's disease (NINCDS-ADRDA) | Combination of rivastigmine transdermal 10cm patch plus memantine 5mg/ day increasing to 20mg/day versus rivastigmine 10cm transdermal patch monotherapy | • Korean MMSE<br>• ADAS-Cog<br>• NPI (carers assessment)<br>• Frontal Assessment Battery<br>• ADCS- ADL<br>• CDR-SB<br>• Koran CMAI<br>• Safety and tolerability | Follow up 16 weeks<br>Location: South Korea<br>Study conducted in 26 centres |
| **Donepezil or galantamine or rivastigmine plus memantine versus memantine only** | | | | | |
| Shao 2015 | Randomised controlled trial | Mild to moderate Alzheimer's disease | Memantine plus donepezil<br>Memantine plus rivastigmine<br>Memantine plus rivastigmine<br>Versus memantine plus placebo | • MMSE<br>• ADCS ADL<br>• Incidence of adverse events | Follow up 24 weeks<br>Location: China |

**Table 52: Included studies for withdrawal of cholinesterase inhibitors or memantine**

| Study reference | Study type | Study population | Intervention and comparator | Relevant outcomes | Comments |
|---|---|---|---|---|---|
| **Donepezil withdrawal** | | | | | |
| Howard 2012 | 2x2 factorial RCT | Community-dwelling people with moderate to severe Alzheimer's disease | Group 1: donepezil continuation (10mg/day) plus initiation of placebo memantine (from week 1)<br><br>Group 2: donepezil discontinuation (donepezil at 5mg for weeks 1-4, placebo donepezil thereafter ) plus initiation of placebo memantine (from week 1)<br><br>Group 3: donepezil discontinuation (donepezil at 5mg for weeks 1-4, placebo donepezil thereafter) plus initiation of memantine (5mg from week 1, increasing in 5 mg increments to reach 20 mg from week 4 onwards)<br><br>Group 4: donepezil continuation plus initiation of memantine (5mg from week 1, increasing in 5 mg increments to reach 20 mg from week 4 onwards) | • Standardised MMSE<br>• Bristol Activities of Daily Living Scale<br>• Neuropsychiatric Inventory<br>• DEM-QOL-proxy<br>• Carer health status (GHQ-12) | 52-week study |
| Howard 2015 (Further analysis of Howard 2012) | | | | • Nursing home placements | Up to 4 years' follow-up |
| **Cholinesterase inhibitor withdrawal (assorted treatments)** | | | | | |
| Herrmann 2016 | Randomised controlled trial | Institutionalised people with | Continuation of existing cholinesterase inhibitor (rivastigmine, galantamine, | • Clinician's Global Impression of Change (CGI/CGI-C) | 8-week study recruiting from 2 |

| Study reference | Study type | Study population | Intervention and comparator | Relevant outcomes | Comments |
|---|---|---|---|---|---|
| | | moderate to severe Alzheimer's disease | donepezil) vs withdrawal and switch to placebo | • Standardised Mini Mental State Examination (sMMSE)<br>• Severe Impairment Battery (SIB)<br>• Neuropsychiatric inventory - Nursing Home version (NPI-NH)<br>• Cohen-Mansfield Agitation Inventory (CMAI)<br>• Apathy Evaluation Scale (AES)<br>• Alzheimer's Disease Co-operative Study - Activities of Daily Living Inventory, modified for severe AD (ADCS-ADL-sev)<br>• Quality of Life in Late-Stage Dementia (QUALID) | long-term care facilities |

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### 11.2.3 Health economic evidence

As for the cost-effectiveness searches, 2 separate systematic searches were undertaken to address the 2 questions in this section. For full details of the search strategies, please see Appendix D.

#### 11.2.3.1 Co-prescription of cholinesterase inhibitors and memantine

The search identified 820 references. After screening on title and abstract, 12 papers were ordered for full-text review; following detailed perusal, 5 cost–utility analyses (CUAs) were included in the final review.

Three CUAs were closely related: **Lachaine et al. (2011)** developed a Markov model comparing co-prescription of cholinesterase inhibitors (AChEs) and memantine with AChE monotherapy from a Canadian perspective, whilst **Pfeil et al. (2012)** and **Touchon et al. (2014)** replicated the analysis from Swiss and French perspectives, respectively. The models adopted a 3-state structure: the modelled cohorts began in community-based care, with a proportion progressing to full-time residential care and the possibility of transition to death from either state. The probability of requiring full-time residential care was estimated from an observational (retrospective cohort) study, based on a US population, which found that people who had received combination therapy were significantly less likely to enter care than people who had received AChE monotherapy (Lopez et al., 2014). Economic evidence profiles for all three CUAs are available in Appendix M.

All 3 analyses were judged to be partially applicable with very serious limitations. Each concluded that combination therapy dominates AChE monotherapy (that is, it is both less expensive and more effective). All 3 CUAs report setting-specific costs from a 'healthcare' perspective and a 'societal' perspective. Neither of these is consistent with the NICE reference case, as the 'healthcare' perspective omits relevant social care costs, and the 'societal' perspective includes these costs but also encompasses estimates of informal carer costs. However, results are not qualitatively different between the 2 perspectives, so it can be inferred that a perspective that sits between the 2 would reach the same conclusions.

**Weycker et al. (2007)** developed a patient-level cohort 'micro-simulation' model, simulating the costs and effects of combination therapy with memantine and donepezil compared with donepezil monotherapy in moderate-to-severe Alzheimer's disease from a US perspective. Treatment effects for combination therapy were based on severe impairment battery (SIB) results from an RCT comparing memantine and donepezil with donepezil monotherapy that is included in our clinical review (Tariot et al. 2004; see above). However, the effects of donepezil were not drawn from the same RCT; rather, they were based on the donepezil arm of a different, placebo-controlled RCT (Feldman et al., 2001). The authors justify this decision by arguing that the benefits of donepezil observed in the Tariot et al. RCT 'are probably an artefact of trial participation and not donepezil therapy *per se*'. SIB results in these 2 trial arms are used to estimate costs, utility and probability of entry to full-time care, via a mapping to MMSE which is, in turn, used to approximate CDR (and, in the case of HRQoL, mapped once again to HUI3).

The CUA was assessed as partially applicable with very serious limitations. It concluded that, over their lifetime, an average patient in the cohort would spend around 2 years in a community setting, followed by a little under 4 years in full-time care, and such a person would accrue a negative QALY aggregate over this period (that is, their remaining quality-adjusted life expectancy should be considered a substantially worse prospect than

immediate death). Incremental results suggest that combination therapy dominates donepezil monotherapy (that is, it is both less expensive and more effective).

The final CUA, reported by **Knapp et al. (2016),** was a UK trial-based analysis conducted alongside the DOMINO-AD RCT, which is described above (Howard et al., 2012). The analysis used directly reported carer-rated EQ-5D results to estimate QALYs over the 1-year duration of the trial. Resource-use data were collected using a comprehensive inventory of health and social care support. Although the trial randomised people to 4 mutually exclusive strategies (donepezil, memantine, donepezil and memantine combination, or placebo), the paper reports incremental results for 3 comparisons that the investigators had pre-specified as of interest: donepezil or combination versus memantine or placebo, combination versus donepezil and memantine versus placebo. The second comparison is of interest for the co-prescription review (see below for analyses of interest to the discontinuation question).

As for the effectiveness review, the investigators shared results stratified by baseline severity, which enabled the committee to consider separate (moderate and severe Alzheimer's disease [AD]) populations. It also made it possible to assess evidence for comparisons not reported in the paper – for example, combination therapy compared with memantine monotherapy (which is a particularly relevant comparison in people with severe AD, given that memantine is licensed in this population, but donepezil is not). Having access to the stratified data had the substantial advantage that the committee could consider analyses of direct relevance to the decision problems with which it was faced. However, it came with the disadvantage that, as data had been subdivided into smaller subsets, it was not feasible to adjust the analyses for the baseline characteristics of the participants, as had been done in the published analysis.

The CUA was assessed as directly applicable with minor limitations. It had the following results:

- In **moderate** disease, combination therapy was associated with increased costs (£1,310 [95%CI: −£3,021 to £5,641]) and reduced quality of life (−0.07 [95%CI: −0.22 to 0.08]) compared with donepezil monotherapy. However, these estimates were subject to substantial uncertainty, as can be seen in the broad confidence intervals with which the disaggregated values are associated.
- In the **severe** AD stratum,
  - combination therapy reduced costs (−£1,658 [95%CI: −£6,399 to £3,082]) and increased QALYs (0.11 [95%CI: −0.06 to 0.28]) compared with memantine monotherapy
  - combination therapy reduced costs (−£240 [95%CI: −£4,759 to 4,279]) and increased QALYs (0.11 [95%CI: −0.06 to 0.28]) compared with donepezil alone

  Once again, these estimates were subject to substantial uncertainty, as seen in the broad confidence intervals.
- Probabilistic analysis is only available in the published analysis, which combines **moderate and severe** AD. This suggested that there is an exactly 50:50 chance that combination therapy or donepezil monotherapy is optimal, if QALYs are valued at £20,000 each.

#### 11.2.3.2 Discontinuation of cholinesterase inhibitors and memantine

The search identified 346 references. After screening on title and abstract, 8 papers were ordered for full-text review; following detailed perusal, 1 was included in the final review.

The one included CUA was Knapp et al.'s, within-trial analysis for the DOMINO-AD RCT (2016), as described above. For the discontinuation question, the comparisons of interest are

donepezil vs placebo and memantine vs placebo in both the moderate and severe subgroups.

The CUA was assessed as directly applicable with minor limitations. It had the following results:

- In **moderate** disease,
  - donepezil monotherapy reduced costs (£974 [95%CI: −£2,383 to £4,332]) and increased QALYs (0.26 [95%CI: 0.08 to 0.45]) compared with placebo
  - memantine monotherapy reduced costs (−£1,472 [95%CI: −£4,273 to £1,329]) and increased QALYs (0.18 [95%CI: −0.02 to 0.37]) compared with placebo
- In **severe** disease,
  - donepezil monotherapy reduced costs (−£5,711 [95%CI: −£19,015 to £7,592]) and increased QALYs (0.05 [95%CI: −0.11 to 0.21]) compared with placebo
  - memantine monotherapy reduced costs (−£4,293 [95%CI: −£17,677 to £9,091]) and increased QALYs (0.07 [95%CI: −0.10 to 0.23]) compared with placebo

These results were typically associated with substantial uncertainty. The one finding that appeared reliable, at a 95% confidence level, is that discontinuing donepezil, in people with moderate AD, results in a loss of QALYs.

### 11.2.4 Evidence statements

#### 11.2.4.1 Cholinesterase inhibitor plus memantine versus cholinesterase inhibitor plus placebo

##### *11.2.4.1.1 Full population*

Low- to high-quality evidence from up to 5 RCTs containing 1,875 people living with Alzheimer's disease found global functioning (CIBIC plus), behavioural and psychological symptoms (NPI), care dependency (Behaviour rating scale for geriatric patients- care dependency subscale), verbal fluency (VFT) and activities of daily living (ADCS-ADL/BADLS) were significantly improved in people treated with combination therapy of cholinesterase inhibitors plus memantine compared with treatment with a cholinesterase inhibitor plus a placebo, but could not differentiate cognition (ADAS-cog; MMSE), global assessment (SIB), health-related quality of life (DEMQOL), global health (Global health questionnaire), carer activity (Caregiver activity survey), adverse events, serious adverse events, discontinuations due to adverse events, entry to long term care or mortality.

##### *11.2.4.1.2 Mild to moderate*

Low- to moderate-quality evidence from up to 3 RCTs containing 740 people living with mild to moderate Alzheimer's disease could not differentiate cognition (ADAS-cog; MMSE), activities of daily living (ADCS-ADL/BADLS), global functioning (CIBIC plus), behavioural and psychological symptoms (NPI), health-related quality of life (DEMQOL), adverse events, serious adverse events, discontinuations due to adverse events or mortality between people treated with combination therapy of cholinesterase inhibitors plus memantine compared with treatment with a cholinesterase inhibitor plus a placebo.

##### *11.2.4.1.3 Moderate to severe*

Very low- to high-quality evidence from up to 4 RCTs containing 1,166 people living with moderate to severe Alzheimer's disease found activities of daily living (ADCS-ADL/BADLS), global functioning (CIBIC plus), behavioural and psychological symptoms (NPI), care dependency (Behaviour rating scale for geriatric patients- care dependency subscale) and verbal fluency (VFT) were significantly improved in people treated with combination therapy

of cholinesterase inhibitors plus memantine compared with treatment with a cholinesterase inhibitor plus a placebo, but could not differentiate cognition (MMSE), global assessment (SIB), health related quality of life (DEMQOL), global health (Global health questionnaire), adverse events, serious adverse events, discontinuations due to adverse events or carer outcomes (Caregiver activity survey).

**Economic evidence**

One directly applicable cost–utility analysis with minor limitations found that combination therapy is associated with small, uncertain increases in both costs and QALYs, with a base-case ICER of £19,967. The probability that either approach is optimal is 50%, if QALYs are valued at £20,000 each.

#### *11.2.4.1.4 Mild only*

Low- to moderate-quality evidence from up to 2 RCTs containing 315 people living with mild Alzheimer's disease could not differentiate global assessment, cognitive function or activities of daily living between people treated with combination therapy of cholinesterase inhibitors plus memantine compared with treatment with a cholinesterase inhibitor plus a placebo.

#### *11.2.4.1.5 Moderate only*

Low- to moderate-quality evidence from up to 4 RCTs containing 663 people living with moderate Alzheimer's disease found cognitive function was significantly improved in people treated with combination therapy of cholinesterase inhibitors plus memantine compared with treatment with a cholinesterase inhibitor plus a placebo, but could not differentiate global assessment, activities of daily living, behavioural and psychological symptoms (NPI), health-related quality of life (DEMQOL) or global health (Global health questionnaire).

**Economic evidence**

One directly applicable cost–utility analysis with minor limitations found that donepezil monotherapy may be associated with lower costs and more QALYs than combination therapy with donepezil and memantine. However, this result is subject to substantial uncertainty, such that the data are consistent with either approach providing better value than the other.

#### *11.2.4.1.6 Severe only*

Moderate- to high-quality evidence from up to 3 RCTs containing 218 people living with severe Alzheimer's disease found cognitive function, activities of daily living and behavioural and psychological symptoms (NPI) were significantly improved in people treated with combination therapy of cholinesterase inhibitors plus memantine compared with treatment with a cholinesterase inhibitor plus a placebo, but could not differentiate global assessment, health-related quality of life (DEMQOL) or global health (Global health questionnaire).

**Economic evidence**

One directly applicable cost–utility analysis with minor limitations found that combination therapy with donepezil and memantine may be associated with lower costs and more QALYs than either agent as monotherapy. However, this result is subject to substantial uncertainty, such that the data are consistent with any approach providing best value.

#### *11.2.4.1.7 Cholinesterase inhibitor plus memantine versus cholinesterase inhibitor monotherapy*

Very low- to moderate-quality evidence from up to 2 RCTs containing 183 people living with Alzheimer's disease found global assessment (Clinical Global Impression-Improvement), cognition (Clock drawing Test), behavioural and psychological symptoms (NPI) and carer burden (Zarit Burden Interview) were significantly improved in people treated with combination therapy of cholinesterase inhibitors plus memantine compared with cholinesterase inhibitor monotherapy, but could not differentiate cognition (MMSE; ADAS-cog), behavioural and psychological symptoms (carer administered), dementia severity (Clinical Dementia rating–sum of boxes; Frontal Assessment Battery), agitation (Cohen Mansfield Agitation Inventory), any adverse events or any serious adverse events.

When data was stratified by baseline dementia severity, cognition (MMSE) was significantly improved for people living with moderate–severe Alzheimer's disease, but could not be differentiated for people living with mild-to-moderate Alzheimer's disease.

**Economic evidence**

Four partially applicable cost–utility analyses with very serious limitations found that, in people with moderate–severe AD, combination therapy with a cholinesterase inhibitor and memantine dominates cholinesterase inhibitor monotherapy (that is, combination therapy is associated with lower costs and more QALYs). All 4 analyses were funded by the manufacturer of memantine, and each derived its estimates of effect from non-randomised comparisons.

#### *11.2.4.1.8 Cholinesterase inhibitor plus memantine versus memantine plus placebo*

Very low to low-quality evidence from 1 RCT with 88 people living with mild to moderate Alzheimer's disease could not differentiate cognition (MMSE); activities of daily living (ADCS-ADL) or number of adverse events for people treated with combination therapy of cholinesterase inhibitors plus memantine compared with people treated with memantine plus a placebo.

**Economic evidence**

One directly applicable cost–utility analysis with minor limitations found that, in people with severe AD, combination therapy with donepezil and memantine may be associated with lower costs and more QALYs than memantine monotherapy. However, this result is subject to substantial uncertainty, such that the data are consistent with either approach providing better value than the other.

### 11.2.4.2 Cholinesterase inhibitor withdrawal

Low- to moderate-quality evidence from up to 2 RCTs containing 148 people living with moderate to severe Alzheimer's disease could not differentiate cognition, activities of daily living, behavioural and psychological symptoms, quality of life or rates of entry to long term care between people continuing with or discontinuing from cholinesterase inhibitors. Significant benefits from continuation were found for cognition in people with moderate Alzheimer's disease.

**Economic evidence**

One directly applicable cost–utility analysis with minor limitations found that

- in people with moderate AD, switching from donepezil to placebo reduces QALYs and may also increase costs, meaning it is likely to be dominated by continued therapy
- in people with severe AD, switching from donepezil to placebo may reduce QALYs and may also increase costs, meaning it may be dominated by continued therapy

#### 11.2.4.3 Cholinesterase inhibitor switch to memantine

Low- to moderate-quality evidence from 1 RCT containing 105 people living with moderate to severe Alzheimer's disease could not differentiate cognition, activities of daily living, behavioural and psychological symptoms, quality of life or rates of entry to long term care between people continuing with cholinesterase inhibitors or switching to memantine. Significant benefits from switching were found for behavioural and psychological symptoms in people with severe Alzheimer's disease.

**Economic evidence**

One directly applicable cost–utility analysis with minor limitations could not differentiate costs and QALYs between switching from donepezil to memantine or continuing donepezil, in people with severe AD.

#### 11.2.4.4 Memantine withdrawal

No evidence was identified looking at the outcomes of memantine withdrawal in people living with dementia.

### 11.2.5 Evidence to recommendations

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| **Relative value of different outcomes** | The committee noted that the primary outcome measures in most of the trials was cognitive function (using one of the MMSE, ADAS-cog and SIB). They recognised that in designing trials, these instruments are used as a measure of identifying disease severity. However, in practice, clinicians are more likely to consider global functioning, quality of life, and the impacts on people's daily activities. In deciding whether to continue treatment, the committee agreed it was important to consider the overall benefit of treatment, rather than simply focusing upon cognitive benefit.<br>The committee also agreed that it was important to consider evidence on behavioural symptoms, and in particular agitation. There is evidence from the literature on memantine monotherapy that it may have positive effects on agitation, and some evidence that cholinesterase inhibitors may worsen agitation in some individuals. These potential effects are also important to consider. |
| **Trade-off between benefits and harms** | **Discontinuation of cholinesterase inhibitors**<br>The committee noted there was clear evidence of harm from discontinuing cholinesterase inhibitors in people with moderate Alzheimer's disease, with a substantial worsening in cognitive function. The committee noted that the trials effectively used an MMSE score as the trigger for discontinuation, and that decisions in clinical practice were likely to be more complex than this, and cover a range of outcomes for the person living with Alzheimer's disease. They therefore agreed the evidence demonstrated that it was not possible to use a set cut-off for disease severity to decide when treatment should be discontinued (as no effective cut-off to use was found). This was supported by the primary analysis of the DOMINO-AD study, which found significant worsening on cholinesterase inhibitor withdrawal. The committee therefore agreed it was appropriate to recommend that |

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| | disease severity should not be used as a reason for treatment discontinuation.<br>The committee agreed that in practice there may be other reasons why treatments are discontinued (e.g. the person is unable or unwilling or distressed by the process of taking the medicine, they are suffering side effects, or they are entering a terminal phase of the illness and harms are felt to outweigh the benefits of treatment). However, it was agreed these discussions were part of normal clinical decision-making, it was not necessary to make any specific recommendations about them.<br>**Co-prescription of cholinesterase inhibitors and memantine**<br>The committee agreed that is was important to separate the population into those with mild Alzheimer's disease and those with moderate/severe disease when considering this question, as the evidence on memantine monotherapy suggests that memantine is not effective in mild Alzheimer's disease.<br>The committee agreed this same pattern was present in the evidence on co-prescription, with no evidence of effect in the mild subgroup, but improvements in cognitive function and global functioning in both the moderate and severe populations (and additionally, improvements in activities of daily living in the severe population). The magnitudes of the effects were approximately half of those seen for cholinesterase inhibitor monotherapy versus placebo in treatment naive individuals, but were still at a level that would be likely to be clinically meaningful, particularly given that there was no evidence of an increase in adverse events from co-prescription.<br>The committee therefore agreed it was appropriate to make positive recommendations for co-prescription in both moderate and severe Alzheimer's disease. A stronger recommendation was made for severe Alzheimer's disease compared with moderate disease for two reasons: firstly, the magnitudes of effects seen were larger in people with more severe Alzheimer's disease; and secondly, the trials in moderate to severe Alzheimer's disease only tended to recruit people at the more severe end of the moderate category, and therefore the evidence of benefit is less clear in people at the milder end of the moderate category.<br>**Switching from cholinesterase inhibitors to memantine**<br>The committee considered the risks and benefits of transferring from monotherapy with cholinesterase inhibitors to monotherapy with memantine. They concluded that, in practice, there may be a risk of doing harm by switching (by moving people off a drug they are known to tolerate), when you have no particular indication to stop. There may be a danger that if a transfer to memantine is not tolerated, people may be left without any prescription, when continuing therapy with cholinesterase inhibitors may have had some benefit. Therefore, the committee agreed the balance of evidence was in favour of co-prescription as opposed to treatment switching in people with severe Alzheimer's disease. |
| **Trade-off between net health benefits and resource use** | The committee noted that, of the economic evaluations identified, only the DOMINO-AD study was directly applicable and subject to only minor limitations: it was the only evidence from the UK, based on an RCT, and that reflected the current prices of the drugs, which have fallen substantially since generic formulations became available. Therefore, the committee agreed it provided more robust evidence than the other studies. The committee noted that the other studies were all judged to be partially applicable with very serious limitations.<br>It agreed that, as the cost of all of these medicines was now extremely low, any intervention that was clinically effective (in improving quality of life) was almost certain to be cost effective. This was supported by evidence from DOMINO-AD, where, with the exception of 1 analysis, interventions associated with more QALYs were also associated with |

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| | lower costs. The committee considered this a predictable finding because, if the intervention is effective in maintaining people's cognition and/or functional independence, the low costs of the drugs themselves will be outweighed by money saved in support required. The committee also noted that the other, lower-quality CUAs were consistent with this pattern, showing that combination therapy dominated monotherapy with a cholinesterase inhibitor alone, resulting in decreased costs and increased QALYs. The committee did not consider these studies to provide convincing evidence, in themselves, that combination therapy provides better value than monotherapy; however, it agreed with the emerging principle that any strategy, in this area, that improves quality of life is also likely to reduce overall costs.<br>**Discontinuation of cholinesterase inhibitors**<br>The committee considered analyses from the DOMINO-AD study comparing donepezil monotherapy versus placebo and memantine monotherapy versus placebo in both moderate and severe AD subgroups. The committee agreed the findings of the analyses agree with the findings of the clinical review that monotherapy in both moderate and severe subgroups with either donepezil or memantine was effective compared with placebo, and resulted in decreased costs and increased QALYs. The committee were confident in the finding that discontinuing donepezil in people with moderate/severe AD resulted in a loss of QALYs, and therefore concluded that donepezil should be not discontinued from people with Alzheimer's disease solely on the basis of disease progression. There was somewhat more uncertainty in the costs associated with these analyses; however, the committee did not think this was a serious issue, as the clinical data were robust, and the cost data clearly pointed in a direction that reflected the previously stated argument that any effective treatment is likely to be cost effective.<br>**Combination therapy**<br>The analyses found that, in moderate AD, combination therapy was associated with increased costs and reduced quality of life, albeit with substantial uncertainty.<br>In the case of severe AD, however, combination therapy appeared to be associated with reduced costs and increased QALYs compared with monotherapy with either memantine or donepezil alone. The committee agreed the level of uncertainty in the evidence meant it was hard to draw definitive conclusions from the economics alone, but again felt that the clear clinical benefits justified making recommendations for co-prescription. The stronger evidence for cost effectiveness in the severe population meant an 'offer' recommendation was made for that group, whilst only a 'consider' recommendation was made for moderate Alzheimer's disease. |
| **Quality of evidence** | The committee agreed that for the co-prescription review question, the evidence that was most relevant for UK practice came from the trials that compared cholinesterase inhibitors plus memantine against cholinesterase inhibitors plus placebo, in people already taking a cholinesterase inhibitor at baseline. The evidence from these trials was general of moderate to high quality, and therefore the committee was comfortable using this evidence to make strong recommendations. The committee agreed that the additional trials of cholinesterase inhibitors plus memantine versus cholinesterase inhibitor monotherapy (without a placebo) were at much higher risk of bias and therefore represented a much lower standard of evidence. They also noted that these trials were excluded from the recent Cochrane review on this topic, and therefore felt it appropriate that these trials not be included as part of the primary analysis looking at the effect of co-prescription.<br>The committee noted that there was also evidence on the effectiveness of adding cholinesterase inhibitors to people already taking memantine at baseline, but agreed this comparison was of much less relevance to |

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| | the UK. Specifically, the technology appraisals for memantine (TA217) state that it is an option in moderate Alzheimer's disease only if cholinesterase inhibitors are contraindicated, and therefore people should only be started on memantine monotherapy ahead of cholinesterase inhibitor monotherapy if they are contraindicated for cholinesterase inhibitors.<br>The committee agreed the DOMINO-AD trial (Howard 2012) was a well-conducted and robust trial that provided evidence directly applicable to the UK on the question of withdrawal of cholinesterase inhibitors in people with moderate to severe Alzheimer's disease. They also noted that this trial was specifically designed to answer questions raised by the 2006 NICE dementia guideline, and therefore was likely to remain the best evidence available to address this question.<br>No evidence was found that looked at the effect of withdrawing memantine in people with severe Alzheimer's disease, and therefore the committee agreed it was not appropriate to make any recommendations on this topic. |
| **Other considerations** | The committee considered the practical arrangements for co-prescription. They agreed it was important to apply the recommendations made for these review questions within the context of the published NICE technology appraisal guidance (TA217) related to the use of cholinesterase inhibitors and/or memantine for the treatment of Alzheimer's disease. They also considered the wording of these recommendations alongside the other TA217 recommendations updated as part of this guideline, on the appropriate people to initiate treatment with cholinesterase inhibitors and/or memantine.<br>The committee agreed that those recommendations (which specify that treatment should only be started on the advice of someone with expertise in diagnosing and treating dementia) were to ensure that prescription is made following a correct diagnosis of dementia. However, this is no longer an important issue when considering the addition of a second medication in people who have an established dementia diagnosis and are living with more advanced stages of disease. For this reason, the committee was happy for co-prescription of these medications to be initiated in primary care, in people who already have an established diagnosis of Alzheimer's disease and are already taking cholinesterase inhibitors.<br>The committee agreed that, whilst the majority of the included evidence was on donepezil, it was reasonable to assume a class effect for cholinesterase inhibitors, and therefore recommendations were made generally for cholinesterase inhibitors. |

### 11.2.6 Recommendations

**67. Do not stop AChE inhibitors in people with Alzheimer's disease because of disease severity alone.**

**68. For people with an established diagnosis of Alzheimer's disease who are already taking an AChE inhibitor:**

- consider memantine in addition to an AChE inhibitor if they have moderate disease
- offer memantine in addition to an AChE inhibitor if they have severe disease.

**69. For people with an established diagnosis of Alzheimer's disease who are already taking an AChE inhibitor, primary care prescribers may start treatment with**

**memantine (see recommendation 68) without taking advice from a specialist clinician.**

# 11.3 Pharmacological management of dementia with Lewy bodies

**Review question**

- What is the comparative effectiveness of donepezil, galantamine, memantine and rivastigmine for cognitive enhancement in dementia associated with Parkinson's disease?

## 11.3.1 Introduction

Dementia (the progressive loss of global cognitive function) is common in Parkinson's disease; 48% to 80% of people develop dementia at some point in their condition. Traditionally, dementia developing more than 1 year after the onset of the motor symptoms of Parkinson's disease is referred to as Parkinson's disease dementia (PDD). Dementia developing within 1 year of the onset of motor symptoms is referred to as dementia with Lewy bodies (DLB).

The relationship between DLB and PDD is unclear, but they have many common clinical features and there is some opinion that they may be the same condition. Therefore, the committee agreed that the population included in this review question should cover people with DLB and PDD. Studies that included people with mild cognitive impairment were excluded.

The aim of this review question was to assess the comparative efficacy of pharmacological interventions for cognitive enhancement in dementia associated with Parkinson's disease, compared with placebo or other active comparator(s). This updates the evidence reviews on:

- Cholinesterase inhibitors for cognitive enhancement in Parkinson's disease from the 2006 guideline on Parkinson's disease (CG35).
- Cholinesterase inhibitors or memantine for the treatment of cognitive symptoms of Dementia with Lewy bodies from the 2006 guideline on Dementia (CG42).
- Cholinesterase inhibitors or memantine for the treatment of non-cognitive symptoms of dementia with Lewy bodies from the 2006 guideline on Dementia (CG42).

This updated review incorporates some studies that were included in the previous guidelines together with newly published evidence.

The review focused on identifying studies that fulfilled the conditions specified in Table 53.

**Table 53: Review summary: effectiveness of pharmacological for cognitive enhancement in dementia associated with Parkinson's disease**

| | |
|---|---|
| **Population** | People with a diagnosis of PDD or DLB |
| **Interventions** | • Donepezil<br>• Galantamine<br>• Memantine<br>• Rivastigmine[1]<br>• Memantine plus cholinesterase inhibitor |
| **Comparators** | • Placebo<br>• Each other<br>• Combination of memantine plus cholinesterase inhibitor |
| **Outcomes** | • Cognitive outcomes, including:<br>○ Mini Mental State Examination (MMSE) |

| | |
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| | ○ Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog)<br>○ Montreal Cognitive Assessment (MoCA)<br>• Global outcomes, including:<br>○ Unified Parkinson's Disease Rating Scale (UPDRS)<br>○ Global impression of change<br>• Activities of daily living (ADL), including:<br>○ Unified Parkinson's Disease Rating Scale – activities of daily living scale (UPDRS-ADL)<br>○ Measures used in DLB research (including those derived from Alzheimer's disease measures)<br>• Other non-cognitive outcomes, including:<br>○ Neuropsychiatric outcomes, such as the Neuropsychiatric Inventory (NPI)<br>○ Motor symptoms, such as tremor and rigidity<br>• Adverse events, such as hallucinations<br>• Study withdrawal<br>• Health-related quality of life<br>• Carer-reported outcomes<br>• Resource use and cost<br>• Time to institutionalised care |

[1] *Rivastigmine capsules are currently the only intervention that is licensed for mild to moderate dementia in Parkinson's disease. No treatments are licensed for dementia with Lewy bodies.*

For full details of the review protocol, please see Appendix C. Randomised controlled trials (RCTs) were considered to be the most appropriate study design to derive treatment effect metrics, and were therefore considered to be the highest quality within a GRADE framework. All other study designs were excluded from this review, including case–control studies, cohort studies, and case reports.

### 11.3.2 Evidence review

A systematic search of the literature was conducted (see appendix D) which identified 1,152 references. This search was restricted to studies published from 2005 onwards to avoid duplicates of studies considered in the previous Parkinson's disease guideline (CG35). After removing duplicates the references were screened on their titles and abstracts and full papers of 130 references were obtained and reviewed against the inclusion and exclusion criteria in the review protocol (see appendix C).

Overall, 121 studies were excluded as they did not meet the eligibility criteria, such as not utilising a randomised-control design. The 9 remaining published papers met the eligibility criteria and were included in the review. A list of excluded studies and reasons for their exclusion is provided in appendix F.

Five RCTs included in previous guidelines on Parkinson's disease (CG35) and Dementia (CG42) were reviewed. Of these, 2 RCTs were already included from the search (McKeith et al., 2000, Ravina et al., 2005) and 2 RCTs (Aarsland et al., 2002; Emre et al., 2004) met the present inclusion and exclusion criteria and were included. The remaining RCT (Leroi et al., 2004) was excluded as people in the study had mild cognitive impairment associated with Parkinson's disease.

Systematic reviews identified in the literature search were also analysed to identify any published papers meeting the eligibility criteria that had not been identified in the search. No further studies were identified. 5 published papers were identified through a rerun of the literature search in June 2016, none of which were included. Therefore, a total of 11 RCTs were included in the evidence review.

Data were extracted into detailed evidence tables (see appendix E), and further summarised in GRADE profiles (appendix G).

#### 11.3.2.1 Description of included studies

See Table 54 for a summary of included studies. References for the included studies are given in appendix I.

##### *11.3.2.1.1 Pharmacological interventions in DLB*

3 double-blind placebo-controlled RCTs assessed the effectiveness of a cholinesterase inhibitor in people with DLB:

- donepezil (Ikeda et al., 2015, Mori et al., 2012)
- rivastigmine (McKeith et al., 2000).

1 double-blind placebo-controlled RCT (Emre et al., 2010) assessed the effectiveness of memantine in people with DLB.

No studies assessed the effectiveness of a combination of cholinesterase inhibitor plus memantine in people with DLB.

##### *11.3.2.1.2 Pharmacological interventions in PDD*

4 double-blind placebo-controlled RCTs (reported in 5 publications) assessed the effectiveness of a cholinesterase inhibitor in people with PDD:

- donepezil (Aarsland et al., 2002, Dubois et al., 2012, Ravina et al., 2005)
- rivastigmine (Emre et al., 2004, Dujardin et al., 2006 [secondary publication]).

1 open-label RCT (Emre et al., 2014) assessed the effectiveness of rivastigmine capsules compared with rivastigmine patches in people with PDD.

2 double-blind placebo-controlled RCTs, reported in 3 publications (Emre et al., 2010; Leroi et al., 2009, Leroi et al., 2014 [secondary publication]) assessed the effectiveness of memantine in people with PDD.

No studies assessed the effectiveness of a combination of cholinesterase inhibitor plus memantine in people with PDD.

##### *11.3.2.1.3 Mixed population (PDD or DLB)*

1 double-blind placebo-controlled RCT assessed the effectiveness of memantine in a mixed population of people with PDD or DLB (Aarsland et al., 2009).

##### *11.3.2.1.4 Prioritisation of outcomes*

A large number of outcomes were reported in the studies, particularly those measuring cognitive function. Some outcomes were reported frequently (for example, MMSE) while others were reported only in a single small RCT. Therefore, the committee prioritised some key critical outcomes for the analyses.

Key critical outcomes prioritised by the committee were:

- Adverse events
- Cognitive function, measured by:

  - Mini Mental State Examination (MMSE)
  - Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog)
  - Mattis Dementia Rating Scale (MDRS)
  - Delis-Kaplan Executive Functions System verbal fluency test (D-KEFS)
  - 10-point clock drawing test
  - Cognitive Drug Research computerised assessment system (CDR)
  - Brief test of attention (BTA)
- Global assessment
- Activities of daily living
- Carer-reported outcomes
- Other non-cognitive outcomes, including
  - Neuropsychiatric Inventory (NPI)
  - Unified Parkinson's Disease Rating Scale – motor subscale (UPDRS III)

**Analyses**

The following analyses were conducted:

- pharmacological interventions in people with DLB:
  - cholinesterase inhibitors versus placebo
  - memantine versus placebo
- pharmacological interventions in people with PDD:
  - cholinesterase inhibitors versus placebo
  - memantine versus placebo
  - rivastigmine patches versus capsules
- combined analyses – pharmacological interventions in a mixed population (PDD or DLB)
  - cholinesterase inhibitors versus placebo
  - memantine versus placebo
  - network meta-analyses of pharmacological interventions versus placebo

The combined analyses were only carried out for outcomes when data were available for both PDD and DLB populations.

For studies which had more than one active treatment arm, for example different doses, the active treatment arms were combined together to give an overall effect.

The evidence across outcomes was appraised using the GRADE framework and forest plots are presented where appropriate (see appendix G and appendix H).

**Table 54: Summary of included studies**

| Study | Population | Intervention | Comparison | Prioritised outcomes |
|---|---|---|---|---|
| **Parkinson's disease dementia (PDD)** | | | | |
| Aarsland et al. (2002) | People aged 45-95 years with cognitive impairment associated with PD (MMSE score 16 to 26 inclusive [mean 20.8]) | Donepezil 5mg daily, increased to 10mg daily after 6 weeks if well tolerated | Placebo | • Adverse events<br>• Cognitive outcome: MMSE<br>• Global outcome: CIBIC+<br>• Non-cognitive outcomes: NPI, UPDRS III |
| Dubois et al. (2012) | People aged 40 years and older with PDD (MMSE score 10 to 26 inclusive [mean 21.4]) | Donepezil 5mg or 10mg daily | Placebo | • Adverse events<br>• Cognitive outcomes: ADAS-cog, MMSE, D-KEFS verbal fluency test, BTA<br>• Global outcomes: CIBIC+<br>• ADL: DAD<br>• Non-cognitive outcomes: NPI, UPDRS III |
| Emre et al. (2004) | People aged at least 50 years old with PDD (MMSE 10 to 24 [mean 19.3]) | Rivastigmine 1.5mg twice daily, increasing to a maximum well tolerated dose (up to 6mg twice daily) | Placebo | • Adverse events<br>• Cognitive outcomes: ADAS-cog, MMSE, D-KEFS verbal fluency test, CDR, 10-point clock drawing test<br>• Global outcome: ADCS-CGIC<br>• ADL: ADCS-ADL<br>• Non-cognitive outcomes: NPI, UPDRS III |
| Emre et al. (2010)[1] | People aged 50 years and older with PDD (MMSE score 10 to 24 inclusive [mean 21.1]) | Memantine 5mg daily, increasing to a maintenance dose of 20mg daily | Placebo | • Adverse events<br>• Global outcome: ADCS-CGIC<br>• ADL: ADCS-ADL<br>• Non-cognitive outcomes: NPI, UPDRS III<br>• Carer-reported outcome: ZBI |
| Emre et al. (2014) | People aged 50 to 85 years with PDD (MMSE score 10 to 26 inclusive [mean 20.9]) | Rivastigmine 4.6mg/24h patch, increasing to 9.5mg/24h patch | Rivastigmine 1.5mg twice daily, increasing to a maximum well tolerated dose (up to 6mg twice daily) | • Adverse events<br>• Cognitive outcome: MDRS<br>• ADL: ADCS-ADL<br>• Non-cognitive outcome: NPI |

| Study | Population | Intervention | Comparison | Prioritised outcomes |
|---|---|---|---|---|
| Leroi et al. (2009) | People with PDD (MMSE score 10 to 27 [mean 19.1]) | Memantine 20mg daily | Placebo | • Adverse events<br>• Cognitive outcomes: MMSE, DRS<br>• Global outcome: CIBIC+<br>• Non-cognitive outcomes: NPI, UPDRS III |
| Ravina et al. (2005) | People aged 40 years and older with PDD (MMSE score 17 to 26 inclusive [mean 22.2]) | Donepezil 5mg daily or 5mg twice daily | Placebo | • Adverse events<br>• Cognitive outcomes: ADAS-cog, MMSE, MDRS<br>• Global outcomes: CGIC, UPDRS (total score)<br>• Non-cognitive outcomes: UPDRS III |
| **Dementia with Lewy bodies (DLB)** | | | | |
| Emre et al. (2010)[1] | People aged 50 years and older with DLB (MMSE score 10 to 24 inclusive [mean 20.4]) | Memantine 5mg daily, increasing to a maintenance dose of 20mg daily | | • Adverse events<br>• Global outcome: ADCS-CGIC<br>• ADL: ADCS-ADL<br>• Non-cognitive outcomes: NPI, UPDRS III<br>• Carer reported outcome: ZBI |
| McKeith et al. (2000) | People with DLB (MMSE score over 9 [mean 17.9]) | Rivastigmine 1.5mg twice daily, increasing to a maximum well tolerated dose (up to 6mg twice daily) | Placebo | • Adverse events<br>• Cognitive outcome: MMSE<br>• Global outcome: CGC+<br>• Non-cognitive outcomes: NPI, UPDRS III |
| Ikeda et al. (2015) | People aged 50 years and older with DLB (MMSE score 10 to 26 inclusive [mean 20.4]) | Donepezil 5mg or 10mg daily | Placebo | • Adverse events<br>• Cognitive outcome: MMSE<br>• Global outcome: CIBIC+<br>• Non-cognitive outcomes: NPI, UPDRS III<br>• Carer-reported outcome: ZBI |
| Mori et al. (2012) | People aged 50 years and older with DLB (MMSE score 10 to 26 inclusive [mean 19.6]) | Donepezil 3mg, 5mg or 10mg daily | Placebo | • Adverse events<br>• Cognitive outcome: MMSE<br>• Global outcome: CIBIC+<br>• Non-cognitive outcomes: NPI, UPDRS III<br>• Carer-reported outcome: ZBI |

| Study | Population | Intervention | Comparison | Prioritised outcomes |
|---|---|---|---|---|
| **Mixed population (PDD or DLB)** | | | | |
| Aarsland et al. (2009) | People with PDD or DLB (MMSE score 12 or above [mean 20.0]) | Memantine 5mg daily, increasing to a maintenance dose of 10mg twice daily | Placebo | • Adverse events<br>• Cognitive outcomes: MMSE<br>• Global outcome: CGIC<br>• ADL: DAD<br>• Non-cognitive outcomes: NPI, UPDRS III |

[1] *Study included people with PDD and DLB; data for PDD, DLB and the mixed population was presented separately in the paper*

*ADAS-cog; Alzheimer's Disease Assessment Scale – cognitive subscale*
*ADCS-ADL; Alzheimer's Disease Assessment Scale – Activities of Daily Living subscale*
*ADCS-CGIC; Alzheimer's disease Cooperation Study – Clinical Global Impression of Change*
*ADL; Activities of daily living*
*BTA; Brief test of attention*
*CDR; Cognitive Drug research computerised assessment system*
*CGC-plus; Clinical Global Change-plus*
*CGIC; Clinical Global Impression of change*
*CIBIC+; Clinician's interview based impression of change*
*DAD; Disability assessment for dementia*
*D-KEFS; Delis-Kaplan Executive Functions System*
*MDRS; Mattis Dementia Rating Scale*
*MMSE; Mini Mental State Examination*
*NPI; Neuropsychiatric Inventory*
*UPDRS; Unified Parkinson's Disease Rating Scale*
*ZBI; Zarit caregiver Burden Interview*

### 11.3.3 Health economic evidence

Literature searches were undertaken to find any existing cost–utility analyses (CUAs) assessing pharmacological interventions for cognitive enhancement in dementia associated with Parkinson's disease. In total, 344 articles were returned, of which 2 were selected as potentially relevant and retrieved for full text review. Both were included. Studies were assessed using the quality appraisal criteria as outlined in the NICE guidelines manual (NICE, 2012).

**Willan et al. (2006)** compared rivastigmine with placebo in people with mild PDD (MMSE 20–24), based on evidence from the EXPRESS RCT (Emre et al. 2004). The analysis concentrated solely on short-term cognitive effect, as measured by MMSE at 24 weeks, which was translated to health-related quality of life (EQ-5D) using a mapping function based on a Scandinavian population with Alzheimer's disease (Jönsson, 2003). For further details, please see the economic evidence profile in Appendix M. The authors' base case adopted a broad societal perspective, including an attempt to value carer time; however, disaggregated results are reported, enabling the recalculation of results with a perspective that is consistent with the NICE reference case (that is, NHS and PSS costs only). This suggests that rivastigmine is associated with an ICER of around £58,600 per QALY gained. However, this analysis comes from a time when rivastigmine was only available as a proprietary product; since then, it has become available generically and costs have decreased substantially. Therefore, to approximate the results of this CUA from a present-day perspective, the developer recalculated results by:

- removing costs borne by patients and carers;
- re-estimating rivastigmine drug cost, assuming the overall change is proportional to the change in price of a 28 x 3 mg pack (£2004=£34.02 [BNF 47]; £2016=£2.57 [NHS Drug Tariff Feb 2016]; reduction of 92.4%);
- inflating all other costs from £2004/05 to £2015/16 using PSSRU hospital & community health services inflators.

This analysis estimated an ICER of approximately £16,000 per QALY gained.

**Gustavsson et al. (2009)** simulated a population with DLB (from which people with PDD were explicitly excluded) receiving unspecified AChE inhibitors. For further details, please see the economic evidence profile in Appendix M. The authors drew treatment effects from a UK observational audit for the first 4 months, and extrapolated these to 5 years using a Scandinavian longitudinal study in Alzheimer's disease (Wallin et al., 2007). Additional non-cognitive symptoms (extra-pyramidal symptoms and psychosis) were assumed for DLB. The authors used 3 separate models, and compared results. The first was a reconstruction of the Southampton Alzheimer's disease model (Loveman et al., 2006); the second was a micro-simulation model; and the third was a Markov model with 4 discrete MMSE states. When applied to people with all severities of dementia, ICERs of between £2,700 and £46,800 per QALY were estimated; when the population was limited to people with moderate dementia (MMSE 10–20), AChE inhibitors were dominant in all 3 models (that is, they were predicted to save money and improve health). Again, it was possible to estimate present-day results for these analyses, by:

- re-estimating AChE inhibitor drug costs, assuming the original model used the cost of donepezil 10 mg daily and assumed 2 monitoring visits per year, and that the overall change in drug costs is proportional to the change in price of a 28 x 10 mg pack of donepezil (£2005=£89.06 [BNF 49]; £2016=£1.45 [NHS Drug Tariff Feb 2016]; reduction of 98.4%);

- inflating all other costs from £2005/06 to £2015/16 using PSSRU hospital & community health services inflators

This recalculation estimated that treatment with AChE inhibitors is less costly and more effective than placebo in all analyses, regardless of population modelled or model preferred.

### 11.3.4 Evidence statements

#### 11.3.4.1 Evidence statements – Dementia with Lewy bodies

##### *11.3.4.1.1 Adverse events*

**Cholinesterase inhibitors**

Moderate-quality evidence from 3 RCTs could not differentiate the risk of any adverse events, serious adverse events or adverse events requiring treatment withdrawal between cholinesterase inhibitors and placebo.

**Memantine**

Moderate-quality evidence from 1 RCT could not differentiate the risk of any adverse events, serious adverse events or adverse events requiring treatment withdrawal between memantine and placebo.

##### *11.3.4.1.2 Cognitive function*

**Cholinesterase inhibitors**

High-quality evidence from 3 RCTs suggests that, compared with placebo, cholinesterase inhibitors significantly improve cognitive function as assessed by the MMSE.

**Memantine**

Moderate-quality evidence from 1 RCT could not differentiate the effect on cognitive function between memantine and placebo, as assessed by the 10-point clock drawing.

##### *11.3.4.1.3 Global assessment*

**Cholinesterase inhibitors**

High-quality evidence from 1 RCT suggests that, compared with placebo, donepezil significantly improves global response as assessed by CIBIC+.

High-quality evidence from 1 RCT suggests that, compared with placebo, donepezil significantly improves global response as assessed by at least minimal improvement in CIBIC+.

**Memantine**

Moderate-quality evidence from 1 RCT could not differentiate the effect on global response between memantine and placebo, as assessed by ADCS-CGIC.

#### *11.3.4.1.4 Activities of daily living*

**Memantine**

Moderate-quality evidence from 1 RCT could not differentiate the effect on activities of daily living between memantine and placebo, as assessed by ADCS-ADL.

#### *11.3.4.1.5 Carer-reported outcomes*

Cholinesterase inhibitors

High-quality evidence from 2 RCTs suggests that, compared with placebo, donepezil significantly improves carer burden as assessed by the Zarit caregiver burden interview.

**Memantine**

Moderate-quality evidence from 1 RCT could not differentiate the effect on carer burden between memantine and placebo, as assessed by the Zarit caregiver burden interview.

#### *11.3.4.1.6 Other non-cognitive outcomes*

**Cholinesterase inhibitors**

Low-quality evidence from 3 RCTs could not differentiate the effect on neuropsychiatric symptoms between cholinesterase inhibitors and placebo, as assessed by the NPI-10 item score.

High-quality evidence from 2 RCTs suggests that, compared with placebo, cholinesterase inhibitors significantly improve neuropsychiatric symptoms (hallucinations, delusions, dysphoria and apathy) as assessed by the NPI-4 item score.

Low-quality evidence from 2 RCTs could not differentiate the effect on neuropsychiatric symptoms (hallucinations, cognitive fluctuation) between donepezil and placebo, as assessed by the NPI-2 item score.

Low-quality evidence from 2 RCTs could not differentiate the effect on motor symptoms between cholinesterase inhibitors and placebo, as assessed by UPDRS III.

**Memantine**

Moderate-quality evidence from 1 RCT could not differentiate the effect on neuropsychiatric symptoms between memantine and placebo, as assessed by the NPI-12 item score.

Moderate-quality evidence from 1 RCT could not differentiate the effect on motor symptoms between memantine and placebo, as assessed by UPDRS III.

#### *11.3.4.1.7 Economic evidence statements*

One partially applicable cost–utility analysis with very serious limitations concluded that, in all people with DLB, AChEs improve QALYs at increased cost, with ICERs ranging from £2,700 to £46,800, depending on modelling assumptions. In a subgroup of people with moderate DLB, AChEs were found to be cost-saving. An approximation to 2016 costs suggests that, now generic AChEs are available at lower cost, treatment would be dominant in all models and all populations. The study undertook no exploration of uncertainty.

### 11.3.4.2 Evidence statements – Parkinson's disease dementia

#### *11.3.4.2.1 Adverse events*

**Cholinesterase inhibitors**

Moderate-quality evidence from 4 RCTs suggests that, compared with placebo, cholinesterase inhibitors significantly increase the risk of any adverse events.

Moderate-quality evidence from 2 RCTs could not differentiate the risk of serious adverse events between cholinesterase inhibitors and placebo.

Moderate-quality evidence from 3 RCTs suggests that, compared with placebo, cholinesterase inhibitors significantly increase the risk of study withdrawal due to adverse events.

Moderate-quality evidence from 2 RCTs suggests that, compared with placebo, cholinesterase inhibitors significantly reduce the risk of hallucinations.

Low-quality evidence from 1 RCT could not differentiate the risk of any adverse events, serious adverse events, study withdrawal due to adverse events or hallucinations between rivastigmine patches and rivastigmine capsules.

**Memantine**

Moderate-quality evidence from 2 RCTs could not differentiate the risk of any adverse events, serious adverse events or study withdrawal due to adverse events between memantine and placebo.

#### *11.3.4.2.2 Cognitive function*

**Cholinesterase inhibitors**

High-quality evidence from 4 RCTs suggests that, compared with placebo, cholinesterase inhibitors significantly improve cognitive function as assessed by the MMSE.

High-quality evidence from 3 RCTs suggests that, compared with placebo, cholinesterase inhibitors significantly improve cognitive function as assessed by ADAS-cog.

Low- to moderate-quality evidence from 1 RCT could not differentiate the effect on cognitive function between rivastigmine patches and rivastigmine capsules at 24 weeks, as assessed by the MDRS total score, but there was a significant benefit for rivastigmine capsules at 76 weeks.

**Memantine**

Low-quality evidence from 1 RCT could not differentiate the effect on cognitive function between memantine and placebo, as assessed by the MMSE and by the 10-point clock drawing test.

#### *11.3.4.2.3 Global assessment*

**Cholinesterase inhibitors**

Moderate-quality evidence from 4 RCTs suggests that, compared with placebo, cholinesterase inhibitors significantly improve global function as assessed by different measures.

High-quality evidence from 3 RCTs suggests that, compared with placebo, cholinesterase inhibitors significantly improve global response as assessed by different measures of at least minimal improvement.

**Memantine**

Moderate-quality evidence from 1 RCT could not differentiate the effect on global function between memantine and placebo, as assessed by ADCS-CGIC.

Low-quality evidence from 1 RCT could not differentiate the effect on global response between memantine and placebo, as assessed by at least minimal improvement in CIBIC+.

#### *11.3.4.2.4 Activities of daily living*

**Cholinesterase inhibitors**

High-quality evidence from 2 RCTs suggests that, compared with placebo, cholinesterase inhibitors significantly improve activities of daily living as assessed by different ADL measures.

Low- to moderate-quality evidence from 1 RCT could not differentiate the effect on activities of daily living between rivastigmine patches and rivastigmine capsules at 24 weeks, as assessed by ADCS-ADL, but there was a significant benefit for rivastigmine capsules at 76 weeks.

**Memantine**

Moderate-quality evidence from 1 RCT could not differentiate the effect on activities of daily living between memantine and placebo, as assessed by ADCS-ADL.

#### *11.3.4.2.5 Carer-reported outcomes*

**Memantine**

Moderate-quality evidence from 2 RCTs could not differentiate the effect on carer burden between memantine and placebo, as assessed by the Zarit caregiver burden interview.

#### *11.3.4.2.6 Other non-cognitive outcomes*

**Cholinesterase inhibitors**

High-quality evidence from 2 RCTs suggests that, compared with placebo, cholinesterase inhibitors significantly improve neuropsychiatric symptoms as assessed by the NPI-10 item score.

Low- to moderate-quality evidence from 1 RCT could not differentiate the effect on neuropsychiatric symptoms between rivastigmine patches and rivastigmine capsules at 24 weeks, as assessed by the NPI-10 item score, but there was a significant benefit for rivastigmine patches at 76 weeks.

Low-quality evidence from 2 RCTs could not differentiate the effect on motor symptoms between donepezil and placebo, as assessed by UPDRS III.

Low-quality evidence from 1 RCT could not differentiate the effect on motor symptoms between rivastigmine patches and rivastigmine capsules, as assessed by UPDRS III.

**Memantine**

Moderate-quality evidence from 2 RCTs could not differentiate the effect on neuropsychiatric symptoms (NPI-10 item or NPI-12 item scores) or motor symptoms (UPDRS III) between memantine and placebo.

#### *11.3.4.2.7 Economic evidence statements*

One partially applicable cost–utility analysis with very serious limitations explored proprietarily-priced rivastigmine for the treatment of PDD. It concluded that rivastigmine is likely to improve quality-adjusted life expectation and may reduce overall costs. However, when an NHS and PSS perspective is adopted, rivastigmine is no longer cost-saving, with an ICER of £58,600/QALY. An approximation to 2016 costs suggests that, now generic rivastigmine is available at lower cost, it would be associated with an ICER of around £16,000/QALY.

### 11.3.4.3 Evidence statements – mixed population (PDD or DLB)

#### *11.3.4.3.1 Adverse events*

**Cholinesterase inhibitors**

High-quality evidence from 7 RCTs suggests that, compared with placebo, cholinesterase inhibitors significantly increase the risk of any adverse events.

Moderate-quality evidence from 5 RCTs could not differentiate the risk of serious adverse events between cholinesterase inhibitors and placebo.

High-quality evidence from 6 RCTs suggests that, compared with placebo, cholinesterase inhibitors significantly increase the risk of adverse events requiring treatment withdrawal.

**Memantine**

Low- to moderate-quality evidence from 2 RCTs could not differentiate the risk of any adverse events, serious adverse events or study withdrawal due to adverse events.

#### *11.3.4.3.2 Cognitive function*

**Cholinesterase inhibitors**

High-quality evidence from 8 RCTs suggests that, compared with placebo, cholinesterase inhibitors significantly improve cognitive function as assessed by the MMSE.

**Memantine**

Low-quality evidence from 2 RCTs could not differentiate the effect on cognitive function between memantine and placebo, as assessed by the MMSE.

#### *11.3.4.3.3 Global assessment*

**Cholinesterase inhibitors**

Moderate-quality evidence from 5 RCTs suggests that, compared with placebo, cholinesterase inhibitors significantly improve global function as assessed by different measures.

High-quality evidence from 4 RCTs suggests that, compared with placebo, cholinesterase inhibitors significantly improve global response as assessed by different measures of at least minimal improvement.

**Memantine**

Moderate-quality evidence from 2 RCTs suggests that, compared with placebo, memantine significantly improves global function as assessed by different measures.

#### *11.3.4.3.4 Activities of daily living*

**Memantine**

Moderate-quality evidence from 2 RCTs could not differentiate the effect on activities of daily living between memantine and placebo, as assessed by different ADL measures.

#### *11.3.4.3.5 Carer-reported outcomes*

**Memantine**

Moderate-quality evidence from 2 RCTs could not differentiate the effect on carer burden between memantine and placebo, as assessed by the Zarit caregiver burden interview.

#### *11.3.4.3.6 Other non-cognitive outcomes*

**Cholinesterase inhibitors**

High-quality evidence from 5 RCTs suggests that, compared with placebo, cholinesterase inhibitors significantly improve neuropsychiatric symptoms as assessed by the NPI-10 item score.

Low-quality evidence from 4 RCTs could not differentiate the effect on motor symptoms between donepezil and placebo, as assessed by UPDRS III.

**Memantine**

Moderate-quality evidence from 3 RCTs could not differentiate the effect on neuropsychiatric symptoms between memantine and placebo, as assessed by the NPI-10 item or NPI-12 item scores.

Moderate-quality evidence from 3 RCTs could not differentiate the effect on motor symptoms between memantine and placebo, as assessed by UPDRS III.

#### *11.3.4.3.7 Network meta-analyses*

Moderate- to high-quality evidence from a network meta-analysis of 9 RCTs showed that cholinesterase inhibitors are associated with a significant increase in any adverse events, compared with placebo, but the data could not differentiate between memantine compared with placebo or cholinesterase inhibitors.

Moderate-quality evidence from a network meta-analysis of 7 RCTs could not differentiate the rates of serious adverse events between any treatment alternative compared with placebo, or between cholinesterase inhibitors and memantine.

Low- to high-quality evidence from a network meta-analysis of 8 RCTs showed that cholinesterase inhibitors are associated with a significant increase in treatment withdrawal due to adverse events, compared with placebo, but the data could not differentiate between memantine compared with placebo or cholinesterase inhibitors.

Low- to high-quality evidence from a network meta-analysis of 10 RCTs showed that cholinesterase inhibitors are associated with a significant improvement in cognitive function assessed by the MMSE, compared with placebo, but the data could not differentiate between memantine compared with placebo or cholinesterase inhibitors.

Moderate- to high-quality evidence from a network meta-analysis of 7 RCTs showed that cholinesterase inhibitors are associated with a significant improvement in global function, compared with placebo, but the data could not differentiate between memantine compared with placebo or cholinesterase inhibitors.

Moderate- to high-quality evidence from a network meta-analysis of 8 RCTs showed that cholinesterase inhibitors are associated with a significant improvement in neuropsychiatric symptoms, compared with placebo, but the data could not differentiate between memantine compared with placebo or cholinesterase inhibitors.

Low- to moderate-quality evidence from a network meta-analysis of 7 RCTs could not differentiate the effect on motor symptoms between any treatment alternative compared with placebo, or between cholinesterase inhibitors and memantine.

### 11.3.5 Evidence to recommendations

| | |
|---|---|
| **Relative value of different outcomes** | Cognitive outcomes were critical to decision-making for this review question. Many different cognitive outcomes were reported in the studies; therefore the committee prioritised those outcomes where more data were available to inform their decision-making. MMSE and ADAS-cog were the most frequently reported cognitive outcomes. However, they recognised the limitations of, for example, MMSE, as a measure of the effectiveness of medication. Frequently, clinicians may be looking for stability, rather than an actual improvement in cognitive function. The committee also recognised that treatments for dementia may have important benefits in non-cognitive outcomes, such as global function, activities of daily living, carer burden and behavioural symptoms. |
| **Trade-off between benefits and harms** | The committee agreed that the evidence overall suggests that the effectiveness of pharmacological interventions is similar in people with PDD and DLB. This supports their original assertion about the similarity between these 2 conditions. The effectiveness of these interventions also appears to be broadly consistent with the effects observed in Alzheimer's disease (AD). Most RCTs ranged from 12 to 24 weeks, which the committee recognised was a |

short duration for a long-term degenerative disease. The committee was also aware that no pharmacological interventions are licensed for managing DLB.

***Cholinesterase inhibitors***

In the previous guideline, the committee was aware that only 1 RCT was identified (McKeith et al., 2000) which showed no significant improvement in cognitive function with rivastigmine, compared with placebo. The new evidence identified for this guideline update shows a significant improvement in cognitive function and other important outcomes with cholinesterase inhibitors, compared with placebo. The committee recognised that caution was needed interpreting the outcomes of RCTs in isolation and patient and clinician factors also needed to be considered.

Overall, evidence was identified for donepezil and rivastigmine; no significant differences were observed between the 2 treatments for any of the outcome measures. The committee discussed whether these results were generalisable for all cholinesterase inhibitors. They were concerned that no efficacy or safety data were available for galantamine in people with DLB, but were aware of data to support its use in AD.

The committee did not expect significant differences to be observed on pharmacological grounds with galantamine compared with either donepezil or rivastigmine. However, they did have concerns about making a recommendation that included galantamine in the absence of evidence, and therefore a first line recommendation was made for donepezil and rivastigmine, with galantamine only given as an option if these agents are not tolerated.

The committee discussed their experience of differences between the cholinesterase inhibitors in their clinical practice. The committee's experience suggests that donepezil is generally better tolerated than rivastigmine. Rivastigmine is generally better in treating neuropsychiatric symptoms. This is also supported by trends observed in the evidence review, although possible differences observed did not reach conventional levels of statistical significance. In the committee's view, galantamine is not widely used in practice, compared with donepezil and rivastigmine. Furthermore, clinicians may take acquisition cost into account when making decisions with people about the choice of treatment. Galantamine is significantly more costly that donepezil or rivastigmine.

The committee discussed the importance of appropriate dose titration when taking cholinesterase inhibitors. Donepezil has a simpler dose titration regime, which may be an important consideration for individual patients. The committee had concerns that many people did not have the initial dose of cholinesterase inhibitor titrated up to the maximum tolerated dose. As cholinesterase inhibitors are being used 'off label' in people with DLB, there is no recommended dose. However, the committee agreed that they would expect it to be consistent with the doses licensed for Alzheimer's disease. To reflect the evidence base, the committee agreed that the dose of cholinesterase inhibitor should be titrated up to the maximum tolerated dose.

The committee recognised that the evidence identified was in people with mild to moderate DLB. In their clinical experience, the committee was aware of cholinesterase inhibitors being started in people with mild or moderate DLB and subsequently stopped in some patients because they had reached the severe stage of the disease. They agreed that treatment should not be stopped on this basis alone. The committee were concerned about the detrimental effects observed in many people in clinical practice when cholinesterase inhibitors were stopped. Although, they were also mindful that some people stay on cholinesterase inhibitors indefinitely without appropriate review.

Some people present with DLB in the advanced stages of the disease. The committee recognised this required careful discussion and consideration on a case-by-case basis, weighing up the possible risks and benefits of treatment. The committee emphasised the importance of medicines being considered appropriately at the right time and right stage of disease.

The RCT (Emre et al., 2014) which compared rivastigmine patches with rivastigmine capsules found that the long-term (76-week) effect on cognitive

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|---|---|
| | function was significantly better with capsules. However, the committee felt that patient factors such as medicines adherence need to be considered on an individual patient basis. There were no other clinically meaningful differences between patches and capsules, including the risk of adverse effects. Therefore, the committee concluded that patches may be an option to consider for some people, but could not make a recommendation specifically on their use.<br>The committee was confident that there is clear evidence of benefit with donepezil and rivastigmine in improving cognition, global function, activities of daily living, carer burden and neuropsychiatric symptoms at a cost that is dominant over placebo. The committee concluded that an 'offer' recommendation should be made to reflect the evidence-base. The recommendation to offer treatment applies to people with mild to moderate DLB as there was no evidence of starting treatment in people with severe DLB. The committee also agreed that the recommendation should inform clinicians that donepezil and rivastigmine are not licensed for DLB.<br>While the committee could not be certain about the effect of galantamine in people with mild to moderate DLB, they agreed that galantamine may be considered for people with mild to moderate DLB if donepezil or rivastigmine are not tolerated. The committee also agreed that the recommendation should inform clinicians that galantamine is not licensed for DLB.<br>Furthermore, although no RCT evidence was identified, the committee discussed and agreed by consensus that a consider recommendation should be made for donepezil and rivastigmine in people with severe DLB. They noted that although no evidence was found, there was no biological or pharmacological reason to expect that the effect would be less in people with severe dementia, and it was therefore appropriate to extrapolate the evidence to that population.<br>***Memantine***<br>The committee recognised that there were far less data for memantine versus placebo, compared with cholinesterase inhibitor versus placebo. The committee was concerned that memantine was only significantly better than placebo on the global assessment scales. However, the committee recognised the limitations of the available data. The committee did agree, however, that it was appropriate to make a 'consider' level recommendation for memantine, but only if cholinesterase inhibitors are not tolerated or are contraindicated.<br>**Combination treatment**<br>Although no studies were identified where participants were randomised to combination treatment with a cholinesterase inhibitor and memantine, the committee recognised that this option was being used in practice. From their clinical experience, some people do respond to combination treatment. As there was no evidence, the committee felt this was an important priority for research and therefore made a research recommendation. |
| **Trade-off between net health benefits and resource use** | The committee agreed that the economic evidence presented had very serious limitations, and lacked direct applicability to the question, particularly because they took place at a time before the generic versions of the drugs were available. However, they also noted that, once appropriate adjustments had been made to the price of the drugs, the fact that cholinesterase inhibitors came out as consistently either cost-effective or cost-saving compared with placebo added additional evidence to support the recommendations made. |
| **Quality of evidence** | Based on the clear and consistent findings for donepezil and rivastigmine, the committee were confident in making an 'offer' recommendation for people with mild to moderate DLB. The evidence-base for memantine was of lower quality and despite a trend towards improvement the committee could not be confident of the effectiveness of memantine. |
| **Other considerations** | The committee noted that the recommendations made here were broadly consistent with those in the NICE Parkinson's disease guideline on managing Parkinson's disease dementia. This was agreed to be important as the evidence did not suggest there was any reason to expect the treatments to |

have different levels of effectiveness in the two groups, and agreed it was appropriate to add a cross-reference to those recommendations in the guideline.

### 11.3.6 Recommendations

**70. Offer donepezil or rivastigmine to people with mild to moderate dementia with Lewy bodies.[a]**

**71. Only consider galantamine[b] for people with mild to moderate dementia with Lewy bodies if donepezil and rivastigmine are not tolerated.**

**72. Consider donepezil or rivastigmine for people with severe dementia with Lewy bodies.[a]**

**73. Consider memantine[c] for people with dementia with Lewy bodies if AChE inhibitors[d] are not tolerated or are contraindicated.**

**74. For guidance on pharmacological management of Parkinson's disease dementia, see Parkinson's disease dementia in the NICE guideline on Parkinson's disease.**

### 11.3.7 Research recommendations

**8. What is the effectiveness of combination treatment with a cholinesterase inhibitor and memantine for people with dementia with Lewy bodies if treatment with a cholinesterase inhibitor alone is not effective or no longer effective?**

For more details on the research recommendation made, and the rationale behind it, see appendix L.

[a] At the time of publication (June 2018), donepezil and rivastigmine did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information

[b] At the time of publication (June 2018), galantamine did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information

[c] At the time of publication (June 2018), memantine did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[d] At the time of publication (June2018), the AChE inhibitors donepezil, rivastigmine and galantamine did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information

# 11.4 Cholinesterase inhibitors and memantine for types of dementia other than typical Alzheimer's disease

**Review question**

- How effective are cholinesterase inhibitors and memantine for types of dementia other than typical Alzheimer's disease?

## 11.4.1 Introduction

The aim of this review question was to determine the comparative effectiveness of donepezil, galantamine, rivastigmine and memantine for cognitive enhancement in dementia types other than typical Alzheimer's disease. The use of cholinesterase inhibitors and memantine for Parkinson's disease dementia is covered in the Parkinson's disease guideline and dementia with Lewy bodies has previously been considered in section 11.3. Therefore these 2 types of dementia were excluded from the evidence review for this question.

The review identified studies that fulfilled the conditions specified in Table 55. For full details of the review protocols, see Appendix C.

**Table 55: Review summary: cholinesterase inhibitors and memantine for non-Alzheimer's dementia**

| | |
|---|---|
| **Population** | People with a diagnosis of dementia other than typical Alzheimer's disease or Lewy-body dementia |
| **Interventions** | • Donepezil<br>• Galantamine<br>• Memantine<br>• Rivastigmine<br>• Memantine plus cholinesterase inhibitor |
| **Comparator** | • Each other<br>• Combination of memantine plus cholinesterase inhibitor<br>• Placebo |
| **Outcomes** | Cognitive outcomes, including:<br>• Mini Mental State Examination (MMSE)<br>• Alzheimer's Disease Assessment Scale –cognitive subscale (ADAS-cog)<br>• Montreal Cognitive Assessment (MoCA)<br>Global outcomes, including:<br>• Global impression of change<br>Activities of daily living<br>Non-cognitive outcomes, e.g.<br>• NPI<br>• Adverse events<br>• Study withdrawal<br>• Health-related quality of life<br>• Carer-reported outcomes<br>• Resource use and cost<br>• Entry to long stay care |

### 11.4.2 Evidence review

A systematic search identified 1,772 references. The references were screened on their titles and abstracts and 99 references were ordered for full text review. Eighty-three papers were subsequently excluded because they did not fit the inclusion criteria (see Appendix F for a detailed list of excluded studies and reasons for their exclusion). Sixteen randomised controlled trials were included in the evidence review.

#### 11.4.2.1 Description of included studies

All included papers considered treatment versus placebo. Nine studies were included for vascular dementia (3 studies compared donepezil versus placebo, 2 studies compared galantamine versus placebo, 2 studies compared rivastigmine versus placebo and 2 studies compared memantine versus placebo).

Three studies were included for frontotemporal dementia (1 paper compared galantamine versus placebo and 2 papers compared memantine versus placebo). The data was stratified into participants with behavioural variant frontotemporal dementia and those with semantic variant frontotemporal dementia.

Three studies were included for cognitive impairment in people with multiple sclerosis (1 study compared donepezil versus placebo, 1 paper considered rivastigmine versus placebo and 1 paper considered memantine versus placebo).

One study was included for Huntington's disease and compared rivastigmine versus placebo.

A summary of the characteristics of the included studies is provided in Table 56. Data from the included studies were extracted into evidence tables. Please see Appendix E for the full evidence tables, and for the full GRADE profiles please see Appendix G. References for the included studies are given in appendix I.

### 11.4.3 Health economic evidence

A total of 381 citations was returned from the search for this question. Following review of titles and abstracts, the full texts of 10 studies were retrieved for detailed consideration, but none met the inclusion criteria. One study, Wong et al. (2009) was considered to be potentially relevant, presenting dominant results from a cost-effectiveness analysis, permissible in some circumstances by *Developing NICE guidelines* (2014). However, its short time horizon (24-28 weeks) and limited costing perspective (only intervention costs and physician costs), in addition to the absence of QALYs, led to the conclusion that the study would not be appropriate to support decision-making. Therefore, no cost–utility analyses were identified for this question.

### 11.4.3.11 Description of included studies

2 **Table 56: Included studies**

| Study reference | Study type | Study population | Intervention and comparator | Relevant outcomes | Authors' conclusions | Comments |
|---|---|---|---|---|---|---|
| **Vascular Dementia** | | | | | | |
| **Galantamine versus placebo** | | | | | | |
| Auchus (2007) GAL-INT-26 | RCT | 786 participants with probable vascular dementia according to NINDSA-AIREN | Intervention: Galantamine 4mg twice daily increasing to 8mg or 12mg twice daily after 4 weeks Control: Placebo | Cognition (ADAS-cog-11, EXIT-25) Functional ability (ADCS-ADL) NPI Adverse events, serious adverse events, mortality and discontinuation due to adverse events | Greater improvement in ADAS-cog/11 at 26 weeks for galantamine treated group No difference in ADCS/ADL at 26 weeks Mean change in baseline of EXIT-25 was significantly greater for galantamine group | Location: USA Follow up 26 weeks |
| Small (2003) | RCT | 1,954 participants with vascular dementia according to NINDSA-AIREN | Intervention: Galantamine 24mg per day Control: Placebo | Cognition (ADAS-cog-11) | Significant improvement in ADAS-cog/11 at 6 months for galantamine group | Location: Multicentre international Follow up 6 months plus additional 6 months open label extension Post hoc sub analysis[1] of Erkinjuntti (2002, 2003) |
| **Rivastigmine versus placebo** | | | | | | |
| Ballard (2008) vantagE study | RCT | 5,723 participants with vascular dementia | Intervention: Rivastigmine 1.5mg twice daily | Cognition (ADAS-cog, MMSE) | Greater improvement in cognitive performance (VaDAS; ADAS-cog; MMSE) | Location: Multicentre international |

| Study reference | Study type | Study population | Intervention and comparator | Relevant outcomes | Authors' conclusions | Comments |
|---|---|---|---|---|---|---|
| | | according to NINDSA-AIREN | dose escalation by 1.5mg every 4 weeks over 16 week period<br>Control:<br>Placebo | Global assessment (VaDAS, ADCS-CGIC, GDS)<br>Functional ability (ADCS-ADL)<br>NPI-12<br>Serious adverse events, mortality and discontinuation due to adverse events | at 24 weeks for rivastigmine group<br>All other outcomes non-significant | Follow up 24 weeks |
| Mok (2007) | RCT | 40 participants with Vascular dementia according to a modification of NINDSA-AIREN | Intervention:<br>Rivastigmine 1.5mg twice daily dose escalating to 3mg twice daily after 4 weeks<br>Control:<br>Placebo | Cognition (MMSE)<br>Global assessment (CDR-SB)<br>Functional ability (IADL, FAB)<br>NPI<br>Adverse events, mortality and discontinuation due to adverse events | No statistical mean difference in in any efficacy measures | Location: China<br>Follow up 26 weeks<br>All outcome measured assessed by Chinese versions of tools |
| **Donepezil versus placebo** | | | | | | |
| Black (2003)<br>Donepezil 307 | RCT | 4,783 participants with Vascular dementia according to NINDSA-AIREN | Intervention:<br>Donepezil 5mg per day or donepezil 10mg per day<br>Control:<br>Placebo | Cognition (ADAS-cog, MMSE)<br>Global assessment (CDR-SB)<br>Functional ability (ADFACS)<br>Adverse events, serious adverse events, mortality and discontinuation due to adverse events | Greater improvement in cognitive performance (ADAS-cog) at 24 weeks for donepezil 5mg and 10mg group<br>Greater improvement in global functional 24 weeks (CIBICplus) for donepezil 5mg (CDR-SB) donepezil 10mg group<br>Significant improvement in ADL (ADFACS) at 24 weeks | Location-international<br>Follow up 24 weeks |

| Study reference | Study type | Study population | Intervention and comparator | Relevant outcomes | Authors' conclusions | Comments |
|---|---|---|---|---|---|---|
| | | | | | for donepezil 5mg and 10mg groups) | |
| Roman 2010 | RCT | 8,183 participants with Vascular dementia according to NINDSA-AIREN | Intervention:<br>Donepezil 5mg per day<br>Control:<br>Placebo | Cognition (ADAS-cog, VaDAS-cog, MMSE, EXIT-25)<br>Functional ability (DAD)<br>Global assessment (CDR-SB)<br>Adverse events, serious adverse events and mortality | Significant improvement in cognition (VaDAS-cog) for donepezil group<br>No significant change in CIBICplus | Location: Multi centre international |
| Wilkinson (2003)<br>Donepezil 308 | RCT | 616 participants with Vascular dementia according to NINDSA-AIREN | Intervention:<br>Donepezil 5mg per day or donepezil 10mg per day<br>Control:<br>Placebo | Cognition (ADAS-cog)<br>Global assessment (CDR-SB)<br>Functional ability (ADFACS, IADL)<br>Adverse events, serious adverse events and mortality | Significant improvements in cognition (ADAS-cog)<br>Significant benefits of global function (CIBICplus and CDRSB)<br>Significant functional benefits (ADFACS) | Location: Multi centre international<br>Follow up 24 weeks |
| **Memantine versus placebo** | | | | | | |
| Orgogozo (2002)<br>MMM300 | RCT | 2,883 participants with Vascular dementia according to NINDSA-AIREN | Intervention:<br>Memantine 20mg per day or<br>Control:<br>Placebo | Cognition (ADAS-cog, MMSE)<br>Global assessment (CIBICplus)<br>Serious adverse events | Significant improvement in cognitive performance (ADAS-cog and MMSE) for memantine group with significant decline in placebo group<br>No significant difference in mean change of global assessment (CIBICplus) | Location: Multicentre (France, Switzerland, Belgium)<br>Follow up 28 weeks |
| Wilcock (2002)<br>MMM500 | RCT<br>MMM500 | 548 participants with Vascular Dementia | Intervention:<br>Memantine 20mg per day | Cognition (ADAS-cog)<br>Adverse events | Significant improvement in cognitive performance (ADAS-cog) | Location: Multicentre UK |

| Study reference | Study type | Study population | Intervention and comparator | Relevant outcomes | Authors' conclusions | Comments |
|---|---|---|---|---|---|---|
| | | according to NINDS-AIREN | Control:<br>Placebo | | No significant difference in mean change of global assessment (CGI-C) | Follow up 28 weeks |
| **Frontotemporal dementia** | | | | | | |
| **Memantine versus placebo** | | | | | | |
| Boxer (2013) | RCT | 64 participants with Frontotemporal dementia | Intervention:<br>Memantine 10mg twice per day<br>Control:<br>Placebo | Cognition (MMSE, EXIT-25)<br>Global assessment (CIGIC, CDR-SB)<br>NPI<br>UPDRS<br>Serious adverse events | No significant difference in outcomes at 26 weeks | Location: USA<br>Follow up 26 weeks |
| Vercelletto (2011) | RCT | 42 participants with Frontotemporal dementia and mean MMSE at baseline of ≥19 | Intervention:<br>Memantine 10mg twice per day<br>Control:<br>Placebo | Cognition (MMSE, MDRS)<br>Global assessment (CIBIC-plus)<br>Carer burden (ZBI)<br>NPI<br>Adverse events, serious adverse events, mortality and discontinuation due to adverse events | No significant difference in outcomes at 52 weeks | Location: Multicentre France<br>Follow up 52 weeks |
| **Galantamine versus placebo** | | | | | | |
| Kertesz (2008): | RCT | 36 participants with Frontotemporal dementia and Primary Progressive Aphasia | Intervention:<br>Galantamine 16-24mg per day<br>Control:<br>Placebo | Cognition (MMSE, DRS)<br>Functional ability (FAB, ADCS-ADL)<br>NPI | No significant difference in outcomes at 26 weeks | Location: USA<br>Follow up 26 weeks<br>Participants completed an initial 18 week open label period ` |

| Study reference | Study type | Study population | Intervention and comparator | Relevant outcomes | Authors' conclusions | Comments |
|---|---|---|---|---|---|---|
| | | | | Adverse events and discontinuation due to adverse events | | |
| **Multiple Sclerosis** | | | | | | |
| **Donepezil versus placebo** | | | | | | |
| Krupp (2011) | RCT | 120 participants with MS and memory impairment | Intervention:<br>10mg per day<br>Control:<br>Placebo | Cognition (total recall on SRT; PASAT2&3)<br>SDMT | No significant difference in neuropsychological outcomes at 24 weeks | Location USA<br>Follow up 24 weeks |
| Rivastigmine versus placebo | | | | | | |
| Maurer (2012) | RCT | 86 participants with MS and cognitive impairment (defined by FST ≥ 3 and/or MUSIC score≤ 19 | Intervention:<br>Rivastigmine patches 4.6mg (5cm$^2$) per day escalating to 9.4mg (10cm$^2$) per day after 4 weeks<br>Control:<br>Placebo | Domain-specific cognition (SRT, PASAT)<br>Global outcomes (CGIC)<br>MS relapse<br>Adverse events, serious adverse events and discontinuation due to adverse events | No significant difference in SRT total recall score at 16 weeks | Location: Germany<br>Follow up 16 weeks |
| Memantine versus placebo | | | | | | |
| Saint-Paul (2016)<br>EMERITE | RCT | 62 participants with MS and cognitive impairment (defined by DRS ≥130 | Intervention:<br>Memantine 10mg per day escalating to 20 mg per day over 3 weeks<br>Control:<br>Placebo | Domain-specific cognition (PASAT)<br>MS progression (EDSS)<br>Adverse events and discontinuation due to adverse events | No significant difference in PASAT scores at 52 weeks<br>No significant difference in EDSS scores | Location: France<br>Multicentre<br>Follow up 16 weeks |
| **Huntington's Disease** | | | | | | |
| Rivastigmine versus placebo | | | | | | |

| Study reference | Study type | Study population | Intervention and comparator | Relevant outcomes | Authors' conclusions | Comments |
|---|---|---|---|---|---|---|
| Sesok (2014) | RCT | 18 participants with Huntington's disease | Intervention:<br>Rivastigmine 1.5mg twice per day increasing to 3mg twice a day after 3 months<br>Control:<br>Placebo | Domain-specific cognition (SDMT, RFCT, RFFT, TOL) | No significant difference in outcomes | Location: Slovenia<br>Follow up 6 months |

Abbreviations: NINDSA-AIREN= National Institute of Neurological Disorders and Stroke-AIREN criteria; ADAS-cog= Alzheimer's disease Assessment cognitive subscale; CIBICplus=Clinician's Interview based Impression of Change plus caregivers assessment; ADCS-ADL= Alzheimer's diseases Cooperative study – Activities of Daily Living; ADCS-CGIC= Alzheimer's disease Cooperative study- Clinician's Global Impression of Change; VaDAS= Vascular Dementia Assessment Scale; MMSE= Mini mental state evaluation; GDS= Global Deterioration scale; NPI= Neuropsychiatric inventory; WMS= Wechsler Memory Scale; DRS = Dementia Rating Scale. PASAT =Paced Auditory Serial Addition Test; EDSSS = Expanded Disability Status Scale; FST= Faces Symbol Test; MUSIC= Multiple Sclerosis Inventarium Cognition Score; SRT= Spatial Recall Test; MDRS = Mattis Dementia Rating Scale; FBI = Frontal Behavioural Inventory; ZBI = Zarit Burden Interview; DAD; Disability assessment Daily; FAQ=Functional Activities Questionnaire; SDMT= Symbol digit modalities test; CVLT= California verbal learning test; RFFT= Ruff figure & fluency test; TOL= Tower of London test of learning and memory; TFLS= Texas Functional Living Scale; [1]Post hoc analysis of population sub group with VaD - original trial based on VaD/mixed treatment

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## 11.4.4 Evidence statements

### 11.4.4.1 Vascular dementia

#### *11.4.4.1.1 Cholinesterase inhibitors versus placebo*

Moderate- to high-quality evidence found global cognition (measured by the MMSE, ADAS-Cog, ADAS-Cog-11, VaDAS-cognitive subscale) was significantly better in people receiving cholinesterase inhibitors compared with placebo, but low-quality evidence found it could not be differentiated when measured by the EXIT-25.

High-quality evidence found neuropsychiatric symptoms (measured by the NPI) were significantly worse in people receiving cholinesterase inhibitors compared with placebo, but moderate-quality evidence found they could not be differentiated when measured by the NPI-12.

Moderate- to high-quality evidence found global assessment (measured by the Clinician's Global Impression of Change, Clinical Dementia Rating-sum of boxes) was significantly better in people receiving cholinesterase inhibitors compared with placebo, but could not be differentiated when measured by the Vascular Dementia Assessment Scale or Global Deterioration Scale.

High-quality evidence found functional ability (measured by the Alzheimer's Disease Functional Assessment and Change Scale) was significantly better in people receiving cholinesterase inhibitors compared with placebo, but very low- to moderate-quality evidence found it could not be differentiated when measured by the ADCS-ADL, Instrumental Activities of Daily Living, Functional Assessment Battery or the Disability assessment for Dementia.

High-quality evidence found the numbers of adverse events and discontinuations due to adverse events were significantly higher in people receiving cholinesterase inhibitors compared with placebo, but low- to moderate-quality evidence could not differentiate the numbers of deaths or serious adverse events.

#### *11.4.4.1.2 Memantine versus placebo*

High-quality evidence found global cognition (measured by the MMSE, ADAS-Cog) was significantly better in people receiving memantine compared with placebo.

Moderate-quality evidence could not differentiate behavioural symptoms (measured by the Nurses' Observational Scale for Geriatric Patients) between people receiving memantine compared with placebo.

Moderate-quality evidence could not differentiate global assessment (measured by the Gottfries-Bråne-Steen scale or CIGIC) between people receiving memantine compared with placebo.

Low- to high-quality evidence could not differentiate the numbers of adverse events or serious adverse events between people receiving memantine compared with placebo.

#### *11.4.4.1.3 Network meta-analyses*

Moderate- to high-quality evidence found cognition (measured by the MMSE, ADAS-Cog) was significantly better in people receiving either cholinesterase inhibitors or memantine

compared with placebo, but could not differentiate scores between cholinesterase inhibitors and memantine.

Moderate-quality evidence found the numbers of adverse events was higher in people receiving cholinesterase inhibitors than placebo, but could not differentiate numbers between memantine and placebo or cholinesterase inhibitors and memantine.

Moderate-quality evidence could not differentiate the numbers of serious adverse events between cholinesterase inhibitors, memantine and placebo.

#### 11.4.4.2 Behavioural variant frontotemporal dementia

##### *11.4.4.2.1 Cholinesterase inhibitors versus placebo*

Low-quality evidence could not differentiate global cognition (measured by the MMSE or DRS), functional ability (measured by the Functional Assessment Battery or ACDS-ADL) or neuropsychiatric symptoms (measured by the NPI) between people receiving cholinesterase inhibitors compared with placebo.

Low-quality evidence could not differentiate the numbers of adverse events or discontinuations due to adverse events between people receiving cholinesterase inhibitors compared with placebo.

#### 11.4.4.3 Memantine versus placebo

Low- to moderate-quality evidence could not differentiate global cognition (measured by the MMSE, Mattis Dementia Rating Scale, EXIT-25), neuropsychiatric symptoms (measured by the NPI), global assessment (measured by CIBIC, CGIC, CDR-SB), motor function (measured by the Unified Parkinson's disease rating scale) or carer burden (measured by the ZBI) between people receiving memantine compared with placebo.

Very low to low-quality evidence could not differentiate the numbers of adverse events, serious adverse events, deaths or discontinuations due to adverse events between people receiving memantine compared with placebo.

#### 11.4.4.4 Network meta-analyses

Moderate-quality evidence could not differentiate global cognition (measured by the MMSE), neuropsychiatric symptoms (measured by the NPI) or the numbers of adverse events or discontinuations due to adverse events between cholinesterase inhibitors, memantine and placebo.

#### 11.4.4.5 Semantic variant frontotemporal dementia

##### *11.4.4.5.1 Memantine versus placebo*

Low-quality evidence could not differentiate global cognition (measured by the MMSE, EXIT-25), neuropsychiatric symptoms (measured by the NPI), global assessment (measured by the CIBIC, CGIC, CDR-SB) or motor function (measured by the Unified Parkinson's disease rating scale) between people receiving memantine compared with placebo.

Low-quality evidence could not differentiate the number of serious adverse events between people receiving memantine compared with placebo.

#### 11.4.4.6 Cognitive impairment in people with multiple sclerosis

##### *11.4.4.6.1 Cholinesterase inhibitors versus placebo*

Moderate-quality evidence could not differentiate global cognition (measured by the Selective Reminding Test, Multiple Sclerosis Inventarium Cognition Score), domain-specific cognition (measured by the Symbol Digit Modalities Test, Paced Auditory Serial Addition Test, Faces Symbol Test) or depressive symptoms (measured by the Montgomery-Åsberg Depression Rating Scale) between people receiving cholinesterase inhibitors compared with placebo.

Low to moderate-quality evidence could not differentiate the numbers of adverse events, serious adverse events, discontinuations due to adverse events or multiple sclerosis relapses between people receiving cholinesterase inhibitors compared with placebo.

##### *11.4.4.6.2 Memantine versus placebo*

Moderate-quality evidence could not differentiate domain-specific cognition (measured by the Paced Auditory Serial Addition Test) or multiple sclerosis progression (measured by the Expanded Disability Status Scale) between people receiving memantine compared with placebo.

High-quality evidence found the number of adverse events was significantly higher in people receiving memantine compared with placebo, but low-quality evidence could not differentiate the number of serious adverse events.

##### *11.4.4.6.3 Network meta-analyses*

High-quality evidence found significantly higher numbers of adverse events in people receiving memantine compared with either cholinesterase inhibitors or placebo, but moderate-quality evidence could not differentiate cognition (measured by the Paced Auditory Serial Addition Test) or the numbers of discontinuations due to adverse events.

#### 11.4.4.7 Huntington's disease

##### *11.4.4.7.1 Cholinesterase inhibitors versus placebo*

Moderate-quality evidence found domain-specific cognition (measured by the Tower of London total times score) was worse in people receiving cholinesterase inhibitors compared with placebo, but low-quality evidence found it could not be differentiated when measured by the Symbol Digit Modalities Test, Tower of London total moves score, Rey Complex Figure Test - delayed recall, Rey Complex Figure Test - immediate recall or Ruff Figural Fluency Test - unique designs.

#### 11.4.4.8 Health economic evidence

No health economic evidence was identified for this review question.

### 11.4.5 Evidence to recommendations

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|---|---|
| **Relative value of different outcomes** | The committee agreed that the following measures (where available) would be prioritised across the various outcome domains:<br>• Global cognition (MMSE, ASAS-cog)<br>• Global assessment (Clinical Dementia Rating scale)<br>• Functional ability (Disability Assessment for Dementia)<br>• Neuropsychiatric symptoms (NPI) |

| | |
|---|---|
| | • Dementia-specific quality of life (DEMQOL)<br>• Generic health-related quality of life (EQ-5D)<br>No outcome was prioritised for domain-specific cognition, as it was agreed that the different outcome measures were often measuring different aspects of cognition, and therefore it would not be appropriate to prioritise 1 measure. |
| **Trade-off between benefits and harms** | **Vascular dementia**<br>The committee recognised there was some evidence of cognitive benefits with treatment, although these were small and often below levels considered clinically significant, such as 1.4 points on the MMSE. Additionally, information on how these differences affect functional ability or quality of life was limited, and the group noted that NPI scores were worse with cholinesterase inhibitors. It was noted that many of the studies (those using a definition of possible or probable vascular dementia) may have included people with underlying Alzheimer's disease, and the committee agreed any effect is likely to be greater in this population than in people with pure vascular dementia, a finding supported by 1 study reporting data on Alzheimer's disease with cerebrovascular legions (which showed an improvement of 3.2 points in the ADAS-cog with treatment, compared with a 1.6 point improvement in people with pure vascular dementia). The committee agreed therefore that it was only clinically justified to consider these drugs in groups of people with vascular dementia where there is clinical suspicion of there also being the presence of another form of dementia where these drugs have been shown to be effective and are recommended by NICE (Alzheimer's disease, Parkinson's disease dementia, dementia with Lewy Bodies). This recommendation was agreed to be important as people may initially be diagnosed with one form of dementia (such as vascular dementia), and then not receive a formal diagnosis of another dementia subtype at a later date. The committee discussed the evidence base and agreed that it was not sufficiently robust to enable making any recommendations about the comparative effectiveness of cholinesterase inhibitors and memantine.<br>**Frontotemporal dementia**<br>The committee noted the evidence base for this population was far smaller than in the population with vascular dementia, and there was no biological hypothesis as to why these treatments would be expected to provide a benefit (there is not usually a cholinergic deficit in people with frontotemporal dementia). No evidence was found of benefit for the use of cholinesterase inhibitors or memantine in behavioural variant or semantic variant frontotemporal dementia, and therefore the committee agreed that, owing to the potential adverse effects associated with these drugs, their use could not be justified in this group. Hence a 'do not use' recommendation was made; however, the committee recognised that it was unlikely that cholinesterase inhibitors or memantine were commonly used in this group, and that the drugs are not licensed for frontotemporal dementia. The committee agreed it was appropriate to extend the recommendation to the third subtype of frontotemporal dementia (progressive non-fluent aphasia) as there is also no underlying cholinergic deficit in this group, and therefore there is no reason to expect that the drugs would be more effective in this group than the other subtypes of frontotemporal dementia.<br>**Multiple sclerosis**<br>The committee discussed whether cognitive impairment associated with multiple sclerosis should be included in this section of the guideline. The committee recognised that the definition of cognitive impairment may not be as clearly defined as in other conditions. They noted there were additional challenges in interpreting the evidence due to the physical impairments associated with the condition when symptoms of cognitive impairment appear. The committee noted that the population in the |

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| | included studies was younger than other subtypes but agreed it was important to include people with multiple sclerosis because the evidence associated with adverse events meant it was important to prevent clinicians from prescribing treatment with cholinesterase inhibitors or memantine to people in this group. They therefore agreed to make a 'do not use' recommendation.<br>**Huntington's disease**<br>The committee noted that the evidence was drawn from a small pilot study and therefore agreed that it would not be appropriate to make any recommendations for this population. |
| **Trade-off between net health benefits and resource use** | No economic evidence was identified for this review question and health economic modelling was not prioritised. The committee noted that all of the named drugs are now generic and off patent and therefore it is unlikely that any significant resource implications would arise from the recommendations made for their use. They also noted that cholinesterase inhibitors and memantine have been found to be cost effective in Alzheimer's disease, Parkinson's Disease dementia and dementia with Lewy Bodies, where they have shown clinical benefit. Therefore, it is reasonable to infer that, in any cases where using cholinesterase inhibitors is clinically effective, the cost of the drugs will be justified. |
| **Quality of evidence** | The committee considered making a research recommendation around vascular dementia (now we are better able to diagnose the subtype of people with pure vascular dementia). However, large RCTs have already been conducted in this group (even if these did not always measure the outcomes we would want nowadays – functional ability and quality of life) so it was felt unlikely that such studies would be conducted.<br>The committee agreed the quality of evidence for vascular dementia was based upon a number of large clinical trials but recognised the evidence was poor for other subtypes, mainly due to the size of the studies. |
| **Other considerations** | The committee agreed that there is generally a need for more research in vascular dementia, but felt the focus is now more on disease modifying agents rather than symptom focused and therefore agreed this was not the forum to pursue such research, as there is not yet sufficient evidence to know which medicines are worth testing for disease modifying purposes. |

### 11.4.6 Recommendations

**75. Only consider AChE inhibitors[e] or memantine[f] to people with vascular dementia if they have suspected comorbid Alzheimer's disease, Parkinson's disease dementia or dementia with Lewy bodies.**

**76. Do not offer AChE inhibitors or memantine for people with frontotemporal dementia.[g]**

[e] At the time of publication (June 2018), the AChE inhibitors donepezil, rivastigmine and galantamine did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[f] At the time of publication (June 2018), memantine did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[g] Note that logopenic aphasia, which has previously been included in some diagnostic guidelines for frontotemporal dementia, has now been shown to most commonly be caused by Alzheimer's disease.

**77. Do not offer AChE inhibitors or memantine to people with cognitive impairment caused by multiple sclerosis.**

# 12 Drugs that may worsen cognitive decline

Dementia is defined by the WHO as a condition where there is a deterioration in cognitive function that adversely affects many aspects of life including memory, understanding, learning capacity, language, behaviour and judgement. Certain classes of drugs, including anticholinergics, have been shown to be associated with an increased risk of dementia in clinical trials and they appear to have more extreme effects in older adults.

Anticholinergics are used to treat a range of conditions including psychosis, depression, urinary incontinence, allergies and COPD. Anticholinergics work by blocking the action of acetylcholine in the nervous system, preventing signal transmission between nerve cells in the brain or nerve cells and muscles in the body. Other side effects include dry mouth, drowsiness, blurred vision, urinary retention and constipation. The mechanism by which anticholinergics could act to increase the risk of dementia remains unclear.

Dementia is usually progressive and chronic with few potentially modifiable risk factors, however, it is possible to alter the level of anticholinergics prescribed to people with dementia and this may improve their cognitive functioning to some extent. The cumulative effect of taking several medicines containing anticholinergics, known as the anticholinergic burden, also increases the risk of cognitive decline and thus it is essential to carefully monitor the use of anticholinergics in older people and those with dementia.

This chapter focuses on identifying which anticholinergics are commonly used for people with dementia with the aim of reducing the level of prescription of these drugs where possible. In addition, it seeks to address whether there are tools which would allow the identification of specific drugs that may be causing cognitive decline.

# 12.1 Drugs that may cause cognitive decline

**Review questions**

- What drugs that may worsen cognitive decline are commonly prescribed in people diagnosed with dementia?
- What are the most effective tools to identify drugs that may be causing cognitive decline?

## 12.1.1 Introduction

The aim of the first specified review question was to identify drugs that may cause cognitive decline that are commonly prescribed in people living with dementia. It was agreed that the main class of drugs that is a cause of concern (anticholinergics) was clear, and the harms of these drugs were well established. Therefore, the key question to answer was not what the harms of these drugs are, but rather which of these drugs are commonly in use, as this may help to focus efforts to reduce levels of inappropriate prescribing.

The aim of the second review question was to identify whether there are appropriate tools available to identify medicines that may be the cause of cognitive decline in a person suspected of having dementia, and therefore prevent false positive diagnoses. The review identified studies that fulfilled the conditions specified in Table 57. The full review protocol is available in Appendix C.

**Table 57: Review summary: drugs that may cause cognitive decline**

| | |
|---|---|
| **Population** | People (aged 40 years and over) with a suspected diagnosis of dementia |
| **Diagnostic variables** | • Standardised tools assessments, instruments and protocols used to identify drugs that cause cognitive decline<br>• Anticholinergic burden scale<br>• Clinical history |
| **Outcomes** | • Incidence of accurately identified dementia<br>• Diagnostic accuracy measures<br>• Change in prevalence of appropriate polypharmacy<br>• Potentially avoidable hospital admissions<br>• Resource use and costs |

## 12.1.2 Evidence review

No literature review was undertaken to identify commonly prescribed drugs that may cause cognitive decline in people with dementia, as it was decided that such a review would only be able to provide data on the well-established harms of certain medicines, rather than identify which of these medicines are currently commonly used in the UK. Therefore, this question was instead supported by evidence provided from an expert witness, the UK Prescribing Observatory for Mental Health. Data were provided on current prescribing patterns in mental health trusts, with the evidence presented to the committee summarised in Appendix N.

A systematic literature search was carried out to identify diagnostic accuracy studies, or systematic reviews of diagnostic accuracy studies for the question considering the tools used to identify drugs that may cause cognitive decline. A total of 6,337 references were screened at the title and abstract level, with 37 potentially relevant references being ordered for full text review. No evidence was identified in a population of people living with dementia, but 1 systematic review of anticholinergic scales in older people (Salahudeen 2015) was included. The excluded studies, with reasons for their exclusion, are listed in Appendix F. Evidence

tables for Salahudeen (2015) and the 7 studies included in that review are presented in Appendix E.

#### 12.1.2.1 Description of included studies

The characteristics of the studies included in Salahudeen (2015) are summarised in Table 58. References for the included studies are given in appendix I.

**Table 58 Summary of studies included in Salahudeen (2015)**

| Study details | Study population | Assessment scales | Methods used to devise scale | Outcome(s) | No of medicines identified |
|---|---|---|---|---|---|
| Ancelin (2006) | 372 people aged >60 years living in the community | Anticholinergic Burden Classification (ABC) | Based on Serum Anticholinergic Activity (SAA) and expert opinion | Cognitive function | 27 |
| Boustani (2008) | 87 nursing home residents with dementia aged ≥65 years | Anticholinergic Cognitive Burden Score (ACB) | Based on published data and expert opinion | Quality of life | 88 |
| Carnahan (2006) | 279 long term care residents | Anticholinergic Drug Score (ADS)[a] | Based on ranking of identified anticholinergic drugs and expert opinion | SAA | 117 |
| Ehrt (2010) | 78 people with Parkinson' | Anticholinergic Activity Scale (AAS) | Based on existing evidence and expert opinion | Cognitive function | 99 |
| Han (2008) | 544 men aged ≥65 years living in the community | Clinician's rated Anticholinergic Scale (CrAS)[a] | Based on published anticholinergic scales and expert opinion | Cognitive function<br>Functional assessment | 60 |
| Rudolph (2008) | 132 people aged ≥65 years in hospital and 117 people aged ≥65 years living in the community | Anticholinergic Risk Score (ARS) | Based on literature review and expert opinion | Central adverse effects (confusion, dizziness, falls) | 49 |
| Sittironarit (2011) | 211 people with Alzheimer's disease;<br>133 people with MCI; 768 healthy controls | Anticholinergic Loading Scale (ACL) | Based on published anticholinergic scales and expert opinion | Executive function<br>Psychomotor speed | 49 |

[a]ADS is a modified version of CrAS

### 12.1.3 Health economic evidence

Standard health economic filters were applied to the clinical search for these questions, and a total of 1,062 citations was returned. Following review of titles and abstracts, no full text

studies were retrieved for detailed consideration. Therefore, no relevant cost–utility analyses were identified for these questions.

### 12.1.4 Evidence statements

Moderate-quality evidence from 1 systematic review of 7 observational studies with 2,325 people (including 297 people diagnosed with dementia) found 7 validated anticholinergic scales developed by expert opinion detected an association between higher scores on anticholinergic scales and harms caused by anticholinergic medicines in older aged populations.

#### 12.1.4.1 Health economic evidence

No health economic evidence was identified for this review question.

### 12.1.5 Evidence to recommendations

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| **Relative value of different outcomes** | The committee agreed there was a need to raise awareness that there are certain groups of drugs that may influence cognitive function and that any recommendations should acknowledge both the minimisation of drugs causing anticholinergic activity and raise awareness of the scales that may be used to detect anticholinergic activity or burden. The committee recognised that there was a clinical issue that older aged populations include a substantial proportion of people with multimorbidities, where more than one condition may be treated with a medicine that has an anticholinergic effect, and the use of multiple medications with anticholinergic burden has a cumulative effect.<br>Two separate settings were identified where anticholinergic burden may be an important factor to consider. The first is when considering a diagnosis of dementia, where the presence of a substantial anticholinergic burden may mimic the symptoms of dementia and therefore lead to false diagnoses. The second, in people with a known diagnosis of dementia, is that the use of anticholinergics may exacerbate the symptoms of cognitive decline, and therefore their use should be carefully monitored. |
| **Trade-off between benefits and harms** | **At the time of diagnosis**<br>The committee agreed that although the evidence they had seen was in relation to a generally older aged population, there should be little difference for people living with dementia. Although the effects of anticholinergic burden may differ by population, the specific drugs that cause the largest anticholinergic burden are likely to remain the same. It noted that there may be implications for community prescribers to assess cognition before prescribing medications, in order to recognise that some drugs may affect anticholinergic burden.<br>The committee agreed that, at the time of considering a diagnosis of dementia, it would be appropriate to reduce the level of anticholinergic drugs being used, if possible alternatives were available, in order to rule out potential false diagnoses, and a ‘consider’ recommendation was made on this point.<br>The committee agreed that, whilst many of the classes of drugs with high anticholinergic activity were understood widely by clinicians, there were other individual drugs where the high level of anticholinergic activity was not well known, particularly when these come from a class of drugs not usually associated with it. Therefore, it agreed that validated, structured tools to assess anticholinergic burden would be useful, as they would make clinicians undertaking reviews aware of drugs they might not otherwise have considered. |

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| | The committee considered the types and classes of drugs listed in each scale. It noted that different drugs may be rated differently in each scale, with some drugs scoring higher for anticholinergic activity than others (this is likely to result from the different methodologies by which the scales were constructed). It agreed that there was currently no evidence to recommend the use of one scale in preference to another, so agreed that it was appropriate only to make clinicians aware of the existence of these scales, rather than make a specific recommendation that one should be used. However, the committee agreed it would be helpful to provide a link to an example of one of these scales, to ensure that non-specialist clinicians could understand the sorts of tools that exist. The Anticholinergic Cognitive Burden Scale was chosen as the most appropriate to reference because it uses standard UK names for drugs, and because it has been updated more recently (2012) than some of the scales identified. It did however, want the recommendation to re-emphasise that this was simply one tool available for determining the anticholinergic activity of specified drugs and not the only tool available for consideration.<br>The committee recognised that awareness of anticholinergic burden should form part of the full patient pathway and acknowledged there were other areas of the guideline (for example when undertaking diagnostic assessments) where this issue would be revisited.<br>**After diagnosis**<br>The committee agreed it remained important to continuously assess the level of anticholinergic burden in people living with dementia, and that an assessment should be made of anticholinergic burden as part of medication reviews. The committee agreed that, again, possible alternatives should be sought for drugs with a high anticholinergic burden, if these are available. It noted that the audit data presented showed that high levels of anticholinergic medicines were still prescribed in people living with dementia, and that while much of this prescribing is likely to be appropriate and necessary, it is likely that there is still inappropriate prescribing of medications with an anticholinergic effect when alternatives without this effect are available.<br>No evidence was identified about how reviews should be conducted and what tools should be used, and therefore the committee agreed the most appropriate action was to cross-reference the NICE guideline on medicines optimisation, which provides guidance on how to undertake medication reviews. |
| **Trade-off between net health benefits and resource use** | The committee agreed that there was potentially a high cost associated with the inappropriate prescription of drugs causing a high level of anticholinergic burden, both due to the side effects they can cause and the costs associated with inaccurate diagnoses. Therefore, appropriate reviews of anticholinergic medicines, both at diagnosis and reviews, would be likely to be cost-saving if it reduced levels of inappropriate prescribing. |
| **Quality of evidence** | The committee agreed that the most appropriate method of validating the scales would have been to consider measures of diagnostic accuracy, such as sensitivity and specificity, but they noted the evidence they had seen did not report validity in this way. This meant it was difficult to assess the overall utility of each scale. After considering the methodologies in each scale, the committee agreed there was an absence of evidence to identify one single well-validated tool over another.<br>The committee noted that the audit data presented on commonly prescribed anticholinergic medicines came from mental health trusts, and therefore there was still a gap in the evidence for which are the most commonly prescribed anticholinergic medicines in primary care. However, the committee agreed the recommendations made for |

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| | medication reviews would still be appropriate in a primary care setting, as the adverse effects to the person treated will be the same. |
| **Other considerations** | The committee acknowledged there is a gap in the current evidence base for considering whether reducing anticholinergic burden can improve the cognitive outcomes for people who have cognitive impairment, as the currently available studies are either cross-sectional or look at populations with a stable or increasing anticholinergic burden over time. It was therefore agreed that randomised control trials comparing a strategy of actively lowering anticholinergic burden, versus usual care, would be useful to fill this gap in the evidence. |

### 12.1.6 Recommendations

78. **Be aware that some commonly prescribed medicines are associated with increased anticholinergic burden, and therefore cognitive impairment.**

79. **Consider minimising the use of medicines associated with increased anticholinergic burden, and if possible look for alternatives:**
    - when assessing whether to refer a person with suspected dementia for diagnosis
    - during medication reviews with people living with dementia.

80. **Be aware that there are validated tools for assessing anticholinergic burden (for example, the Anticholinergic Cognitive Burden Scale), but there is insufficient evidence to recommend one over the others.**

81. **For guidance on carrying out medication reviews, see medication review in the NICE guideline on medicines optimisation.**

### 12.1.7 Research recommendations

9. **Does actively reducing anticholinergic burden in people living with dementia improve cognitive outcomes compared with usual care?**

For more details on the research recommendation made, and the rationale behind it, see appendix L.

# 13 Non-pharmacological interventions for people living with dementia

Dementia is a progressive, long-term condition that people live with, often for many years. Enabling and supporting people to live as well as possible with the condition is an important priority.

Living with dementia brings many challenges. The symptoms of dementia make it harder to participate in activities and engage socially, to maintain independence, to communicate effectively, to feel in control and, ultimately, to care for oneself. Experiencing symptoms of dementia has consequences, such as loss of confidence or tensions in family relationships, which compound the original disability. All of this can profoundly threaten a person's sense of identity and security, especially where the person's environment is not well-adapted or the surrounding community is not inclusive, and can impact on the ability of families to provide care. There is potential for people with dementia to live meaningful and satisfying lives and to experience a good quality of life, but this requires support both to promote inclusion and to manage disability.

In recent years a growing social movement has focused on changing public attitudes, inspired the creation of dementia-friendly communities, and promoted inclusion of people with dementia and awareness of the rights of people with dementia, for example through the development of peer support and advocacy groups. Involvement can provide enormous benefits for those people with dementia who wish to engage in this way.

Alongside this, there has been an increasing focus on enabling individuals with dementia and their families through providing interventions, suitable for the stage of dementia and tailored to personal needs and preferences, that promote functioning and well-being and help to sustain positive family relationships. A wide range of interventions has been proposed with these general aims in mind. At the time of diagnosis, supportive interventions offer an opportunity to process emotions, adjust to the condition and plan for the future. In the mild to moderate stages of dementia, personalised support with maintaining independence and managing everyday activities aims to ensure continued engagement and participation, while bringing people together in groups aims to enhance functioning as well as providing important opportunities for social contact. At all stages of the condition, engaging in enjoyable, creative and health-enhancing activities offers a means of promoting well-being. Nevertheless, there remains a significant gap in provision of non-pharmacological interventions which is compounded by inequity of access to services, for example for people living in rural areas or areas with poor transport links.

This chapter focuses on the range of non-pharmacological interventions for which rigorous evidence from randomised controlled trials is available. The evidence covered here excludes studies of interventions targeted at people experiencing specific illness-emergent non-cognitive symptoms such as depression, anxiety, or agitation; these are covered in section 14. This chapter reviews evidence from studies involving broader groups of people with dementia, at different stages of the condition, and aiming to produce benefits in cognition, functioning or well-being. In translating this evidence to practice it is vital to acknowledge that each person is different, and hence a one-size-fits-all approach is inappropriate. It is essential to seek the views of people living with dementia and their carers about the kinds of interventions they consider to be feasible and acceptable. Decisions about which non-pharmacological interventions are likely to be suitable and helpful for a given individual need to be based on an understanding of that individual's unique set of life experiences, circumstances, preferences, strengths and needs, with interventions personalised and tailored as far as possible to each individual and, where relevant, each family.

# 13.1 Pre-, peri- and post-diagnostic counselling and support for people living with dementia and their families

**Review question**

- How effective are pre-, peri- & post-diagnostic counselling and support on outcomes for people living with dementia and their families?

## 13.1.1 Introduction

The aim of this review question was to determine the effectiveness and cost-effectiveness of pre-, peri- and post-diagnostic counselling and support for improving outcomes for people living with dementia and their families and to identify the most effective and cost-effective ways of providing it. The review identified studies that fulfilled the conditions specified in Table 59. For full details of the review protocol, see appendix C.

**Table 59: Review summary: post-diagnostic counselling and support**

| | |
|---|---|
| **Population** | People (aged 40 years and over) living with dementia and having been diagnosed within the previous 12 months |
| **Interventions** | Counselling and support for people living with dementia and their families, which may include elements such as:<br>• Diagnostic counselling<br>• Psychosocial support<br>• Peer support groups<br>• Information and advice<br>• Signposting |
| **Comparator** | • Each other<br>• Standard care |
| **Outcomes** | • Clinical outcomes including cognitive, functional and behavioural ability<br>• Access to health and social care support<br>• Patient and carer experience and satisfaction<br>• Patient and carer health-related quality of life<br>• Resource use and costs |

## 13.1.2 Evidence review

A systematic literature search for systematic reviews and RCTs identified 2,662 references. These were screened at title and abstract level, with 4 systematic reviews ordered as potentially relevant and 17 ordered as potentially relevant RCTs of counselling and support interventions for people living with dementia and their families. Finally, because of the limited RCT data available, a separate search was conducted to look for comparative observational studies. This identified 1,942 references, of which 9 were judged to be potentially relevant and ordered for full-text review. Six additional references were also identified from excluded systematic reviews, the search for health economics evidence, and a related included reference. In total, 4,604 references were identified, of which 36 were judged to be potentially relevant and ordered for full-text review.

Three RCTs were included (reported in 4 publications), with 32 excluded at full-text review. Excluded studies are listed, with reasons for exclusion, in appendix F, and evidence tables are available in appendix E.

Two different types of post-diagnostic support interventions were found aimed at people who were recently diagnosed with dementia (within the previous 12 months):

- Psychosocial interventions – These interventions included elements of counselling, psychosocial support, information and advice to people living with dementia and their carers.
- Self-management interventions – These interventions included elements of psychosocial support, information and advice to people living with dementia and their carers.

No evidence was found on pre- and peri-diagnostic counselling and support for people living with dementia and their families.

#### 13.1.2.1 Analyses

Data from different studies were meta-analysed where possible, with GRADE tables and meta-analysis results given in appendices G and H, respectively. References for the included studies are given in appendix I.

A minimal clinically important difference of ≥0.03 points was considered by Koivisto (2016) for quality of life as measured with the 15D questionnaire (Sintonen 2001).

A difference of 3 points was considered by Laakkonen (2016) as clinically important for the physical component summary of the RAND-36 survey of health-related quality of life (Hays and Morales 2001).

### 13.1.2.21 Description of included studies

2 **Table 60: Summary of included studies**

| Study reference | Intervention<br>Control | Study population<br>Location<br>Follow-up | Included participants | Outcomes of interest |
|---|---|---|---|---|
| Koivisto (2016) | Intervention: Psychosocial<br>Control: Basic counselling at diagnosis | Study population: People with Alzheimer's disease diagnosis for an average of 5 months and clinical dementia rating of 0.5 (very mild) or 1.0 (mild) and their carers.<br>Setting: Brain Research and Rehabilitation Centre<br>Location: Finland<br>Follow-up: 36 months. | n=236 dyads (patient-carer)<br>n=84 allocated to intervention<br>n=152 allocated to control | People with dementia:<br>• Quality of life (QoL-AD and VAS)<br>• Cognitive impairment (MMSE)<br>• Memory disorder severity(CDR-SOB)<br>• Activities of daily living (ADCS-ADL)<br>• Behavioural disturbances (NPI)<br>• Nursing home placement<br>• Mortality<br>Carers:<br>• Quality of life (15D and VAS)<br>• Psychological distress during caregiving (GHQ)<br>• Orientation to life (SOC)<br>• Depression (BDI) |
| Laakkonen (2016) | Intervention: Self-management<br>Control: Usual care (including basic post-diagnostic counselling if needed) | Study population: People with a recent diagnosis of dementia and their spouses.<br>Setting: Primary care and memory clinics<br>Location: Finland<br>Follow-up: 9 months. | n=136 couples<br>n=67 allocated to intervention<br>n=69 allocated to control | People with dementia:<br>• Health-related quality of life (15D)<br>• Cognitive function (CDR, VF, CDT)<br>Spouses:<br>• Health-related quality of life (RAND-36 PCS) |
| Waldorff (2012)<br>Phung (2013) | Intervention: Psychosocial<br>Control: Follow-up support (including basic post-diagnostic counselling if needed) | Study population: People diagnosed with Alzheimer's disease, mixed Alzheimer's disease or Lewy body dementia within the previous 12 months of | n=330 patient-carer dyads<br>n=163 allocated to intervention | Patients:<br>• Quality of life (QoL-VAS and QoL-AD)<br>• Cognitive function (MMSE)<br>• Activities of daily living (ADCS-ADL) |

| Study reference | Intervention<br>Control | Study population<br>Location<br>Follow-up | Included participants | Outcomes of interest |
|---|---|---|---|---|
| | | recruitment in the trial and their primary carers.<br>Setting: Study centres (hospitals; community health centre)<br>Location: Denmark<br>Follow-up: 12 months<br>Follow-up: 36 months. | n=167 allocated to control | • Behavioural disturbances (NPI-Q)<br>• Depression (CDS)<br>• Nursing home placement<br>• Mortality<br>Carers:<br>• Quality of life (QoL-VAS)<br>• Depression (GDS) |

15D: 15-dimensional health-related quality of life instrument; ADCS-ADL: Alzheimer's Disease Cooperative Study-Activities of Daily Living; BDI: Beck Depression Inventory; CDR-SOB: clinical dementia rating global and the sum of boxes score; CDS: Cornell scale for depression in dementia; CDT: clock drawing test; GDS: geriatric depression scale; GHQ: general health questionnaire; MMSE: mini-mental state examination; NPI: neuropsychiatric inventory; NPI-Q: brief clinical form of the neuropsychiatric inventory; QoL-AD: quality of life in Alzheimer's disease; RAND-36 PCS: Research and Development Corporation 36 item health survey physical component survey; SOC: sense of coherence; VAS: visual analogue scale; VF: verbal fluency test.

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### 13.1.3 Health economic evidence

A systematic literature search was undertaken to identify existing cost–utility analyses (CUAs) evaluating the effectiveness of pre-, peri- and post-diagnostic counselling and support on outcomes for people living with dementia and their families. In total, 1,392 articles were returned, of which 2 were selected as potentially relevant and retrieved for full text review. Of these studies, 1 study considering psychosocial intervention was deemed relevant and included.

#### 13.1.3.1 Psychosocial interventions

**Søgaard et al. (2014)** conducted a cost–utility analysis alongside the Danish Alzheimer's Intervention Study (DAISY) (n=300), an RCT conducted in 2004 in Denmark, which collected health care utility data using the EQ-5D. They compared the cost effectiveness of a psychosocial intervention with control support (usual care). Details of the psychosocial intervention and control support (usual care) can be found in the reported Waldorff et al. (2012) study. Primary outcome measures were QALYs and costs over 36 months. For further details, please see the economic evidence profile in Appendix M.

The authors' base case adopted a broad societal perspective, including an attempt to value informal care and associated production loss costs; however, disaggregated results are reported, enabling the recalculation of results with a perspective that is consistent with the NICE reference case (that is, NHS and PSS costs only). All costs were valued according to 2008 prices and converted into euros (€). Healthcare costs were based on national registers and Danish governmental tariffs.

The EQ-5D was administered to carers at baseline and at 6, 12 and 36 months of follow-up for reporting of carers' health-related quality of life and for proxy reporting of participants' health-related quality of life. Lifetime was measured in days based on register data from the national registry of death causes.

Base-case results (Table 61) suggest that, over a period of 36 months, psychosocial intervention resulted in decreased costs and a loss of QALYs.

**Table 61: Base-case cost–utility results from Søgaard et al. (2014), based on multiple imputation-based analysis over 36 months with informal care costs and production loss costs excluded**

| | Absolute | | Incremental | | |
|---|---|---|---|---|---|
| **Treatment** | **Cost** | **Effect** | **Cost** | **Effect [a]** | **ICER** |
| Psychosocial intervention | €35,040 | 3.26 QALYs | | | |
| Control | €39,473 | 3.46 QALYs | €4,433 | 0.09 QALYs | €49,256 / QALY |

[a] *difference adjusted for baseline utility*

The results of the complete case analysis showed a relatively smaller savings of cost compared with the multiple imputation-based analysis of -€958 and the loss of 0.38 QALYs (when adjusted for baseline utility) for the psychosocial intervention compared with usual care. This results in an ICER of €2,521 saved per QALY forgone.

Amongst the authors' probabilistic sensitivity analyses, 1 set of results represents a 'formal care' perspective that is most closely comparable to the NICE reference case. This suggests

that there is a 78% probability that the intervention reduced health and social care costs and a 60% chance that the intervention is associated with an ICER of €30,000/QALY or better (arising because the amount of money it is predicted to save would, in a majority of cases, be judged to outweigh the harm it is predicted to cause).

The authors concluded that a psychosocial intervention is unlikely to be cost effective in a Danish setting because it did not generate additional QALYs and it led to higher average use of informal care. When the costs of such care (which are not consistent with the NICE reference case) are removed, it appears that, although the use of psychosocial interventions results in fewer QALYs than usual care, it may save sufficient money to offset this. These findings are subject to considerable uncertainty, and should be understood in the context that any cost savings that may be associated with the intervention arose by shifting cost burden from health and social care budgets to informal carers.

### 13.1.4 Evidence statements

No evidence was found on pre- and peri-diagnostic counselling and support for people living with dementia and their families.

#### 13.1.4.1 Psychosocial interventions

##### *13.1.4.1.1 People living with dementia*

Moderate- to high-quality evidence from 2 RCTs containing 566 people diagnosed with dementia within the last year found that people offered psychosocial interventions had better quality of life (measured with a dementia specific scale) at 12 months compared with people offered follow-up support. However they could not differentiate quality of life (measured with a visual analogue scale) at 12 months, or using a quality of life instrument at 36 months.

Moderate- to high-quality evidence from 2 RCTs containing 601 people diagnosed with dementia within the last year found that people offered psychosocial interventions had lower levels of depressive symptoms at 12 months (measured with the Cornell depression scale) compared with people offered follow-up support, but could not differentiate levels of depressive symptoms at 36 months.

High-quality evidence from 1 RCT containing 236 people diagnosed with dementia within the last year found that people offered psychosocial interventions had more severe memory disorder at 36 weeks compared with people offered basic counselling.

High-quality evidence from 2 RCTs containing 566 people diagnosed with dementia within the last year found people offered psychosocial interventions had worse functioning in their daily activities at 36 months compared with people offered follow-up support or basic counselling at diagnosis, but could not differentiate activities of daily living at 12 months.

Low- to moderate-quality evidence from 2 RCTs containing 566 people diagnosed with dementia within the last year could not differentiate numbers of nursing home placements, mortality, cognition or behavioural and psychological symptoms of dementia at 12 or 36 months between people offered psychosocial interventions and people offered follow-up support or basic counselling at diagnosis.

##### *13.1.4.1.2 Carers*

Low- to moderate-quality evidence from 2 RCTs containing 566 carers for people diagnosed with dementia within the last year could not differentiate quality of life, psychological distress

during caregiving, orientation to life, and depressive symptoms at either 12 or 36 months between people offered psychosocial interventions compared with follow-up support or basic counselling at diagnosis.

#### 13.1.4.2 Self-management interventions

##### *13.1.4.2.1 People with dementia*

Moderate-quality evidence from 1 RCT containing 134 people diagnosed with dementia within the last year found that people offered self-management interventions had better cognitive function (measured with the verbal fluency and clock drawing tests) compared with people offered usual care.

Low-quality evidence from 1 RCT containing 134 people diagnosed with dementia within the last year could not differentiate quality of life and cognitive function (measured with the clinical dementia rating scale) between people offered self-management interventions or usual care.

##### *13.1.4.2.2 Carers*

Low-quality evidence from 1 RCT containing 134 carers for people diagnosed with dementia within the last year could not differentiate quality of life between people offered self-management interventions or usual care.

#### 13.1.4.3 Health economic evidence

##### *13.1.4.3.1 Psychosocial interventions*

One partially applicable trial-based cost–utility analysis with potentially serious limitations explored the cost effectiveness of psychosocial intervention over 36 months. When compared with usual care, the intervention resulted in a loss of 0.09 QALYs and a decrease in health and social care costs of €4,433 per person, resulting in an ICER of €49,255 saved per QALY forgone. In probabilistic sensitivity analysis, the intervention has a 60% probability of being considered cost effective, if QALYs are valued at €30,000 each.

### 13.1.5 Evidence to recommendations

| | |
|---|---|
| **Relative value of different outcomes** | The committee agreed that long-term outcomes capturing the experiences of people living with dementia and their carers, including quality of life and cognitive function, were the most important to address this question. It noted that, since these studies were recruiting people with comparatively minor problems at baseline, studies may need to have long follow-up periods in order to detect meaningful differences, whereas in a more advanced population symptomatic benefit may be detectable over a shorter timeframe.<br>The committee agreed that differences in mortality and entry into full time care would also be important, but that it would be unlikely that studies recruiting people at or around the time of diagnosis would be able to detect differences in these outcomes. |
| **Trade-off between benefits and harms** | The committee agreed that the evidence presented did not provide clear evidence of benefits for either of the post-diagnostic interventions identified (psychosocial support or self-management). Whilst there were short-term improvements in quality of life, cognition and depression as measured by some of the instruments included in the trials, these effects did not persist, nor were they replicated on other instruments in trials measuring similar outcomes. The committee therefore agreed |

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|---|---|
| | there was not sufficient confidence in the evidence to make a positive recommendation for either of the interventions considered.<br>Conversely, the committee also agreed it would not be appropriate to make a negative recommendation, as only a small number of RCTs were identified, covering only a narrow range of the different types of interventions that have been developed and tested for people living with dementia over the whole lifetime of the condition. The committee agreed that even though the particular interventions considered in these trials had not been shown to be effective, this could not be used as evidence that other interventions would not prove to be so. Therefore, the committee agreed the current evidence did not enable them to make either positive or negative recommendations.<br>The committee agreed the lack of effectiveness in the trials meant there was no evidence that the period around diagnosis should be treated as a separate, discrete phase in the dementia pathway, requiring specifically different interventions. It agreed that the severity of dementia was likely to be a more important factor in which interventions were effective, rather than the time since diagnosis. In particular, if an intervention was shown to be effective for people with mild dementia, it was likely to also be effective for people with mild dementia around the time of diagnosis. The committee therefore agreed that the population considered in this section would be covered by recommendations made for mild dementia in the section of this guideline on non-pharmacological interventions for cognition, functional ability and wellbeing. |
| **Trade-off between net health benefits and resource use** | The committee noted that the DAISY trial did not find any significant or clinically meaningful differences in health outcomes between the intervention (psychosocial intervention) and control groups. The economic evaluation conducted alongside the trial (Søgaard et al., 2014) found that the psychosocial intervention was a dominated strategy (as it cost more money than control and produced fewer QALYs). However, as Søgaard et al (2014) considered costs that were not relevant to the NICE reference case, we conducted an analysis where these costs were removed. Under these circumstances, it was found that the psychosocial intervention was cost saving compared with the control group, but still produced fewer QALYs. The committee agreed that it would not be appropriate to make a recommendation based on evidence which showed that the psychosocial intervention produced fewer treatment benefits than the control, when any cost savings expected from the intervention were (a) extremely uncertain and (b) appear to be achieved by shifting costs from health and social care budgets to people living with dementia and their carers. |
| **Quality of evidence** | No evidence was identified about pre- and peri-diagnostic counselling and support for people living with dementia and their families. The committee agreed that this was not surprising because although this is recognised as being good practice, there has been little research in this area.<br>The committee highlighted an issue with the control arms in the studies. The control arm participants would very likely receive an enhanced version of usual care (often a limited version of the intervention), and this would reduce the estimated effect sizes.<br>The committee also highlighted that a possible confounding factor in the included studies was whether or not people had received pre-diagnostic counselling and support before entering the included interventions for post-diagnostic support, as it is not known what the earlier part of the process was like for the participants. Whilst appropriate randomisation should mean that the level of pre-diagnostic support is approximately balanced between the trial arms, the committee agreed that high levels of pre-diagnostic support may reduce the incremental benefit of the |

| | |
|---|---|
| | intervention, as people having already received support would have less potential to gain. |
| **Other considerations** | The committee highlighted that the use of 1 year post-diagnosis as a cut-off for this question was an arbitrary figure, but it was not possible to robustly define the transition from the post-diagnostic phase to more general support services, as this trajectory would differ considerably between individuals. It also highlighted that as people with dementia are now being diagnosed earlier than has been the case historically, this means that over time the populations in the studies may no longer be representative of the real world post-diagnosis population.<br>The committee agreed the key issue for many individuals was not about the specifics of post-diagnostic support, but rather around continuity of care as people move from diagnosis in to more general support services. These issues are considered in the section of this guideline on the co-ordination of health and social are services. |

### 13.1.6 Recommendations

No recommendations were made

## 13.2 Interventions to promote cognition, independence and wellbeing

**Review questions**

- What are the most effective non-pharmacological interventions for supporting cognitive functioning in people living with dementia?
- What are the most effective non-pharmacological interventions for supporting functional ability in people living with dementia?
- What are the most effective non-pharmacological interventions to support wellbeing in people living with dementia?
- What are the most effective methods of supporting people living with dementia to reduce harm and stay independent?

### 13.2.1 Introduction

The aim of these review questions was to determine the most effective and cost-effective non-pharmacological interventions for supporting people living with dementia. This review covered separate questions, looking at interventions to support cognition, functional ability, independence and wellbeing, with all the interventions identified considered across all these categories.

The review identified studies that fulfilled the conditions specified in Table 62. For full details of the review protocol, see Appendix C.

**Table 62: Review summary: non-pharmacological interventions to support independence, cognition, functional ability and wellbeing in people living with dementia**

| | |
|---|---|
| **Population** | People (aged 40 years and over) living with dementia |
| **Interventions** | Non-pharmacological interventions which may have a positive impact on cognitive functioning |
| **Comparator** | • Each other<br>• Standard care |
| **Outcomes** | • Clinical outcomes including cognitive, functional and behavioural ability<br>• Admissions to hospitals/care homes<br>• Access to health and social care support<br>• Patient and carer experience and satisfaction<br>• Patient and carer health-related quality of life<br>• Adverse events<br>• Resource use and costs |

### 13.2.2 Evidence review

The identification of studies was conducted in two stages for these review questions. First, a systematic review of systematic reviews was conducted by the York Health Economics consortium, looking to identify the most recent high-quality systematic reviews published on non-pharmacological interventions for people living with dementia. Where a newer systematic review was available that completely covered the subject of an earlier review, the earlier review was not included. In total, 33 relevant reviews were identified, and these reviews were then used as a source of primary RCTs. In addition, a separate RCT search was conducted to identify trials published after the search dates of the included reviews,

which found a total of 204 records, which were then screened on title and abstract, as described in the separate sections for each intervention below. Full details of this review are available in appendix O.

Finally, an additional systematic literature search was carried out to identify any randomised controlled trials or systematic reviews of randomised controlled trials, where the stated intention of the intervention was to promote independence in people living with dementia. A total of 5,152 references were screened at the title and abstract level, with 51 potentially relevant references being ordered for full text review. Of these references, 15 were selected for inclusion based on their relevance to the review protocol. The excluded studies are listed, with reasons for their exclusion, in Appendix B. All data included in the review was extracted from the primary studies, regardless of from which source the primary paper was identified. References for the included studies are given in appendix I.

Data was extracted for the outcomes of cognition, activities of daily living, behavioural and psychological symptoms, global assessment, health-related quality of life, dementia severity, depression, agitation, carer burden and mortality. In each case, a standardised mean difference was used to combine all outcomes measures on that scale, and additionally data were reported on the mean difference scale for the pre-specified primary outcome measure in each domain. These primary outcomes were:

- Cognition – MMSE
- Behavioural and psychological symptoms – NPI
- Activities of daily living – ADCS-ADL
- Global assessment – CIBIC+
- Health-related quality of life – QoL-AD (dementia-specific), EQ-5D (generic)
- Dementia severity (CDR)
- Depression (CSDD)
- Agitation (CMAI)
- Carer burden (ZBI)

Where papers did not contain any of the outcome domains of interest in an extractable format, the paper was excluded. When studies reported outcome measures at multiple time points, data were extracted post-intervention (the first measurement time after completion of the intervention) and at long-term follow-up (the final time point of the study).

#### 13.2.2.1 Cognitive stimulation, cognitive training and cognitive rehabilitation

There is considerable inconsistency in the terminology used in the literature around cognitive stimulation, cognitive training and cognitive rehabilitation for people living with dementia. In particular, the terms cognitive training and rehabilitation have often been used interchangeably despite arising from different disciplines and having very different intentions in what they are trying to achieve. For the purposes of the guideline, the following definitions of these interventions have been used:

- Cognitive stimulation: Engaging in a range of activities and discussions (usually in a group) that are aimed at general improvement of cognitive and social functioning.
- Cognitive training: Guided practice on a set of standard tasks that are designed to reflect particular cognitive functions. There may be a range of difficulty levels, to fit the tasks to each person's level of ability.
- Cognitive rehabilitation: Identifying functional goals that are relevant to the person living with dementia, and working with them and their family members or carers to achieve these. The emphasis is on improving or maintaining functioning in everyday

life, building on the person's strengths and finding ways to compensate for impairments, and supporting independence. Cognitive rehabilitation does not aim to improve cognition, but addresses the disability resulting from the impact of cognitive impairment on everyday functioning and activity. Rehabilitation is sometimes referred to as 'reablement'.

In total, 86 potentially relevant papers were identified for full-text review. Of these, 44 were excluded (with reasons for exclusion given in appendix B), and 40 were included for the three relevant interventions. Of these, 25 reported data on cognitive stimulation, 13 on cognitive training and 5 on cognitive rehabilitation (1 paper reported data on both cognitive training and cognitive rehabilitation). Evidence tables for these studies are given in appendix E, and GRADE profiles in appendix G.

#### 13.2.2.2 Self-management groups

In total, 6 potentially relevant papers were identified for full-text review. Of these, 3 were excluded (with reasons for exclusion given in appendix B), and 3 were included. These papers provided data on self-management groups for people living with dementia. Evidence tables for these studies are given in appendix E, and GRADE profiles in appendix G.

#### 13.2.2.3 Reminiscence therapy

In total, 21 potentially relevant papers were identified for full-text review. Of these, 10 were excluded (with reasons for exclusion given in appendix B), and 11 were included. These papers provided data on either individual or group reminiscence therapy for people living with dementia. An additional paper was identified at the re-run stage which included both group and individual therapy and was included. Therefore, 12 papers were included in total. Some interventions only focused on the person living with dementia, whilst others were dyadic and also included a component for carers. Evidence tables for these studies are given in appendix E, and GRADE profiles in appendix G.

#### 13.2.2.4 Occupational therapy

In total, 12 potentially relevant papers were identified for full-text review. Of these, 8 were excluded (with reasons for exclusion given in appendix B), and 4 were included. These papers provided data on occupational therapy for people living with dementia. Evidence tables for these studies are given in appendix E and GRADE profiles in appendix G.

#### 13.2.2.5 Psychotherapy

In total, 20 potentially relevant papers were identified for full-text review. Of these, 17 were excluded (with reasons for exclusion given in appendix B), and 3 were included. These papers provided data on psychotherapy for people living with dementia, where the trials did not require people to have a diagnosis of a non-cognitive symptom (such as depression or anxiety) at baseline. Trials looking at the treatment of anxiety or depression in people living with dementia are covered in the section of this guideline on managing non-cognitive symptoms. Evidence tables for these studies are given in appendix E, and GRADE profiles in appendix G.

#### 13.2.2.6 Exercise

In total, 50 potentially relevant papers were identified for full-text review. Of these, 28 were excluded (with reasons for exclusion given in appendix B), and 22 were included. Of these, 1 primarily focused on tai chi, 2 on dance therapy, 2 on non-aerobic exercise, 5 on aerobic

exercise, 9 on combined aerobic/non-aerobic exercise, and 3 on multimodal interventions with a primary exercise component, but also containing other interventions such as occupational therapy or cognitive behavioural therapy. In all analyses including multimodal interventions, a sensitivity analysis was also conducted excluding those trials, to estimate the effect of studies with exercise only as the intervention. Evidence tables for these studies are given in appendix E, and GRADE profiles in appendix G.

#### 13.2.2.7 Nutrition

In total, 68 potentially relevant papers were identified for full-text review. Of these, 29 were excluded (with reasons for exclusion given in appendix B), and 39 were included. Studies comparing nutritional supplements with either placebo or usual care were included, but studies comparing to pharmacological interventions (such as cholinesterase inhibitors or memantine) were excluded.

Evidence tables for these studies are given in appendix E, and GRADE profiles in appendix G.

#### 13.2.2.8 Music therapy

In total, 47 potentially relevant papers were identified for full-text review. Of these, 31 were excluded (with reasons for exclusion given in appendix B), and 16 were included. Nine publications specified non-cognitive symptoms such as anxiety as an inclusion criteria. Twelve publications compared music therapy to standard care with one also including an active comparator arm. Four publications compared music therapy to active comparator sessions, such as cooking. Music therapy varied widely across the publications; differences were observed for example in the type (active or receptive therapy), the delivery setting (individualised or small group sessions), number of sessions (1 to around 60), as well as the length of sessions (10 min to 90 min) and experimental period (10 min to 4 months). Eight publications included a follow-up period which varied from 1 hour after treatment session to 6 months. Evidence tables for these studies are given in appendix E, and GRADE profiles in appendix G.

#### 13.2.2.9 Aromatherapy

In total, 11 potentially relevant papers were identified for full-text review. Of these, 9 were excluded (with reasons for exclusion given in appendix B), and 2 were included. These papers provided data on aromatherapy, in particular Melissa and Lavendula, for people living with dementia and non-cognitive symptoms. Evidence tables for the included studies are given in appendix E, and GRADE profiles in appendix G.

#### 13.2.2.10 Light therapy

In total, 17 potentially relevant papers were identified for full-text review. Of these, 14 were excluded (with reasons for exclusion given in appendix B), and 3 were included. These papers provided data on light therapy for people living with dementia. Evidence tables for the included studies are given in appendix E, and GRADE profiles in appendix G.

#### 13.2.2.11 Motor-cognitive dual-task training

In total, 3 potentially relevant papers were identified looking at motor-cognitive dual-task training (which involves the addition of cognitive tasks to mobility interventions aimed at domains such as gait to balance) for full-text review. All 3 of these papers were excluded (with reasons for exclusion given in appendix F), and 0 were included.

#### 13.2.2.12 Non-invasive brain stimulation

In total, 24 potentially relevant papers were identified for full-text review. Of these, 18 were excluded (with reasons for exclusion given in appendix B), and 6 were included. Five of the included publications reported on people with Alzheimer's disease of varying severity and 1 on people with mild vascular dementia. In 4 publications the investigators used rTMS (repetitive transcranial magnetic stimulation) of 1 Hz, 10 Hz or 20 Hz intensity; in 2 studies tDCS (transcranial direct current stimulation), of 2 mA, was used. All publications included multiple sessions with the length of active phase varying from 4 days to 6 weeks. All publications included a follow-up period which varied from 18 days to 4.5 months with 1 study including maintenance treatment during the follow-up. Evidence tables for these studies are given in appendix E, and GRADE profiles in appendix G.

#### 13.2.2.13 Acupuncture

In total, 20 potentially relevant papers were identified for full-text review. Of these, 18 were excluded (with reasons for exclusion given in appendix B) and 2 were included. These papers provided data on acupuncture for people living with dementia. Evidence tables for the included studies are given in appendix E, and GRADE profiles in appendix G.

#### 13.2.2.14 Assistive technology

A 2017 Cochrane review identified no randomised controlled trials studying the effectiveness of assistive technology in people living with dementia. This review looked for studies evaluating the efficacy of assistive technology for supporting memory, daily performance of personal and instrumental activities of daily living (ADL) independence, behavioural and psychological symptoms, need for informal and formal care, quality of life and carer burden.

#### 13.2.2.15 Assisted animal therapy

One paper was identified during the re-run stage and was included in the review. This paper evaluated the effectiveness of animal assisted therapy by interaction with a dog compared with usual treatment. Reported outcomes were: depression, anxiety and quality of life. Evidence tables for the included studies are given in appendix E, and GRADE profiles in appendix G.

#### 13.2.2.16 Robotic pet therapy

One paper was identified during the re-run stage and was included in the review. This paper evaluated the effectiveness of robotic pet therapy using PARO (personal robot), a FDA-approved device designed to look like a baby harp seal. Individual interaction by the participants was encouraged at group sessions. Evidence tables for the included studies are given in appendix E, and GRADE profiles in appendix G.

#### 13.2.2.17 Adapted mindfulness program

One paper was identified during the re-run stage and was included in the review. This paper evaluated the effectiveness of an adapted mindfulness program plus treatment as usual versus treatment as usual alone and reported outcomes on cognition, quality of life and depression. Evidence tables for the included studies are given in appendix E, and GRADE profiles in appendix G.

#### 13.2.2.18 Home safety toolkit

One paper was identified, evaluating the effectiveness of a home safety toolkit for promoting independence and reducing harm in people living with dementia. Evidence tables for the included studies are given in appendix E, and GRADE profiles in appendix G.

### 13.2.3 Health economic evidence

#### 13.2.3.1 Systematic review of published economic evaluations

A systematic literature search was undertaken to identify existing cost–utility analyses (CUAs) evaluating non-pharmacological interventions for people living with dementia. In total, 3,229 articles were returned, of which 57 were selected as potentially relevant and retrieved for full-text review. Additionally, a committee member made available a pre-publication manuscript detailing an NIHR-funded RCT. A final literature search performed to identify any newly indexed papers found 1 new paper. In total, 4 publications were judged to be at least partially applicable to the review questions and were therefore included. Of these studies, 1 evaluated cognitive rehabilitation, 1 evaluated maintenance cognitive stimulation therapy, 1 evaluated joint reminiscence group therapy and 1 evaluated exercise. Details of the literature search are provided in Appendix D.

##### *13.2.3.1.1 Cognitive rehabilitation*

**Clare et al. (in press)** conducted a cost–utility analysis alongside the GREAT RCT. The inclusion criteria were that participants had an ICD-10 diagnosis of Alzheimer's disease, vascular or mixed dementia with mild to moderate cognitive impairment (MMSE score ≥ 18). Cognitive rehabilitation was administered in additional to usual treatment. It was delivered by therapists with experience of rehabilitative interventions in 10 individual sessions over 3 months, followed by 4 maintenance sessions over the next 6 months. For further details, please see the economic evidence profile in Appendix M.

To cost the intervention, the Client Services Receipt Inventory was completed by the person with dementia and carer together. Costs of health and social care were calculated by applying relevant, nationally generalisable unit costs, including data from NHS reference costs and PSSRU.

Cost–utility analysis was undertaken separately for participants with dementia and their carers using QALYs generated from the EQ-5D-3L for carers and DEMQOL-U for the person with dementia. Cases included imputed costs and QALYs where data were missing.

Base-case results (Table 63) suggested that cognitive rehabilitation was associated with increased health and social care costs (though the data were also consistent with no difference at a 95% confidence level), but no additional benefit could be detected. For carers, there was no difference in utility scores between the control group and the cognitive rehabilitation group.

**Table 63: Base-case cost–utility results (person with dementia) from Clare et al. (in press)**

| Treatment | Absolute | | Incremental | | |
|---|---|---|---|---|---|
| | Cost [95%CI] | Effect [95%CI] | Cost [95%CI] | Effect [95%CI] | ICER |
| Usual care | £4,286 [3,353 to 5,672] | 0.45 QALYs [0.44 to 0.46] | | | |
| Cognitive rehabilitation | £5,397 [4,563 to 6,388] | 0.45 QALYs [0.44 to 0.46] | £1,110 [-382 to 2,187] | 0.001 QALYs [-0.01 to 0.01] | £1,110,000 /QALY |

In probabilistic analysis, the probability that cognitive rehabilitation is cost effective was very low, regardless of the value that was assumed for QALYs, from the health and social care perspective

The authors noted that the attainment of personally set goals did not bring about changes in those domains that are measured in the dementia-specific quality of life measure (DEMQOL), nor did it bring about changes in carer health-related quality of life (measured by EQ5D). They authors concluded that, for commissioning purposes, they did not find that cognitive rehabilitation is cost-effective when gauged against QALY gains for either participants with dementia or carers.

#### *13.2.3.1.2 Maintenance cognitive stimulation therapy*

D'Amico et al. (2015) conducted a cost–utility analysis alongside the Orrell et al. (2014) RCT investigating 24 weeks of weekly maintenance cognitive stimulation therapy (CST) versus no additional therapy following a 7-week, 14-session initial CST programme (see 13.2.2, above).

The authors' base case adopted a health and social care perspective. The Client Service Receipt Inventory was used to capture resource use. The cost of maintenance CST itself included a 1-day training course for facilitators, materials and equipment, costs of 2 co-facilitators and transport costs for participants.

Unit costs were taken from the PSSRU and BNF and from market sources for equipment and adaptations. Costs were expressed in 2011 British pounds.

QALYs were calculated from both generic and dementia-specific quality of life measures, using both participant- and proxy-reported measures, by 'area under the curve' analysis, with linear interpolation between assessment points.

Base-case results (Table 64) show that maintenance CST was associated with a non-significant increase in both costs and QALYs. The ICER approached levels that might be considered a reasonable use of health and social care funds only when QALYs were estimated using the proxy-rated EQ-5D. Probabilistic sensitivity analysis showed that, using this measure, there was a 40% chance that maintenance CST was associated with an ICER of £20,000 or better. There was no evidence that maintenance CST would be considered cost effective when any of the other QALY measures was used.

**Table 64: Base-case cost–utility results from D'Amico et al. (2015)**

| Treatment | Absolute | | Incremental | | |
|---|---|---|---|---|---|
| | Cost | Effect | Cost [95%CI] | Effect [95%CI] | ICER |
| **EQ-5D** | | | | | |
| Usual care | NR | NR | | | |
| Maintenance CST | NR | NR | £475 [−314 to 1,264] | 0.0013 QALYs [−0.020 to 0.022] | £365,276 /QALY |
| **Proxy-rated EQ-5D** | | | | | |
| Usual care | NR | NR | | | |
| Maintenance CST | NR | NR | £474 [−315 to 1,263] | 0.0176 [−0.005 to 0.040] | £26,835 /QALY |
| **DEMQOL** | | | | | |
| Usual care | NR | NR | | | |
| Maintenance CST | NR | NR | £518 [−347 to 1383] | 0.0039 QALYs [−0.009 to 0.017] | £132,539 /QALY |
| **Proxy-rated DEMQOL** | | | | | |
| Usual care | NR | NR | | | |
| Maintenance CST | NR | NR | £402 [−442 to 1,245] | 0.0062 QALYs [−0.005 to 0.017] | £64,785 /QALY |

#### *13.2.3.1.3 Joint reminiscence group therapy*

Woods et al. (2016) conducted a cost–utility analysis alongside the REMCARE RCT. To be included in the study, patients had to have mild/moderate dementia diagnosed using DSM-IV criteria.

Joint reminiscence group therapy followed the 'Remembering Yesterday, Caring Today' manual. Group sessions were held weekly over 12 consecutive weeks, followed by 7 monthly maintenance group sessions. Sessions were led by 2 trained facilitators in each centre, supported by trained volunteers.

The authors undertook a micro-costing of the intervention by recording the types and quantities of resource input including: staff time, materials, room rental, training and supervision of staff. Appropriate national salary scales were used for staff who were NHS or university employees. Costs were adjusted to the price year 2010 and expressed in British pounds.

Cost–utility analysis was undertaken separately for participants with dementia and their carers using QALYs generated from the self-completed EQ-5D-3L. Carers completed the measure from their own perspective and for the person with dementia, who would also complete it whenever possible.

Base-case results (Table 65) showed that reminiscence therapy was associated with substantial extra costs of over £1,000 per participant, but did not produce any meaningful QALY gains for people living with dementia or carers.

**Table 65: Base-case cost–utility results from Woods et al. (2016)**

| Treatment | Absolute | | Incremental | | |
|---|---|---|---|---|---|
| | Cost (£) | Effect (QALYs) | Cost (£) | Effect (QALYs) | ICER (£/QALY) |
| **Person living with dementia** | | | | | |
| Usual care | 4,309 | 0.643 | | | |
| Reminiscence | 5,853 | 0.644 | 1,544 | 0.001 | 1,544,000 |
| **Carer** | | | | | |
| Usual care | 1,359 | 0.633 | | | |
| Maintenance CST | 2,495 | 0.632 | 1,136 | -0.001 | dominated |

The authors stated that, whilst a full probabilistic analysis had been planned, the results showed that generating cost-effectiveness acceptability curves would not be meaningful. The authors concluded that the REMCARE trial does not support the clinical effectiveness or cost-effectiveness of joint reminiscence group therapy.

#### *13.2.3.1.4 Exercise*

Sopina et al. (2017) conducted a cost–utility analysis alongside a Danish RCT (Hoffmann et al., 2013). To be included in the study, participants had to have a confirmed diagnosis of Alzheimer's disease and an MMSE of 20 or more. The control group received treatment as usual while the intervention group performed 1 hour of supervised moderate-to-high intensity aerobic exercise 3 times weekly for 16 weeks.

Health-related quality of life was measured using the 5-level version of the EQ-5D (EQ-5D-5L), with ratings elicited from participants and the primary caregivers as proxy respondents. The study had relatively short follow-up period and did not include cost of health and social care used by the participants.

Base-case cost–utility results (Table 66) suggested that the intervention was associated with significant cost increases but very small QALY benefits, leading to high ICERs in excess of €100,000/QALY.

**Table 66: Base-case cost–utility results from Sopina et al. (2017)**

| Treatment | Absolute | | Incremental | | |
|---|---|---|---|---|---|
| | Cost | Effect | Cost [95%CI] | Effect | ICER |
| **EQ-5D-5L** | | | | | |
| Usual care | NR | NR | | | |
| Exercise | NR | NR | €496 [495 to 497] | 0.00313 QALYs | €158,520 /QALY |
| **Proxy-rated EQ-5D-5L** | | | | | |
| Usual care | NR | NR | | | |
| Exercise | NR | NR | €496 [495 to 497] | 0.00411 QALYs | €120,790 /QALY |

In probabilistic analysis, the authors found that, using participant-rated EQ-5D-5L, the chance of the intervention being cost effective only reached 50% when QALYs were valued at €175,000 or greater each.

#### 13.2.3.2 Original economic analysis

##### *13.2.3.2.1 Methods*

Owing to the paucity of published health economic studies for non-pharmacological interventions in dementia, the GDG prioritised these questions for original economic modelling.

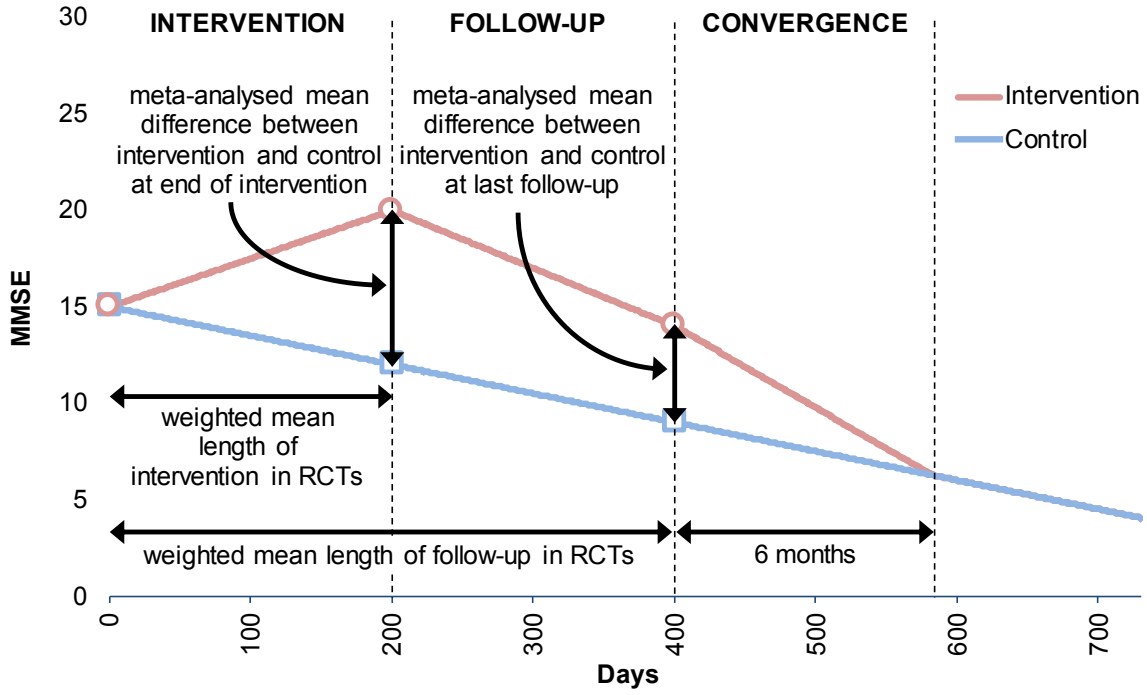
A series of simple cost–utility models was developed that sought to simulate the average patient receiving each intervention of interest, compared with usual care. The models used a simple area-under-the-curve method to estimate differences, over time, between a person receiving the intervention and one receiving usual care in multiple clinical outcomes that could then be used to estimate health-related quality of life (and, consequently, QALYs).

The systematic reviews undertaken for this chapter (see 13.2.2, above) were used to identify non-pharmacological interventions for which sufficient data were available for modelling. Single summary estimates for each continuous variable of interest were drawn from the meta-analyses, which were then substituted into published models (2 univariable and 1 multivariable), drawn from a review of available literature, to estimate the health-related quality of life that could be expected for the typical person living with dementia receiving the intervention in question. The constraints of available utility models dictated that clinical outcomes of interest were effects in cognitive, functional and behavioural domains. Data synthesised as standardised mean differences (SMDs) were re-expressed in units needed for the utility models (e.g. cognition→MMSE, functional→DAD, behavioural→NPI), using pooled standard deviations from the assembled evidence-base.

Two datapoints were used to estimate treatment effect: change at the end of the intervention and (where available) change at post-intervention follow-up. For each outcome-within-intervention, these timepoints were defined by a weighted average of intervention length and follow-up length, respectively, in each trial contributing to the effect estimate, with weights defined by the relevant meta-analysis.

To extrapolate any observed benefits of treatment beyond the empirical data, advice from the *Guide to the methods of technology appraisal* (2013) was followed. This stipulates that a range of assumptions should be explored, ranging from no additional benefit to an indefinite preservation of gains achieved over the course of the intervention. For the base case, a scenario between these extremes was adopted: patients revert to natural history 6 months after the longest follow-up period available in a linear fashion.

Figure 1 provides a schematic depiction of the method, using the example of change in MMSE (where the multivariable utility model was used, similar analyses were performed for other relevant outcomes and the joint effect of intervention on all domains estimated).




*Model shown reflects base-case assumptions; alternative scenarios (including immediate onset of treatment benefit, and longer and shorter durations of post-follow-up benefit) were explored in sensitivity analysis*
*NB some quantities have been exagerrated, compared with empirical data, for schematic clarity*

**Figure 1: Schematic depiction of model**

In the base case, the effect difference between any 2 time points occurred in a linear fashion. In instances where the average follow-up period exceeded 18 months, patients in the control and interventions arms were assumed to converge at 24 months (730 days), the maximal time horizon for the model.

Costs included in the analyses only related to the costs of delivering the interventions themselves. While it may be expected that effective interventions may reduce other health and social care costs (for example, improvements in functional ability might reduce requirement for domiciliary support), there was no evidence of significant differences in costs between treatment and control in any of the within-trial analyses summarised above (13.2.3.1). Therefore, it was assumed that, aside from the expense incurred in delivering the intervention in question, there would be no difference in total costs between people who do and do not receive the intervention. Resource use for each of the interventions was estimated, where possible, using evidence from the assembled RCTs. This included the number of sessions, length of sessions, grade of staff required to deliver the intervention. Where data were not available from clinical papers, the guideline committee was consulted to provide estimates of resource use in the English NHS setting. Where unit cost data were not available from study papers and PSSRU unit costs, the guideline committee were consulted to provide estimates of unit costs in the English NHS setting. Resource use and unit cost data were combined to produce a cost for each intervention modelled.

Probabilistic sensitivity analyses and one-way sensitivity analyses were conducted to examine the effects of model input parameters that were subject to uncertainty. Scenario analyses were also conducted to examine the effects of varying several parameters at the same time. A full description can be found in Appendix J.

The analyses used a patient perspective for outcomes and an NHS+PSS perspective for costs, in line with *Developing NICE guidelines* (2014). Costs and outcomes were discounted at the rate of 3.5% per annum.

Some of the key assumptions of the model include:

- Non-pharmacological interventions are unable to alter the disease process or mortality rates in patients with dementia.
- The maximal effects of the intervention are likely to be limited to the duration for which the patient receives it.
- Clinical measures – and, by extension, utility scores – change in a linear fashion between points at which measurements are estimated.
- The model does not consider any difference of resource use (i.e. hospital inpatient stays, GP appointments etc.) or disutility as a result of interventions.

More information about the model can be found in appendix J.

#### *13.2.3.2.2 Results*

**Group cognitive stimulation therapy**

The base-case model suggested that group CST was associated with a benefit of a little over 0.033 QALYs relative to control, at an additional cost of £653, leading to an ICER of £19,966/QALY (Table 67). One-way sensitivity analysis found that the model was extremely sensitive to almost all parameters in the model: varying any parameter within plausible range generates results lying on either side of a £20,000/QALY threshold.

**Table 67: Incremental costs and effects for group cognitive stimulation therapy versus control**

| | Absolute | | Incremental | | | Ceiling £ for this benefit[a] |
|---|---|---|---|---|---|---|
| | Costs | QALYs | Costs | QALYs | ICER | |
| **Base case (multivariable model)** | | | | | | |
| Control | £0 | 1.164 | | | | |
| Intervention | £653 | 1.197 | £653 | 0.033 | £19,966 | £654 |
| **Univariable model (MMSE)** | | | | | | |
| Control | £0 | 1.069 | | | | |
| Intervention | £653 | 1.080 | £653 | 0.010 | £62,973 | £207 |
| **Univariable model (ADCS-ADL)** | | | | | | |
| Control | £0 | 1.007 | | | | |
| Intervention | £653 | 1.029 | £653 | 0.022 | £29,986 | £435 |

[a] *The maximum intervention cost at which benefits of the magnitude estimated here would lead to an ICER of £20,000/QALY or better*

Probabilistic sensitivity analysis (Figure 2) suggested that the probability that intervention is cost-effective is around 50%, if QALYs are valued at £20,000 each, or 70%, if a higher threshold of £30,000/QALY is used.

In a scenario analysis where costs relating to staff training, staff travel, venue, and administration were set to zero (that is, only staff time and participant travel expenses were accounted for), group CST was found to cost an additional £554 compared with control, and produced an ICER of £16,942/QALY.

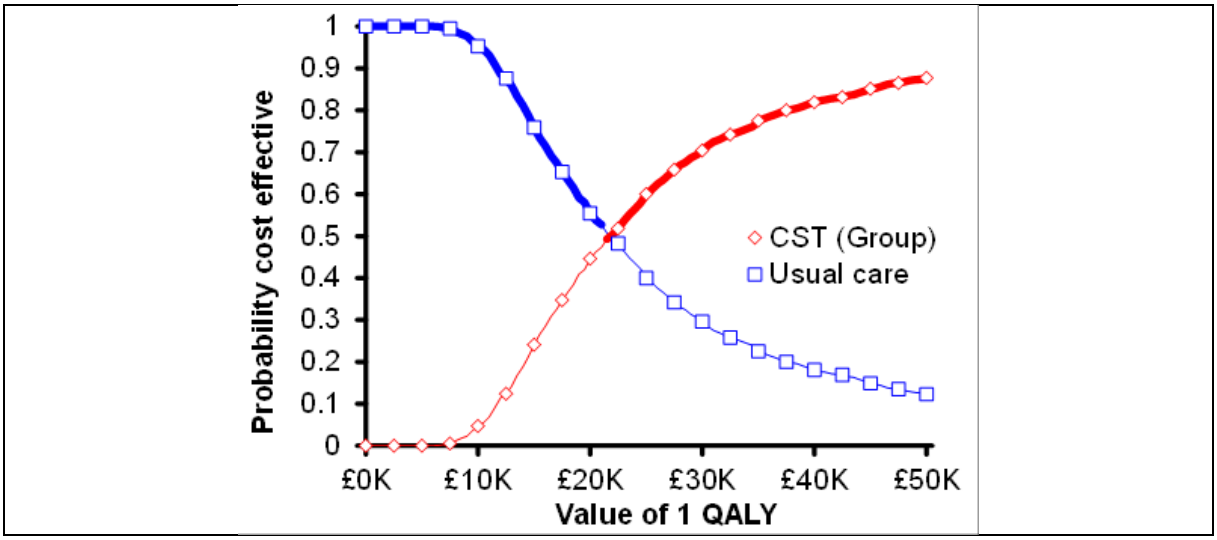



**Figure 2: Cost-effectiveness acceptability curve – group cognitive stimulation versus usual care**

### Cognitive rehabilitation (individual)

The base-case model suggested that cognitive rehabilitation was associated with a benefit of a little over 0.027 QALYs relative to control, at an additional cost of £1,827, leading to an ICER of £66,863/QALY (Table 68). One-way sensitivity analysis found that the model was most sensitive to the SMD value for BPSD at long term follow-up; however, no parameter variations resulted in an ICER lower than £20,000/QALY.

**Table 68: Incremental costs and effects for individual cognitive rehabilitation versus control**

| | Absolute | | Incremental | | | Ceiling £ for this benefit[a] |
|---|---|---|---|---|---|---|
| | Costs | QALYs | Costs | QALYs | ICER | |
| **Base case (multivariable model)** | | | | | | |
| Control | £0 | 1.164 | | | | |
| Intervention | £1,827 | 1.191 | £1,827 | 0.027 | £66,863 | £546 |
| **Univariable model (MMSE)** | | | | | | |
| Control | £0 | 1.069 | | | | |
| Intervention | £1,827 | 1.113 | £1,827 | 0.044 | £41,900 | £872 |
| **Univariable model (ADCS-ADL)** | | | | | | |
| Control | £0 | 1.031 | | | | |
| Intervention | £1,827 | 1.101 | £1,827 | 0.070 | £26,006 | £1,405 |

[a] *The maximum intervention cost at which benefits of the magnitude estimated here would lead to an ICER of £20,000/QALY or better*

Probabilistic sensitivity analysis (Figure 3) suggested that the probability that intervention is cost-effective is around 2%, if QALYs are valued at £20,000 each, or 15%, if a higher threshold of £30,000/QALY is used.

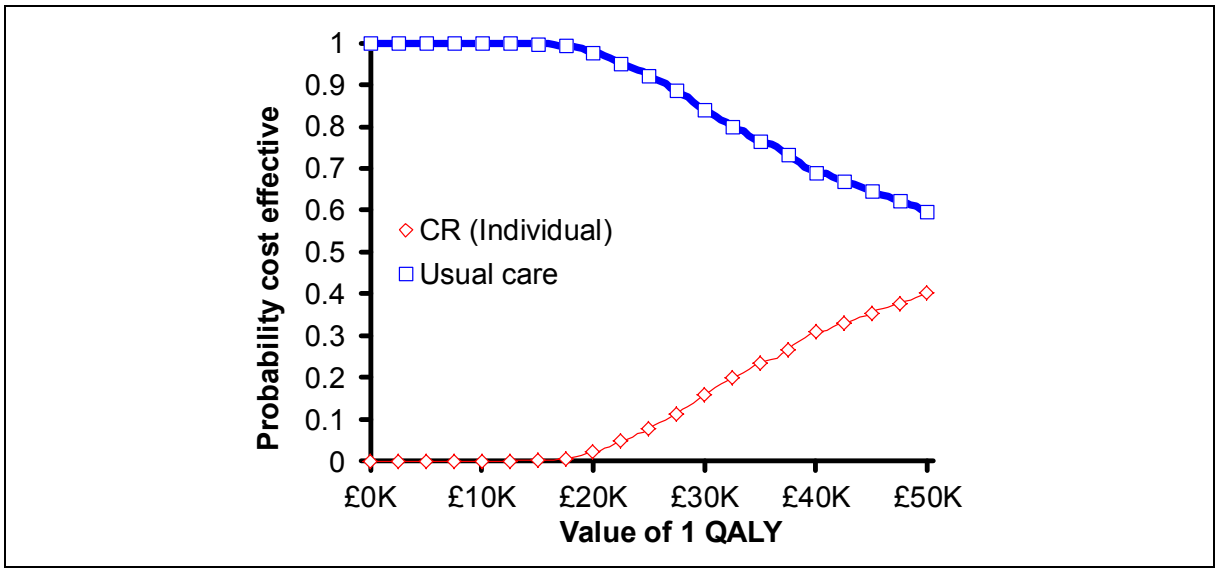



**Figure 3: CEAC for individual cognitive rehabilitation versus control**

### Cognitive training for groups

The base-case model suggested that cognitive training for groups was associated with a benefit of a little over 0.003 QALYs relative to control, at an additional cost of £653, leading to an ICER of £254,615/QALY. One-way sensitivity analysis found that the model was most sensitive to the use of the univariable MMSE model and the SMD for cognition at the end of the intervention. If the MMSE values in the univariable MMSE model and the SMD for cognition at the end of the intervention were increased to their highest plausible value, cognitive training may be a cost-effective treatment as the incremental net monetary benefit would be greater than zero.

**Table 69: Incremental costs and effects for group cognitive training versus control**

| | Absolute | | Incremental | | | Ceiling £ for this benefit[a] |
|---|---|---|---|---|---|---|
| | Costs | QALYs | Costs | QALYs | ICER | |
| **Base case (multivariable model)** | | | | | | |
| Control | £0 | 1.164 | | | | |
| Intervention | £653 | 1.166 | £653 | 0.003 | £251,615 | £52 |
| **Univariable model (MMSE)** | | | | | | |
| Control | £0 | 1.069 | | | | |
| Intervention | £653 | 1.163 | £653 | 0.094 | £6,978 | £1,871 |
| **Univariable model (ADCS-ADL)** | | | | | | |
| Control | £0 | 1.031 | | | | |
| Intervention | £653 | 1.039 | £653 | 0.008 | £78,324 | £167 |

[a] *The maximum intervention cost at which benefits of the magnitude estimated here would lead to an ICER of £20,000/QALY or better*

Probabilistic sensitivity analysis (Figure 4) suggested that the probability that intervention is cost-effective is around 11%, if QALYs are valued at £20,000 each, or 20%, if a higher threshold of £30,000/QALY is used.

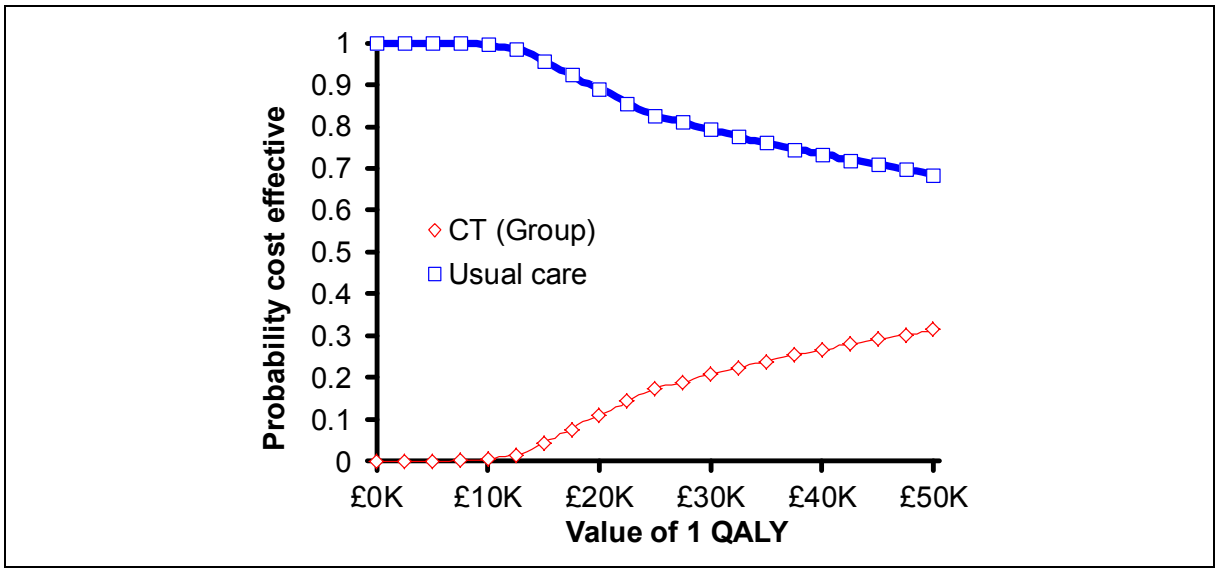



**Figure 4: CEAC for group cognitive training versus control**

### Reminiscence therapy in a group setting

Reminiscence therapy in a group setting relative to control was dominated in the base case, and had high ICERs in the univariable MMSE and ADCS-ADL models (Table 70). One-way sensitivity analysis found that the model was most sensitive to a lower cost per participant per course; however, variations to any single parameter did not result in ICERs below a £20,000/QALY threshold.

**Table 70: Incremental costs and effects for group reminiscence therapy versus control**

| | Absolute | | Incremental | | | Ceiling £ for this benefit[a] |
|---|---|---|---|---|---|---|
| | Costs | QALYs | Costs | QALYs | ICER | |
| **Base case (multivariable model)** | | | | | | |
| Control | £0 | 1.164 | | | | |
| Intervention | £964 | 1.160 | £964 | -0.004 | dominated | -£74 |
| **Univariable model (MMSE)** | | | | | | |
| Control | £0 | 1.069 | | | | |
| Intervention | £964 | 1.087 | £964 | 0.018 | £52,853 | £365 |
| **Univariable model (ADCS-ADL)** | | | | | | |
| Control | £0 | 1.031 | | | | |
| Intervention | £964 | 1.032 | £964 | 0.001 | £809,456 | £24 |

[a] *The maximum intervention cost at which benefits of the magnitude estimated here would lead to an ICER of £20,000/QALY or better*

Probabilistic sensitivity analysis (Figure 5) suggested that the probability that intervention is cost-effective is around 0%, if QALYs are valued at £20,000 each, or 0%, if a higher threshold of £30,000/QALY is used.

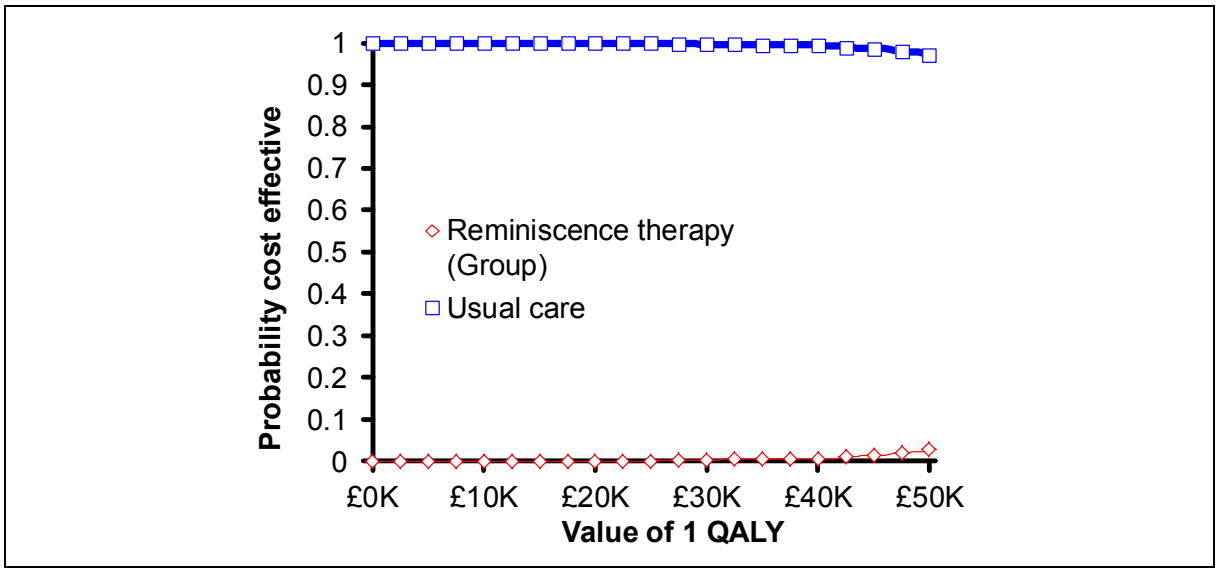



**Figure 5: CEAC for group reminiscence therapy versus control**

### One-to-one exercise therapy

The base-case model suggested that one-to-one exercise therapy was associated with a benefit of a little over 0.023 QALYs relative to control, at an additional cost of £1,776, leading to an ICER of £76,678/QALY(Table 71). One-way sensitivity analysis found that the model was most sensitive to a lower cost per course of individualised exercise therapy, but would still not make individualised exercise therapy a cost-effective treatment at the £20,000/QALY threshold.

**Table 71: Incremental costs and effects for one-to-one exercise therapy versus control**

| | Absolute | | Incremental | | | Ceiling £ for this benefit[a] |
|---|---|---|---|---|---|---|
| | Costs | QALYs | Costs | QALYs | ICER | |
| **Base case (multivariable model)** | | | | | | |
| Control | £0 | 1.164 | | | | |
| Intervention | £1,776 | 1.187 | £1,776 | 0.023 | £76,678 | £463 |
| **Univariable model (MMSE)** | | | | | | |
| Control | £0 | 1.069 | | | | |
| Intervention | £1,776 | 1.101 | £1,776 | 0.032 | £55,573 | £639 |
| **Univariable model (ADCS-ADL)** | | | | | | |
| Control | £0 | 1.031 | | | | |
| Intervention | £1,776 | 1.058 | £1,776 | 0.027 | £65,402 | £543 |

[a] *The maximum intervention cost at which benefits of the magnitude estimated here would lead to an ICER of £20,000/QALY or better*

Probabilistic sensitivity analysis (Figure 6) suggested that the probability that intervention is cost-effective is around 0%, if QALYs are valued at £20,000 each, or 2%, if a higher threshold of £30,000/QALY is used.

In a scenario analysis where costs relating to staff training, staff travel, venue, and administration were set to zero – and only staff time and participant travel expenses were accounted for, one-to-one exercise therapy was found to cost an additional £1,445 compared to control, and produced an ICER of £62,382/QALY.

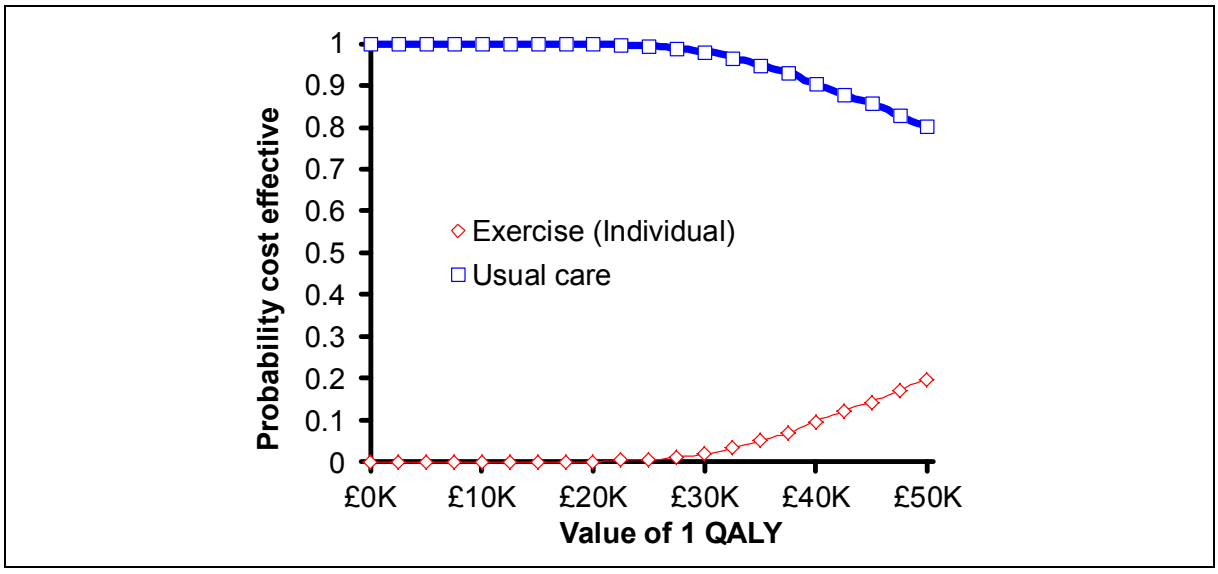



**Figure 6: CEAC for one-to-one exercise therapy versus control**

### Group exercise therapy

The base-case model suggested that group exercise therapy was associated with a benefit of a little over 0.042 QALYs relative to control, at an additional cost of £1,727, leading to an ICER of £41,359/QALY (Table 72). One-way sensitivity analysis found that the model was most sensitive to the cost per group session but only the indefinite long-term extrapolation scenario resulted in an ICER lower than £20,000/QALY.

**Table 72: Incremental costs and effects for group exercise versus control**

| | Absolute | | Incremental | | | Ceiling £ for this benefit[a] |
|---|---|---|---|---|---|---|
| | Costs | QALYs | Costs | QALYs | ICER | |
| **Base case (multivariable model)** | | | | | | |
| Control | £0 | 1.164 | | | | |
| Intervention | £1,727 | 1.206 | £1,727 | 0.042 | £41,359 | £835 |
| **Univariable model (MMSE)** | | | | | | |
| Control | £0 | 1.069 | | | | |
| Intervention | £1,727 | 1.124 | £1,727 | 0.054 | £31,791 | £1,087 |
| **Univariable model (ADCS-ADL)** | | | | | | |
| Control | £0 | 1.031 | | | | |
| Intervention | £1,727 | 1.049 | £1,727 | 0.019 | £92,373 | £374 |

[a] *The maximum intervention cost at which benefits of the magnitude estimated here would lead to an ICER of £20,000/QALY or better*

Probabilistic sensitivity analysis (Figure 7) suggested that the probability that intervention is cost-effective is around 15%, if QALYs are valued at £20,000 each, or 22%, if a higher threshold of £30,000/QALY is used.

In a scenario analysis where costs relating to staff training, staff travel, venue, and administration were set to zero – and only staff time and participant travel expenses were accounted for, group exercise therapy was found to cost an additional £1,529 compared to control, and produced an ICER of £36,600/QALY.

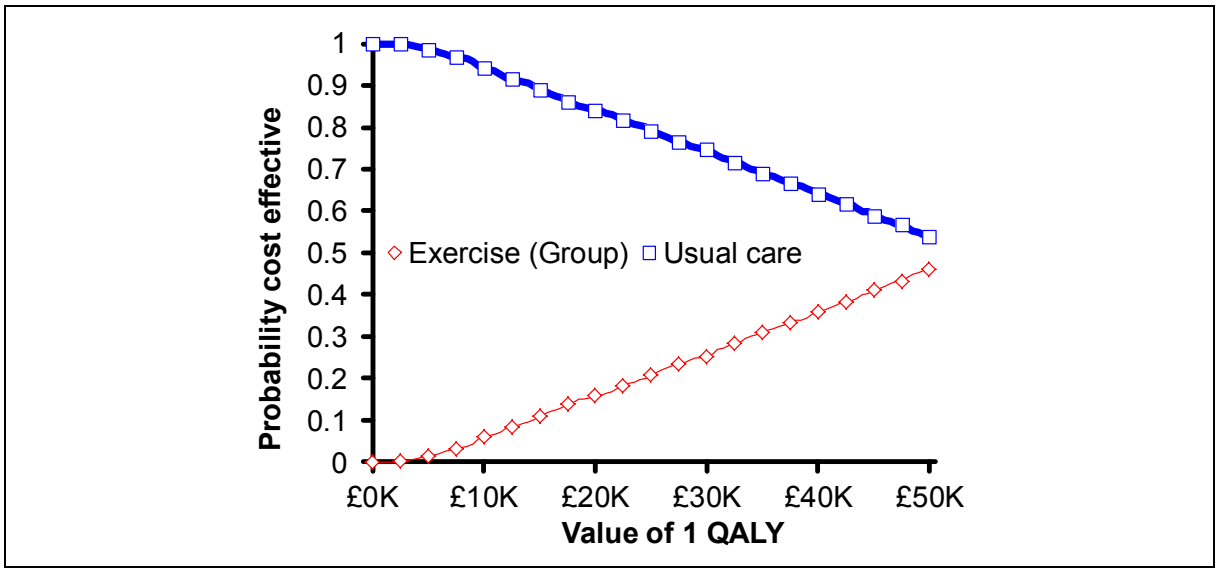



**Figure 7: CEAC for group exercise versus control**

### Group exercise therapy for people with severe dementia

The base-case model suggested that group exercise therapy for people with severe dementia was associated with a benefit of a little over 0.05 QALYs relative to control, at an additional cost of £1,510, leading to an ICER of £329,685/QALY (Table 73). One-way sensitivity analysis found that the model was most sensitive to the cost per patient per course, but no parameter variations suggested that the intervention would cost effective at a £20,000/QALY threshold.

**Table 73: Incremental costs and effects for group exercise therapy for people with severe dementia versus control**

| | Absolute | | Incremental | | | Ceiling £ for this benefit[a] |
|---|---|---|---|---|---|---|
| | Costs | QALYs | Costs | QALYs | ICER | |
| **Base case (multivariable model)** | | | | | | |
| Control | £0 | 1.164 | | | | |
| Intervention | £1,510 | 1.168 | £1,510 | 0.005 | £329,685 | £92 |
| **Univariable model (MMSE)** | | | | | | |
| Control | – | – | | | | |
| Intervention | – | – | – | – | – | – |
| **Univariable model (ADCS-ADL)** | | | | | | |
| Control | £0 | 1.031 | | | | |
| Intervention | £1,510 | 1.045 | £1,510 | 0.014 | £105,987 | £285 |

[a] *The maximum intervention cost at which benefits of the magnitude estimated here would lead to an ICER of £20,000/QALY or better*

Probabilistic sensitivity analysis (Figure 8) suggested that the probability that intervention is cost-effective is around 0%, if QALYs are valued at £20,000 each, or 0%, if a higher threshold of £30,000/QALY is used.

In a scenario analysis where costs relating to staff training, staff travel, venue, and administration were set to zero – and only staff time and participant travel expenses were accounted for, group exercise therapy for people with severe dementia was found to cost an

additional £1,367 compared to control, and produced an ICER of £298,488/QALY.

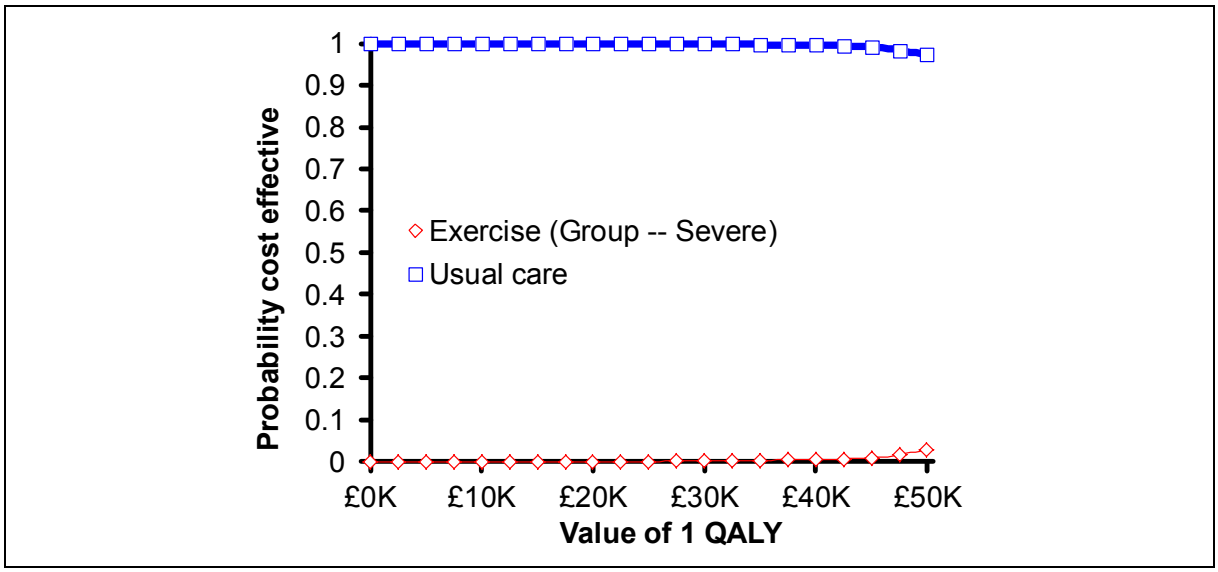



**Figure 8: CEAC for group exercise therapy for people with severe dementia versus control**

### Group music therapy (participatory)

The base-case model suggested that participatory group music therapy was associated with a benefit of a little over 0.016 QALYs relative to control, at an additional cost of £434, leading to an ICER of £26,944/QALY (Table 74). One-way sensitivity analysis found that plausible variations to 8 parameters resulted in ICERs lower than £20,000/QALY, including those relating to long-term extrapolation of treatment effects, lower costs of treatment, and treatment effects at the upper 95% confidence interval of synthesised estimates.

**Table 74: Incremental costs and effects for group music therapy versus control**

| | Absolute | | Incremental | | | Ceiling £ for this benefit[a] |
|---|---|---|---|---|---|---|
| | Costs | QALYs | Costs | QALYs | ICER | |
| **Base case (multivariable model)** | | | | | | |
| Control | £0 | 1.164 | | | | |
| Intervention | £434 | 1.180 | £434 | 0.016 | £26,944 | £322 |
| **Univariable model (MMSE)** | | | | | | |
| Control | £0 | 1.069 | | | | |
| Intervention | £434 | 1.083 | £434 | 0.014 | £31,369 | £276 |
| **Univariable model (ADCS-ADL)** | | | | | | |
| Control | £0 | 1.031 | | | | |
| Intervention | £434 | 1.059 | £434 | 0.028 | £15,599 | £556 |

[a] *The maximum intervention cost at which benefits of the magnitude estimated here would lead to an ICER of £20,000/QALY or better*

Probabilistic sensitivity analysis (Figure 9) suggested that the probability that intervention is cost-effective is around 22%, if QALYs are valued at £20,000 each, or 40%, if a higher threshold of £30,000/QALY is used.

In a scenario analysis where costs relating to staff training, staff travel, venue, and administration were set to zero – and only staff time and participant travel expenses were

accounted for, participatory group music therapy was found to cost an additional £364s compared to control, and produced an ICER of £22,623/QALY.

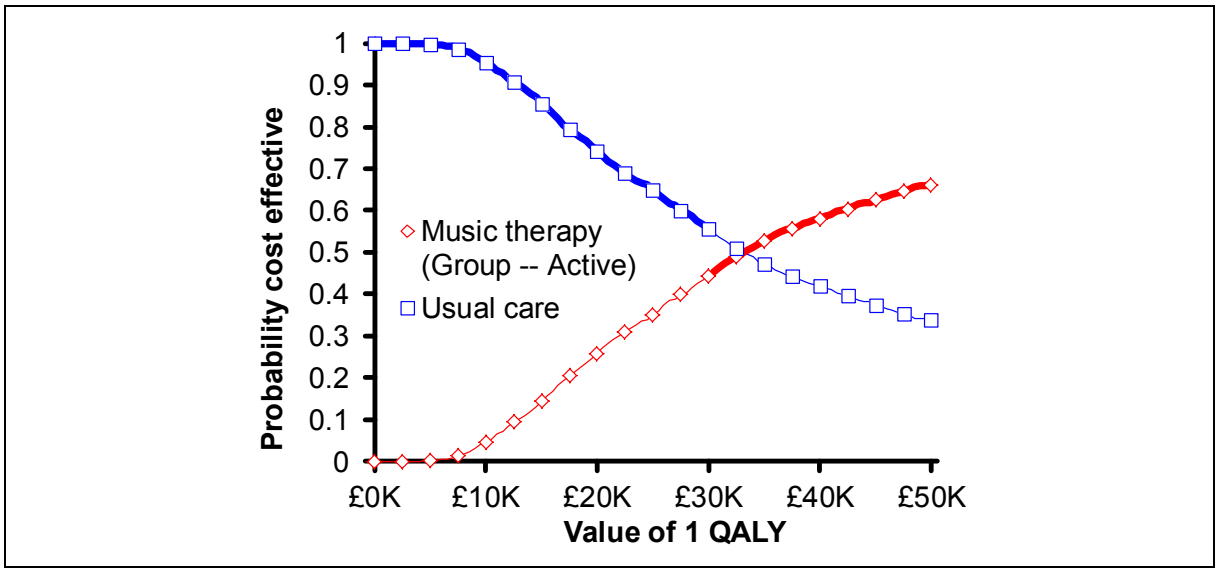



**Figure 9: CEAC for group music therapy versus control**

### One-to-one music therapy

The base-case model suggested that one-to-one music therapy was associated with a benefit of a little over 0.019 QALYs relative to control, at an additional cost of £1,010, leading to an ICER of £52,970 (Table 75). One-way sensitivity analysis found that the model was most sensitive to the long-term extrapolation scenario, with indefinitely projected benefit producing ICERs below £20,000/QALY.

**Table 75: Incremental costs and effects for one-to-one music therapy versus control**

| | Absolute | | Incremental | | | Ceiling £ for this benefit[a] |
|---|---|---|---|---|---|---|
| | Costs | QALYs | Costs | QALYs | ICER | |
| **Base case (multivariable model)** | | | | | | |
| Control | £0 | 1.164 | | | | |
| Intervention | £1,010 | 1.183 | £1,010 | 0.019 | £52,970 | £381 |
| **Univariable model (MMSE)** | | | | | | |
| Control | £0 | 1.069 | | | | |
| Intervention | £1,010 | 1.145 | £1,010 | 0.076 | £13,243 | £1,525 |
| **Univariable model (ADCS-ADL)** | | | | | | |
| Control | – | – | | | | |
| Intervention | – | – | – | – | – | – |

[a] *The maximum intervention cost at which benefits of the magnitude estimated here would lead to an ICER of £20,000/QALY or better*

Probabilistic sensitivity analysis (Figure 10) suggested that the probability that intervention is cost-effective is around 0%, if QALYs are valued at £20,000 each, or 10%, if a higher threshold of £30,000/QALY is used.

In a scenario analysis where costs relating to staff training, staff travel, venue, and administration were set to zero – and only staff time and participant travel expenses were

accounted for, one-to-one music therapy was found to cost an additional £883 compared to control, and produced an ICER of £46,329/QALY.

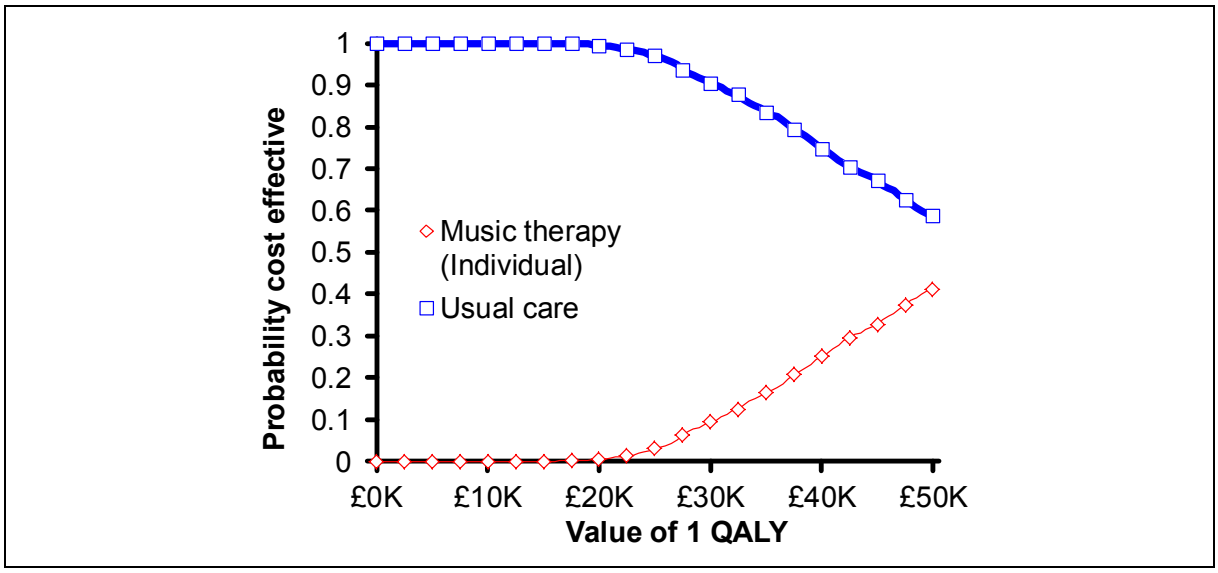



**Figure 10: CEAC for one-to-one music therapy versus control**

### Occupational therapy

The base-case model suggested that occupational therapy was associated with a benefit of a little over 0.010 QALYs relative to control, at an additional cost of £1,241, leading to an ICER of £130,349/QALY (Table 76). One-way sensitivity analysis found that the model was most sensitive to the MMSE and ADL variables, but no sensitivity analysis resulted in an ICER lower than £20,000/QALY.

**Table 76: Incremental costs and effects for occupational therapy versus control**

| | Absolute | | Incremental | | | Ceiling £ for this benefit[a] |
|---|---|---|---|---|---|---|
| | Costs | QALYs | Costs | QALYs | ICER | |
| **Base case (multivariable model)** | | | | | | |
| Control | £0 | 1.164 | | | | |
| Intervention | £1,241 | 1.173 | £1,241 | 0.010 | £130,249 | £191 |
| **Univariable model (MMSE)** | | | | | | |
| Control | – | – | | | | |
| Intervention | – | – | – | – | – | – |
| **Univariable model (ADCS-ADL)** | | | | | | |
| Control | £0 | 1.031 | | | | |
| Intervention | £1,241 | 1.055 | £1,241 | 0.025 | £50,509 | £491 |

[a] *The maximum intervention cost at which benefits of the magnitude estimated here would lead to an ICER of £20,000/QALY or better*

Probabilistic sensitivity analysis (Figure 11) suggested that the probability that intervention is cost-effective is around 0%, if QALYs are valued at £20,000 each, or 0%, if a higher threshold of £30,000/QALY is used.

In a scenario analysis where costs relating to staff training, staff travel, venue, and administration were set to zero – and only staff time and participant travel expenses were

accounted for, occupational therapy was found to cost an additional £1,176 compared to control, and produced an ICER of £123,393/QALY.

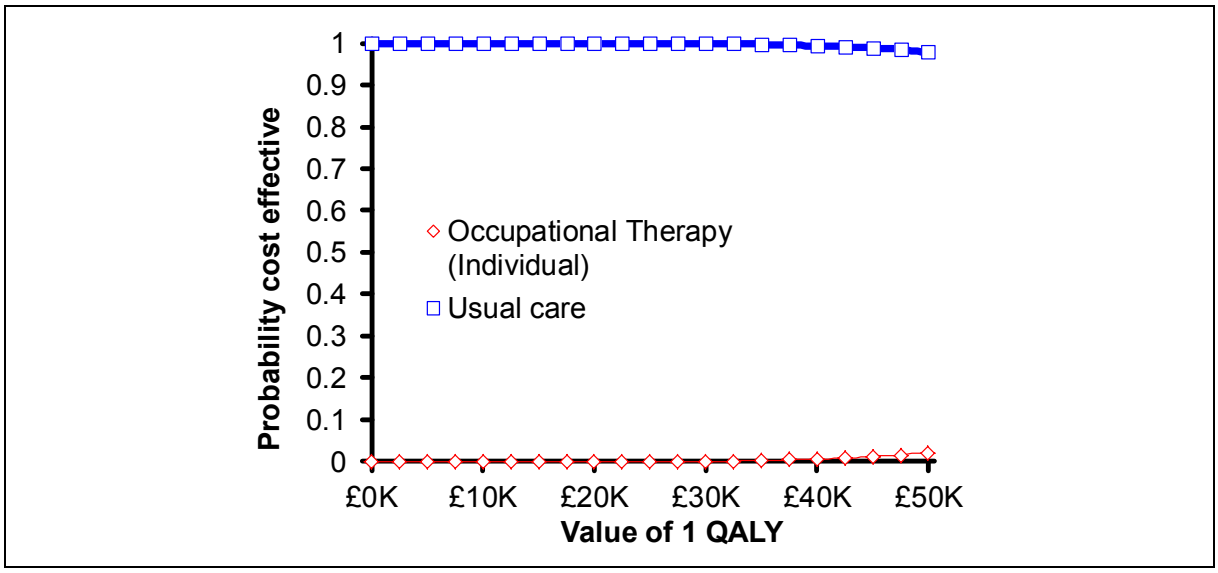



**Figure 11: CEAC for occupational therapy versus control**

### 13.2.4 Evidence statements

#### 13.2.4.1 Cognitive stimulation therapy

Moderate-quality evidence from up to 23 RCTs containing 1,398 participants found a clinically meaningfully improvement in cognition in people living with mild/moderate dementia offered cognitive stimulation therapy versus usual care.

Low- to high-quality evidence from up to 11 RCTs containing 895 participants could not detect clinically meaningful differences in activities of daily living, behavioural and psychological symptoms, depressive symptoms, quality of life or carer burden between people living with mild/moderate dementia offered cognitive stimulation therapy versus usual care.

##### *13.2.4.1.1 Economic evidence*

One directly applicable original cost–utility model with potentially serious limitations comparing high-intensity group cognitive stimulation therapy with usual care suggested that group cognitive stimulation therapy is associated with an ICER of approximately £20,000/QALY. However, one-way sensitivity analysis found that this finding was extremely sensitive; varying almost any parameter within a plausible range generates results lying on either side of a £20,000/QALY threshold. A scenario analysis where costs relating to staff training, staff travel, venue and administration were set to zero resulted in an ICER of £17,000/QALY.

One directly applicable cost–utility analysis with minor limitations conducted alongside a 6-month RCT explored the cost effectiveness of maintenance cognitive stimulation therapy in patients in England. Only where QALYs were calculated from proxy EQ-5D was maintenance CST associated with an ICER of less than £30,000 per QALY. When QALYs were calculated using the person living with dementia's own rating, the intervention was not cost-effective at 6 months.

#### 13.2.4.2 Cognitive training

Very low- to moderate-quality evidence from up to 12 RCTs containing 608 participants could not detect clinically meaningful differences in cognition, activities of daily living, behavioural and psychological symptoms, depressive symptoms, quality of life or carer burden between people living with mild/moderate dementia offered cognitive training versus usual care.

##### *13.2.4.2.1 Economic evidence*

One directly applicable original cost–utility model with potentially serious limitations comparing high-intensity group cognitive training with usual care suggested that the intervention is associated with a base-case ICER of around £250,000/QALY. Alternative model assumptions resulted in a much more favourable of ICER of around £7,000/QALY; however, this was based on an estimated effect in the cognitive domain that was heavily influenced by 1 small RCT's extremely large but uncertain estimate of benefit. Other sensitivity analyses suggested a low probability of the intervention being associated with an ICER of £20,000/QALY or better.

#### 13.2.4.3 Cognitive rehabilitation

Moderate-quality evidence from up to 3 RCTs containing 527 participants found a clinically meaningfully improvement in activities of daily living in people living with mild/moderate dementia offered cognitive rehabilitation versus usual care.

Very low- to moderate-quality evidence from up to 5 RCTs containing 831 participants could not detect clinically meaningful differences in cognition, behavioural and psychological symptoms, depressive symptoms, quality of life or carer burden between people living with mild/moderate dementia offered cognitive rehabilitation versus usual care.

##### *13.2.4.3.1 Economic evidence*

One directly applicable original cost–utility model with potentially serious limitations comparing high-intensity cognitive rehabilitation with usual care showed that cognitive rehabilitation was associated with an ICER of around £67,000/QALY. One-way and probabilistic sensitivity analyses showed there is a very low probability of the intervention being associated with an ICER of £20,000/QALY or better.

One directly applicable cost–utility analysis with minor limitations conducted alongside an RCT explored the cost effectiveness of cognitive rehabilitation compared with usual care. For persons with dementia, the intervention was associated with substantial additional costs and negligible QALY gains, leading to an ICER in excess of £1m/QALY. There was no difference in quality of life between the cognitive rehabilitation group and the control group for carers of the person with dementia.

#### 13.2.4.4 Self-management groups

Low- to moderate-quality evidence from up to 3 RCTs containing 291 participants could not detect clinically meaningful differences in cognition, depressive symptoms or quality of life between people living with mild dementia offered access to self-management groups versus usual care.

#### 13.2.4.5 Reminiscence therapy

Very-low to moderate-quality evidence from up to 8 RCTs containing 1,432 participants found clinically meaningful post-intervention improvements in cognition and depressive symptoms in people living with dementia offered reminiscence therapy versus usual care, but the effects on depressive symptoms did not persist at long-term follow-up.

Low- to moderate-quality evidence from up to 5 RCTs containing 1,071 participants could not detect clinically meaningful differences in activities of daily living, behavioural and psychological symptoms, quality of life, agitation or carer burden between people living with dementia offered reminiscence therapy versus usual care.

##### *13.2.4.5.1 Economic evidence*

One directly applicable original cost–utility model with potentially serious limitations suggested that high-intensity group reminiscence therapy was a dominated strategy as it cost more and produced fewer QALYs than usual care. One-way and probabilistic sensitivity analyses showed no probability of the intervention being associated with an ICER of £20,000/QALY or better.

One directly applicable cost–utility analysis with minor limitations conducted alongside an RCT found that, when compared with usual care, joint reminiscence group therapy was associated with substantial extra costs of over £1,000 per participant, but did not produce any meaningful QALY gains for people living with dementia or carers, leading to an ICER in excess of £1m/QALY.

#### 13.2.4.6 Occupational therapy

Low- to high-quality evidence from up to 4 RCTs containing 491 participants found clinically meaningful post-intervention improvements in depressive symptoms and quality of life in people living with dementia offered occupational therapy versus usual care, but the effect on quality of life did not persist at long-term follow-up.

Very low- to moderate-quality evidence from up to 2 RCTs containing 313 participants could not detect clinically meaningful differences in activities of daily living, agitation or carer burden between people living with dementia offered occupational therapy versus usual care.

##### *13.2.4.6.1 Economic evidence*

One directly applicable original cost–utility model with potentially serious limitations comparing occupational therapy with usual care suggested that the intervention was associated with a base-case ICER of around £130,000/QALY. One-way, probabilistic and scenario analyses showed no probability of the intervention being associated with an ICER of £20,000/QALY or better.

#### 13.2.4.7 Psychotherapy

Moderate-quality evidence from up to 3 RCTs containing 125 participants found a clinically meaningful post-intervention improvement in depressive symptoms in people living with dementia offered psychotherapy versus usual care, but these effects did not persist at long-term follow-up.

Low- to moderate-quality evidence from up to 2 RCTs containing 95 participants could not detect clinically meaningful differences in cognition, activities of daily living, or quality of life between people living with dementia offered psychotherapy versus usual care.

#### 13.2.4.8 Exercise

Low- to high-quality evidence from up to 16 RCTs containing 1,474 participants found clinically meaningful post-intervention improvements in cognition, activities of daily living, global assessment and behavioural and psychological symptoms in people living with dementia offered exercise interventions versus usual care, but these effects did not persist at long-term follow-up.

Very low- to moderate-quality evidence from up to 7 RCTs containing 762 participants could not detect clinically meaningful differences in depressive symptoms, quality of life or carer burden between people living with dementia offered exercise interventions versus usual care.

##### *13.2.4.8.1 Economic evidence*

One directly applicable original cost–utility model with potentially serious limitations comparing high-intensity group exercise therapy with usual care suggested that the intervention was associated with a base-case ICER of around £41,000/QALY. Probabilistic sensitivity analysis showed less than 20% probability of the intervention being associated with an ICER of £20,000/QALY or better. A scenario analysis where costs relating to staff training, staff travel, venue, and administration were set to zero resulted in an ICER of £36,600/QALY. The only deterministic sensitivity analysis reducing the ICER to below £20,000/QALY was when the benefits of exercise were assumed to last indefinitely.

One directly applicable original cost–utility model with potentially serious limitations comparing high-intensity one-to-one exercise therapy with usual care suggested that the intervention was associated with a base-case ICER of around £77,000/QALY. One-way, probabilistic, and scenario analyses showed little probability of the intervention being associated with an ICER of £20,000/QALY or better.

One directly applicable original cost–utility model with potentially serious limitations comparing high-intensity group exercise therapy for people with severe dementia with usual care suggested that the intervention was associated with a base-case ICER of over £300,000/QALY. One-way, probabilistic and scenario analyses showed no probability of the intervention being associated with an ICER of £20,000/QALY or better.

One partially applicable cost-utility analysis with potentially serious limitations examined the cost-effectiveness of a moderate-to-high intensity aerobic exercise for patients with mild Alzheimer's disease in Denmark. The study found that exercise was associated with significant cost increases but very small QALY benefits, leading to high ICERs in excess of €100,000/QALY.

#### 13.2.4.9 Nutrition

##### *13.2.4.9.1 Ginkgo biloba*

Low- to moderate-quality evidence from up to 4 RCTs containing 319 participants could not detect clinically meaningful differences in cognition, activities of daily living or global assessment between people living with mild to moderate Alzheimer's disease offered ginkgo biloba versus placebo.

Low- to moderate-quality evidence from up to 6 RCTs containing 1,922 participants found clinically meaningful differences in cognition, activities of daily living, behavioural and psychological symptoms, global assessment and quality of life in people living with mild to moderate Alzheimer's disease or vascular dementia offered ginkgo biloba compared with placebo. The evidence was primarily from a population who had defined non-cognitive symptoms at baseline.

#### *13.2.4.9.2 Omega-3 fatty acids*

Moderate-quality evidence from up to 3 RCTs containing 604 participants could not detect clinically meaningful differences in cognition, activities of daily living, behavioural and psychological symptoms or dementia severity between people living with dementia offered omega-3 fatty acid supplementation versus placebo.

#### *13.2.4.9.3 Souvenaid*

Low- to moderate-quality evidence from up to 3 RCTs containing 879 participants could not detect clinically meaningful differences in cognition, activities of daily living, quality of life or dementia severity between people living with dementia offered souvenaid versus placebo.

#### *13.2.4.9.4 Huperzine A*

Very low- to low-quality evidence from up to 7 RCTs containing 648 participants found clinically meaningful improvements in cognition and activities of daily living in people living with mild to moderate Alzheimer's disease offered Huperzine A versus placebo or no intervention.

Moderate-quality evidence from 1 RCT containing 210 participants could not detect clinically meaningful differences in behavioural and psychological symptoms between people living with mild to moderate Alzheimer's disease offered Huperzine A versus placebo or usual care.

#### *13.2.4.9.5 Tailored nutritional guidance*

Moderate-quality evidence from 1 RCT containing 78 participants found a clinically meaningful post-intervention improvement in quality of life in people living with dementia offered tailored nutritional guidance versus usual care.

#### *13.2.4.9.6 Other nutritional interventions*

Moderate-quality evidence from up to 3 RCTs containing 226 participants could not detect clinically meaningful differences between people living with dementia offered ginseng, vitamin E supplements or other nutritional or herbal formulations and those offered placebo or no intervention.

### 13.2.4.10 Music therapy

#### *13.2.4.10.1 Music therapy versus usual care*

Very low- to moderate-quality evidence from up to 5 RCTs containing 322 participants found clinically meaningful post-intervention improvements in cognition and activities of daily living in people living with mild/moderate dementia offered music therapy versus usual care. These effects were consistent when trials only recruiting people with non-cognitive symptoms at baseline were excluded, but did not persist at long-term follow-up.

Very low- to moderate-quality evidence from up to 2 RCTs containing 236 participants found clinically meaningful long term follow-up improvements in agitation, quality of life and carer

burden in people living with mild/moderate dementia offered music therapy versus usual care. These effects were consistent when trials only recruiting people with non-cognitive symptoms at baseline were excluded, but were not found in post-intervention measurements.

Very low- to low-quality evidence from up to 2 RCTs containing 124 participants could not detect clinically meaningful differences in behavioural, psychological or depressive symptoms, or, between people living with mild/moderate dementia offered music therapy versus usual care.

**Economic evidence**

One directly applicable original cost–utility model with potentially serious limitations comparing group participatory music therapy with usual care showed that participatory group music therapy was associated with a base-case ICER of around £27,000/QALY. One-way sensitivity analysis found that varying several parameters within plausible ranges generated ICERs lying on either side of a £20,000/QALY threshold. Probabilistic sensitivity analysis showed a 26% probability that the intervention is associated with an ICER of £20,000/QALY or better. A scenario analysis where costs relating to staff training, staff travel, venue and administration were set to zero resulted in an ICER of £23,000/QALY.

One directly applicable original cost–utility model with potentially serious limitations comparing one-to-one music therapy with usual care suggested that the intervention was associated with a base-case ICER of around £53,000/QALY. Some alternative model assumptions resulted in much more favourable ICERs; however, probabilistic sensitivity analyses showed very little probability of the intervention being associated with an ICER of £20,000/QALY or better. A scenario analysis where costs relating to staff training, staff travel, venue and administration were set to zero resulted in an ICER of £46,000/QALY.

#### *13.2.4.10.2 Music therapy versus active control*

Very low- to low-quality evidence from up to 3 RCTs containing 104 participants could not detect clinically meaningful differences in cognition, behavioural and psychological symptoms, depressive symptoms, agitation, quality of life or carer burden between people living with mild/moderate dementia offered music therapy versus an active control intervention.

### 13.2.4.11 Aromatherapy

Low-quality evidence from 1 RCT containing 56 participants found a clinically meaningfully improvement in depressive symptoms in people living with dementia offered aromatherapy versus usual care.

Very low to low-quality evidence from up to 3 RCTs containing 190 participants could not detect clinically meaningful differences in behavioural and psychological symptoms, agitation, activities of daily or quality of life between people living with dementia offered aromatherapy versus usual care.

### 13.2.4.12 Light therapy

Very-low to low-quality evidence from up to 2 RCTs containing 103 participants could not detect clinically meaningful differences in cognition, behavioural and psychological symptoms, depressive symptoms, agitation or activities of daily living between people living with dementia offered bright light therapy versus usual care.

#### 13.2.4.13 Non-invasive brain stimulation

##### *13.2.4.13.1 Alzheimer's disease*

Very-low to low quality evidence from up to 5 RCTs containing 105 participants could not detect clinically meaningful differences in cognition, activities of daily living, or depressive symptoms between people living with mild, moderate or severe dementia offered non-invasive brain stimulation versus usual care.

##### *13.2.4.13.2 Vascular dementia*

Very-low quality evidence from 1 RCT containing 21 participants could not detect clinically meaningful differences in cognition between people living with mild vascular dementia offered non-invasive brain stimulation versus usual care.

#### 13.2.4.14 Acupuncture

Very-low to low-quality evidence from up to 2 RCTs containing 223 participants could not detect clinically meaningful differences in cognition or activities of daily living between people living with dementia offered acupuncture versus no treatment.

#### 13.2.4.15 Animal assisted therapy

Very-low to moderate-quality evidence from 1 RCT containing 50 participants found a clinically meaningful improvement in depressive symptoms at long-term follow-up in people living with dementia offered animal-assisted therapy versus usual care, but could not detect a difference post-intervention, or in quality of life at any time point.

#### 13.2.4.16 Robotic pet therapy

High-quality evidence from 1 RCT containing 61 participants found a clinically meaningful improvement in depressive symptoms in people living with dementia offered robotic pet therapy versus usual care.

#### 13.2.4.17 Adapted mindfulness program

Very low- to low-quality evidence from 1 RCT containing 28 participants found a clinically meaningful improvement in quality of life, but could not detect a difference post-intervention in cognition or depressive symptoms in people living with dementia who took part in an adapted mindfulness program plus treatment as usual versus treatment as usual alone.

#### 13.2.4.18 Home Safety Toolkit

Moderate-quality evidence from 1 RCT containing 108 people could not differentiate caregiver self-efficacy, caregiver strain, home safety or risky behaviour scales between people offered a home safety toolkit intervention versus usual care.

### 13.2.5 Evidence to recommendations

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| **Relative value of different outcomes** | The committee noted that there were four primary outcomes of relevance to the questions considered in this review: cognition, functional ability, independence and wellbeing (most commonly measured through quality of life). They noted that different interventions often primarily targeted different domains and would therefore be most likely to have an impact on those domains, but it would be appropriate |

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| | to measure the impact of all interventions across all domains, as there are considerable levels of interaction between each of the different outcomes.<br>The committee also noted that it is important to separate out the short term benefits of the interventions (i.e. those that only persist for as long as the intervention is delivered) from any longer term benefits that remain after the intervention is stopped. The evidence was therefore divided in to two time points; outcomes measured at the end of an intervention, and any long-term follow-up measured after the intervention was stopped. |
| **Trade-off between benefits and harms** | **Cognitive stimulation therapy and reminiscence therapy**<br>The committee noted there were improvements in cognition in people offered cognitive stimulation therapy, and the average improvement was around the level that would be considered meaningful for an individual (approximately 1.4 points on the MMSE). Only a small number of trials reported follow-up after the intervention stopped, but there was no evidence the effects went away again after the intervention, with very similar (and still statistically significant) effect sizes. The effects of group interventions seemed to be larger than those of individual interventions, and no evidence of benefit was found on outcomes other than cognition.<br>Similar short-term results were found for reminiscence therapy, with again an improvement in cognition, though in this case with no evidence of those effects persisting after the end of the intervention, and the number of included studies was smaller. Again, group interventions appeared to provide more benefits on average than those delivered individually. The committee noted that in practice the two interventions were not mutually exclusive, with cognitive stimulation therapy often including elements of reminiscence.<br>The committee agreed there was evidence of benefits from both interventions, but the evidence was stronger for cognitive stimulation than for reminiscence, and therefore agreed it was appropriate to make a strong ('offer') recommendation for cognitive stimulation therapy, and a weaker ('consider') recommendation for reminiscence therapy.<br>**Cognitive training**<br>The committee noted there was now a considerable body of evidence on cognitive training providing no evidence of value in any of the relevant domains, and therefore agreed it was appropriate to make a recommendation that cognitive training not be offered. The majority of the evidence base was in people with mild to moderate Alzheimer's disease, and therefore the committee agreed to restrict the recommendation to this population, as they noted there were other types of dementia (e.g. semantic dementia) where cognitive training might have benefits, and where it has not yet been tested.<br>**Cognitive rehabilitation and occupational therapy**<br>The committee noted that both the large studies of cognitive rehabilitation showed improvements in activities of daily living, with particularly large benefits shown in the recent UK HTA study. Benefits for depression and quality of life were also shown with occupational therapy, although a difference in activities of daily living could not be demonstrated here, as a number of the trials did not measure this as an outcome. However, the committee agreed that since the primary focus of occupational therapy interventions was on ADL, the impairments in quality of life seen were highly likely to be mediated through improvements in ADL.<br>The committee agreed the evidence was sufficient to make 'consider' recommendations for both cognitive rehabilitation and occupational therapy, and also agreed it was important to stress these interventions were designed to target functional ability, as they would be unlikely to be effective for people who do not have concerns about functional limitations. |

**Individualised activities**

The committee noted there was evidence of some benefits across a range of domains from exercise, aromatherapy, music therapy, mindfulness and animal assisted therapy. However, the magnitudes of these benefits were uncertain, and there was considerable variability in both the structure and intensity of the interventions tested. The committee also noted that taking one particular activity and offering that to all people living with dementia is unlikely to be the most effective approach, nor is this what is done in practice.

The committee agreed the more appropriate recommendation was that people should be offered access to a range of activities that should be tailored to their individual preferences. They agreed such an approach was likely to be more effective than the blanket provision of a specific activity (such has music therapy being provided to everyone), and was justified by the evidence showing evidence of benefits across a range of different activities. They also agreed that it was appropriate not to list any specific activities under this heading, as the important part of the recommendation was about the activities being individualised, rather than what they actually are.

The individual activity with the strongest evidence of benefits individually was exercise, but the committee were aware of the soon to be published DAPA (Dementia and Physical Activity) study looking at the effectiveness and cost-effectiveness of structured exercise provision in the UK, and felt that in the absence of those results it was not appropriate to make a specific positive recommendation for exercise.

**Nutrition**

The committee noted there was no evidence of benefits from a range of supplements and nutritional interventions, including omega-3 fatty acids, souvenaid, ginseng and various vitamin and herbal supplements. The committee therefore agreed it was appropriate to make a ‘do not offer’ recommendation for these for the purposes of treating dementia. Some evidence was identified showing potential benefits of huperzine A, but this evidence was of low quality and conducted in populations often not directly comparable to the UK (in particular, it was unclear if people were taking cholinesterase inhibitors in the study, and how robust the diagnosis of Alzheimer’s disease in many of the studies was). The committee agreed the evidence was therefore not sufficient to make either a positive or a negative recommendation.

The studies did not suggest any evidence of benefits from ginkgo biloba supplements in a population of people with Alzheimer’s disease alone. In a mixed population with Alzheimer’s disease, vascular dementia, or comorbid Alzheimer’s disease and vascular dementia, there was evidence of benefits, but the majority of the evidence in these studies came from studies where people were only recruited if they had behavioural symptoms at baseline (defined as being above a certain threshold on the NPI). The committee therefore agreed this evidence was best considered in the section of the guideline on managing non-cognitive symptoms in people living with dementia (section 14).

**Other interventions**

The committee noted that there were no meaningful benefits found in trials of psychotherapy (specifically interpersonal therapy), acupuncture or non-invasive brain stimulation, and therefore it was appropriate to make ‘do not offer’ recommendations for these interventions even in the absence of proven clinical harm, as money spent on these interventions would be better used on interventions where there is evidence of benefits. However, they noted that non-invasive brain stimulation is still an active area of research, and therefore added a caveat to that recommendation to allow it still to be used within the context of clinical trials. No positive evidence was found in this section for light therapy either, but since this was already recommended within the section of the

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| | guideline on managing sleep problems, the committee agreed it was appropriate to make no comment on this within this section.<br>Finally, the committee considered the evidence on self-management groups was insufficient to make either a positive or a negative recommendation. In particular, self-management interventions were agreed to comprise such a wide range of possible interventions that the literature currently available did not cover the full range of possible interventions adequately to be able to make recommendations, and therefore the committee agreed the appropriate action was to make a research recommendation around the effectiveness of self-management for people living with dementia and their carers. |
| **Trade-off between net health benefits and resource use** | For these review questions, the systematic literature reviews identified one economic study each for the interventions of cognitive rehabilitation, maintenance cognitive stimulation therapy, joint reminiscence group therapy and exercise.<br>The committee noted that a commonly cited paper assessing the cost effectiveness of cognitive stimulation therapy, Knapp et al. (2006) had not been included as evidence for this guideline, but understood this was because it did not meet the NICE reference case, as health outcomes were not measured using QALYs. The committee were satisfied that the trial data underpinning Knapp et al. (2006) was considered in the original economic modelling using quantitative synthesis techniques.<br>Although cognitive rehabilitation as per the Clare et al (in press) trial was found to be more expensive than usual care, and was unable to demonstrate a statistically significant benefit in terms of QALYs, the committee were not convinced that the clinical benefit that this treatment provided was adequately captured. The committee agreed that a similar situation existed for joint reminiscence group therapy as per the Woods et al. (2016) study and exercise as per the Sopina et al. (2017) study.<br>Although cognitive rehabilitation, maintenance cognitive stimulation therapy and joint reminiscence group therapy and exercise were not found to be cost effective at conventional thresholds in the primary analyses, the guideline committee questioned the robustness of these studies in the light of a systematic review and meta-analyses that indicated positive benefits on clinically important domains. These interventions were therefore prioritised for original economic modelling.<br>All interventions selected for original economic modelling were associated with QALY gains in the region of 0.03 QALYs with the exceptions of cognitive training (0.003 QALYS) and reminiscence therapy (-0.004).<br>However, interventions varied in terms of costs and resultant ICERs, with most of the high-intensity interventions modelled never likely to be a cost-effective option even if QALYs are valued at £50,000 or more each. The committee noted that the interventions tested in the trials (and therefore on which the costs in this analysis were based) were considerably more intensive than those currently offered in UK practice. Therefore, the evidence was agreed to demonstrate that high-intensity, long-term interventions were unlikely to be an effective use of resources.<br>However, the committee noted that there was no clear pattern in the evidence that high intensity interventions were more effective than lower intensity ones. In particular, a number of recent trials of intensive interventions (e.g. reminiscence therapy - Woods 2016) did not show larger effects than trials of less intensive interventions. Therefore, the committee was confident that these interventions could be delivered in a much cheaper way than those measured in the more intensive trials, whilst still providing benefits for people living with dementia.<br>When uncertainty in model parameters was explored, some of these intensive interventions had the potential to be cost-effective. |

In the base case, group cognitive stimulation therapy was found to be marginally cost effective at the £20,000/QALY threshold. However, the one-way sensitivity analysis conducted for group cognitive stimulation therapy found that the model was extremely sensitive to many parameters in the model, and varying any parameter within plausible range generates results lying on either side of a £20,000/QALY threshold. The case for group cognitive stimulation therapy was strengthened by a scenario analysis where costs relating to staff training, staff travel, venue and administration were set to zero –that is, only staff time and participant travel expenses were accounted for. This too resulted in group cognitive stimulation therapy being associated with an ICER of less than £20,000/QALY. Furthermore, the committee reported that many CCGs did not pay for participant travel and used staff at band 2 and band 4 on the agenda for change pay scale, rather than the staff at band 4 and band 6 as assumed in the original model. Assuming that the effectiveness of the intervention remains the same, these further modifications would only reduce the cost and increase the cost effectiveness of group cognitive stimulation therapy. Furthermore, the committee noted that one of the cost–utility analyses from the included study by D'Amico (2015) found that maintenance CST was associated with an ICER of between £20,000 and £30,000/QALY (health and social cares perspective; effects measured using proxy-EQ-5D). The committee therefore felt it appropriate to create a strong ('offer') recommendation for group cognitive stimulation therapy.

The committee also noted that the original models were likely to be somewhat conservative, as there were potential benefits they did not capture such as impact on carers, and potential cost savings to other services that may result from providing people with appropriate support.

Although reminiscence therapy was associated with a negative QALY gain, and was technically dominated, this was driven by a loss in the behavioural domain larger than we would expect, which was only partially offset by a benefit in the cognitive domain larger than we would expect. The committee also took into account the very small loss of QALYs associated with the model (-0.004) and did not believe that reminiscence therapy would result in any harm, and considered it misleading to think of it as a dominated strategy.

The committee also considered the original economic evidence for cognitive training in detail and found the high ICER of the base-case model to be an unacceptable use of NHS resources. The committee considered the univariable sensitivity analysis, which only took into account effects in the cognitive domain, and produced an ICER well below traditionally acceptable cost-effectiveness thresholds. However, the committee was not convinced that this evidence was reliable, as the meta-analysis on which it was based was disproportionately influenced by a single, small RCT (Bergamaschi et al., 2013), which showed a very large positive effect on the MMSE scale of 6.3 points in favour of cognitive training. The committee did not believe that the intervention could feasibly have an effect of this magnitude, and noted that the apparent cost effectiveness of cognitive training, in this sensitivity analysis, disappeared when this datapoint was excluded from analysis. Therefore, the committee was confident in making a strong ('do not') recommendation against cognitive training.

The committee also considered the original evidence for cognitive rehabilitation and occupational therapy and agreed that, although the base-case analyses resulted in ICERs higher than £30,000/QALY, use of alternate model structures could result in more favourable ICERs. The committee noted that, using the univariable ADL model (that is, focusing only on the domain in which cognitive rehabilitation aims to achieve its effect), cognitive rehabilitation resulted in an ICER of £26,006/QALY compared with standard care. Furthermore, the committee agreed that, while large ADL benefits had been shown in the

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|---|---|
| | recent UK HTA study, these had not translated into quality of life benefits as measured by the instrument used in that RCT (DEMQOL-U). As ADL measurements had been specifically targeted at factors that affected each participant's day-to-day life, committee members expressed a belief that a more sensitive quality of life instrument would have reflected the benefits in ADL shown. The committee also agreed that the available analyses did not adequately capture the benefits of occupational therapy. The committee noted that the role of occupational therapy is well established for a broad range of people who have restricted ADL. It noted that, in some analogous conditions (for example, Parkinson's disease) NICE committees had reviewed evidence that enabled them to make strong ("offer") recommendations for occupational therapy. The committee concluded that this was supportive evidence that patients with dementia are likely to obtain cost-effective benefit from this intervention, too. Overall, the committee believed that both these interventions are most likely to benefit people with mild or moderate dementia. As a result of this, the committee felt a 'consider' recommendation was most appropriate for cognitive rehabilitation and occupational therapy.<br>The committee also noted that resources were already spent in the current system on providing both group activities and support with activities of daily living for people living with dementia. The recommendations were therefore agreed not to be likely to be associated with a substantial resource impact associated with new investment, but were rather advising people on the most effective ways to use the resources already allocated to supportive interventions for people living with dementia. They also noted there would be potential savings from the number of 'do not' recommendations made for ineffective interventions. |
| **Quality of evidence** | The committee noted that the evidence around cognitive stimulation, reminiscence therapy, occupational therapy and cognitive rehabilitation was predominantly in a population of people with mild to moderate dementia, and agreed it was likely that interventions would need to be delivered in different ways for people with more severe dementia. Therefore, they agreed it was appropriate to focus those recommendations on people with mild to moderate dementia. The evidence on individual activities (particular music and exercise) came from a more varied population and did include studies in people with severe dementia, and therefore the committee were comfortable for that recommendation to apply to the whole population.<br>The committee noted that, for the interventions that were not found to be effective, some of the trials were conducted solely or predominantly in people with Alzheimer's disease (cognitive training, interpersonal therapy and non-invasive brain stimulation), and therefore the recommendations made should be specific to that population. The trials on acupuncture and nutrition tended to recruit a more general population of people living with dementia, and therefore the committee were confident to apply those recommendations to the broader group. |
| **Other considerations** | The committee noted that one possible interpretation of the evidence base identified for this review question was that the benefits of many of these interventions were driven less by the specific content of the interventions, and more by the benefits from support groups more generally. Therefore, the committee agreed it was appropriate to make a research recommendation around the effectiveness of unstructured activities as an intervention, to test this hypothesis. |

### 13.2.6 Recommendations

82. **Offer a range of activities to promote wellbeing that are tailored to the person's individual preferences.**

83. **Offer group cognitive stimulation therapy to people living with mild to moderate dementia.**

84. **Consider group reminiscence therapy for people living with mild to moderate dementia.**

85. **Consider cognitive rehabilitation or occupational therapy to support functional ability in people living with mild to moderate dementia.**

86. **Do not offer acupuncture to treat dementia.**

87. **Do not offer ginseng, vitamin E supplements or herbal formulations to treat dementia.**

88. **Do not offer cognitive training to treat mild to moderate Alzheimer's disease.**

89. **Do not offer interpersonal therapy to treat the cognitive symptoms of mild to moderate Alzheimer's disease.**

90. **Do not offer non-invasive brain stimulation (including transcranial magnetic stimulation) to treat mild to moderate Alzheimer's disease, except as part of a randomised controlled trial.**

### 13.2.7 Research recommendations

10. **What are the most effective psychosocial interventions for improving cognition, independence, activities of daily living and wellbeing in people living with dementia?**

11. **What is the effectiveness of unstructured community activities on wellbeing for people living with dementia?**

12. **What is the effectiveness and cost-effectiveness of self-management training for people living with dementia and their carers?**

For more details on the research recommendations made, and the rationale behind them, see appendix L.

# 14 Managing non-cognitive symptoms

The cognitive problems associated with dementia are well established, but up to 90% of people with dementia may also be affected by non-cognitive symptoms of dementia. These symptoms can lead to significant changes in behaviour that include increased aggression, anxiety, apathy, agitation, depression, delusions, hallucinations and sleep disturbances.

These behaviours often reflect a high level of distress being felt by the person with dementia that they may not be able to communicate or understand, but these behaviours can also have significant adverse effects on the people involved in caring for the person with dementia. For example, the occurrence of sleep problems and wandering by people with dementia will disrupt their carer's sleep patterns and is likely to have a severe effect on their carer's mental state and ability to cope over time. Carer responses to these non-cognitive symptoms can also increase distress for the person with dementia and may lead to their being prescribed medication to try to control these behaviours. The inability of these treatments to successfully manage the non-cognitive behavioural symptoms may ultimately result in the institutionalisation of the person with dementia when the carer becomes unable to cope. However, staff within these care homes may also struggle to manage these behavioural issues and may in turn refer the person with dementia to specialist nursing care.

Thus, the non-cognitive symptoms associated with dementia have severe adverse effects on the person with dementia, family and both paid and unpaid carers. If these could be treated successfully this would have a big impact on the quality of life for everyone concerned and could lead to people with dementia being able to remain in their homes or with family.

There are a range of potential treatments for the non-cognitive symptoms of dementia which can be divided into two groups: pharmacological and non-pharmacological interventions. Pharmacological interventions are targeted to the problematic behaviour of the person with dementia and include the use of antidepressants, antipsychotics, mood stabilisers and drugs to modify sleep patterns. In contrast, non-pharmacological interventions take a wider view and may include approaches aimed at: resetting sleep patterns using bright light therapy or by increasing the activity levels of the person with dementia; calming and distracting an agitated person; and altering the carer's behaviour to better cope with and manage the person with dementia. In addition, anxiety and depression may be treated using cognitive behavioural therapy, multisensory stimulation, relaxation and animal-assisted therapies.

This chapter focuses on the range of pharmacological and non-pharmacological interventions to address non-cognitive symptoms for which rigorous evidence from randomised controlled trials is available. The non-cognitive symptoms examined include depression, which is the subject of specific NICE guidance in its own right. However, it was decided that there were additional factors that needed to be taken into consideration for people with dementia and as a result depression was addressed in this specific context.

# 14.1 Interventions for treating illness emergent non-cognitive symptoms in people living with dementia

**Review questions**

- What are the most effective pharmacological interventions for managing illness emergent non-cognitive symptoms, such as psychosis, depression, behavioural changes in people living with dementia?
- What are the most effective non-pharmacological interventions for managing illness emergent non-cognitive symptoms, such as psychosis, depression, behavioural changes in people living with dementia?

## 14.1.1 Introduction

The aim of these review questions was to determine the effectiveness of different pharmacological and non-pharmacological interventions for treating illness emergent non cognitive symptoms in people living with dementia. The review identified studies that fulfilled the conditions specified in Table 77 and Table 78. For full details of the review protocols, see appendix C.

**Table 77: Review summary: pharmacological interventions**

| | |
|---|---|
| **Population** | People (aged 40 years and over) living with dementia |
| **Interventions** | Pharmacological interventions for treating illness emergent non-cognitive symptoms, which may include:<br>• Antipsychotics<br>• Cholinesterase inhibitors<br>• Memantine<br>• Carbamazepine<br>• Valproate (mood stabilisers)<br>• Antidepressants<br>• Anxiolytics<br>• Propranolol<br>• Hypnotics |
| **Comparator** | • Each other<br>• Standard care |
| **Outcomes** | • Change in/resolution of non-cognitive symptoms<br>• Clinical outcomes including cognitive, functional and behavioural ability<br>• Adverse events<br>• Access to health and social care support<br>• Patient and carer experience and satisfaction<br>• Patient and carer health-related quality of life<br>• Resource use and costs |

**Table 78: Review summary: non-pharmacological interventions**

| | |
|---|---|
| **Population** | People (aged 40 years and over) living with dementia |
| **Interventions** | • Non-pharmacological interventions for treating illness emergent non-cognitive symptoms |
| **Comparator** | • Each other<br>• Standard care |

| | |
|---|---|
| **Outcomes** | • Change in/resolution of non-cognitive symptoms<br>• Clinical outcomes including cognitive, functional and behavioural ability<br>• Adverse events<br>• Access to health and social care support<br>• Patient and carer experience and satisfaction<br>• Patient and carer health-related quality of life<br>• Resource use and costs |

### 14.1.2 Evidence review

This review was conducted as an update from the previous dementia guideline (CG42). All included RCTs and systematic reviews from the previous guideline, together with all RCTs in included systematic reviews, were screened at title and abstract level. RCTs from included systematic reviews were excluded if they did not meet the criteria of enrolling patients with dementia and an illness-emergent non-cognitive symptom at baseline.

In addition, a systematic literature search for randomised controlled trials since the time of the last guideline identified 2,645 references. These were screened at title and abstract level, with 103 papers ordered as potentially relevant systematic reviews, 196 ordered as potentially relevant RCTs; 40 systematic reviews and 104 RCTs were ordered for pharmacological interventions; 63 systematic reviews and 92 RCTs were ordered as potentially relevant for non-pharmacological interventions. Finally, 21 papers identified through the literature search for the question on the management of pre-existing mental health conditions were also included as part of this question. Summaries of the included studies are provided below, with details of all excluded studies given in Appendix F.

For the full evidence tables and full GRADE profiles for included studies, please see Appendix E and Appendix G. References for the included studies are given in appendix I.

#### 14.1.2.1 Description of included studies

##### *14.1.2.1.1 Anxiety, depression, antidepressants and antipsychotics*

Twenty-seven studies were included in the evidence review for this question, 16 on depression and/or anxiety (including 5 systematic reviews containing an additional 32 RCTs), 1 on antidepressants for other behavioural symptoms (a systematic review containing 9 RCTs), and 9 on the use of antipsychotics (including 3 systematic reviews containing an additional 33 RCTs). A systematic review of memantine for mild Alzheimer's disease was also identified, containing 3 RCTs. A summary of the included studies is given in Table 79.

##### *14.1.2.1.2 Sleep problems*

Nine studies were included in the evidence review for this question, consisting of 7 RCTs and 2 systematic reviews containing 5 additional RCTs. A summary of the included studies is given in Table 80. One additional study was identified during the rerun process, but this was excluded at full text screening.

##### *14.1.2.1.3 Agitation and aggression*

Twenty-eight studies were included in the evidence review for this question, 22 RCTs and 6 systematic reviews containing 42 additional RCTs. A summary of the included studies is given in Table 81.

### 14.1.2.21 Summary tables for included studies

#### *4.1.2.2.12 Anxiety, depression, antidepressants and antipsychotic*

3 **Table 79: Included studies for anxiety, depression, antidepressants and antipsychotics**

| Study reference | Study design | Study population | Intervention & comparator | Relevant outcomes | Comments |
|---|---|---|---|---|---|
| Ballard (2008) | RCT | 165 people with dementia and taking antipsychotics | Intervention: Antipsychotic withdrawal<br>Comparator: Continuation | Cognition<br>Functional ability | Location: UK<br>Follow up: 12 months |
| Ballard (2009) | RCT | 165 people with dementia and taking antipsychotics | Intervention: Antipsychotic withdrawal<br>Comparator: Continuation | Mortality | Location: UK<br>Follow up: 24-54 months |
| Ballard (2015) | RCT | 199 people in care homes taking antipsychotics | Intervention: Memantine<br>Comparator: Antipsychotics | Cognition<br>Behavioural symptoms<br>Anxiety<br>Adverse events<br>Mortality | Location: UK/Norway<br>Follow up: 24 weeks |
| Banerjee (2011) | RCT | 326 people with Alzheimer's disease | Intervention: Sertraline or mirtazapine<br>Comparator: Placebo | Depression<br>Cognition<br>Quality of life<br>Adverse events | Location: UK<br>Follow up: 35 weeks |
| Boström (2015) | RCT | 186 people with dementia | Intervention: High-Intensity Functional Exercise program<br>Comparator: Non-exercise activity program | Depression | Location: Sweden<br>Follow up: 7 months |
| Brodaty (2003) | RCT | 86 people with dementia | Intervention: Psychogeriatric management<br>Comparator: Usual care | Depression | Location: Australia<br>Follow up: 12 weeks |
| Cooke (2010) | RCT | 47 people with confirmed or probable dementia | Intervention: Music therapy<br>Comparator: Reading therapy | Quality of life<br>Depression | Location: Australia<br>Follow up: 16 weeks |

| Study reference | Study design | Study population | Intervention & comparator | Relevant outcomes | Comments |
|---|---|---|---|---|---|
| Fossey (2006) | RCT | 349 people with dementia | Intervention: Psychosocial intervention<br>Comparator: Usual care | Neuroleptic use<br>Agitation<br>Aggression | Location: UK<br>Follow up: 12 months |
| Hickman (2007) | RCT | 66 people with dementia | Intervention: Ambient bright lighting<br>Comparator: Standard lighting | Depression | Location: USA<br>Follow up: 3 weeks |
| Holmes (2007) | RCT | 27 people with Alzheimer's disease | Intervention: Risperidone<br>Comparator: Rivastigmine | Anxiety | Location: UK<br>Follow up: 6 weeks |
| Ing-Randolph (2015) | Systematic review | 9 studies in people with dementia-associated anxiety | Intervention Group music<br>Comparator: Usual care | Anxiety | Location: N/A<br>Follow up: 5 weeks-6 months |
| Kiosses (2015) | RCT | 74 people with cognitive impairment (39 with dementia) | Intervention: PATH<br>Comparator: ST:CI | Depression<br>Disability | Location: USA<br>Follow up: 12 weeks |
| Leong (2014) | Systematic review | 10 RCTs in people with depression and dementia | Intervention: Antidepressants<br>Comparator: Placebo | Depression | Location: N/A<br>Follow up: 6-24 weeks |
| Leontjevas (2013) | RCT | 403 residents of dementia units | Intervention: Multidisciplinary care programme<br>Comparator: Usual care | Depression<br>Quality of life | Location: Netherlands<br>Follow up: 20 months |
| Lyketsos (2003) | RCT | 44 people with Alzheimer's disease | Intervention: Sertraline<br>Comparator: Placebo | Depression<br>Cognition<br>Adverse events | Location: USA<br>Follow up: 12 weeks |
| Ma (2014) | Systematic review | 19 studies in people with dementia | Intervention: Antipsychotics<br>Comparator: Placebo | Behavioural symptoms<br>Anxiety<br>Adverse events<br>Mortality | Location: N/A<br>Follow up: 6 weeks-26 weeks |
| Moulton (2014) | Systematic review | 11 studies in people with Huntington's disease | Intervention: Pharmacological treatment<br>Comparator: Placebo | Depression | Location: N/A<br>Follow up: 4 weeks-1 year |

| Study reference | Study design | Study population | Intervention & comparator | Relevant outcomes | Comments |
|---|---|---|---|---|---|
| Orgeta (2015) | Systematic review | 6 RCTs in people with anxiety/ depression and dementia | Intervention: Psychological treatment<br>Comparator: Usual care | Anxiety<br>Depression | Location: N/A<br>Follow up: 6 weeks-1 year |
| Pan (2014) | Systematic review | 10 RCTs in people with dementia and taking antipsychotics | Intervention: Antipsychotic withdrawal<br>Comparator: Continuation | Behavioural symptoms<br>Mortality | Location: N/A<br>Follow up: 4 weeks-54 months |
| Petrovsky (2015) | Systematic review | 10 studies in people with anxiety/depression and dementia | Intervention: Active music interventions<br>Comparator: Usual care | Anxiety<br>Depression | Location: N/A<br>Follow up: <24 weeks |
| Porsteinsson (2014) | RCT | 186 people with probably Alzheimer's disease | Intervention: Citalopram<br>Comparator: Usual care | Anxiety<br>Agitation | Location: US/Canada<br>Follow up: 9 weeks |
| Richter (2012) | Systematic review | 4 RCTs in care homes | Interventions: Psychosocial interventions<br>Comparator: Usual care | Antipsychotic use<br>Behavioural symptoms | Location: N/A<br>Follow up: 30 days-12 months |
| Schneider (2011) | Systematic review | 3 RCTs in mild Alzheimer's disease | Intervention: Memantine<br>Comparator: Placebo | Cognition<br>Behavioural symptoms | Location: N/A<br>Follow up: 24 weeks |
| Seitz (2011) | Systematic review | 9 RCTs in people with psychosis/agitation | Interventions: Antidepressants<br>Comparator: Usual care | Psychosis<br>Agitation | Location: N/A<br>Follow up: 4 weeks-12 weeks |
| Sung (2010) | RCT | 52 people with dementia | Intervention: Preferred music listening<br>Comparator: Usual care | Anxiety | Location: Taiwan<br>Follow up: 6 weeks |
| Verhey (2006) | RCT | 58 people with dementia and agitation | Intervention: Olanzapine<br>Comparator: Haloperidol | Anxiety | Location: Netherlands<br>Follow up: 5 weeks |
| Weintraub (2010) | RCT | 131 people with Alzheimer's disease | Intervention: Sertraline<br>Comparator: Placebo | Depression<br>Cognition<br>Adverse events | Location: USA<br>Follow up: 24 weeks |

#### *4.1.2.2.2*1 *Sleep problems*

2 **Table 80: Included studies for sleep problems**

| Study reference | Study design | Study population | Included studies | Outcomes of interest |
|---|---|---|---|---|
| Alessi (2005) | RCT | Nursing home residents with abnormal sleep/wake patters | Intervention: Multicomponent nonpharmacological intervention<br>Comparator: Usual care | Acitgraph measurements |
| Chong (2005) | RCT | Community-dwelling patients with mild to moderate Alzheimer's disease and sleep disordered breathing. | Intervention: continuous positive airway pressure (CPAP) for 6 weeks<br>Comparator: sham CPAP for 3 weeks then CPAP for 3 weeks | Epworth sleepiness scale |
| Forbes (2009) | Systematic Review | Dementia patients treated with light therapy to manage sleep, cognitive, functional, psychiatric and behavioural disturbances | 10 RCTs included in final review<br>Sleep relevant RCTs = 6<br>Intervention: light therapy<br>Comparator: | Acitgraph measurements (or equivalent systems) |
| Harris (2012) | RCT | Nursing home patients with dementia and sleep disturbances | Intervention: slow-stroke back massage<br>Comparator: usual care | Acitgraph measurements |
| Larsson (2010) | RCT | Parkinson's Disease and dementia with Lewy bodies patients suffering from sleep disorders enrolled in psychiatric and neurological out-patient clinics. | Intervention: Memantine<br>Comparator: Placebo | Stavanger sleep questionnaire<br>Epworth sleepiness scale |
| McCleery (2016) | Systematic Review | Pharmacological interventions in patients with Alzheimer's Disease and sleeping problems in nursing homes, long-term care facilities and hospital geriatric centres. | 5 RCTs included in final review:<br>Melatonin n=4<br>Trazadone n=1 | Acitgraph measurements |
| McCurry (2005) | RCT | AD patients living at home with carers and suffering from sleep disturbances. | Intervention: Night-time insomnia treatment and education (NITE-AD) | Epworth sleepiness scale<br>PSQI<br>Actigraph measurements: |

| Study reference | Study design | Study population | Included studies | Outcomes of interest |
|---|---|---|---|---|
| | | | Comparator: general dementia education and carer support | Night awakenings<br>Time in bed (hrs)<br>Daytime sleep (hrs)<br>Total sleep/night (hrs) |
| McCurry (2011) | RCT | Patients in an independent community living setting suffering from AD and sleep problems. | Intervention(s): walking, light or NITE-AD<br>Comparator: contact control (non-directive dementia care support) | Actigraph measurements:<br>Total wake time/night<br>Sleep %<br>Total sleep time<br>Number of awakenings<br>Sleep disorders inventory (SDI) |
| Richards (2005) | RCT | Patients in a nursing home setting suffering from dementia and sleep problems | Intervention: individualised social activities<br>Comparator: usual care | Actigraph measurements:<br>Day/night sleep ratio<br>Night-time sleep efficiency,%<br>Night-time minutes to sleep onset<br>Night-time minutes slept<br>Night-time awake<br>Daytime minutes slept |

#### *4.1.2.2.3*1 *Agitation and aggression*

2 **Table 81: Included studies for agitation and aggression**

| Study reference | Study design | Study population | Included studies | Outcomes of interest |
|---|---|---|---|---|
| Brown (2015) | Systematic review | RCTs comparing opioids to placebo for agitation in dementia | 0 RCTs included in final review | N/A |
| Forrester (2014) | Systematic Review | RCTs of aromatherapy for people living with dementia | 5 RCTs in review | Agitation (CMAI; NPI; PAS<br>Aggression (NPI)<br>Behavioural symptoms (NPI)<br>Quality of life (Blau QOL scale)<br>Activities of Daily living (Barthel scale of ADL) |

| Study reference | Study design | Study population | Included studies | Outcomes of interest |
|---|---|---|---|---|
| Jutkowitz (2016) | Systematic review | Non-pharmacological care delivery interventions to reduce and manage agitation and aggression in people living with dementia in nursing homes and assisted living | 19 RCTs included in final review:<br>Dementia care mapping (DCM) n=3;<br>Person centred care<br>(PCC) n=3;<br>Clinical protocols for antipsychotic use n=3;<br>Emotion oriented care n=2;<br>Unique interventions n=11 | Frequency of agitation and aggression (measured by CMAI) |
| Kong (2009) | Systematic review | RCTs of non-pharmacological interventions for agitation in people living with dementia | 14 RCTs included in final review:<br>Sensory interventions (n=3);<br>Social contact activities (n=5);<br>Environmental modification carer training (n=3)<br>Behavioural interventions (n=2)<br>Combination therapy (n=1) | Agitation (measured by CMAI and short CMAI; Pittsburgh Agitation Scale PAS; Agitation Behaviour Mapping Instrument ABMI; Agitated Behaviour Inventory for Dementia ABID; Agitation Visual Analogue Scale; AVAS; Observed Agitation Scale ; OAS Scale for the Observation of Agitation in Dementia SOAD)<br>Aggression (measured by the Ryden Aggression Scale (RAS)<br>Behavioural symptoms (measured by Burke Dementia Behavioral Rating Scale BDBRS; Behavioral Pathology in Alzheimer's Disease Rating Scale BEHAVE-AD; Disruptive Behavior Scale DBS; Need Driven Compromised Behavior Model NDB |
| Von Gunten (2015) | Systematic review | RCTs comparing Ginkgo biloba extract EGb 761 to placebo for people living with dementia and behavioural and psychological symptoms | 4 RCTs included in final review | Cognition (based on SKT short cognitive performance test)<br>BPSD (based on NPI) |

| Study reference | Study design | Study population | Included studies | Outcomes of interest |
|---|---|---|---|---|
| | | | | Activities of daily living (based on Gottfries Brane Steen scale (GBS) and Activities of Daily living-International scale (ADL-IS)<br>Clinical Global Impression of change (based on GBS total score and Alzheimer's disease Cooperative Study-Clinical Global Impression of Change (ADCS-CIGIC)<br>Quality of life – DEMQOL=-PROXY) |
| Xiao (2010) | Systematic review | RCTs comparing use of mood stabilisers for agitation in Alzheimer's disease | 5 RCTs included in final review | Agitation<br>Functional Ability<br>Neuropsychiatric profile<br>Cognition<br>Adverse events |

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| Study reference | Study design | Study population | Intervention | Outcomes of interest | Other |
|---|---|---|---|---|---|
| Burns 2009 | RCT | 48 people with dementia and agitation | Bright light therapy versus normal light | Agitation (CMAI)<br>MMSE<br>Cornell scale for depression<br>Behavioural psychopathology (MOUSEPAD) | Study location UK<br>Follow up 3 weeks |
| Cohen Mansfield 2007 | RCT | 167 people with dementia and exhibiting agitation several times a day | TREA – individualised interventions for unmet needs versus usual care | Overall agitation | Study location USA<br>Follow up / duration 10 days |
| Cohen Mansfield 2012 | RCT | 125 people with dementia and exhibiting agitation at least several times a day | TREA – individualised interventions for unmet needs versus usual care | Overall Agitation (CMAI)<br>Overall BPSD (LMBS) | Study location USA<br>Follow up 2 weeks |

| Study reference | Study design | Study population | Intervention | Outcomes of interest | Other |
|---|---|---|---|---|---|
| Cummings 2015 | RCT | 194 [people with Alzheimer's disease and behavioural symptoms interfering with daytime routine | Dextromethorphan quinidine versus placebo | Agitation (NPI)<br>NPI total score<br>Cornell scale for depression<br>Global assessment (CGIC) | Study location USA<br>Follow up 10 weeks |
| Deudon 2009 | RCT | 306 people with dementia presenting with at least one BPSD once a week | Staff training programme versus usual care | NPI | Study location France<br>Follow up 10 weeks |
| Fox 2012 | RCT | 153 people with Alzheimer's disease with significant agitation | Memantine versus matched placebo | Agitation (CMAI)<br>NPI<br>Cognition (MMSE)<br>Global assessment (CIGIC) | Study location UK<br>Follow up 12 weeks |
| Frakey 2012 | RCT | 22 people with Alzheimer's disease and displaying apathetic outcomes | Modafinil versus matched placebo | Apathy (FrSBe)<br>Activities of Daily Living (ADLQ)<br>Functional status (DAFS) | Study location USA<br>Follow up 8 weeks |
| Holmes 2004 | RCT | 96 people with Alzheimer's disease and showing neuropsychiatric symptoms | Donepezil versus matched placebo | NPI<br>NPI distress scale<br>Adverse events | Study location UK<br>Follow up 24 weeks |
| Howard 2007 | RCT | 249 people with Alzheimer's disease and agitation | Donepezil versus matched placebo | Agitation (CMAI)<br>NPI<br>CGIC<br>MMSE | Study location UK<br>Follow up 8 weeks |
| Lin 2011 | RCT | 100 people with dementia and agitated behaviours | Group music versus usual care | Agitation (CMAI) | Study location Taiwan<br>Follow up 6 weeks |

| Study reference | Study design | Study population | Intervention | Outcomes of interest | Other |
|---|---|---|---|---|---|
| Mahlberg 2007 | RCT | 20 people with Alzheimer's disease and showing agitated behaviour | Rivastigmine versus matched placebo | NPI agitation<br>NPI<br>NOSGER | Study location Germany<br>Follow up 2 weeks |
| McCabe 2015 | RCT | 189 people with dementia and agitation and/or aggression | Staff training protocol versus usual care | Agitation (CMAI ) | Study location Australia<br>Follow up 12 weeks |
| Porsteinsson 2001 | RCT | 56 people with dementia and agitated symptoms | Divalproex sodium versus usual care | BPRS<br>CMAI<br>PSMS<br>MMSE | Study location USA<br>Follow up 6 weeks |
| Rapp 2013 | RCT | 304 people with dementia and agitation | Training support and activity therapy<br>Usual care | Agitation (CMAI) | Study location Germany<br>Follow up 10 weeks |
| Rea 2015 | RCT | 113 people with Alzheimer's disease showing apathetic signs | Donepezil plus choline alphoscerate versus donepezil | Apathy<br>NPI<br>Frontal Assessment Battery | Study location Italy<br>Follow up 2 years |
| Ridder 2013 | RCT | 21 people diagnosed with dementia and symptoms of agitation | Music therapy versus standard care | Anxiety (CMAI)<br>Activities of daily living (ADRQL) | Study location Netherlands<br>Follow up 6 weeks |
| Sung 2006 | RCT | 36 people with dementia and presence of agitated behaviours | Group music and movement versus standard care | Agitation (CMAI) | Study location Taiwan<br>Follow up 4 weeks |
| Van der Ploeg (2013) | RCT | 44 people with dementia showing physical agitated behaviour several times a day | Individualised activity session versus non personalise intervention | Agitation<br>Positive affect<br>Negative affect<br>Constructive engagement<br>Negative engagement | Study location Australia<br>Follow up 4 weeks |

| Study reference | Study design | Study population | Intervention | Outcomes of interest | Other |
|---|---|---|---|---|---|
| Van den Elsen (2015) | RCT | 50 people with dementia and showing agitated, aggressive or aberrant behaviour | Tetrahydrocannabinol versus placebo Study location | Agitation (CMAI)<br>NPI total<br>CGIC<br>QoL-AD | Study location Netherlands<br>Follow up 3 weeks |
| Wang 2008 | RCT | 22 people with Alzheimer's disease and exhibiting agitation or aggression at least twice a week | Prazosin versus matched placebo | GCIC<br>BPRS<br>NPI | Study location USA<br>Follow up 8 weeks |
| Yang (2015) | RCT | 186 people with dementia and symptoms of agitation | Aroma acupressure versus control<br>Aromatherapy versus control | Agitation (CMAI) | Study location Taiwan<br>Follow up 4 weeks |
| Zwijsen (2014) | RCT | 659 people with dementia and showing challenging behaviours (specifically agitation) | Staff protocol versus usual care | Agitation (CMAI)<br>NPI | Study location Netherlands<br>Follow up 20 months |

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### 14.1.3 Health economic evidence

#### 14.1.3.1 Systematic review of published economic evaluations

A systematic literature search was undertaken to identify existing cost–utility analyses (CUAs) evaluating the most effective pharmacological and non-pharmacological interventions for managing illness emergence non-cognitive symptoms in people living with dementia. In total, 2,385 articles were returned. In total, 4 publications were judged to be at least partially applicable to the review questions and were therefore included. Details of the literature search are provided in Appendix D.

#### 14.1.3.2 Antidepressants

**Banerjee et al. (2013)** compared the cost effectiveness of sertraline and of mirtazapine with placebo, for the treatment of depression in people with Alzheimer's disease referred to old-age psychiatry services. Romeo et al. (2013) present the same study and analysis in a separate publication. The authors conducted a cost–utility analysis alongside the HTA-SADD RCT of 326 participants, collecting primary service-use and EQ-5D data. The primary analysis was a cost-effectiveness analysis with change in the Cornell Scale for Depression and Dementia as the health outcome. A secondary analysis considered incremental QALYs. A 39-week time horizon was taken for this secondary analysis, matching the trial duration. There was no extrapolation beyond the trial duration. For further details, please see the economic evidence profile in Appendix M.

Service-use data included direct costs associated with hospital-based care, community-based care and day services recorded during the follow-up period. Informal care data (unpaid carer costs) were also collected. QALYs were estimated using data obtained from the EQ-5D questionnaire. The authors performed non-parametric bootstrapping to generate additional pairs of incremental cost and QALY outcomes in order to present a cost-effectiveness acceptability analysis. The mean results with informal care costs excluded are presented in Table 82.

**Table 82: Base-case cost–utility results – Banerjee (2013) and Romeo (2013)**

| | Absolute | | Incremental | | |
|---|---|---|---|---|---|
| Treatment | Costs | Effects (QALYs) | Costs (£)[95% CI] | Effects (QALYs) [95% CI] | ICER (£/QALY) |
| Placebo | £2,146 | 0.55 QALYs | | | |
| Mirtazapine | £2,550 | 0.60 QALYs | £404 [-972, 1,626] | 0.05 QALYs [-0.10, 0.10] | £8,080 /QALY |
| Sertraline | £2,839 | 0.57 QALYs | £289 [-1,545, 1,151] | -0.02 QALYs [-0.07, 0.03] | Dominated |

The base-case analysis produces an ICER of £8,080 per QALY for mirtazapine compared with placebo, and shows sertraline to be dominated by mirtazapine. There is large uncertainty around the incremental costs and QALYs, with all 95% confidence intervals crossing zero. In addition, some estimates are conspicuously skewed, especially estimated incremental QALYs for mirtazapine compared with placebo: the 95% confidence interval ranges from −0.1 to +0.1, but the mean is +0.05 QALYs. Despite its low mean ICER compared with placebo, mirtazapine is shown to have only approximately 20% probability of being cost-effective at a threshold value of £20,000/QALY. Mirtazapine is shown to have a probability in excess of 90% of being cost-effective compared with sertraline at all threshold values. Deterministic sensitivity analysis was not presented for analyses which excluded

informal care costs. The authors conclude that their analysis provides no support for the use of antidepressants as first-line therapy for depression in people with Alzheimer's disease referred to old-age psychiatry services.

#### 14.1.3.3 Antipsychotics

**Rosenheck et al. (2007)** compared the cost effectiveness of olanzapine, quetiapine and risperidone with placebo, for the treatment of psychosis and aggression in people with Alzheimer's disease in ambulatory outpatients living at home or in assisted living. The authors conducted a cost–benefit analysis alongside Schneider et al. (2006) (n=421), assessing quality-adjusted life-years (QALYs) using the Health Utilities Index Mark. This was supplemented by the Alzheimer's Disease Related Quality of Life Scale, the Alzheimer's disease Cooperative Study Activities of Daily Living Scale (ADCS-ADL) and the AD Dependence Scale. A secondary analysis excluded observations after the first medication change. For further details, please see the economic evidence profile in Appendix M.

Service-use data included direct costs associated with experimental medication costs. Concomitant medication cost and monthly health service costs were also collected. The authors performed an analyses of net health benefits when the value of health benefits was valued at $50,000 per QALY and $100,000 per QALY. The mean results with concomitant medication cost and monthly health service costs excluded are presented in Table 83.

**Table 83: Base-case cost–utility results – Rosenheck et al., (2007)**

| | Absolute | | Incremental | | |
|---|---|---|---|---|---|
| Treatment | Costs | Effects | Costs | Effects | ICER |
| Placebo | $4,923 | 0.14 QALYs | | | |
| Olanzapine | $6,480 | 0.12 QALYs | $1,557 | -0.02 QALYs | Dominated |
| Quetiapine | $7,839 | 0.15 QALYs | $2,916 | 0.01 QALYs | ext. dom. |
| Risperidone | $10,215 | 0.16 QALYs | $5,292 | 0.02 QALYs | $264,600 /QALY |

The base-case analysis suggests that olanzapine is dominated by placebo as placebo is cheaper and produces more health benefits. Quetiapine and risperidone both produced a very small incremental health benefit (of +0.01 and +0.02 QALY, respectively), but also result in relatively large costs, with the result that risperidone produces an ICER of $264,600/QALY compared with placebo, and quetiapine is extendedly dominated by placebo and risperidone. At the cost-effectiveness thresholds of $50,000 and $100,000 per QALY considered by the authors, no intervention was found to be cost-effective.

**Kirbach et al. (2008)** compared the cost effectiveness of olanzapine with no treatment, for the treatment of agitation and psychosis in people with Alzheimer's disease in the USA. The authors created a Markov model, with a 6-month cycle length and a 13-year treatment horizon Transition probabilities for Alzheimer's disease progression were taken from the Consortium to Establish a Registry for Alzheimer's disease (CERAD) cohort, in which there was a 70% prevalence for agitation and up to 36% prevalence for varying psychoses. In common with Rosenheck et al. (2007), Kirbach et al. (2008) used results from Schneider et al. (2006) to estimate olanzapine cost-effectiveness. Economic evidence profiles for both studies are available in Appendix M.

The study considered both 'direct' and 'indirect' costs, though did not specify what each comprised. The results presented here are from analyses of 'direct' costs only, as these were judged less likely to include items that are beyond the NICE reference case. Utility weights used to estimate QALYs were provided by Murman and Colenda (2005).

**Table 84: Base-case cost–utility results – Kirbach et al (2008)**

| | Absolute | | Incremental | | |
|---|---|---|---|---|---|
| Treatment | Costs | Effects | Costs | Effects | ICER |
| No olanzapine | $34,215 [a] | NR | | | |
| Olanzapine | $39,781 | NR | $5,566 [a] | 0.15 QALYs | $37,104 /QALY |

[a] *Not reported in paper, but may be inferred from ICER, incremental QALYs and absolute costs of olanzapine*

The base-case analysis (Table 84) suggests that treatment with olanzapine incurs additional costs (primarily due to cost of the drug itself) but also provides QALY gains, with an ICER of $37,104 per QALY. Several 1-way, 2-way and 3-way deterministic sensitivity analyses produced ICERs ranging from $31,336 to $42,039.

However, this finding is at odds with Rosenheck et al. (2007) (see above), which is noteworthy, given that both models relied on the same evidence to estimate the effectiveness of olanzapine.

#### 14.1.3.4 Non-pharmacological interventions

**Livingston et al. (2014)** compared the cost effectiveness of a 6-month, multimodal, non-pharmacological intervention with usual care, for reducing agitation in people with dementia. The intervention comprised music-based group therapy, structured teaching with a therapist, psychoeducational staff training by a psychologist and intensive family member–staff communication comprising provision of basic information, everyday availability of professional carers to answer family members' questions, and a 1-hour session of psychoeducational counselling by a psychologist to a close family member of each participant. For further details, please see the economic evidence profile in Appendix M.

Service-use data included direct costs associated with providing the treatment including staff time. Data from a longitudinal epidemiological study (LASER-AD) were used to quantify the relationship between agitation and health and social care costs and agitation and utility. The analysis adopted a 12-month time horizon.

**Table 85: Base-case cost–utility results – Livingston et al. (2015)**

| | Absolute | | Incremental | | |
|---|---|---|---|---|---|
| Treatment | Costs | Effects | Costs | Effects | ICER |
| Multimodal intervention | NR | NR | | | |
| Usual care | NR | NR | £716 | -0.00583 QALYs | dominated |

Base-case results (Table 85) suggest that, although the treatment cost £406 to provide to each patient, the net cost impact was a saving of £716 compared with usual care. This was due to a reduction in the costs of managing agitation. The intervention was also more effective than the comparator, so is considered dominant. PSA suggested that the intervention had an 82.2% probability of being cost effective, if QALYs are valued at £20,000 each.

This analysis, however, had some serious limitations. Critically, data for treatment effects were from a paper published by Fischer-Terworth and Probst (2011), a non-randomised study with a small number of participants (n=49).

**Zwijsen et al. (2016)** compared the cost effectiveness of a non-pharmacological intervention ('Grip on Challenging Behaviour'; GRIP), for the management of challenging behaviour in dementia special care units in comparison with usual care in the Netherlands. The economic evaluation was performed from a societal perspective alongside a cluster-randomised controlled trial (Zwijsen et al., 2011; see 14.1.2, above). QALYs were estimated using the EQ-5D. Challenging behaviour and quality of life was assessed on 5 different occasions, each 4 months apart. For further details, please see the economic evidence profile in Appendix M.

Costs were estimated using standard Dutch sources. Staff time was estimated using prospective 1-monthy diaries.

**Table 86: Base-case cost–utility results – Zwijsen et al. (2016)**

| | Absolute | | Incremental | | |
|---|---|---|---|---|---|
| **Strategy** | **Cost** | **Effect** | **Cost** | **Effect** | **ICER** |
| Usual care | 483 EUR€ | NR | | | |
| GRIP | 931 EUR€ | NR | 276 EUR€ | -0.02 QALYs | dominated |

The base-case analysis (Table 86) suggests that GRIP is associated with increased costs and less QALYs compared with usual care. Probabilistic analysis showed that the probability of GRIP being cost-effective in comparison with usual care was zero regardless of the value placed on a QALY. The authors concluded that GRIP was not considered cost-effective in comparison with usual care.

#### 14.1.3.5 Exercise

**D'Amico et al. (2016)** conducted a cost–utility analysis alongside EVIDEM-E RCT, evaluating a 12-week trial of a dyadic exercise regimen (tailored walking) for people living with dementia and their main carer as therapy for behavioural and psychological symptoms of dementia. For further details, please see the economic evidence profile in Appendix M.

Data on care and support service use were collected using an adapted version of the Client Service Receipt Inventory. Unit costs were taken from standard sources (PSSRU, BNF), if possible, and estimated from market sources if not. All costs were expressed in 2011 UK pounds. QALYs were calculated for participants with dementia only, using the DEMQOL-Proxy, completed by the carer, with societal weights.

**Table 87: Base-case cost–utility results from a health and social care perspective for exercise compared with control for D'Amico et al. (2016)**

| | Absolute | | Incremental | | |
|---|---|---|---|---|---|
| **Strategy** | **Cost** | **Effect** | **Cost [a] [95%CI]** | **Effect [a] [95%CI]** | **ICER** |
| Control | £1,984 | NR | | | |
| Exercise | £2,122 | NR | £-169.70 [−1240.0, 900.5] | 0.0055 QALYs [-0.0031, 0.0140] | Dominant |

Base-case results from a health and social care perspective (Table 61) show that exercise was associated with lower costs and higher QALYs than control, resulting in the being a

dominant. However, findings were very uncertain in both cost and effect dimensions. The cost savings of the exercise group compared with the control group appear to be driven by less usage of hospital services by those in the exercise group; however, the authors note that neither the costs or QALY difference were statistically significant.

### 14.1.4 Evidence statements

#### 14.1.4.1 Anxiety and depression

##### *14.1.4.1.1 Pharmacological treatment*

**Sertraline vs placebo**

Low-quality evidence from up to 3 RCTs containing 348 people could not differentiate levels of depressive symptoms (Cornell Scale for Depression in Dementia/Hamilton Depression rating Scale) between people taking sertraline and placebo at any time between 12 and 39 weeks.

Low- to moderate-quality evidence from up to 2 RCTs containing 217 people could not differentiate global impression of change scores (mADCS-CGIC), cognition (MMSE), activities of daily living, neuropsychiatric symptoms (NPI) or quality of life (self- or carer-reported) between people taking sertraline and placebo at any time between 12 and 39 weeks.

Moderate- to high-quality evidence from 1 RCT containing 173 people found worse levels of carer mental health (GHQ/SF-12) in carers of people taking sertraline compared with placebo at 13 weeks, but could not differentiate levels at 39 weeks, or carer burden or physical health at 13 or 39 weeks.

Moderate-quality evidence from 3 RCTs containing 385 people found higher levels of adverse events in people taking sertraline compared with placebo, but very low-quality evidence from 2 RCTs containing 348 people could not differentiate levels of serious adverse events.

**Mirtazapine vs placebo**

Low-quality evidence from 1 RCT containing 158 people could not differentiate levels of depressive symptoms (Cornell Scale for Depression in Dementia) between people taking mirtazapine and placebo at 13 or 39 weeks.

Low- to moderate-quality evidence from 1 RCT containing 158 people could not differentiate cognition (MMSE), activities of daily living, neuropsychiatric symptoms (NPI) or quality of life (self- or carer-reported) between people taking mirtazapine and placebo at 13 or 39 weeks.

Moderate-quality evidence from 1 RCT containing 158 could not differentiate levels of carer burden, physical or mental health between carers of people taking mirtazapine and placebo at 13 or 39 weeks.

Moderate-quality evidence from 1 RCT containing 215 people found higher levels of adverse events in people taking mirtazapine compared with placebo, but low-quality evidence from the same study could not differentiate levels of serious adverse events.

**Antidepressants vs placebo**

Low-quality evidence from a systematic review containing 10 RCTs could not identify evidence of significant benefit with antidepressants compared with placebo for the management of depressive symptoms in people with dementia.

Low-quality evidence from a systematic review containing 11 studies (5 RCTs) could not identify evidence of significant benefit with pharmacological treatment compared with placebo for the management of depressive symptoms in people with Huntington's disease.

#### *14.1.4.1.2 Psychological treatment vs usual care*

Low-quality evidence from 6 RCTs containing 439 people found lower levels of depressive symptoms in people offered psychological treatment compared with usual care.

Low- to moderate-quality evidence from up to 2 RCTs containing 65 people found lower levels of anxiety (RAID) in people offered psychological treatment compared with usual care, but could not differentiate levels of anxiety as measured by self-rating or the NPI-A.

Very-low to low-quality evidence from up to 4 RCTs containing 381 people could not differentiate levels of quality of life (self-report or proxy), activities of daily living, neuropsychiatric symptoms, cognition (MMSE) or carer depressive symptoms between people offered psychological treatment compared with usual care.

#### *14.1.4.1.3 PATH vs ST-CI*

Low- to moderate-quality evidence from 1 RCT containing 74 people with either dementia (n=39) or mild cognitive impairment (n=35) found lower levels of depressive symptoms and disability in people offered the PATH intervention compared with the ST-CI intervention for depression.

#### *14.1.4.1.4 Structured depression management vs usual care (in nursing homes)*

Moderate-quality evidence from 1 RCT containing 393 people could not differentiate levels of depressive symptoms (Cornell Scale for Depression in Dementia/Geriatric Depression Scale) or severe depression between people offered structured depression management compared with usual care.

High-quality evidence from 1 RCT containing 393 people found higher levels of quality of life (EQ-VAS) in people offered structured depression management compared with usual care.

#### *14.1.4.1.5 Psychogeriatric management vs usual care*

Moderate-quality evidence from 1 RCT containing 45 people could not differentiate levels of depressive symptoms or psychosis between people offered psychogeriatric case management, psychogeriatric consultation or usual care.

#### *14.1.4.1.6 Ambient bright lighting*

Very low- to low-quality evidence from 1 RCT containing 66 people found higher levels of depressive symptoms (Cornell Scale for Depression in Dementia) in men exposed to bright morning light compared with standard lighting, but could not differentiate levels in those exposed to bright evening or all-day light compared with standard lighting, or in women in any lighting conditions.

#### *14.1.4.1.7 Music therapy*

**Group music therapy**

Moderate-quality evidence from a systematic review containing 8 studies (5 RCTs) could not identify evidence of significant benefit of group music therapy compared with standard therapy or non-music interventions for the management of anxiety in people with dementia.

**Active music therapy**

Low-quality evidence from a systematic review containing 10 studies (3 RCTs) could not identify evidence of significant benefit with active music therapy compared with usual care or non-music interventions for the management of anxiety and depressive symptoms in people with dementia.

**Active music therapy vs reading**

Low-quality evidence from 1 RCT containing 47 people could not differentiate levels of quality of life (DQOL) or depressive symptoms (Geriatric Depression Scale) between people offered active music therapy compared with reading therapy.

**Preferred music listening vs usual care**

Very-low quality evidence from 1 RCT containing 52 people could not differentiate levels of anxiety (RAID) between people offered preferred music listening compared with usual care.

#### *14.1.4.1.8 High-intensity exercise vs non-exercise activity program*

Low- to moderate-quality evidence from 1 RCT containing 184 people could not differentiate levels of anxiety (RAID) or depressive symptoms (Geriatric Depression Scale/MADRS) between people offered high-intensity exercise compared with a non-exercise activity program.

### 14.1.4.2 Antidepressants for other non-cognitive symptoms

Very low- to moderate-quality evidence from up to 4 RCTs containing 419 people found improvements in scores on the Cohen-Mansfield Agitation Inventory with SSRIs versus placebo, but could not differentiate total neuropsychiatric symptoms, behavioural symptoms or adverse events.

Very low- to moderate-quality evidence from up to 2 RCTs containing 103 people could not differentiate any outcome measures between SSRIs and atypical antipsychotics, SSRIs and typical antipsychotics, trazodone and placebo, or trazadone and typical antipsychotics.

### 14.1.4.3 Antipsychotics

#### *14.1.4.3.1 Atypical antipsychotics versus placebo*

Moderate- to high-quality evidence from up to 17 RCTs containing 5,028 people found improvements in the NPI, Brief Psychiatric Rating Scale, Cohen-Mansfield Agitation Inventory and Clinical Global Impression of Change with atypical antipsychotics versus placebo, but higher rates of mortality, somnolence, and extrapyramidal and cerebrovascular adverse events.

#### *14.1.4.3.2 Olanzapine vs haloperidol*

Low-quality evidence from 1 RCT containing 58 people could not differentiate cognition (MMSE), anxiety (CMAI) or neuropsychiatric symptoms (NPI) between people taking olanzapine and haloperidol.

#### *14.1.4.3.3 Risperidone vs rivastigmine*

Moderate-quality evidence from 1 RCT containing 27 people found lower levels of anxiety in people taking risperidone versus rivastigmine.

#### *14.1.4.3.4 Antipsychotic withdrawal*

High-quality evidence from 7 RCTs containing 366 people found a higher proportion of people who discontinued antipsychotics had a worsening of behavioural and psychological symptoms of dementia compared with those who continued, but low- to moderate-quality evidence from up to 6 RCTs containing 462 people could not differentiate overall levels of behavioural and psychological symptoms of dementia, or rates of early study termination or mortality.

Moderate-quality evidence from 1 RCT containing 109 people could not differentiate levels of cognition (SIB/MMSE), neuropsychiatric symptoms (NPI), Parkinsonism (modified UPDRS), activities of daily living (BADL) or language difficulties (STALD/FAS) between people who continued antipsychotic medication compared with those who discontinued.

High-quality evidence from 1 RCT containing 109 people found higher levels of neuropsychiatric symptoms (NPI) in people who discontinued antipsychotic medication compared with those who continued, but moderate-quality evidence from the same study could not differentiate levels of cognition (SIB)

High-quality evidence from 1 RCT containing 165 people found lower levels of mortality in people who discontinued antipsychotic medication compared with those who continued.

#### *14.1.4.3.5 Antipsychotic switch to memantine*

Moderate-quality evidence from 1 RCT containing 164 people could not differentiate levels of agitation (CMAI), neuropsychiatric symptoms (NPI), cognitions (MMSE), activities of daily living (BADL), serious adverse events or mortality between people on antipsychotics at baseline who either continued on antipsychotics or were switched to memantine.

#### *14.1.4.3.6 Enhanced psychosocial care*

Moderate-quality evidence from 1 RCT containing 338 people found a lower proportion of people taking antipsychotics in homes that offered an enhanced psychosocial care intervention compared with usual care, but very low- to low-quality evidence from the same study could not differentiate rates of falls or levels of aggression and wellbeing.

### 14.1.4.4 Memantine vs placebo

Low-quality evidence from 3 RCTs containing 427 people could not differentiate cognition (ADAS-cog), activities of daily living (ADCS-ADL) or neuropsychiatric symptoms (NPI) between people with mild Alzheimer's disease taking memantine versus placebo.

#### 14.1.4.5 Sleep problems

##### *14.1.4.5.1 Melatonin vs placebo*

Very low- to moderate-quality evidence from up to 3 RCTs containing 195 people could not detect a difference in total night-time sleep time, ratio of daytime to night-time sleep, sleep efficiency, nocturnal time awake, number of night-time awakenings, carer-rated sleep activity, activities of daily living, sleep latency or numbers of adverse events between people with sleep problems taking melatonin versus placebo.

##### *14.1.4.5.2 Trazadone vs placebo*

Moderate- to high-quality evidence from 1 RCT containing 30 people found higher levels of total night-time sleep and better sleep efficiency in people with sleep problems taking trazadone versus placebo over a two week period, but could not differentiate numbers of night-time awakenings, total daytime sleep, number of daytime naps or activities of daily living.

##### *14.1.4.5.3 Memantine vs placebo*

Low- to moderate-quality evidence from 1 RCT containing 60 people found a reduction in REM sleep behaviour disorder (measured using the Stavanger Sleep Questionnaire) in people with sleep problems taking memantine versus placebo, but could not differentiate scores on the Epworth Sleepiness Scale.

##### *14.1.4.5.4 Light therapy*

Low-quality evidence from 2 RCTs containing 48 people could not detect a difference in total sleep duration, sleep latency, night-time activity counts or the number of night-time awakenings in people with dementia and sleep problems exposed to bright light therapy.

##### *14.1.4.5.5 Slow-stroke back massage*

Moderate-quality evidence from 1 RCT containing 40 people could not detect a difference in total night-time sleep time or sleep efficiency in people with dementia and sleep problems exposed to massage therapy for 2 nights.

##### *14.1.4.5.6 Multicomponent non-pharmacological interventions vs usual care*

Moderate- to high-quality evidence from up to 3 RCTs containing 207 people found improvements in total night-time sleep, total night-time awake time and scores on the Sleep Disorders Inventory in people offered a multicomponent non-pharmacological intervention including light exposure, exercise, environmental modification and sleep hygiene advice versus usual care, but could not differentiate number of night-time awakenings, total daytime sleep or depressive symptoms.

##### *14.1.4.5.7 Individualised activities*

Low- to moderate-quality evidence from 1 RCT containing 50 people found a reduction in the amount of daytime sleep in people with dementia and a sleep efficiency of <50% at baseline exposed to individualised social activities for 21 days, but could not differentiate the day/night sleep ratio or the number of night-time minutes to sleep onset, night-time minutes slept, night-time sleep efficiency or night-time minutes awake.

#### *14.1.4.5.8 Continuous positive air pressure*

Moderate-quality evidence from 1 RCT containing 39 people did not detect a difference in the Epworth Sleepiness Scores in people with dementia and sleep disordered breathing treated with continuous positive air pressure compared with sham intervention for 3 weeks.

### 14.1.4.6 Non-pharmacological management of agitation, aggression and apathy

#### *14.1.4.6.1 Sensory interventions*

Moderate-quality evidence from up to 5 RCTs containing 446 people could not differentiate levels of agitation, positive affect, negative affect, depressive symptoms, quality of life, behavioural pathology or cognition between people offered sensory interventions or usual care.

#### *14.1.4.6.2 Social contact*

Very low-quality evidence from 1 RCT containing 164 people could not differentiate levels of agitation between people offered social contact interventions (simulated presence or pet therapy) or usual care.

#### *14.1.4.6.3 Activities*

Low- to moderate-quality evidence from up to 6 RCTs containing 465 people found reduced levels of negative affect and increased levels of pleasurable and interested affect in people offered activity based intervention versus usual care, but very low- to low-quality evidence could not differentiate levels of agitation, constructive engagement or negative engagement.

#### *14.1.4.6.4 Care delivery interventions*

Very low-to moderate quality evidence from up to 5 RCTs containing 71 people could not differentiate levels of agitation, aggressive behaviours, or rates of psychotropic prescription in centres offered or not offered a care delivery intervention, but found higher rates of antidepressant and cholinesterase inhibitor prescriptions in centres that offered the intervention.

#### *14.1.4.6.5 Staff training*

Moderate- to high-quality evidence from 1 RCT containing 272 people found reduced levels of anxiety and verbally aggressive behaviours in centres offered a staff training intervention, but could not differentiate levels of physically aggressive behaviours.

#### *14.1.4.6.6 Herbal extracts*

Low- to high-quality evidence from up to 4 RCTs containing 1,596 people found improved NPI scores, activities of daily living, quality of life and cognition in people offered ginkgo biloba extract versus placebo.

### 14.1.4.7 Pharmacological management of agitation, aggression and apathy

#### *14.1.4.7.1 Mood stabilisers vs placebo*

Very low- to high-quality evidence from up to 4 RCTs containing 254 people found NPI scores, cognition (MMSE) and adverse events were significantly worse in people offered mood stabilisers versus placebo, but could not differentiate levels of agitation (CMAI; NPI BPRS subscale), total neuropsychiatric symptoms or physical self-maintenance.

#### *14.1.4.7.2 Cholinesterase inhibitors versus usual care*

Low- to high-quality evidence from up to 3 RCTs containing 317 people found global assessment, agitation (NPI subscale) and cognition were significantly better in people offered cholinesterase inhibitors versus placebo, but could not differentiate levels of agitation (CMAI) or total neuropsychiatric symptoms (NPI).

#### *14.1.4.7.3 Memantine versus placebo*

Moderate- to high-quality evidence from 1 RCT containing 149 people found significantly lower NPI scores in people offered memantine versus placebo but could not differentiate levels of agitation, global assessment, clinician assessment or cognition.

#### *14.1.4.7.4 Tetrahydrocannabinol versus placebo*

Moderate-quality evidence from 1 RCT containing 47 people could not differentiate levels of agitation (CMAI; NPI agitation aggression subscale), neuropsychiatric profile, aberrant behaviours, clinician global assessment, activities of daily living or quality of life in people offered tetrahydrocannabinol versus placebo.

#### *14.1.4.7.5 Prazosin versus placebo*

Very low- to low-quality evidence from 1 RCT containing 13 people found improvements in psychiatric assessment and global assessment in people offered prazosin versus placebo, but could not differentiate neuropsychiatric profile (NPI).

#### *14.1.4.7.6 Dextromethorphan-quinidine vs placebo*

Moderate- to high-quality evidence from 1 RCT containing 279 people found improved neuropsychiatric symptoms (NPI), agitation/aggression and depressive symptoms (Cornell scale) but higher levels of adverse events in people offered dextromethorphan-quinidine versus placebo. The evidence could not differentiate global assessment, cognition, quality of life, serious adverse events or mortality.

#### *14.1.4.7.7 Modafinil vs placebo*

Moderate-quality evidence from 1 RCT containing 22 people could not differentiate levels of apathy, function, activities of daily living or carer burden between people offered modafinil versus placebo.

#### *14.1.4.7.8 Donepezil and choline alphoscerate vs donepezil*

High-quality evidence from 1 RCT containing 113 people found improved levels of apathy, neuropsychiatric symptoms (NPI) and cognition (MMSE, ADAScog) in people offered donepezil and choline alphoscerate versus donepezil alone.

### 14.1.4.8 Health economic evidence

#### *14.1.4.8.1 Antidepressants*

One directly applicable cost–utility analysis with very serious limitations found that mirtazapine has a probability in excess of 90% of being superior to sertraline, regardless of the assumed value of a QALY, but it only had a probability of approximately 20% of being associated with an ICER of £20,000 per QALY or better compared with placebo. The study undertook only limited exploration of uncertainty and had a short time horizon.

#### *14.1.4.8.2 Antipsychotics*

Two partially applicable cost–utility analyses from the USA explored the cost effectiveness of second-generation antipsychotics compared with each other and/or usual care.

- One RCT-based analysis with potentially serious limitations found that there were no significant differences in QALYs across the treatment groups, with olanzapine being worse than placebo. Both risperidone and sertraline produced very small increases in QALYs which were insufficient to outweigh additional costs even when QALYs are valued at $100,000 each.
- One analysis with very serious limitations, based on an observational study, found that, assuming QALYs are valued at $50,000 each or more, olanzapine is likely to be considered cost-effective, compared with usual care, for the treatment of agitation and psychosis in Alzheimer's disease. However, effect data were drawn from a study that found that olanzapine resulted in a loss of QALYs.

#### *14.1.4.8.3 Non-pharmacological interventions*

One directly applicable cost–utility analysis with very serious limitations explored a multimodal, non-pharmacological intervention consisting of music therapy, sensory interventions and training. The intervention was found to have a 82% probability of being cost effective if QALYs are valued at £20,000 each. However, the analysis relied on a non-randomised study with a small number of participants (n=49) for effects.

One partially applicable economic evaluation with potentially serious limitations, which was performed alongside a cluster RCT in the Netherlands, found that the Grip on Challenging Behaviours care programme (GRIP) was less effective and more expensive than usual care.

#### *14.1.4.8.4 Exercise*

One partially applicable cost–utility analysis with minor limitations conducted alongside an RCT explored the cost effectiveness of a dyadic exercise regimen for people living with dementia and their main carer as therapy for behavioural and psychological symptoms of dementia. Exercise was found to result in lower costs and higher QALYs than control, resulting in the exercise intervention being dominant. The authors noted that neither the costs nor QALY difference were statistically significant.

### 14.1.5 Evidence to recommendations

#### 14.1.5.1 Pharmacological interventions

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| **Relative value of different outcomes** | The committee agreed that evaluations of most interventions depended on 3 components; whether the intervention improves the specific symptom(s) it is targeting; whether there are any broader impacts on cognition, function or wellbeing; and adverse events. Many pharmacological treatments are known to have worse adverse event profiles in people with cognitive decline than in people without, and therefore the committee agreed this trade-off was always an important one to consider.<br>**Sleep disturbances**<br>The committee agreed that whilst daytime sleep was a relevant outcome, the most important individual measure would be of nocturnal time awake, as this is a particular issue that can impact on carer quality of life. It also agreed that it would be important to consider participant and carer reported outcomes alongside the actigraph measurements which are commonly reported in trials of sleep disturbances. |

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| **Trade-off between benefits and harms** | **Depression and anxiety**<br>The committee agreed the evidence did not show significant benefits from using antidepressants to treat mild to moderate depression in people with mild to moderate dementia. In particular, the large DIADS-2 and HTA-SADD studies did not produce any positive findings. Whilst only 2 specific antidepressants were tested in these trials, the committee agreed this was likely to represent a class effect, and therefore any recommendation made should apply to all antidepressants. There were, however, specific caveats that the committee agreed were important. First, it agreed that it would not be appropriate to extrapolate these findings to people with either severe depression (where there may be an urgent need for treatment) or severe dementia. Second, it agreed that if someone had previously responded well to antidepressant treatment, then it would be appropriate to use the same treatment if the person later develops dementia.<br>**Antipsychotics**<br>The committee agreed there was a clear pattern in the evidence for antipsychotics. They showed clear evidence of efficacy (reductions in agitation and NPI scores), but also evidence of significant harms, with increase in rates of all types of adverse events, and mortality. The committee agreed that the significant risks of treatment meant their use should be restricted as much as possible, and limited only to situations either where there is an urgent need for treatment to prevent harm to the person living with dementia or others, or where the use is for the treatment of an underlying psychosis, and would be equally appropriate in a person who does not have dementia. The committee also agreed that a specific discussion is necessary with the person living with dementia and their carers/family members about the benefits and harms of treatment. It agreed that treatment should be restricted to the lowest effective does and the shortest possible time, in order to reduce adverse events as far as possible.<br>The committee agreed that it was necessary to regularly review people taking antipsychotics to ensure the treatment is still necessary, and to encourage a discussion about discontinuation wherever this is possible. It also agreed that the use of an antipsychotic was not a reason to discontinue non-pharmacological treatment, and that people either taking or being discontinued from antipsychotics should have access to the same range of non-pharmacological options as people not being treated with antipsychotics.<br>It was noted that the majority of the included studies were for non-cognitive symptoms such as agitation or similar behavioural symptoms, rather than as treatments for psychosis.<br>It was also agreed to be appropriate to add a specific recommendation in the guideline around the risk of worsening motor features and antipsychotic sensitivity reactions in people with Parkinson's disease dementia or dementia with Lewy bodies taking antipsychotics. This recommendation links to the NICE guideline on Parkinson's disease, which contains additional recommendations on this topic.<br>**Sleep disturbances**<br>The committee agreed the evidence did not show significant benefit from using melatonin to treat insomnia in people with Alzheimer's disease, and that the evidence base contained a sufficiently large sample size that any meaningful benefit would have been detected. As a result of this and the known adverse events associated with melatonin treatment (including headaches and dizziness) the committee agreed it should not be used to manage insomnia. The committee agreed it was not appropriate to extrapolate this evidence to other subtypes of dementia. For example, melatonin is used to treat REM sleep disorder in people with Parkinson's disease, and the committee did not want to |

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| | restrict its use for people with Parkinson's disease dementia or dementia with Lewy bodies without robust evidence.<br>The committee agreed that the evidence for trazadone was promising, but noted that since the trial only had a 2 week duration it was unclear whether the increase in night-time sleep time would be sustained long-term. The committee agreed that the full effects of trazodone could take longer to be detected and that the increase in night-time sleep detected here could be due to the sedative effect of the drug rather than an effect on sleeping per se. In addition it agreed that the lack of improvement in carer reported outcomes was an issue and that the side-effects of trazadone treatment should also be considered before prescription. It therefore decided against recommending the use of trazadone, but included a research recommendation to examine the effectiveness of pharmacological interventions to treat sleep problems in people with dementia who had failed to respond to non-pharmacological interventions.<br>**Agitation, aggression and apathy**<br>The committee agreed the evidence relating to the use of valproate was demonstrably robust. It noted the significant presence of adverse events in people living with dementia receiving the intervention, but recognised that this was contrary to the beneficial effect mood stabilisers can have in non-dementia specific populations. As a result, the committee agreed it would be appropriate to recommend limiting the use of valproate in people living with dementia to those with pre-existing mood disorders only (specifically, in situations where they had already shown effectiveness before the onset of cognitive decline). The committee noted there was only very limited evidence on other mood stabilisers, and therefore it was appropriate to restrict the recommendation solely to valproate.<br>In addition, the committee noted that preliminary findings regarding the use of dextromethorphan-quinidine for agitation in people living with dementia, and donepezil plus choline alphoscerate for the management of apathy in people living with dementia did show some positive preliminary results. Although these results were limited the committee agreed it would be beneficial to pursue these lines of research and suggested these would be appropriate topics in which to make research recommendations. |
| **Trade-off between net health benefits and resource use** | **Depression and anxiety**<br>The committee noted that the findings of the economic evaluation conducted alongside the HTA-SADD trial were also negative, with mirtazapine only having a 20% probability of being cost-effective versus placebo at £20,000/QALY, and sertraline an even lower probability. The committee agreed this added further justification to their conclusion that antidepressants not be routinely used in this population.<br>**Antipsychotics**<br>The committee agreed that the most robust economic evidence available in this area came from the Rosenheck et al publication conducted alongside the CATIE-AD trial. This study concluded that antipsychotic treatment was not cost-effective for the trial population, and the committee agreed this further supported their conclusion that treatment should be restricted to those cases where it is urgently needed.<br>**Sleep disturbances**<br>No economic evidence was identified for sleep disturbances, but the implementation of the negative recommendation for melatonin was agreed to be likely to be cost-saving.<br>**Agitation, aggression and apathy** |

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| | No positive recommendations were made for pharmacological treatment for agitation, aggression and apathy, and therefore the committee was not concerned by the lack of economic evidence identified. |
| **Quality of evidence** | **Depression and anxiety**<br>The committee agreed that both the DIADS-2 and HTA-SADD trials were of good quality, with sufficiently large sample sizes that it would be reasonable to expect an effect to have been detected, if a meaningful one was present at the population level. It agreed that whilst there may be individual people who respond well to antidepressants, it is not usually possible to identify these people prospectively, and therefore no specific recommendations could be made for this group.<br>**Antipsychotics**<br>The committee agreed that there were good quality studies with large sample sizes looking at both antipsychotic efficacy and the effects of antipsychotic discontinuation. There were also long-term studies looking at the effects of antipsychotics on mortality, and therefore the committee agreed there was a robust evidence base behind the recommendation made.<br>**Sleep disturbances**<br>The committee noted that since the trazadone trial only ran for 2 weeks and involved a small number of participants, care was needed in interpreting the positive findings presented.<br>The committee were concerned about the use of the Epworth Sleepiness Scale and Stavanger Sleep Questionnaire as primary outcome measures in the Larsson study. Combined with the lack of actigraph data and carer outcomes this led it to rate the study quality as poor and as a result they lacked confidence in the reported improvement in REM sleep disorder presented.<br>**Agitation, aggression and apathy**<br>The committee observed that aside from the evidence relating to mood stabilisers, the evidence from all other pharmacological interventions associated with the management of agitation, aggression or apathy came from a limited number of RCTs or single studies only. For this reason the committee were cautious and agreed it would be inappropriate to make broad based recommendations on these interventions without a more comprehensive evidence base. |
| **Other considerations** | A common exclusion criteria across many of the trials in this review was either people who were deemed to need treatment sufficiently urgently that they could not be included in the study, or had sufficiently severe symptoms that randomisation was not considered appropriate. Therefore, the majority of the evidence base consists of people not considered at urgent need of treatment, and it is unlikely that RCTs would be conducted in this very severe population. Therefore, the committee agreed it was important to note that the recommendations made focus on this non-urgent population, and individual clinician judgement would be important in those people where it was felt there was an urgent need for intervention to prevent harm to the individual. |

#### 14.1.5.2 Non-pharmacological interventions

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| **Relative value of different outcomes** | The committee agreed that evaluations of most interventions depended on 3 components; whether the intervention improves the specific symptom(s) it is targeting; whether there are any broader impacts on cognition, function or wellbeing; and adverse events. |
| **Trade-off between benefits and harms** | **Depression and anxiety**<br>The committee agreed there was evidence of efficacy for psychological treatments in the management of depression and anxiety. There were significant reductions in overall levels of depression across the studies, as well as reductions in the primary anxiety measure in the 2 studies |

where people were required to have elevated levels of anxiety at study entry. The population in the studies was composed of people with mild to moderate dementia and mild to moderate depression, and therefore the committee agreed it was appropriate to make a recommendation for this group.

The only other intervention which showed evidence of benefit was the PATH intervention, but this was conducted in a setting where only around 50% of the people had dementia (the rest having mild cognitive impairment), and since the results were not reported separately for the 2 populations, the committee were not confident to conclude the intervention was specifically effective for people living with dementia.

**Managing distress**

The committee agreed that reactions which are classified as behavioural symptoms of dementia were often responses to other underlying problems in the context of difficulty in communicating needs effectively. For example, people with pain or delirium or who are responding to inappropriate care may be labelled as having behavioural problems when in fact there is a need to treat the underlying pain or delirium, and/or to improve the environment. The committee therefore agreed that, before any interventions for distress are considered, it is important that a thorough structured assessment of the person and their environment be conducted to try and identify and address the underlying causes of distress.

If this assessment is unsuccessful in identifying approaches that can resolve the problem, then in view of the clearly established harms of antipsychotics, the committee agreed it was appropriate that non-pharmacological management (both environmental and psychosocial) be offered before any thought is given to the use of antipsychotics. The committee also noted that the evidence showed that staff training in appropriate use of non-pharmacological methods showed the use of antipsychotics could be significantly reduced without any subsequent increase in neuropsychiatric symptoms, and therefore it was agreed this would form an appropriate part of the training staff should receive in managing non-cognitive symptoms (this is included as part of a recommendation in section 16 on staff training).

The committee also noted the evidence on two somewhat different approaches to managing symptoms; more structured psychosocial interventions and less structured interventions based around offering enjoyable and personalised activities. The committee agreed it was appropriate for both to be mentioned in the recommendations as they may each be useful in different situations.

**Sleep disturbances**

The committee agreed there was a lack of evidence in support of the use of light therapy for people with dementia and sleep problems.

The benefits of multicomponent interventions, including NITE-AD, were considered and the committee agreed that although the participants showed an increase in sleep at night-time and a reduction in awake-time at night, the importance of these improvements was hard to judge in the absence of data on the effect on participant or carer quality of life. Since the evidence suggested that light therapy alone was ineffective at increasing sleep the committee attributed the changes seen to the other interventions included in the programme, namely improved sleep hygiene and daily exercise. The discussion expanded to include the reduction in day-time sleep associated with individualised social activities, which despite not being associated with a significant increase in night-time sleep could have an important effect on people's quality of life by enriching their environment. The committee commented on the value of improved sleep hygiene, exposing people to daylight, physical and other pleasurable activities on general health and wellbeing of people with dementia. The committee agreed the positive results of the

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| | 3 trials looking at multicomponent interventions justified a recommendation in favour of an intervention involving sleep hygiene, daylight exposure and exercise, but in the absence of robust data on quality of life felt this recommendation should be kept at the “consider” level.<br>**Agitation, aggression and apathy**<br>The committee recognised there was some overlap in symptoms experienced by people living with dementia; managing symptoms is not necessarily discrete.<br>Overall, the committee agreed that staff training studies demonstrated the most positive findings. The committee considered the relevance of training implementation. It noted that the health technology assessment presented for Livingston (2014) had demonstrated similar findings and consequently the committee concluded that the focus for implementation should rest upon care providers where group training sessions could be offered. It recognised that the evidence reported in Deudon (2009) suggested that supporting and mentoring staff could have positive effects. For this reason the committee agreed it was appropriate to incorporate specific aspects of that reported intervention within a recommendation. Specifically, the committee recognised the benefit of face to face interventions rather than e-learning interventions. It agreed that it was important for initial sessions to be followed by on the job support sessions, focusing upon specific content.<br>In addition, the committee considered the evidence for ginkgo biloba in treating symptoms of agitation in people with dementia. It acknowledged that the pooled outcomes from 4 trials demonstrated positive outcomes for treating behavioural and psychological symptoms of dementia but was also mindful that evidence from non-dementia specific populations had observed effects from drug interactions. The committee also noted that ginkgo biloba is on a list of items that currently cannot be prescribed in primary care, and therefore agreed it was not appropriate to make any recommendations on its use. |
| **Trade-off between net health benefits and resource use** | **Depression and anxiety**<br>No economic evidence was identified for non-pharmacological management of depression and anxiety. However, the committee agreed that the recommendation made was broadly similar to that in the NICE guideline for depression, and therefore it was unlikely there would be significantly higher resource use in this group.<br>**Managing distress**<br>The committee noted there was no specific evidence available on the cost-effectiveness of non-pharmacological interventions for managing distress. However, it did note the evidence from the 2014 Livingston HTA report which demonstrated that successful non-pharmacological interventions for managing non-cognitive symptoms could be cost-saving, due to the reductions in subsequent treatment costs for those receiving early interventions. The committee agreed that this recent HTA report represented the best quality economic evidence available, and supported the recommendation for the first line use of non-pharmacological management.<br>**Agitation and aggression**<br>The committee noted that the Grip on Challenging Care programme (GRIP) (trialled by Zwijsen in 2011), a non-pharmacological treatment strategy for patients with dementia who display symptoms of agitation and aggression, resulted in a loss of QALYs, despite incurring a small but modest cost for the treatment. GRIP is therefore a dominated strategy. The committee also took note of the EVIDEM-E study and concluded that evidence for exercise for behavioural and psychological symptoms of dementia did not show a significant difference in terms of costs or benefits and were therefore unable to recommend it. |

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| | **Sleep problems**<br>The potential cost of a programme similar to NITE-AD was discussed by the committee with concern being raised about the cost of multiple sessions with a geropsychologist. It was suggested that another suitably trained person could deliver these sessions instead and at less cost to the health system. In addition, the committee noted that the study by Alessi 2005, which contained a similar multicomponent intervention but without the same extensive input from a geropsychologist, appeared to be equally effective, and was therefore confident that such an intervention could be delivered without imposing a large additional resource burden. |
| **Quality of evidence** | **Depression and anxiety**<br>The committee noted that the trials included in the meta-analysis of psychological interventions were heterogeneous, both in terms of the entry criteria into the trial and the interventions studied. Unfortunately, the sample sizes of the individual trials were small, so it was not possible to identify which individual interventions (e.g. CBT, counselling, psychodynamic interpersonal therapy) were likely to have the most robust effects, and therefore the committee agreed that only a general recommendation for psychological treatments was appropriate. The committee agreed it was appropriate to make a research recommendation about the most effective psychological treatments for anxiety and depression, in order to identify which of this class of interventions is most appropriate to offer to people living with dementia.<br>**Managing distress**<br>The committee noted that the evidence on using enhanced psychosocial care to reduce antipsychotic prescribing rates came from a single study. Therefore, whilst it was confident to recommend that this should form part of the training given to staff to manage anxiety, it did not feel that it was appropriate to recommend any specific form these interventions should take based on this single study.<br>**Sleep problems**<br>The committee commented that the short time frame of 2 days used in the slow-stroke back massage pilot study (Harris 2012) was probably insufficient to determine effects on sleep problems. The committee agreed that it was difficult to fully disentangle the effects of the individual components of the NITE-AD intervention, and therefore it was not possible to make recommendations about which parts of the intervention were the most important.<br>The committee was concerned that patients with sleep disordered breathing in the Chong 2005 study were not generally representative of people with dementia and a sleep problem, and that the use of a mask in people with dementia would be both problematic and potentially distressing. |
| **Other considerations** | The committee agreed that one of the factors leading to sleep problems for people with dementia is likely to be a lack of stimulation during the day. This can lead to day-time sleepiness and therefore affect sleep patterns at night. The committee therefore agreed that the non-pharmacological interventions considered elsewhere in this guideline for the improvement of function and wellbeing in people which dementia would be likely to also have an impact on sleep problems for some people.<br>The committee noted that only very limited evidence as found on managing non-cognitive symptoms in people with Parkinson's disease dementia or dementia with Lewy bodies, and therefore agreed it was appropriate to cross-refer to the advice in the NICE Parkinson's disease guideline. However, the committee noted these interventions may need to be modified to be appropriate or a population of people living with |

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| | dementia, and agreed it was important to highlight this within the recommendation. |

### 14.1.6 Recommendations

**Agitation, aggression, distress and psychosis**

**91. Before starting non-pharmacological or pharmacological treatment for distress in people living with dementia, conduct a structured assessment to:**

- explore possible reasons for the person's distress **and**
- check for and address clinical or environmental causes (for example pain, delirium or inappropriate care).

**92. As initial and ongoing management, offer psychosocial and environmental interventions to reduce distress in people living with dementia.**

**93. Only offer antipsychotics[h,i] for people living with dementia who are either:**

- at risk of harming themselves or others **or**
- experiencing agitation, hallucinations or delusions that are causing them severe distress.

**94. Be aware that for people with dementia with Lewy bodies or Parkinson's disease dementia, antipsychotics can worsen the motor features of the condition, and in some cases cause severe antipsychotic sensitivity reactions. For more guidance, see the advice on managing delusions and hallucinations in the NICE guideline on Parkinson's disease. Be aware that interventions may need to be modified for people living with dementia**

**95. Before starting antipsychotics, discuss the benefits and harms with the person and their family members or carers (as appropriate). Consider using a decision aid to support this discussion.**

**96. When using antipsychotics:**

- use the lowest effective dose and use them for the shortest possible time
- reassess the person at least every 6 weeks, to check whether they still need medication.

**97. Stop treatment with antipsychotics:**

- the person is not getting a clear ongoing benefit from taking them **and**

[h] The MHRA (2012) has given advice for health and social care professionals on prescribing antipsychotics to people living with dementia to treat the behavioural and psychological symptoms of dementia.

[i] At the time of publication (June 2018), the only antipsychotics with a UK marketing authorisation for this indication were risperidone and haloperidol. The marketing authorisation for risperidone only covers short-term treatment (up to 6 weeks) of persistent aggression in people with moderate to severe Alzheimer's disease unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others. The marketing authorisation for haloperidol only covers treatment of persistent aggression and psychotic symptoms in people with moderate to severe Alzheimer's dementia and vascular dementia when non-pharmacological treatments have failed and when there is a risk of harm to self or others. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

- after discussion with the person taking them and their family members or carers (as appropriate).

**98. Ensure that people living with dementia can continue to access psychosocial and environmental interventions for distress while they are taking antipsychotics and after they have stopped taking them.**

**99. For people living with dementia who experience agitation or aggression, offer personalised activities to promote engagement, pleasure and interest.**

**100. Do not offer valproate to manage agitation or aggression in people living with dementia, unless it is indicated for another condition.[j]**

**Depression and anxiety**

**101. For people living with mild to moderate dementia who have mild to moderate depression and/or anxiety, consider psychological treatments.**

**102. Do not routinely offer antidepressants to manage mild to moderate depression in people living with mild to moderate dementia, unless they are indicated for a pre-existing severe mental health condition.**

**Sleep problems**

**103. Do not offer melatonin to manage insomnia in people living with Alzheimer's disease.**

**104. For people living with dementia who have sleep problems, consider a personalised multicomponent sleep management approach that includes sleep hygiene education, exposure to daylight, exercise and personalised activities.**

**Parkinson's disease dementia and dementia with Lewy bodies**

**105. For guidance on the management of Parkinson's disease symptoms in people with Parkinson's disease dementia and Dementia with Lewy bodies, see the NICE guideline on Parkinson's disease. Be aware these interventions may need to be modified for people living with dementia.**

### 14.1.7 Research recommendations

**13. What are the most effective psychological treatments for managing depression or anxiety in people living with dementia at each stage of the condition?**

**14. What is the effectiveness and cost-effectiveness of dextromethorphan-quinidine for managing agitation in people living with dementia?**

**15. What is the effectiveness and cost-effectiveness of choline alphoscerate for managing apathy in people living with dementia?**

[j] If relevant, follow MHRA advice that valproate medicines are contraindicated in women and girls of childbearing potential unless a Pregnancy Prevention Programme is in place.

16. **What is the effectiveness of pharmacological treatments for sleep problems in people who have not responded to non-pharmacological management?**

For more details on the research recommendations made, and the rationale behind them, see appendix L.

# 15 Supporting informal carers

Informal carers are the wives, husbands, partners, children, other family members, and friends who provide vital unpaid care and support for people with dementia living in the community. In the UK, informal carers provide 1.34 billion hours of unpaid care to people with dementia each year, equating to a cost of £11.6 billion per year, or 44% of the total cost of dementia (Dementia UK, 2nd Edition, Alzheimer's Society, 2014). People with dementia have particular needs for care which are greater and more complex than those of other users of long-term care (World Alzheimer Report 2013), but provision of home care for people with dementia is not keeping pace with rising need (Carers UK, 2015). This places significant demands on informal carers.

For many carers, providing care has positive aspects, such as feeling closer to the person with dementia and fulfilling commitments made in lasting relationships. However, caring also brings many challenges (Merrilees, 2016). Carers experience loss and grief at the changes in the person they care for and in their relationship. Many feel isolated and lonely, and lack confidence in their ability to cope. Caregiving can be mentally and physically exhausting, especially where the person's behaviour causes concern or personal care needs are high. Many carers also have other responsibilities, such as caring for children or grandchildren, or experience practical problems such as lack of financial resources or unsuitable accommodation. Some carers, especially older carers, have health and mobility problems of their own.

Consequently, carers of people with dementia experience high levels of stress, and this impacts on their own physical and mental well-being. It is essential that carers have good support to enable them to manage the stresses and demands of caregiving and enable them to fulfil their role. This includes both support for the specific challenges of caregiving and support to address their own needs. Effective support will be tailored to the carer's personal circumstances and needs as well as the characteristics of the person with dementia for whom they are providing care; for example support needs will differ at different stages of dementia progression, and will continue after the person with dementia has moved into residential care. Carers are entitled under the Care Act 2014 to an assessment of their own needs and to have these needs addressed. The key questions for this review therefore focus firstly on how carers' needs can best be assessed and secondly on what kinds of interventions and services are effective in supporting carers' well-being and hence enabling them, if they so choose, to continue providing care..

# 15.1 Supporting informal carers of people living with dementia

**Review questions**

- How effective are carers' assessments in identifying the needs of informal carers of people living with dementia?
- What interventions/services are most effective for supporting the wellbeing of informal carers of people living with dementia?

## 15.1.1 Introduction

The aim of these review questions was to determine the effectiveness of different methods of assessing the needs of carers, and the effectiveness of interventions and services for supporting informal carers of people living with dementia. The 2014 Care Act gives carers a legal right to an assessment if they request one, and therefore the focus of the assessments question was on how and by whom these assessments should be conducted. The review identified studies that fulfilled the conditions specified in Table 88 and Table 89. For full details of the review protocols, see appendix C.

**Table 88: Review summary: informal carers' assessments**

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| **Population** | Carers of people (aged 40 years and over) living with dementia |
| **Interventions** | Formal assessments of the needs of carers of people living with dementia |
| **Comparator** | • Alternative assessment methods<br>• No formal assessment |
| **Outcomes** | • Access to health and social care support<br>• Carer burden and stress<br>• Carer experience and satisfaction<br>• Carer health-related quality of life<br>• Resource use and costs |

**Table 89: Review summary: interventions/services for informal carers**

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| **Population** | Carers of people (aged 40 years and over) living with dementia |
| **Interventions** | Interventions or services designed to improve the wellbeing of informal carers of people living with dementia, which may include:<br>• Peer support groups<br>• Training/information courses<br>• Information<br>• Psychosocial support<br>• Cognitive behavioural therapy<br>• Respite breaks |
| **Comparator** | • Each other<br>• Standard care |
| **Outcomes** | • Carer burden and stress<br>• Carer experience and satisfaction<br>• Carer health-related quality of life<br>• Resource use and costs |

### 15.1.2 Evidence review

This review was conducted as an update from the previous dementia guideline (CG42). All included RCTs and systematic reviews from the previous guideline were considered. Relevant RCTs, together with identified RCTs in the included systematic reviews, were screened at title and abstract level, with 112 potentially relevant references ordered for full-text review. The previous guideline included interventions for all carers, whilst this update only considered interventions for carers of people living with dementia, and therefore not all papers included in the previous guideline were eligible for inclusion in this update.

In addition, a systematic literature search for RCTs published since the last guideline identified 6,738 references. These were screened at title and abstract level, with 63 papers ordered as potentially relevant systematic reviews, 247 ordered as potentially relevant RCTs of interventions/services for carers, and 3 ordered as potentially providing relevant data on carers' assessments. Finally, because of the limited RCT data available on carers' assessments, a separate search was conducted to look for comparative observational studies on carers' assessments, identified from the full set of observational studies related to carers of people living with dementia using a keyword search for variations on the terms assess/assessment. In total, 1,477 references were identified, of which 7 were judged to be potentially relevant and ordered for full-text review.

#### 15.1.2.1 Interventions/services for informal carers

Interventions were classified into one of 7 different types, based on a classification by Sörensen et al 2002 used in the previous guideline, but updated to take into account the changes in types of interventions available, in particular the increasing using of technology and more formal models of case management. These intervention types were defined as follows:

- Psychoeducational interventions – Structured programmes providing information about how to effectively respond to dementia-related difficulties, such as memory or behavioural problems.
- Skills training – Training and information on specific practical aspects of care for a person living with dementia.
- Psychoeducation and skills training – Interventions containing both of the components listed above.
- Supportive interventions – Professionally or peer-led unstructured support groups
- Respite care – In-home or site-specific assistance with care, designed to give the carer time off from providing care.
- Psychotherapy – Formal therapeutic interaction between a trained professional and the carer. This category includes both cognitive-behavioural therapy and interventions modelled on a cognitive-behavioural approach.
- Case management – A specified case manager is responsible for the assessment, planning, facilitation, coordination and evaluation of an individual's care, to ensure this care is optimised.
- Multicomponent intervention – Any intervention containing elements of at least two of the categories above (with the exception of the combined psychoeducation and skills training category). Interventions containing multiple components from the same category (e.g. an intervention containing both group and individual psychoeducation) would be classified under that rather than as a multicomponent intervention. Interventions were sub-categorised according to whether all components of the interventions were aimed at the carer, or whether some components were aimed at the carer and some the care receiver. A table summarising what components were contained in multicomponent studies is given in Appendix E.

Where appropriate, these types were further sub-categorised accordingly to the way they were delivered (individual versus group, in person versus telephone versus online).

The most recent, high quality systematic reviews in each of these areas were included as part of the analysis, with older systematic reviews being excluded if they did not provide additional relevant data. All RCTs contained within those systematic reviews were retrieved to check for additional relevant data, which was also included in any analyses undertaken. Any additional identified RCTs not contained in any included systematic reviews were included separately. Some interventions did not fit anywhere within the classification, and were therefore kept separate. These interventions were:

- Exercise
- Attendance at a memory clinic
- Meditation/mindfulness
- Cranial electrotherapy stimulation

In total, 8 systematic reviews and 38 additional RCTs were included, with 112 studies from the old guideline excluded at full-text review, and 266 studies (55 systematic reviews and 210 RCTs) from the new search excluded at full-text review. Studies excluded from both the old dementia guideline and the new search are listed, with reasons for exclusion, in appendix F, and evidence tables for both systematic reviews and RCTs are available in appendix E. Evidence was further summarised in GRADE profiles, which are given in appendix G.

#### 15.1.2.2 Carers' assessments

The 10 identified papers (from both the RCT and observational searches) were screened at full-text level, with 10 excluded due to not matching the study protocol, and therefore no studies were included in the final review. Studies excluded are listed, with reasons for exclusion, in appendix F.

#### 15.1.2.3 Analyses

For both questions, data from different studies were meta-analysed when possible, with GRADE tables and meta-analysis results given in appendices G and H, respectively. References for the included studies are given in appendix I.

##### *15.1.2.3.1 Meta-regression*

A meta-regression analysis was additionally carried out for the question on interventions for informal carers. In this analysis, rather than the separate categories of intervention being compared to usual care (or another active intervention) independently, all the studies are combined into a single network meta-analysis, with a regression model being fitted to the effect sizes from each trial to estimate the contribution of different intervention components to the overall effect size. This analysis has the advantage of being able to decompose multicomponent interventions, and estimate the effect of individual components within those interventions, rather than treating multicomponent interventions as a single homogeneous class. Sufficient data were only available to undertake this analysis for the outcome of carer depression, with the following analyses being conducted:

- An analysis containing the full list of all components included within any intervention.
- A restricted analysis, only including those intervention components included in enough studies to provide reliable estimates of effect.
- An analysis of the effect of the mode of intervention delivery (individual, group, telephone, technology-based).

- An analysis of the effect of the target of an intervention (carer only, or dyadic for the person living with dementia and their carer).
- An analysis including both intervention components and mode of delivery.
- An analysis including both intervention components and the target of an intervention.
- Two analyses looking at intervention components, and also including specific parameters for the numbers of components in an intervention, to test for either an additive effect of multiple interventions, or for a diminution of effect, where the overall effectiveness of a multicomponent intervention is less than the sum of its components.

Further details on and result of this analysis are given in appendix H.

#### 15.1.2.4 Description of included studies

##### *15.1.2.4.1 Carers' assessments*

No evidence was identified evaluating the effectiveness of carers' assessments. Many of the multicomponent interventions identified did include a structured assessment, but it was not possible to isolate the effect of one particular component of the interventions.

##### *15.1.2.4.2 Interventions/services for informal carers*

**Systematic reviews**

**Table 90: Summary of included studies**

| Study reference | study design | Study population | Included studies | Outcomes of interest |
|---|---|---|---|---|
| Jensen (2015) | Systematic review | RCTs comparing educational interventions with usual care for informal carers of people living with dementia | 7 RCTs comparing educational interventions for carers of people living with dementia versus usual care | Carer burden<br>Carer depression<br>Carer quality of life<br>Admissions to long stay facility |
| Laver (2016) | Systematic review | RCTs comparing the efficacy of multicomponent interventions for the carer and dyadic interventions for the carer and person living with dementia to usual care | 17 RCTs included for carer only multicomponent interventions versus usual care<br>23 RCTs included for dyadic multicomponent interventions versus usual care | Carer depressive symptoms<br>Carer quality of life<br>Carer reaction to behavioural and psychological symptoms of dementia |
| Lins (2014) | Systematic review | RCTs comparing the efficacy of telephone counselling for informal carers of people living with dementia to usual care | 9 RCTs included in the review | Carer depression<br>Carer burden<br>Distress<br>Anxiety<br>Quality of life<br>Care-giving self-efficacy |
| Maayan (2014) | Systematic review | RCTs comparing respite care with a control intervention for carers of people living with dementia | 3 RCTs compared respite care for carers of people living with | Carer Burden (ZBI)<br>Carer psychological stress and health |

| Study reference | study design | Study population | Included studies | Outcomes of interest |
|---|---|---|---|---|
| | | | dementia versus a control intervention | |
| Parker (2008) | Systematic review | Studies assessing the effectiveness of interventions that assist carers to provide support for people living with dementia in the community | 13 studies considered psycho educational interventions;<br>7 studies considered support;<br>12 studies reported multicomponent interventions | Psychological morbidity<br>Self-reported perceptions of knowledge<br>Quality of life<br>Health service utilisation (including carer satisfaction |
| Scott (2016) | Systematic review | Studies considering trials of pure technology based CBT interventions for carers of people living with dementia | 4 studies included in the review | Carer depression |
| Thompson (2007) | Systematic review | RCTs evaluating the efficacy of individual or group based technology interventions | 4 studies classed as technology based;<br>13 studies classed as group based;<br>27 studies classed as individual based | Quality of life<br>Physical and mental health<br>Burden or satisfaction<br>Time spent on caring activities |
| Vernooij-Dassen (2011) | Systematic review | Studies using cognitive reframing to reduce carer's problems by changing their beliefs and interpretations. | 11 RCTs included in the review | Depression<br>Anxiety<br>Quality of life<br>Self-efficacy<br>Burden |

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**Randomised controlled trials**

A total of 111 unique RCTs containing relevant data were identified, of which 107 compared the following interventions with either standard care or a less intensive intervention:

- 9 RCTs of psychoeducational interventions (4 group, 2 individual, 2 technology-based, 1 telephone-based)
- 12 RCTs of skills training interventions (4 group, 5 individual, 2 technology-based, 1 telephone-based)
- 20 RCTs of combined psychoeducation and skills training interventions (6 group, 9 individual, 2 technology-based, 3 telephone-based)
- 7 RCTs of supportive interventions (3 group, 1 individual, 3 telephone-based)
- 3 RCTs of respite care
- 15 RCTs of psychotherapy interventions (8 group, 3 individual, 4 technology-based)
- 3 RCTs of case management
- 30 RCTs of multicomponent interventions (14 carer only, 16 in carer and care receiver dyads)
- 2 RCTs of exercise interventions (1 individual, 1 telephone-based)
- 1 RCT of attendance at a memory clinic
- 5 RCTs of meditation/mindfulness interventions
- 1 RCT of cranial electrotherapy stimulation

Additionally, 4 RCTs compared different intervention types at the same intensity of intervention:

- 3 RCTs compared psychotherapy with a psychoeducational intervention
- 1 RCT compared cognitive behavioural therapy with acceptance and commitment therapy

At the re-runs stage 1 RCT of a spiritual care educational program was identified.

### 15.1.3 Health economic evidence

A systematic literature search was undertaken to identify existing cost–utility analyses evaluating interventions targeted on informal carers of people living with dementia or carers' assessments that have been published since the literature reviews in CG42. In total, 2,454 articles were returned, of which 22 were selected as potentially relevant and retrieved for full-text review. Additionally, 2 studies included in CG42 were deemed to be suitable for full-text review against the current protocol. In total, 8 publications, reporting on 5 studies, were judged to be at least partially applicable to the review question regarding interventions/services for supporting the wellbeing of informal carers, and were therefore included. Of these studies, 2 evaluated psychoeducation and skills training interventions, 2 evaluated multicomponent carer interventions and 1 evaluated a supportive intervention. No relevant CUAs were identified evaluating carers' assessments.

Details of the literature search are provided in Appendix D.

### 15.1.3.1 Interventions/services for informal carers

#### *15.1.3.1.1 Supportive interventions*

**Charlesworth et al. (2008)** compared the befriending of carers by trained lay workers with usual care, which was all normal available care without the befriending intervention. The trained lay workers offered emotional support and a degree of informational support. The economic evaluation was conducted alongside a UK RCT (BECCA; n=236), over a time horizon of 15 months. Utilities were elicited from carers using the EQ-5D. Carers also provided resource use data, with unit costs from standard UK sources (price year 2005). For further details, please see the economic evidence profile in Appendix M.

Trained lay workers befriending carers was associated with 0.017 additional carer QALYs, and £2,003 of additional costs, compared with usual care over 15 months. The resulting ICER was £117,039. Cost-effectiveness acceptability analysis, conducted only from a societal perspective (including the cost of informal carer time), showed the intervention to have a 29.4% probably of achieving an ICER of £30,000 per QALY or better. Including QALY gains for the person living with dementia appeared to increase its likelihood of being cost-effective; however this analysis was only presented with societal costs included, such as informal carer time forgone.

#### *15.1.3.1.2 Multicomponent interventions*

**Martikainen et al. (2004)** compared a programme of short psychoeducation courses with counselling support for carers, including physical and recreational training for their relatives with Alzheimer's disease, with existing community services. A 5-year Markov model based on nursing home placement used effectiveness data from 1 US RCT. Resource use and costs were from Finnish sources. Utilities were informed by a published HUI-2 values. Cost-effectiveness results focused on the PWD's outcomes; however, carer QALYs were reported such that an ICER including them can be estimated. For further details, please see the economic evidence profile in Appendix M.

The analysis found that family meetings reduce carer QALYs by 0.01 and reduces costs by €2992, meaning €299,200 is saved for every 1 QALY lost. Combining QALYs from carers and people living with dementia, this analysis suggests that the intervention dominates usual care.

**Drummond et al. (1991)** conducted an economic evaluation of a multicomponent support programme for carers of people with dementia. The intervention included weekly visits by carer support nurses, weekly periods of respite care, monthly family meetings, and education about dementia and caregiving. The programme was compared with conventional nursing in a Canadian RCT (n=60) with 6 months of follow-up. The CUA, conducted concurrently, collected resource use data from carer interviews and health records. Unit costs were obtained from Canadian national sources (price year 1988). Utilities were elicited from RCT participants using the Caregiver Quality of Life Index by time trade-off. For further details, please see the economic evidence profile in Appendix M.

The carer support intervention was found to be associated with an ICER of $20,036 per QALY gained compared with conventional care. No sensitivity analysis or cost-effectiveness acceptability analysis was presented.

#### *15.1.3.1.3 Psychoeducation and skill training*

**Livingston et al. (2014)** reported on the cost-effectiveness of a programme of manual-based coping strategy sessions for carers of PWD, compared with usual care. The CUA was conducted alongside a UK RCT (START; n=260), over a time horizon of 24 months. Utilities were elicited from carers using the EQ-5D questionnaire. Carers also provided resource use data, with unit costs from standard UK sources (price year 2009). For further details, please see the economic evidence profile in Appendix M.

The intervention was associated with 0.03 additional QALYs per carer, and an additional £336 of carer-related costs, resulting in an ICER of £11,200 compared with usual care. In probabilistic sensitivity analysis, the intervention was found to have a 65% probably of achieving an ICER of £20,000 per QALY or better. Methodological sensitivity analyses conducted, varying the time horizon and approach to missing data, did not materially impact upon results.

**Joling et al. (2013)** compared a programme of 6 counselling sessions held every 2–3 months, 4 of which could include the carer's family and friends, with usual care. The CUA was conducted alongside a 12-month Dutch RCT (n=192). Resource use was collected using cost diaries, with unit costs from standard Dutch tariffs (price year 2009). A societal perspective was taken; however, the value of productivity losses can be subtracted from total costs to estimate a health and social care perspective. Utilities for carers and people living with dementia were informed by the SF-12 for the estimation of QALYs. For further details, please see the economic evidence profile in Appendix M.

Using carer outcomes only, Joling et al. suggest that the family meetings intervention dominates usual care. Including carer-PWD dyad outcomes, Joling et al. found the intervention to have an ICER of €1,875.

### 15.1.3.2 Carers' assessments

No relevant CUAs were identified evaluating carers' assessments, therefore there is no economic evidence for this review question.

## 15.1.4 Evidence statements

### 15.1.4.1 Psychoeducational interventions

Very low- to moderate-quality evidence from up to 3 RCTs containing 373 people could not differentiate levels of burden (carer), depressive symptoms (carer), anxiety (carer), stress (carer), quality of life (carer), self-efficacy (carer), social support (carer), severity of memory, behavioural and psychological symptoms (person living with dementia), reactions to memory, behavioural and psychological symptoms of dementia (carer), activities of daily living (person living with dementia) or the proportion of people entering long stay care (person living with dementia) between people offered psychoeducational interventions or usual care.

### 15.1.4.2 Skills training

Low- to moderate-quality evidence from up to 6 RCTs containing 360 people found people offered skills training had improvements in burden (carer) and quality of life (carer) compared with people offered usual care.

Very low- to moderate-quality evidence from up to 8 RCTs containing 496 people could not differentiate levels of depressive symptoms (carer), anxiety (carer), stress (carer), self-efficacy (carer), social support (carer), severity of memory, behavioural and psychological symptoms (person living with dementia) or reactions to memory behavioural and psychological symptoms (carer) between people offered skills training or usual care.

#### 15.1.4.3 Psychoeducation and skills training

Low- to moderate-quality evidence from up to 14 RCTs containing 2,031 people found people offered psychoeducation and skills training had improvements in burden (carer), depressive symptoms (carer), anxiety (carer), stress (carer) and severity of memory, behavioural and psychological symptoms (person living with dementia) compared with people offered usual care.

Very low- to moderate quality evidence from up to 7 RCTs containing 973 people could not differentiate levels of quality of life (carer), self-efficacy (carer), reactions to memory, behavioural and psychological symptoms (carer), activities of daily living (person living with dementia) or the proportion of people entering long stay care (person living with dementia) between people offered psychoeducation and skills training or usual care

#### 15.1.4.4 Supportive interventions

Low- to moderate-quality evidence from up to 5 RCTs containing 475 people could not differentiate burden (carer), depressive symptoms (carer), anxiety (carer), stress (carer), quality of life (carer), social support (carer) or severity of memory, behavioural and psychological symptoms (person living with dementia) between people offered supportive interventions or usual care.

#### 15.1.4.5 Respite care

Moderate-quality evidence from 1 RCT of 55 people could not differentiate burden (carer), depressive symptoms (carer) or anxiety (carer) between people offered respite care or usual care.

Moderate-quality evidence from 1 RCT of 38 people found people offered polarity therapy had less severe depressive symptoms (carer), and stress (carer) compared with people offered respite care.

#### 15.1.4.6 Psychotherapy

Low- to high-quality evidence from up to 14 RCTs containing 1,034 people found people offered psychotherapy had improvements in burden (carer), depressive symptoms (carer), anxiety (carer), quality of life (carer), self-efficacy (carer) and reactions to memory, behavioural and psychological symptoms (carer) compared with people offered usual care.

Low- to moderate-quality evidence of up to 3 RCTs containing 298 people could not differentiate stress (carer) or severity of memory, behavioural and psychological symptoms (person living with dementia) between people offered psychotherapy or usual care.

#### 15.1.4.7 Case management

High-quality evidence from 1 RCT of 61 people found people offered case management had improvements in anxiety (carers) and severity of memory, behavioural and psychological symptoms (person living with dementia) compared with people offered usual care.

Low- to moderate-quality evidence from up to 3 RCTs of 229 people could not differentiate levels of burden (carers), depressive symptoms (carers), quality of life (carers), self-efficacy (carers) or proportions of people entering long stay care (person living with dementia) between people offered case management or usual care.

#### 15.1.4.8 Multicomponent interventions

Low- to moderate-quality evidence from up to 20 RCTs containing 5,220 people found people offered multicomponent interventions had improvements in burden (carer), depressive symptoms (carer), quality of life (carer), social support (carer), severity of memory, behavioural and psychological symptoms (person living with dementia) and reactions to memory, behavioural and psychological symptoms (carer) compared with people offered usual care.

Low- to moderate-quality evidence of up to 7 RCTs containing 992 people could not differentiate levels of anxiety (carer), self-efficacy (carer), activities of daily living (person living with dementia) or the proportion of people entering long stay care (person living with dementia) between people offered multicomponent interventions or usual care.

#### 15.1.4.9 Exercise

Low- to moderate-quality evidence from up to 2 RCTs containing 161 people could not differentiate burden (carer), depressive symptoms (carer) or stress (carer) between people offered exercise or usual care.

#### 15.1.4.10 Memory clinic

Moderate-quality evidence from 1 RCT of 30 people could not differentiate burden (carer) or reactions to memory, behavioural and psychological symptoms (carer) between people offered access to a memory clinic or usual care.

#### 15.1.4.11 Mindfulness/meditation

High-quality evidence from up to 5 RCTs containing 192 people found people offered meditation/mindfulness interventions had improvements in depressive symptoms (carer) but worsening in the severity of memory, behavioural and psychological symptoms (person living with dementia) compared with people offered usual care.

Low-to moderate-quality evidence from up to 3 RCTs containing 133 people could not differentiate burden (carer), anxiety (carer), stress (carer), self-efficacy (carer), social support (carer) or reactions to memory, behavioural and psychological symptoms between people offered meditation/mindfulness interventions or usual care.

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#### 15.1.4.12 Cranial electrotherapy stimulation

Very low-quality evidence from 1 RCT of 38 people could not differentiate burden (carer) or depressive symptoms (carer) between people offered cranial electrotherapy stimulation or usual care.

#### 15.1.4.13 Psychotherapy versus psychoeducational interventions

Low- to moderate-quality evidence from up to 3 RCTs containing 127 people could not differentiate burden (carer), depressive symptoms (carer), anxiety (carer), self-efficacy (carer), severity of memory, behavioural and psychological symptoms (person living with dementia) or reactions to memory, behavioural and psychological symptoms (carer) between people offered cognitive behavioural therapy or psychoeducational interventions

#### 15.1.4.14 Cognitive behavioural therapy versus acceptance and commitment therapy

Low-quality evidence from 1 RCT of 87 people could not differentiate depressive symptoms (carer) or anxiety (carer) between people offered cognitive behavioural therapy or acceptance and commitment therapy.

#### 15.1.4.15 Spiritual care

Low-quality evidence from 1 quasi experimental RCT of 54 people found carer self-efficacy improved for carers of people with Alzheimer's disease who took part in a spiritual care education program compared with those who did not receive the intervention.

#### 15.1.4.16 Meta-regression (carer depression)

Moderate-quality evidence from a meta-regression 73 RCTs found that skills training, mindfulness and psychotherapy significantly reduced carer depressive symptoms compared to usual care, with the largest effects found in group interventions offered to carers alone (rather than in a dyad with the person living with dementia also present).

#### 15.1.4.17 Health economic evidence

##### *15.1.4.17.1 Psychoeducational and skill training*

One directly applicable cost-utility analysis with minor limitations compared a manual-based programme of coping strategy sessions for carers with usual care. The intervention was associated with 0.03 additional QALYs per carer, and an additional £336 of carer-related costs. The ICER was £11,200. The intervention had an ICER of no more than £20,000 per QALY in 65% of analysis replications (designed to capture uncertainty in the sample), and no more than £30,000 per QALY in 75%.

One partially applicable cost–utility analyses with very serious limitations compared programmes of family meetings for carers of PWD with usual care. One found that family meetings provide 0.02 additional carer QALYs at a lower cost (-€845) compared with usual care over 12 months.

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#### *15.1.4.17.2 Supportive interventions*

One directly applicable cost-utility analysis with potentially serious limitations compared lay workers befriending carers with usual care. Befriending carers generated 0.017 additional carer QALYs, and incurred an additional £2,003, over 15 months. The ICER was £117,039.

#### *15.1.4.17.3 Multicomponent interventions*

One partially applicable cost-utility analyses with very serious limitations compared programmes of family meetings for carers of PWD with usual care. It found that family meetings cause a loss of 0.01 carer QALYs, with a cost saving of €299,200 per lost QALY. Both interventions were found to be dominant when QALYs of the PWD were included.

One partially applicable cost-utility analysis with very serious limitations compared a multicomponent intervention of support for carers with usual care. The intervention was associated with a gain of 0.11 carer QALYs, estimated using the Caregiver Quality of Life Index, and an additional cost of Can$2204 (price year 1988). The ICER was Can$20,036.

### 15.1.5 Evidence to recommendations

#### 15.1.5.1 Interventions/services for informal carers

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| **Relative value of different outcomes** | The committee acknowledged the variety of measures used to assess each outcome and agreed the use of a standardised mean difference was the appropriate method of interpretation. A value of 0.2 was used as the cut-off for a meaningful effect size throughout the discussions.<br>The committee recognised there were some limitations in linking the outcomes with clinical experience. Some interventions may be more fitted to specific situations: for example, the interpretation of depression as an outcome may have to be qualified within the context of the recruited population; in mixed carer populations, both depressed and non-depressed people may have been included in the sample (combined with the general underdiagnosing of depression in carers of people living with dementia). In other instances, disaggregation of data meant it was possible to interpret outcomes at the subgroup level, whereby the use of skills training demonstrated significant benefits for carer burden at the group and individual level, but did not differentiate for the use of technology based interventions.<br>Of the outcomes available, the committee agreed that carer burden and carer quality of life would be the most directly applicable for decision making, as they are both overall measures of the impact that caring for someone living with dementia has on the life of the carer. They also agreed that measures of behavioural and psychological symptoms would be valuable, as these would identify if any changes interventions introduced in the way carers interact with the person they are caring for would impact on the person living with dementia themselves (with positively or negatively), as well as on the carer. |
| **Trade-off between benefits and harms** | **Psychoeducation and skills training**<br>The committee noted that skills training was closely linked to psychoeducation and agreed that the stratification of evidence into individual, group based or technology based interventions was the most appropriate means of presentation. However, the committee acknowledged that individual, group based and technological interventions involve different approaches and interactions. The committee noted the choice of intervention technique may reflect the |

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carer's individual or personal preference and specific approaches may be more considerate of different cultural needs.

The committee agreed that whilst there was no evidence of benefits from psychoeducation alone, and only limited evidence of benefits from skills training alone, interventions combining psychoeducation and skills training showed meaningful benefits across a range of domains, and included benefits for both the carer and the person living with dementia.

**Respite care**

The committee acknowledged the limited evidence on respite care meant it was difficult to come to a conclusion about its overall benefit. It noted that respite can be very difficult to measure because it does not benefit all carers in exactly the same way. Some people may find respite a relief from stress, whereas, for others, stress levels may remain high. The committee noted there were caveats on the interpretation of the results and observed that if carers do not find respite care helpful they might be unlikely to continue in a trial. In real world examples, respite care packages will probably evolve based on an individual's needs or personal preference. The overall consensus from the committee was that although it was hard to measure and capture real world outcomes, the lack of evidence does not mean we should conclude that respite care does not work. Further, it noted that the trials only included a very specific type of respite care (small respite periods of short duration, as opposed to an extended single period of respite). Finally, it noted that many of the other interventions examined will necessarily have involved a level of respite care being provided in order for the carer to be able to attend the intervention.

**Psychotherapy and counselling**

The committee recognised that psychotherapy and counselling were distinct interventions and therefore should be classified discretely. The committee recognised there is a distinction between psychotherapy for specific mental health issues and post-diagnostic counselling aimed at supporting adjustment to the diagnosis, and acknowledged that the evidence that had been presented was mostly related to cognitive behavioural therapy (CBT). The committee had concerns about the applicability of the trials to the current UK context; the trials often included people without problems at baseline, whilst in the UK, people often only receive these interventions when demonstrating and showing signs of a specific need which prompts a referral (a situation where larger gains may well be expected, as the carer has more potential to benefit). The committee queried whether these interventions would be most effective for selective groups of carers or everyone. In particular, they felt that carers with a diagnosis of depression would receive standard psychological treatments, and therefore the relevant question for this guideline was whether a specific group of people with sub-threshold depression would benefit from earlier psychological interventions, and the committee felt it was not possible to answer this from the current evidence due to the heterogeneous nature of the populations involved in the trials.

The committee discussed the applicability of technology based interventions and raised the need to be mindful of selection of participants, as people with skills in using web based technologies may experience interventions differently to others. On the other hand, the committee noted anecdotal evidence that, in general, web based CBT may be as effective as face to face delivery – this may especially be the case for younger people with dementia and their carers who are seen to be increasingly using web based resources.

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However, the committee noted there was evidence that group CBT may provide benefits, particularly in levels of depression, and therefore agreed it was appropriate to make a research recommendation, looking at the effectiveness of these interventions in a more targeted group of people at risk of depression.

**Case management**

The committee agreed there was limited evidence available on case management interventions. It was agreed that the effectiveness of case management was best assessed as part of the questions on non-pharmacological treatments for people living with dementia, as there is a larger volume of evidence available in this context.

**Multicomponent interventions**

Multi-component interventions were described as encompassing at least 2 or more elements to the intervention, both aimed at the carer. The committee noted that an intervention containing only a course of psychoeducation and skills training would not normally be classified as multicomponent, therefore this was considered in its own category as part of the review.

The committee agreed that many multicomponent interventions demonstrated moderate significant effects, yet when each of the individual components was considered, they were only able to demonstrate a small or negligible effect. One possible explanation for this is that some of the multicomponent intervention trials may be better designed than some of the individual component studies, where a structured package has been developed (and tailored to individual needs), rather than simply offering a single individual intervention. It may also be the case either that the effects of the interventions are additive, or that the higher levels of contact time usually seen with multicomponent interventions lead to better results.

**Psychoeducation and skills training interventions**

The committee agreed that there was clear evidence of benefits from interventions containing both psychoeducation and skills training, and the findings were broadly similar to those for more general multicomponent interventions. The committee agreed that it was therefore appropriate to recommend psychoeducation and skills training interventions, and the content of these should include at least those features which were commonly present in the clinical data showing the effectiveness of these interventions. It also agreed that recommending a specific psychoeducation and skills training intervention was more appropriate than making a more generic recommendation around multicomponent interventions, both because of the economic evidence described in the “trade-off between net health benefits and resource use” section below, and because it was a clearly defined intervention type that should be practical to implement in practice.

**Mindfulness and meditation**

The committee agreed with the evidence seen on mindfulness although noted that the high quality status would need to be qualified alongside the small to moderate effect that was observed. It did not believe the evidence was sufficiently robust to suggest recommending these interventions over the psychoeducation and skills training interventions discussed above.

**Supportive interventions; exercise; memory clinics; cranial electrical stimulation**

The committee noted there were non-significant effects across a range of interventions including exercise, cranial electrical stimulation, memory

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| | clinics and supportive interventions, and therefore did not feel it appropriate to recommend any of these approaches.<br>**Spiritual care**<br>The committee agreed that, although a significant result was found in the one study looking at spiritual care, the fact this came from only one small study meant the evidence was insufficient for any positive recommendations to be made. |
| **Trade-off between net health benefits and resource use** | **Supportive interventions**<br>The committee discussed the health economic evidence for supportive interventions, which was based on one trial of a carer befriending intervention. The committee discussed the importance of capturing the resource impact of interventions preventing carer breakdown and delaying or avoiding the need for residential care for the person living with dementia. The committee recognised that the mean ICER was significantly higher than would usually be considered an effective use of NHS resources, and agreed that the expected additional resource use required for the intervention would be likely to cause a net loss of health within the wider health care system.<br>The committee discussed the importance of critiquing health economic evaluations of very specific interventions, and agreed that is it important to determine the degree to which any single intervention is representative of that wider category of interventions.<br>**Multicomponent interventions**<br>The committee discussed the two CUAs evaluating multicomponent interventions. The committee discussed the extent to which the studies could be used to inform present decision making, for example given the publication date (1991) of the Drummond et al. study, and ultimately felt that they could not rely on the economic evidence to support a recommendation. The committee understood that some estimation of ICERs by the NICE technical team had been necessary in order to present results that satisfied the reference case, and that this added to the overall uncertainty.<br>**Psychoeducation and skill training**<br>The committee discussed the Livingston et al. evaluation of individual, manual-based carer support. The results were robust to probabilistic sensitivity analysis, with the intervention having a 65% probability of being cost effective at a threshold of £20,000/QALY and a 75% probability of being cost effective at £30,000/QALY. The committee discussed whether this was sufficient to determine whether an intervention should be recommended. The committee agreed that the study provided evidence to recommend a psychoeducation and skills training intervention for carers, but not necessarily the specific intervention evaluated (START), as it was acknowledged that a substantial number of possible alternative interventions were not captured in the clinical or economic evidence. The committee agreed that the topics covered by START are a good representation of the topics that should be covered in this type of intervention. |
| **Quality of evidence** | The committee noted that the evidence in relation to respite care consisted of fairly poor examples of respite interventions; the trials may not have been long enough to actually allow carers to use the time as they desire. Furthermore, polarity therapy was agreed to be not directly relevant as an intervention for the UK health and social care setting. With the exception of respite care, no other real overarching concerns with the overall quality of the evidence were raised.<br>The committee recognised that the vast array of interventions and outcomes meant it was very hard to present outcomes for interventions |

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| | in a truly meaningful way, and recommendations could only really be made at the class level.<br>The committee discussed the potential impact of the placebo effect on outcome effect sizes, as the evidence consisted of studies where the intervention recipient and provider were not blinded. However, they noted that in the case of the types of supportive interventions considered, the benefits gained simply from taking part in an activity regardless of the content of it, could reasonably be considered a part of the intervention itself, rather than a confounding factor.<br>The committee noted that the fact the results of the meta-regression analysis were consistent with the pairwise analyses was a useful validation of the findings, and gave further justification to the recommendations made around skills training and group interventions, and the research recommendation on group CBT. |
| **Other considerations** | The committee agreed that carer interventions were generally considered to be clinically beneficial. They were confident that the evidence they had seen on multicomponent interventions was sufficient to enable an 'offer' recommendation to be made. This could be achieved by taking into consideration specific elements drawn from individual components which had been found to be effective on their own, together with the common elements from the psychoeducation and skills training interventions evaluated, and the elements found in psychoeducation and skills training interventions shown to be cost-effective. The committee agreed it was not appropriate to provide a prescriptive list of requirements, but felt comfortable providing a minimum set of domains which should be covered in any psychoeducation and skills training intervention package.<br>The committee acknowledged that specific attention should be paid to carers' individual and personal preferences. For example different people will prefer face to face, web based, or group based support. A personalised approach may identify issues which had not been observed in the evaluated interventions. The committee therefore agreed the recommendation should consider personalised strategies. However, they also noted the evidence suggested the largest benefits would be found in group interventions, and therefore agreed it was appropriate to make an awareness raising recommendation on this point.<br>The committee discussed wording around the use of 'pleasant activities' and agreed it was best applied jointly as a collaborative statement focusing on both the carer and the person living with dementia. The committee also discussed the relevance of psychotherapy. They agreed it was important for carers to have access to a range of interventions to manage any serious issues, rather than automatically being referred for psychotherapy. The use of Improving Access to Psychological Therapies (IAPT) was highlighted as it is often accessed via self-referral if people have knowledge of it.<br>It was noted there is a legal necessity to place carers at the centre of the decision making process. The committee were mindful that any intervention offered should be easily accessible although noted that intervention choice may be influenced by mode and/or setting.<br>The committee also agreed it was appropriate to cross-refer to the NICE guideline depression in this section, due to the established higher risk of depression in carers of people living with dementia. |

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#### 15.1.5.2 Carers' assessments

| | |
|---|---|
| **Relative value of different outcomes** | The committee recognised the Care Act 2014 sets out best practice but noted that different local authorities may interpret the Act differently, with statutory guidance used to help support implementation. Guideline recommendations can highlight or support specific parts of the Act. |
| **Trade-off between benefits and harms** | The committee acknowledged that carers' assessments are a legal requirement and noted that assessing carers and identifying appropriate interventions were two separate issues. For the former, reading the Care Act may help in identifying appropriate wording. However, the committee were reminded that the purpose of any recommendation should not simply be to explain legislative requirements, but should be used to enable a practical application of carers' assessments.<br>The committee noted there are very practical implications which inhibit any standardisation in the application of carers' assessments across the board. In some areas there has been the expectation that numbers of carer's assessments would increase, given the requirements of the Care Act, but in some cases carers are not coming forward or making use of their entitlement to receive an assessment. This may be a consequence of accessibility or awareness issues. The committee noted that some carers may be unaware of their rights and of the services that are available.<br>The committee highlighted issues with continuity of care that may arise from 'artificial' divisions between under and over 65s in care organisations. Changing demographics and funding arrangements may have an impact upon considerations regarding repeat reviews. |
| **Trade-off between net health benefits and resource use** | No economic evidence was identified for this review question and economic modelling was not prioritised. Since the recommendations made were only about ensuring people were aware of their legal rights, the committee agreed it was not necessary to consider the resource implications of those rights being accessed. |
| **Quality of evidence** | The committee noted the lack of evidence from research in this area but received a contextual presentation placing carers' assessments within the framework of the Care Act 2014, delivered by one of the Local Authority Commissioners on the committee. This covered both the legal rights people have and the extent to which the legislation has been fully implemented in practice. |
| **Other considerations** | The committee agreed that recommendations within this area needed to be considered within an equality impact framework. It was noted that young carers in particular often do not access the support to which they are entitled, and that they often feel that support is not appropriate for their age group. Culturally appropriate approaches may be needed and the committee raised awareness of issues facing ethnic groups; for example people from black African and Caribbean family origin often do not access the levels of support to which they are entitled. The committee recognised there is variation/inequality around the country regarding who does the assessment which needs to be highlighted.<br>Sections of recommendations referring to younger people were also informed by the evidence review on the specific needs of younger people living with dementia (section 17). |

### 15.1.6 Recommendations

**106. Offer carers of people living with dementia a psychoeducation and skills training intervention that includes:**

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- education about dementia, its symptoms and the changes to expect as the condition progresses
- developing personalised strategies and building carer skills
- training to help them provide care, including how to understand and respond to changes in behaviour
- training to help them adapt their communication styles to improve interactions with the person living with dementia
- advice on how to look after their own physical and mental health, and their emotional and spiritual wellbeing
- advice on planning enjoyable and meaningful activities to do with the person they care for
- information about relevant services (including support services and psychological therapies for carers) and how to access them
- advice on planning for the future.

**107. Ensure that the support offered to carers is:**

- tailored to their needs and preferences and to what they want it to achieve (for example, providing information on carer's employment rights for carers who work or want to work)
- designed to help them support people living with dementia
- available at a location they can get to easily
- provided in a format suitable for them (for example individual or group sessions, or online training and support)
- available from diagnosis and as needed after this.

**108. Be aware that carer interventions are likely to be most effective when provided as group sessions.**

**109. Advise carers about their right to the following and how to get them:**

- a formal assessment of their own needs (known as a 'Carer's Assessment'), including their physical and mental health
- an assessment of their need for short breaks and other respite care .

**110. Be aware that carers of people living with dementia are at an increased risk of depression. For guidance on identifying and managing depression, see the NICE guideline on depression in adults.**

### 15.1.7 Research recommendations

**17. What is the effectiveness and cost-effectiveness of group-based cognitive behavioural therapy for carers of people living with dementia who are at high risk of developing depression?**

For more details on the research recommendation made, and the rationale behind it, see appendix L.

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# 16 Staff training

The need for improvement in dementia care has increasingly become a focus of research, development and policy initiatives. The demand for high quality dementia care through a skilled workforce will increase as both dementia prevalence and diagnosis rates rise.

The focus of the Prime Minister's Challenge on Dementia 2020 (DH, 2015) and the 2015–16 Mandate from Government to Health Education England (HEE) is the requirement for an informed and effective workforce for people living with dementia. This means all health and social care staff involved in the care of people who may have dementia should have the necessary dementia core skills, education and training to provide the best quality care in the roles and settings where they work.

The Prime Minister's Challenge on Dementia 2020 Implementation Plan (DH, 2016) presents the progress that has been made in ensuring that the dementia workforce is fully equipped through the development of such initiatives as the Core Skills, Education and Training Framework led by Skills for Health and HEE. One of the questions often raised, however, is what difference does a well-developed workforce make to the experiences of people living with dementia and their carers?

The Implementation Plan, supported by other reports such as the "Fix Dementia Care" (Alzheimer's Society, 2016), demonstrate a direct correlation between poor skills, education and training to poor outcomes, poor effectiveness and poor experience.

A skilled educated and trained workforce can improve the experience of the person living with dementia and their carers throughout the dementia pathway, from diagnosis, care and treatment to living well and the end of life. The experience can potentially be improved at:

- First contact, as primary care has an increased focus and understanding of dementia leading to a timely diagnosis and increased diagnosis rates.
- Assessment and treatment, as memory assessment services improve their response times, discharge plans and ongoing care and support plans and coordination.
- Acute care, as staff understand the alternative options to hospital admission and, if admission is necessary, ensure people with dementia and their carers receive personalised care helping to reduce length of stay, hospital incidents, improved satisfaction, co-ordinated discharge and reduced readmissions.
- Post-diagnostic care, as staff working in communities support people living with dementia to remain independent and active citizens for as long as possible delaying the possible need for residential care and improving the quality of life both of the person living with dementia and their carers/families.
- Care homes, as care home staff deliver personalised co-ordinated and dignified care and support reducing the possible need for hospital admission, reducing incidents and improving satisfaction.
- End of Life, as palliative care and hospice teams include the care and support of people living with dementia as part of their commissioned services and service offer increasing choice and control for people with dementia at the end of life.

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# 16.1 Staff training

### Review question

What effect does training for staff working with people living with dementia have upon the experiences of people living with dementia in their care?

## 16.1.1 Introduction

This question considered both quantitative and qualitative evidence on effective models of staff training for improving the care and experiences of people living with dementia. The quantitative part of this review included a collaboration between the NICE Guideline Updates Team and the Cochrane Dementia and Cognitive Impairment Group.

**Table 91: Review summary: qualitative evidence**

| | |
|---|---|
| **Population** | • People (aged 40 years and over) living with dementia |
| **Phenomena of interest** | Aspects of training programmes for staff caring for people living with dementia, which may include training on:<br>• The natural history of dementia, different subtypes, prognosis etc.<br>• Communication skills<br>• Principles of person-centred care<br>• Roles of different health and social care professionals, and how care should be co-ordinated between these different services<br>• Adult protection policies and procedures<br>• Awareness of abuse and neglect<br>• Principles of palliative care<br>• Appropriate prescribing (antipsychotics)<br>• Avoiding unnecessary hospital admissions<br>• Managing behaviour and non-cognitive symptoms<br>• Enablement and reablement<br>• Nutrition and swallowing difficulties<br>• Legislative rights |
| **Outcomes** | • Experiences and satisfaction of people living with dementia<br>• Experiences and satisfaction of carers of people living with dementia |

**Table 92: Review summary: quantitative evidence**

| | |
|---|---|
| **Population** | People (aged 40 years and over) living with dementia |
| **Interventions** | • Training interventions for formal, paid staff working with people living with dementia |
| **Comparator** | • No specific training intervention |
| **Outcomes** | • Appropriate use of procedures/medicines<br>• Patient and carer experience and satisfaction<br>• Patient and carer health-related quality of life<br>• Resource use and costs |

Qualitative studies needed to report the views of either people living with dementia or their carers, and match the criteria given in Table 91. The aims of this review were to establish the

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most effective ways of managing the transition between different settings for people living with dementia, and their carers. The review focused on identifying studies that fulfilled the conditions specified in Table 40. For full details of the review protocol, see Appendix C.

Randomised controlled trials were included if they explored the effectiveness of staff training interventions for improving the experiences of people living with dementia and meet the criteria given in Table 92. Papers were excluded if they:

- did not include the views of people living with dementia or their carers
- were not in the English language
- were abstracts, conference proceedings or other unpublished studies.

For the purposes of this question, a care provider is defined as an organisation that delivers health and/or social care. This includes all providers registered with the Care Quality Commission as well as unregistered providers such as Community Based Support Services which may be delivering health and social care through a commissioning agreement.

### 16.1.2 Evidence review

#### 16.1.2.1 Qualitative evidence

A single search was conducted for all the qualitative questions included in this guideline, which returned a total of 10,085 references. References were screened based on their titles and abstracts, and the full texts of 11 references that were potentially relevant to the review question were requested. All of these studies were excluded on full text review, with reasons for exclusion presented in Appendix F.

#### 16.1.2.2 Quantitative evidence

The RCT data included in this review primarily came from an ongoing Cochrane review on 'Educational interventions for improving clinical competencies of medical practitioners to detect, diagnose, and manage people with cognitive impairment and dementia'. Whilst this review was not published at the time this question was considered in the guideline, the list of included studies was provided by the Cochrane Dementia and Cognitive Impairment Group, and these studies were screened at full text level to identify relevant studies. In addition, the studies included in 4 other recent, high-quality systematic reviews were also screened to identify any additional studies not included in the Cochrane review, particularly studies primarily targeted at social care rather than healthcare staff. The systematic reviews used as sources for RCT data are summarised in Table 93. For the full evidence tables and full GRADE profiles of included RCTs, please see Appendix E and Appendix G. References for the included studies are given in appendix I.

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**Table 93: Systematic reviews used to identify primary studies**

| Study details | Study population | Interventions |
|---|---|---|
| Belisario (2013) – Protocol for an ongoing review<br>Educational interventions for improving the skills of medical practitioners to detect, diagnose, and manage people with cognitive impairment and dementia | Generalist clinicians working in either primary care or secondary care settings, and specialist consultants in any related medical field and who are working in any clinical setting. | Educational interventions whose primary objective is to improve clinicians' skills in evaluating, diagnosing, managing (or a combination of these) people with cognitive impairment or dementia. |
| Bird (2016)<br>Do interventions with staff in long-term residential facilities improve quality of care or quality for life people with dementia? A systematic review of the evidence | Staff working in residential dementia care | Interventions in long-term facilities helping staff develop their capacity to provide better care and/or QOL for residents living with dementia |
| Machiels (2017)<br>Interventions to improve communication between people with dementia and nursing staff during daily nursing care: A systematic review | Nursing staff working with people living with dementia | Interventions that aim to improve communication (verbal and/ or non-verbal) between nursing staff and people living with dementia |
| Scerri (2016)<br>Dementia training programmes for staff working in general hospital settings - a systematic review of the literature | Staff working in a ‘general hospital’, defined as ‘a hospital not specialising in the treatment of a particular illness or of patients of a particular sex or age group’ | Any dementia training programmes directed to staff working in general hospital settings |
| Spector (2013)<br>A systematic review of staff training interventions to reduce the behavioural and psychological symptoms of dementia | Paid care staff in nursing or residential care homes | Training interventions designed to help staff manage behavioural and psychological symptoms of dementia |

A total of 88 unique studies were identified from these reviews, and these studies were themselves screened at full text level. Twenty-five RCTs met the criteria for inclusion (reported in 26 papers), with the remaining 62 studies excluded, with reasons for exclusion given in Appendix F. The included studies are summarised in Table 94.

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**Table 94: Summary of included studies – RCT evidence**

| Study details | Study population | Methods | Outcomes |
|---|---|---|---|
| Beer (2011) | 351 people living with dementia. Living in residential care. | Intervention: Training to meet the perceived need of GPs and residential care staff. Main topics of the educational programs were: communication, personal care and activities, positive values, behaviours of concern, pain management, dementia, depression and delirium, and effective working between GPs and residential care facility staff.<br>Comparison: No training. | Quality of life, behavioural and psychological symptoms of dementia, pain, use of physical restraint. |
| Burgio (2002) | 88 people living in residential care who displayed behavioural disturbances. Their mean MMSE was approximately 7. 106 nursing assistants. | Intervention: Behaviour management skills training of residential care staff.<br>Comparison: Conventional staff management. | Resident agitation observations. |
| Chang (2005) | 20 people living with dementia in residential care identified as having eating problems. | Intervention: Feeding skills training program.<br>Comparison: No training. | Food intake. |
| Chenoweth (2009) | 289 people living with dementia in residential care. | Intervention 1: Dementia care mapping. Staff carers received training.<br>Intervention 2: Person-centred care. Staff carers received training.<br>Comparison: Usual care. | Agitation, measured with the Cohen-Mansfield agitation inventory. Psychiatric symptoms, neuropsychological status, quality of life, falls. |
| Chenoweth (2014) | 601 people living with dementia in residential care. | Intervention 1: Person-centred care. Nurses received training.<br>Intervention 2: Person-centred dementia environment.<br>Comparison: Usual care. | Quality of life (DEMQOL), agitation, emotional responses, depression scores. |
| Clare (2013) | 65 people living with dementia in residential care. 65 care staff. | Intervention: Care staff training to observe and identify signs of awareness in participants with advanced dementia<br>Comparison: No training. | Quality of life, well-being, behaviour and cognition. |
| Davison (2007) | 113 people living with dementia in residential care. 90 care staff. | Intervention 1: Care staff received training to manage dementia-related challenging | Frequency of challenging behaviours. |

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| Study details | Study population | Methods | Outcomes |
|---|---|---|---|
| | | behaviours. In addition, there was a peer-support group.<br>Intervention 2: Care staff received training to manage dementia-related challenging behaviours.<br>Comparison: Wait-list control. | |
| Deudon (2009) | 306 people living with dementia in residential care. | Intervention: Care staff education to manage the behavioural and psychological symptoms of dementia.<br>Comparator: No training. | Cohen-Mansfield Agitation Inventory (CMAI) and an Observation Scale (OS) score. |
| Döpp (2015) | 71 people living with dementia. 71 informal carers. | Intervention: A training package for occupational therapists including the usual postgraduate course, outreach visits, regional meetings, and access to a reporting system.<br>Physicians and managers received newsletters, had access to a website.<br>Comparison: A postgraduate course for occupational therapists only. | Daily functioning, carers' sense of competence, quality of life, and self-perceived performance of daily activities of both people living with dementia and carers. |
| Finnema (2005) | 146 people living with dementia in psychogeriatric wards in residential care. 99 nursing assistants. | Intervention: Care staff training to provide integrated emotion-orientated care.<br>Comparison: No training. | Behaviour and mood related to adaptation to the illness and the institutionalisation. |
| Fossey (2006) | 246 people living with dementia in residential care. | Intervention: Training and support delivered to residential care staff, focusing on alternatives to drugs for the management of agitated behaviour in dementia.<br>Comparison: Usual care. | Proportion of residents in each home who were prescribed neuroleptics and mean levels of agitated and disruptive behaviour (Cohen-Mansfield agitation inventory). |
| Huizing (2006) | 167 people living with dementia. Living in psychogeriatric residential care wards. | Intervention: Training care staff to reduce their use of physical restraints.<br>Comparison: No training. | Restraint use. |
| Leone (2013) | 230 people living with dementia with apathy. | Intervention: Care staff education to manage apathy.<br>Comparison: No training. | Katz ADL Scale, neuropsychiatric symptoms, The Apathy Inventory-Clinician to measure apathy, behavioural disturbance. |

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| Study details | Study population | Methods | Outcomes |
|---|---|---|---|
| Magai (2002) | 91 people living with dementia. Living in residential care. | Intervention: Training staff carers in sensitivity to nonverbal communication.<br>Comparison 1: “Training” on cognitive and behavioural aspects.<br>Comparison 2: No training group. | Symptoms (depression, agitation, behavioural symptoms), facial expressions of emotion. |
| McCallion (1999) | 105 people living with dementia. Living in residential care. | Intervention: Nursing assistants underwent a Nursing Assistant Communication Skills Program.<br>Comparison: No training. | Penn State Mental Health Questionnaire, turnover rates, signs and symptoms of depression and aggressive behaviours, disorientation, irritability, agitation, psychotropic medication and restraint use. |
| Pellfolk (2010) | 353 people living with dementia in group dwelling units for people living with dementia. | Intervention: Nursing staff underwent a restraint minimisation education program.<br>Comparison: No training. | Use of physical restraints, number of falls, use of psychoactive medication. |
| Robison (2007) | 388 family members of people living with dementia in residential care. | Intervention: Nursing staff received training that was designed to improve communication and cooperation between staff and families of people living with dementia.<br>Comparison: No training. | Ease of communicating with staff, staff behaviours, and care involvement of the family. |
| Sloane (2004) | 69 people living with dementia, who had agitation during bathing, living in residential care. | Intervention 1: Care staff were educated to deliver person-centred showering.<br>Intervention 2: Care staff were educated to deliver towel bathing.<br>Comparison: Usual care. | Agitation, and aggression, discomfort, bath completeness, skin condition, skin microbial flora. |
| Testad (2005) | 142 people living with dementia. Living in residential care. | Intervention: Care staff training on restraint use and alternatives.<br>Comparison: No training. | Number of restraints used and agitation. |
| Testad (2010) | 90 people living with dementia. Living in residential care. | Intervention: Care staff were trained using the Relation-Related Care course to reduce agitation and restraint use.<br>Comparison: No training. | Use of restraints, agitation and use of antipsychotics. |
| van de Ven (2013) | 192 people living with dementia. Living in residential care. | Intervention: Staff were trained to use dementia care mapping.<br>Comparison: Usual care. | Agitation, neuropsychiatric symptoms, and quality of life. |

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| Study details | Study population | Methods | Outcomes |
|---|---|---|---|
| van Weert (2005) | 121 people living with dementia. Living in residential care. | Intervention: Care staff were trained in verbal and non-verbal communication, and in multisensory stimulation.<br>Comparison: No training. | Smiling, gaze, negative verbal behaviours and verbal expressed autonomy. |
| Verkaik (2011) | 97 people living with dementia. Living in residential care. | Intervention: Nurses were trained to apply a guideline to their residents who had depression. The aim of the guideline was to individualise pleasant activities and decrease unpleasant events<br>Comparison: No training. | Depression, observed mood. |
| Visser (2008) | 76 people living with dementia. Living in residential care. | Intervention 1: Care staff attended a behaviourally-based education programme.<br>Intervention 2: Care staff attended a behaviourally-based education programme. They also participated in a peer support group.<br>Comparison: No training. | Agitation, quality of life. |
| Wenborn (2013) | 210 people living with dementia. Living in residential care. | Intervention: Adjusting care homes to improve residents' engagement in activities, care staff training to promote residents' engagement in activities.<br>Comparison: Usual care. | Quality of life, anxiety, depression and challenging behaviour. |

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### 16.1.3 Health economic evidence

Standard health economic filters were applied to the clinical search for this question, and a total of 1,414 citations was returned. Following review of titles and abstracts, no full text studies were retrieved for detailed consideration. Therefore, no relevant cost–utility analyses were identified for this question

### 16.1.4 Evidence statements

#### 16.1.4.1 Residential care staff training

##### *16.1.4.1.1 Flexible education*

Low- to moderate-quality evidence from 1 RCT containing 351 people could not differentiate quality of life, pain, behavioural and psychological symptoms of dementia or the use of physical restraint between people living with dementia in residential care where staff were offered a flexible training package, and people living with dementia in residential care where no specific additional training was offered.

##### *16.1.4.1.2 Activity provision*

Moderate-quality evidence from 1 RCT containing 159 people could not differentiate quality of life, cognition, challenging behaviours, depression, anxiety or the total number of medicines prescribed between people living with dementia in residential care where staff were offered training in activity provision, and people living with dementia in residential care where no specific additional training was offered.

##### *16.1.4.1.3 Multisensory stimulation*

Moderate-quality evidence from 1 RCT containing 121 people found improvements in verbal communication and increases in the duration of morning care for people living with dementia in residential care where staff were offered training in multisensory stimulation, compared with people living with dementia in residential care where no specific additional training was offered.

##### *16.1.4.1.4 Behaviour management*

Very low-quality evidence form 1 RCT containing 79 people could not differentiate between levels of agitation in people living with dementia in residential care where staff were offered behavioural management training, and people living with dementia in residential care where no specific additional training was offered.

##### *16.1.4.1.5 Feeding skills*

Very low-quality evidence from 1 RCT containing 20 people found higher levels of feeding difficulties in people living with dementia in residential care where staff were offered feeding skills training, compared with people living with dementia in residential care where no specific additional training was offered.

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#### *16.1.4.1.6 Dementia care mapping*

Moderate- to high-quality evidence from 1 RCT containing 159 people found reductions in agitation and the number of falls in people living with dementia in residential care where staff were offered training in dementia care mapping, compared with people living with dementia in residential care where no specific additional training was offered, but could not differentiate quality of life or behavioural and psychological symptoms of dementia.

#### *16.1.4.1.7 Person-centred care*

Moderate- to high-quality evidence from up to 2 RCTs containing 269 people found less agitation and improvements in quality of life, behavioural and psychological symptoms of dementia and the number of falls in people living with dementia in residential care where staff were offered training in person-centred care, compared with people living with dementia in residential care where no specific additional training was offered.

#### *16.1.4.1.8 Awareness and communication*

Low- to moderate-quality evidence from 1 RCT containing 65 people found improvements in quality of life in people living with advanced dementia in residential care who had little or no verbal communication where staff were offered training in identifying signs of awareness in people with advanced dementia and improving their communication skills, compared with people living with dementia in residential care where no specific additional training was offered, but could not differentiate wellbeing, cognition or behavioural symptoms.

#### *16.1.4.1.9 Challenging behaviours*

Very low- to moderate-quality evidence from up to 2 RCTs containing 350 people found less agitation in people living with dementia in residential care where staff were offered training in managing challenging behaviours, compared with people living with dementia in residential care where no specific additional training was offered, but could not differentiate aggressive behaviours, quality of life, numbers of hospitalisations or numbers of psychotropic medicines prescribed.

Very low- to low-quality evidence from 1 RCT containing up to 67 people could not differentiate agitation, aggressive behaviours or quality of life between people living with dementia in residential care where staff were offered training in managing challenging behaviours and additional peer support, and people living with dementia in residential care where no specific additional training was offered.

#### *16.1.4.1.10 Communication skills*

Low- to moderate-quality evidence from 1 RCT containing 105 people found improvements in depression and verbally aggressive behaviours and reduced use of mechanical restraints in people living with dementia in residential care where staff were offered training in communication skills, compared with people living with dementia in residential care where no specific additional training was offered, but increased levels of disorientation. The evidence could not differentiate physically aggressive behaviours, use of chemical restraints or levels of irritability or withdrawal.

#### *16.1.4.1.11 Emotion-oriented care*

Moderate- to high-quality evidence from 1 RCT containing 146 people could not differentiate cognition, agitation, affect or satisfaction between people living with dementia in residential care where staff were offered training in emotion-oriented care, and people living with dementia in residential care where no specific additional training was offered.

#### *16.1.4.1.12 Reducing antipsychotic drug use*

Very low- to moderate-quality evidence from 1 RCT containing 338 people found a lower proportion of people taking antipsychotics in residential care homes where staff were offered psychosocial care training, compared with people living with dementia in residential care where no specific additional training was offered, but could not differentiate rates of falls or levels of aggression and wellbeing.

#### *16.1.4.1.13 Towel bathing and person-centred showering*

Low- to moderate-quality evidence from 1 RCT containing 73 people found improvements in levels of aggression and discomfort in people living with dementia in residential care where staff were offered training in either towel bathing or person-centred showering, compared with people living with dementia in residential care where no specific additional training was offered, but could not differentiate agitation or specific types of aggression.

#### *16.1.4.1.14 Apathy management*

Low- to moderate-quality evidence from 1 RCT containing 230 people found reduced levels of apathy in people living with dementia in residential care where staff were offered training in managing apathy, compared with people living with dementia in residential care where no specific additional training was offered, but could not differentiate other measures of apathy, activities of daily living or behavioural and psychological symptoms of dementia.

#### *16.1.4.1.15 Non-verbal emotion signals*

Very low-quality evidence from 1 RCT containing up to 68 people could not differentiate dementia symptoms or emotions between people living with dementia in residential care where staff were offered training in sensitivity to non-verbal emotion signals, and people living with dementia in residential care where no specific additional training was offered.

### 16.1.4.2 Residential care staff and nurse training

#### *16.1.4.2.1 Communication, empathy and conflict resolution*

Low- to moderate-quality evidence from 1 RCT containing 325 people found improvements in communication and interaction between people living with dementia in residential care where nurses and other staff were offered training in communication, empathy development and conflict resolution, compared with people living with dementia in residential care where no specific additional training was offered, but could not differentiate the level of involvement of other family members in care.

Staff training

#### 16.1.4.3 Restraint use reduction

Very low- to moderate-quality evidence from up to 2 RCTs containing 288 people found reductions in the use of physical restraints on people living with dementia in residential care where nurses and other staff were offered training in restraint use reduction, compared with people living with dementia in residential care where no specific additional training was offered, but could not differentiate numbers of medicines prescribed, functional ability, falls, agitation or aggressive behaviours.

#### 16.1.4.4 Residential care nurse training

##### *16.1.4.4.1 Managing depression*

Moderate-quality evidence from 1 RCT containing 97 people could not differentiate levels of depression between people living with dementia in residential care where nurses were offered training in managing depression, and people living with dementia in residential care where no specific additional training was offered.

##### *16.1.4.4.2 Restraint use reduction*

Low-quality evidence from 1 RCT containing 126 people could not differentiate levels of restraint use between people living with dementia in residential care where nurses were offered training in restraint use reduction, and people living with dementia in residential care where no specific additional training was offered.

##### *16.1.4.4.3 Dementia care mapping*

Low- to moderate-quality evidence from 1 RCT containing 192 people found improvements in behavioural and psychological symptoms in people living with dementia in residential care where staff were offered training in dementia care mapping, compared with people living with dementia in residential care where no specific additional training was offered, but could not differentiate agitation or quality of life.

#### 16.1.4.5 Occupational therapist training

##### *16.1.4.5.1 Interdisciplinary training*

Low- to moderate-quality evidence from 1 RCT containing 33 people could not differentiate activities of daily living or quality of life between people living with dementia offered occupational therapy by therapists who had been given specific additional training in dementia, and people living with dementia offered occupational therapy by therapists who had been given no specific additional training.

#### 16.1.4.6 GP training

##### *16.1.4.6.1 Flexible education*

Low- to moderate-quality evidence from 1 RCT containing 351 people could not differentiate quality of life, pain, behavioural and psychological symptoms of dementia or the use of physical restraint between people living with dementia in residential care where GPs were offered a flexible training package, and people living with dementia in residential care where no specific additional GP training was offered.

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#### 16.1.4.7 Pooled analysis: person-centred care versus control

Moderate- to high-quality evidence from up to 5 RCTs containing 941 people found improvements in quality of life and levels of agitation in people living with dementia in residential care where staff were offered training falling under the broad category of person-centred care, compared with people living with dementia in residential care where no specific additional training was offered, but low-quality evidence could not differentiate levels of behavioural and psychological symptoms of dementia.

#### 16.1.4.8 Health economic evidence

No health economic evidence was identified for this review question.

### 16.1.5 Evidence to recommendation

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| **Relative value of different outcomes** | The committee agreed that, since the aim of this review question was to identify staff training interventions that improve the experience of the person living with dementia, outcomes for that individual (such as quality of life or behavioural and psychological symptoms) would be most relevant. They noted that the review was not focused on identifying interventions that improve the experience of staff and, therefore, trials that only reported on outcomes for staff would not be relevant to include within the review. |
| **Trade-off between benefits and harms** | **Person-centred and outcome-focussed care**<br>The committee agreed there were a number of trials (Chenoweth 2009 and 2014, Davison 2007, Deudon 2009, Finnema 2005, Fossey 2006 and van de Ven 2013) that, whilst including quite disparate training interventions, could be grouped under the general heading of person-centred care. Whilst the committee acknowledged that there were difficulties in combining the data from these studies, it was agreed that is was an appropriate thing to do, as the studies reported a range of positive and negative findings without obvious differences in study design which could explain the different outcomes. Therefore, it was agreed to be appropriate to calculate the average effectiveness across this group of studies, to ensure biased recommendations were not made by focusing only on the positive studies. The meta-analysis found significant improvements in both agitation and quality of life in people treated by staff offered person-centred training interventions, and the committee agreed it was therefore appropriate to recommend such interventions.<br>No clear evidence was identified for any individual training programme (such as dementia care mapping) being more effective than another, and therefore the committee agreed it was appropriate to make a more general recommendation which highlighted the key elements of the interventions, rather than being more prescriptive on exactly how an intervention should be structured or delivered.<br>The committee agreed that concerns had been raised by the LGBT community that their needs are not being addressed. Therefore, the bullet point “Respecting the person’s identity, sexuality and culture” was included.<br>In the recommendation on training for care providers, the committee agreed it was appropriate to specify those components which were consistently included as part of the trials in the evidence base. This included general education about dementia, assessing and responding to individual’s symptoms and needs and understanding and managing non-cognitive symptoms such as agitation, aggression |

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| | and pain. These trials also all included some follow-up sessions to provide feedback to staff, and give advice on specific complex cases. This recommendation also included items on antipsychotics and restraint (explained below), and a specific recommendation for younger people living with dementia, based on evidence from and explained in section 17.<br>**Antipsychotics and restraint use**<br>Trials which focused primarily on managing agitation and/or aggression whilst reducing the use of ether antipsychotics medicines or physical restraint were also identified. The aim of these trials was somewhat different, in that rather than trying to improve symptoms, they focused on reducing the use of potentially harmful medicines or procedures, without an increase in symptoms over a defined time period. The committee noted there was clear evidence from these studies that an approximately 50% reduction could be achieved in the use of either antipsychotics or physical restraint without any significant increase in behavioural or other symptoms, and the committee therefore agreed it was appropriate to include this in the recommendation for training interventions.<br>**Multi-sensory stimulation**<br>The committee agreed there was some evidence of benefits from a multisensory stimulation intervention in people with moderate to severe dementia. It noted that in practice these interventions are sometimes used across a wider range of individuals, but agreed the evidence was not sufficient to extrapolate beyond this more limited population (particularly, since it was only based on evidence from a single trial). Since the same quantity of evidence was not available as for person-centred care, they agreed that it was appropriate to restrict this recommendation to a 'consider' recommendation.<br>**Other interventions**<br>The evidence base also contained a number of more specific targeted interventions. These again were often presented under the broad heading of person-centred care, but only focused on a specific subset of care rather than a whole person-centred approach. The committee agreed these trials did not demonstrate the same positive results as the more inclusive training programmes and agreed that it was not possible to establish whether this was because these interventions are less effective, or because the trials were too small to detect an effect. It was therefore agreed that the evidence was not sufficient to make any recommendations based on this evidence. |
| **Consideration of health benefits and resource use** | **Person-centred and outcome-focussed care**<br>The committee noted there was a lack of cost-effectiveness evidence available to support recommendations on this topic, and therefore were conscious that it was important not to impose substantial additional costs. The committee therefore agreed that it was appropriate to subdivide the recommendation into two specific target groups.<br>The first group is comprised of staff directly providing care and support to people living with dementia. The committee agreed it was this group for whom training would have the highest impact, and therefore it was appropriate, in line with the interventions shown to be effective in the trials, to recommend this training be face-to-face and include the option for mentoring or additional support after the initial intervention is delivered. It noted that there were a number of ways in which training was delivered within the context of the trials whereby in some studies all staff were trained by an external provider, whilst in others the provider only trained a small number of staff, who then |

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| | passed on that knowledge to their colleagues. The committee agreed that both of these approaches were appropriate to consider in practice.<br>The second group of individuals considered in the recommendations consists of care and support providers more generally. This may include staff working in care environments or with people living with dementia, but not directly involved in providing care and support themselves. The committee agreed this group would also benefit from training, but it was not possible to justify the costs associated with providing face-to-face training in this larger group. The committee noted that in practice this was often provided as online training, and agreed that for this broader group this was an appropriate approach to take.<br>**Antipsychotics and restraint use**<br>The committee agreed that, even though there would be additional costs associated with delivering this training, this would be offset by considerable reductions in the costs of antipsychotic prescribing, provided that reductions similar to those found in the studies could be achieved in practice.<br>**Multi-sensory stimulation**<br>The committee noted that the primary cost associated with multisensory stimulation is the initial cost of purchasing the equipment, and staff training costs. It therefore agreed it was important the recommendation focus on training staff in the use of such equipment and techniques (which would only be relevant if the equipment was available at their site), rather than recommending additional sites purchase that equipment as there was not sufficient evidence to justify the purchase of such equipment as part of the recommendation. |
| **Quality of evidence** | The committee agreed the evidence underpinning the recommendations on person-centred care and multisensory stimulation was of moderate to high quality. However, it noted that the evidence base was entirely composed of studies conducted in care homes, and not in other clinical or community settings. The committee agreed that the principles of good training would be similar across these different settings, and therefore it was appropriate to extrapolate the evidence base from care homes to being applicable to all care and support providers. However, it also agreed that there may be other interventions that are more effective in these other settings, and therefore made research recommendations to look at the most effective training interventions for community staff and acute hospital staff. |
| **Other considerations** | The committee noted that in a number of the included studies, carers were also invited to attend the training alongside staff. Whilst there was no direct evidence that this led to improved outcomes, the committee agreed that it was a positive thing to encourage, both because of the gains that carers could make themselves, and because they provided a valuable additional perspective at any training. The committee agreed the evidence did not justify recommending additional resources be devoted to training specifically organised for carers but agreed it was appropriate to consider inviting carers along to training sessions that were already being run, provided sufficient capacity is available.<br>Sections of recommendations referring to younger people were also informed by the evidence review on the specific needs of younger people living with dementia (section 17). |

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### 16.1.6 Recommendations

**111. Care and support providers should provide all staff with training in person-centred and outcome-focused care for people living with dementia, which should include:**

- understanding the signs and symptoms of dementia, and the changes to expect as the condition progresses
- understanding the person as an individual, and their life story
- respecting the person's individual identity, sexuality and culture
- understanding the needs of the person and their family members or carers
- the principles of the Mental Capacity Act 2005 and the Care Act 2014.

**112. Care providers should provide additional face-to-face training and mentoring to staff who deliver care and support to people living with dementia. This should include:**

- understanding the organisation's model of dementia care and how it provides care
- how to monitor and respond to the lived experience of people living with dementia, including adapting communication styles
- initial training on understanding, reacting to and helping people living with dementia who experience agitation, aggression, pain, or other behaviours indicating distress
- follow-up sessions where staff can receive additional feedback and discuss particular situations
- advice on interventions that reduce the need for antipsychotics and allow doses to be safely reduced
- promoting freedom of movement and minimising the use of restraint
- if relevant to staff, the specific needs of younger people living with dementia and people who are working or looking for work.

**113. Consider giving carers and/or family members the opportunity to attend and take part in staff dementia training sessions.**

**114. Consider training staff to provide multi-sensory stimulation for people with moderate to severe dementia and communication difficulties.**

### 16.1.7 Research recommendations

**18. What is the cost effectiveness of using a dementia-specific addition to the Care Certificate for community staff, including dementia-specific elements on managing anxiety, communication, nutritional status and personal care?**

**19. What is the effectiveness of training acute hospital staff in managing behaviours that challenge in people living with dementia on improving outcomes for people and their carers?**

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For more details on the research recommendation made, and the rationale behind it, see appendix L.

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# 17 Needs of younger people living with dementia

It is estimated that at least 40,000 people in the UK are living with young-onset dementia, defined as symptom onset before the age of 65 (Dementia UK, 2nd edition). Young-onset dementia differs from dementia in later life in several important respects. Less typical clinical syndromes (such as behavioural, language-led, dyspraxic or visuospatial presentations) and underlying pathologies (such as frontotemporal dementia) contribute a higher proportion of cases. A family history of young-onset dementia, or related conditions such as motor neuron disease or Parkinson's disease, may be relevant in this age group, as dementias caused by single gene mutations typically have a lower age of onset than sporadic forms.

The onset of dementia at an earlier age has a range of consequences that require particular consideration from health and social care professionals and systems. These include, but are not limited to, loss of employment (and hence income and status), reduced ability to care for elderly parents or dependent children, a need to reconsider plans for retirement, and stigma from having an illness more typically associated with later life. Carers of people living with young-onset dementia also have particular needs. They are most commonly spouses of a similar age, so may also experience difficulty maintaining employment and other responsibilities. But elderly parents and children can also become carers and face particular challenges as a result. It is incumbent on professionals working with people affected by young-onset dementia to be mindful of the additional challenges faced by this group, and to respond to these in a personalised way. For example, some people living with young onset dementia may be able to continue working if appropriately supported.

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# 17.1 The specific needs of younger people living with dementia

**Review question**

- What are the specific needs of younger people living with dementia?

## 17.1.1 Introduction

**Table 95: Review summary: needs of younger people living with dementia**

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|---|---|
| **Population** | • People (aged between 40 years and 65 years) living with dementia<br>• Carers of people (aged between 40 years 65 years) living with dementia |
| **Phenomena of interest** | Any factors which either uniquely impact on younger people living with dementia or have a disproportionate impact on this group, which may include:<br>• Being in work at time of diagnosis<br>• Having a partner who still works<br>• Dependent children<br>• Caring for older relatives<br>• Large financial commitments (e.g. mortgage) |
| **Outcomes** | • Experiences and satisfaction of people living with dementia<br>• Experiences and satisfaction of carers of people living with dementia |

Qualitative studies and qualitative evidence syntheses were included if they explored the specific needs of younger people living with dementia and focussed upon improving outcomes for people with dementia and their carers. Studies needed to contain participants from the UK, report the views of either people living with dementia or their carers, and match the criteria given in either Table 95. Full details of the review protocol are given in appendix C. Papers were excluded if they:

- did not include the views people living with dementia or their carers in the UK
- included only quantitative analysis of the collected information
- were not in English
- were abstracts, conference proceedings and other unpublished studies.

## 17.1.2 Evidence review

A single search was conducted for all the qualitative questions included in this guideline, which returned a total of 10,085 references. References were screened based on their titles and abstracts, and the full texts of 25 references that were potentially relevant to these review questions were requested. Seven qualitative studies exploring care coordination were included in the review. The included studies are summarised in Table 96. For the full evidence tables and full CERQual profiles please see Appendix E and Appendix G. References for the included studies are given in appendix I. The 18 excluded papers, with reasons for exclusion, are presented in Appendix F.

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**Table 96: Summary of included studies**

| Study details | Study population | Subject of study | Outcomes |
|---|---|---|---|
| Chaplin 2016 | 5 younger people living with dementia | Topic: the experiences of people with dementia in employment<br>Method of data collection: interviews | The opinions of younger people living with dementia |
| Clayton-Turner 2015 | 28 younger people living with dementia and 15 carers | Topic: standard care<br>Method of data collection: Interviews | The opinions of younger people living with dementia and their carers |
| Clemerson 2014 | 8 younger people living with dementia | Topic: comparing a memory service and a young onset dementia service<br>Method of data collection: semi-structured interviews | The opinions of younger people living with dementia |
| Hegarty 2014 | 4 men and 2 women who were younger people living with dementia, and their carers | Topic: a walking group for younger people living with dementia<br>Method of data collection: focus group interview for younger people living with dementia. A questionnaire for their spouses. | The opinions of younger women living with dementia and their carers |
| Higgins 2010 | 5 younger people living with dementia and 6 carers | Topic: a club for younger people with dementia<br>Method of data collection: interviews | The opinions of younger people living with dementia and their carers |
| Johnson 2008 | 16 younger women living with dementia and their carers | Topic: a service for younger women living with dementia<br>Method of data collection: written and verbal feedback | The opinions of younger women living with dementia and their carers |
| Pipon-young 2011 | 8 younger people living with dementia | Topic: the experiences of younger people with dementia<br>Method of data collection: interviews and group discussions | The opinions of younger people living with dementia |

### 17.1.3 Health economic evidence

As this review question was qualitative in nature, it was not appropriate to conduct a search for economic literature.

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### 17.1.4 Evidence statements

#### 17.1.4.1 Experiences and coping in employment

The following themes were identified for 'experiences and coping in employment' for people living with dementia and their carers:

- People needed information about their rights in the workplace, and employers also needed to be educated about the same (low confidence)
- People living with dementia had an awareness of changes in their functioning in the work place as they developed dementia. (low confidence)
- People living with dementia experienced a shock at losing their expected future. (low confidence)
- A reluctance from people living with dementia to acknowledge the signs of cognitive decline (low confidence)
- Attempting to self-manage – developing coping strategies, and spending more time and effort in planning and organising tasks (low confidence)
- Feeling under scrutiny by managers and colleagues (low confidence)
- A lack of consultation about management decisions – not feeling they were offered the reasonable adjustments they were entitled to (low confidence)
- Feeling abandoned by the workplace and consequent feelings of resentment towards the workplace (low confidence)
- Financial hardship and consequent worry (low confidence)

#### 17.1.4.2 General experiences and coping

The following themes identified for 'general experiences and coping' for people living with dementia and their carers:

- Feelings of shock and a sense of loss at receiving the diagnosis, but also relief at having the diagnosis confirmed (low confidence)
- Experiences of feeling 'too young' – assuming dementia was something that affected older people (high confidence)
- Sense of pressure at still having responsibility for children, a mortgage or a business to run (low confidence)
- Coping by normalising the situation - creating an identity as an older person, even transiently, allowed people to make sense of developing Alzheimer's disease by normalising the life-cycle (very low confidence)
- Loss of adult competency - emerged through people's experience of either feeling more 'childlike' due to a loss of skills or being treated this way by others (very low confidence)
- Negative impact of other's perceptions (low confidence)
- A reduced sense of self-worth (very low confidence)
- Trying to hold on to their existing self-concept - the importance of acknowledging that although they have dementia, there were many aspects of their lives that remained the same (high confidence)
- A fear of disclosing the diagnosis and a desire to hide it from others (low confidence)
- The importance of remaining independent, active and involved (low confidence)

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- The importance of knowing other people with dementia and being able to share understandings through similar experiences (low confidence)
- Lack of age-appropriate services (very low confidence)
- The intention to regain control emerged as a common coping strategy in response to the experience of loss of agency (very low confidence)
- People may well still be driving, and this should be discussed (low confidence)

#### 17.1.4.3 Group activities (walking group, day service and lunchtime social group)

The following themes identified for 'group activities designed specifically for young people living with dementia' for people living with dementia and their carers:

- Benefits of building supportive and positive relationships, and a social network (low confidence)
- Provided a sense of belonging, purpose and achievement (low confidence)
- Improved self-confidence by being able to interact with a group of people similar to themselves (low confidence)

#### 17.1.4.4 Health economic evidence

As this review question was qualitative in nature, it was not appropriate to conduct a search for economic literature.

### 17.1.5 Evidence to recommendations

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| **Relative value of different outcomes** | The committee agreed the key finding of the review would be any specific needs identified for younger people living with dementia that were different to those of the main dementia population. This would then be used to ensure the pathway was equally relevant to and accessible for, younger people living with dementia (and their carers). |
| **Trade-off between benefits and harms** | Chaplin (2016) and Clayton-Turner (2015) provided evidence that at diagnosis, the person and their family members or carers should be offered oral and written information that explains the person's rights and needs for reasonable adjustments if they are in work or looking for work. In the committee's experience, with reasonable adjustments, some younger people living with dementia are able to continue to work for many years. The committee noted that in their experience Disability Employment Advisors have little experience in this area and it agreed that a recommendation in this area would be useful. The committee agreed that the phrase 'needs for reasonable adjustments' should be included in the recommendation as this infers that the person's needs should be assessed. The committee agreed that the 'employment' being undertaken could be voluntary and therefore, the word 'work' was used rather than 'employment' to reflect this. The committee agreed that care providers should provide face-to-face training and mentoring to staff who deliver care and support to people living with dementia. This should include the specific needs of younger people living with dementia (where this is relevant to their role).<br>Pipon-Young (2012) and Clayton-Turner (2015) discussed the issues around younger people living with dementia and financial commitments such as mortgages they may still have. The committee agreed that this adds further importance to the recommendations |

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| | which have already been drafted to offer information regarding financial and legal advice services to all people living with dementia.<br>Some of the studies either involved peer support groups (Clayton-Turner 2015, Hegarty 2014, Higgins 2010, Johnson 2008) or discussed a need for them (Pipon-Young 2012). The committee agreed that the recommendations already include offering information regarding local support groups.<br>The committee agreed that people living with dementia who work during office hours may find it difficult to access services. Therefore, the committee agreed that service providers should design services to be accessible to as many people living with dementia as possible, including people who are in work.<br>The committee noted that the carers of younger people living with dementia might still be in employment. Therefore, the committee agreed that the support offered to carers should be tailored to their needs and preferences and to what they want it to achieve, for example, carer's employment rights. |
| **Consideration of health benefits and resource use** | The committee discussed the potential impact of the recommendations and agreed that they should not result in additional expenditure. |
| **Quality of evidence** | The committee agreed that the overall quality of the evidence was low or very low, because of the paucity of studies in this area and the low numbers of study participants. However, the committee agreed that the findings of the review did match their experience and therefore were confident they would be replicated in larger studies. They agreed that, due to the relatively low quality of the evidence available, it was more appropriate to make modifications to recommendations made in other sections with stronger evidence bases to ensure they appropriately considered the needs of younger people, rather than writing a separate set of recommendations to cover younger people.<br>The committee agreed that the work-related issues raised in the study Chaplin 2016 were very important to people living with dementia and very common for younger people. Therefore, this study had a high value. |
| **Other considerations** | No specific equality issues were identified for this review question. |

### 17.1.6 Recommendations

Additional comments around the needs of younger people living with dementia were added to the sections on 'involving people living with dementia in decisions about their care' (section 6), 'staff training' section (section 16) and 'care planning, review and co-ordination' (section 7).

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# 18 Assessing and managing comorbidities

Dementia is primarily a condition of old age and as such many people with dementia will have additional long term illnesses also associated with increasing age.

People with dementia often have several additional long term conditions; a UK based study found that, on average, people with dementia had 4.6 chronic illnesses in addition to their dementia (Guthrie 2012) and other geriatric conditions such as delirium, falls and incontinence are also more frequent.

The most common chronic illnesses in people with dementia include diabetes, hypertension, cardiovascular disease and age-related musculoskeletal disorders.

The increasing multi-morbidity associated with older age leads to a higher level of clinical complexity which health care professionals may find challenging especially within health care systems where clinical guidelines and service organisation are often focused on a single illness. In addition, research to date has often considered dementia in isolation with little, if any, regard as to how other complex health needs might impact on the person living with dementia and their family's needs and experiences and service use and provision. Also certain comorbid medical conditions may exacerbate the progression of dementia; for example, there is evidence that cognitive decline may be accelerated in older people with type 2 diabetes. The presence of dementia may also adversely affect the clinical care of other conditions by limiting their ability to self-care, take medication, attend specialist care appointments and engage in health promotion. There has been little research investigating the effect of co-existent multi-morbidity on a person living with dementia's health, well-being and clinical care and what 'good practice' would look like to both service users and providers.

Healthcare professionals who do not work in mental health often have little understanding of the needs and experiences of people with dementia and consequently their care needs are frequently not met with evidence of service duplication, delays in the identification of problems and unnecessary interventions. Whilst improving quality of care for people with dementia remains a key government target, there is a growing concern that current health care service organisation is not meeting the needs of an increasing ageing population. Key questions to be addressed include the optimal ways to manage both co-existing long term illnesses after a diagnosis of dementia, and how best to manage intercurrent illness in people living with dementia.

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Assessing and managing comorbidities


# 18.1 Assessing and treating intercurrent illness in people living with dementia

**Review questions**

- Are there effective methods for assessing intercurrent illness in people living with dementia that are different from those already in use for people who do not have dementia?
- Are there effective methods for treating intercurrent illness in people living with dementia that are different from those already in use for people who do not have dementia?

## 18.1.1 Introduction

The aim of these review questions was to identify the most effective methods for assessing the symptoms and severity of intercurrent illness and to identify the most effective interventions and strategies for treating intercurrent illness in people living with dementia.

Both review questions considered whether the methods used for assessing and treating intercurrent illness in people living with dementia are different from those used for people who do not have dementia. They sought to explore the methods of assessing and treating an unrelated acute condition presenting in people living with dementia and specifically focused on people showing symptoms of the following.

- Pain
- Falls (& loss of mobility)
- Delirium
- Urinary tract infections

The review identified studies that fulfilled the conditions specified in Table 97 or Table 98. For full details of the review protocols, see Appendix C.

**Table 97: Review summary: assessing intercurrent illness in people living with dementia**

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| **Population** | • Studies containing people (aged 40 years and over) with and without a diagnosis of dementia, and showing symptoms of an intercurrent illness |
| **Interventions** | • Standardised observations, assessments, scales or tools used to assess the presentation and severity of an acute condition specifically for people living with dementia |
| **Comparator** | • Standardised observations, assessment scales or tools used to assess the presentation and severity of an acute condition for people with an intercurrent illness who do not have dementia<br>• Usual care |
| **Outcomes** | • Rates of accurately identified intercurrent illness in people living with dementia<br>• Diagnostic test accuracy (including sensitivity, specificity, PPV, NPV etc.)<br>• Clinical outcomes including cognitive, functional and behavioural ability<br>• Health-related quality of life of people living with dementia |

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| | • Resource use and cost |

**Table 98: Review summary: managing intercurrent illness in people living with dementia**

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|---|---|
| **Population** | • People (aged 40 years and over) with a diagnosis of dementia and showing symptoms of an intercurrent illness |
| **Interventions** | • Pharmacological interventions/self-care strategies/monitoring or observational strategies specifically designed for people living with dementia and an intercurrent illness |
| **Comparator** | • Pharmacological interventions/self-care strategies/monitoring or observational strategies for people with an intercurrent illness but not specific to people living with dementia<br>• Usual care |
| **Outcomes** | • Symptom resolution/reduction of intercurrent illness<br>• Clinical outcomes including cognitive, functional and behavioural ability<br>• Change in appropriate polypharmacy<br>• Intervention-related problems such as potentially avoidable hospital admissions and re-admissions, errors, poor adherence and potentially avoidable adverse effects (e.g. pressure sores)<br>• Intervention related outcomes including concordance, compliance satisfaction of person living with dementia and their informal carers<br>• Health related quality of life of person living with dementia and his/her informal carers<br>• Resource use and cost |

### 18.1.2 Evidence review

A systematic search identified 8,833 references. The references were screened on their titles and abstracts and 285 references were ordered for full text across both review questions. 258 papers were subsequently excluded because they did not fit the inclusion criteria (see Appendix F for a detailed list of excluded studies and reasons for their exclusion).

Seven studies were included in the evidence review for the question considering assessments for an intercurrent illness. Five studies were included for assessing pain, 1 study for assessing falls and 1 study for assessing delirium. No studies were identified as relevant to consider assessments for urinary tract infections in people living with dementia compared with those who do not have dementia.

Fourteen studies were included in the evidence review for the question considering management of an intercurrent illness. Eight studies were included for falls, 3 for pain, 2 for hip fractures and 1 for delirium.

A summary of the characteristics of the included studies for assessment is provided in Table 99 and for management in Table 100. For the full evidence tables and full GRADE profiles

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please see Appendix E and Appendix G. References for the included studies are given in appendix I.

## 18.1.2.11 Description of included studies

2 **Table 99: Included studies - assessment of intercurrent illness**

| Study reference | Study design | Study population | Intervention & comparator (including study aim) | Assessment scales | Relevant outcomes | Comments |
|---|---|---|---|---|---|---|
| **Pain assessment** | | | | | | |
| Mosele et al (2012) | Prospective cohort | Participants with MMSE≥24 (n=290)<br>versus participants with MMSE<24=310) | To assess the psychometric properties of PAINAD scale compared with the NRS in people with different stages of cognitive impairment | Pain assessment in advanced dementia (PAINAD) versus<br>Numerical rating scale (NRS) and verbal descriptor scale (VDS)<br>(observational pain assessment versus self-report assessment) | • Presence of pain as assessed by PAINAD and NRS | All participants were admitted to the acute geriatric section of Padua University.<br>Study location Italy |
| Horgas et al (2007) | Cross sectional study | Cognitively intact participants with a mean MMSE score of 27 (n=20)<br>Versus<br>Cognitively impaired participants with mean MMSE score of 17 (n=20) | To compare NOPPAIN ratings with self-report in participants with and without cognitive impairment | Non Communicative Patients Pain Assessment (NOPPAIN) versus numerical rating scale (NRS and verbal descriptor scale (VDS)<br>(observer reported versus self- report assessment) | • Pain verification – correlation between observational and self-reported pain scores | All participants were selected as a subsample from a larger parent study. Participants were enrolled in assisted living facilities, nursing facilities or retirement apartments.<br>Study location USA |
| De Waters et al (2008) | Correlational design | Cognitively intact participants with a mean MMSE score of 26 (n=13)<br>Versus | To psychometrically evaluate the PAINAD alongside the NRS in participants with and | Pain assessment in advanced dementia (PAINAD) versus<br>Numerical rating scale (NRS) | • Pain verification - correlation between observational | All participants hospitalised for a hip fracture.<br>Study location USA |

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| Study reference | Study design | Study population | Intervention & comparator (including study aim) | Assessment scales | Relevant outcomes | Comments |
|---|---|---|---|---|---|---|
| | | Cognitively impaired participants with a mean MMSE score of14 (n=12) | without cognitive impairment | (observational pain assessment versus self-report assessment) | and self-reported pain scores | |
| Van Herk et al (2009) | Multi centre case control study | Participants without cognitive impairment with MMSE ≥18 (n=50) versus participants with cognitive impairment with MMSE< 18 (n=124) | To assess reliability and validity of a newly developed observational pain assessment tool for people whom self-report is impossible in people with and without cognitive impairment | Rotterdam Elderly Pain Observation Scale (REPOS)<br>Versus NRS and PAINAD<br>(observational pain assessment versus observational and self-report assessment) | • Pain verification<br>• Comparison of pain scores | Study location Netherlands |
| Lukas et al (2013) | Retrospective cohort | Participants with MMSE ≥24 (n=60) versus participants with MMSE<20 (n=65) | To determine the comparative ability of observer-rated pain assessment tools to identify the presence or intensity of pain in cognitively intact older people or people with moderate to severe cognitive impairment | Abbey pain scale<br>Pain Assessment in Advanced Dementia (PAINAD)<br>Non communicative Patients Pain Assessment (NOPPAIN)<br>(observational pain assessment versus observational pain assessment versus self-report assessment) | • Pain verification: level of agreement regarding presence of pain<br>• Correlation regarding pain intensity | Study location Australia |
| **Falls assessment** | | | | | | |

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| Study reference | Study design | Study population | Intervention & comparator (including study aim) | Assessment scales | Relevant outcomes | Comments |
|---|---|---|---|---|---|---|
| Kato-Narita et al (2011) | Case control study | Participants without cognitive impairment (based on Mayo Older American Normative Studies Criteria ;n=40)<br>versus<br>participants with Alzheimer's disease (based on Clinical Dementia Rating; n=48) | To analyse the correlation between falls and loss of functional capacity in people with Alzheimer's disease and those without cognitive impairment | Berg Balance Scale (BBS)<br>Disability Assessment for Dementia (DAD) | Number of falls<br>Performance on scale | Alzheimer's disease diagnosed by CDR rating.<br>Participants recruited from an out-patients service at a university hospital.<br>Study location<br>Brazil |
| **Delirium assessment** | | | | | | |
| Sepulveda et al (2015) | Cross sectional analysis | Participants without cognitive impairment (diagnostic criteria not reported; n=40)<br>versus<br>participants with possible Dementia based on IQCD score >85 (n= 85) | To assess Delirium rating scale- revised 98 against other assessment scales in people with dementia and those without cognitive impairment | DRS-R98<br>versus<br>ICD-10<br>DSM-III-R<br>DSM-IV<br>DSM-5 | • DRS-R98 scores<br>• ROC analyses | Participants with dementia were identified as a subsample of whole population based on a classification by Spanish Informant questionnaire on cognitive decline (score >85).<br>Study location Spain |

1 **Table 100 Included studies for management of intercurrent illness**

| Study reference | Study design | Study population | Intervention & comparator (including study aim) | Relevant outcomes |
|---|---|---|---|---|
| **Pain management** | | | | |
| Fuchs-Lacelle et al (2008) | Cluster RCT | 173 people over 65 with dementia and severe communication impairment | Intervention:<br>• Completion of the Pain Assessment Checklist for Seniors with Limited | • Medication level<br>• Nursing stress scale |

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| Study reference | Study design | Study population | Intervention & comparator (including study aim) | Relevant outcomes |
|---|---|---|---|---|
| | | | Ability to Communicate (PACSLAC) every other day for 3 months<br>Comparator:<br>• Completion of an Activity Log every other day for 3 months | |
| Husebo et al (2014) | Cluster RCT | 352 people with dementia (MMSE < 20) | Intervention:<br>• Stepwise protocol for treating pain<br>Comparator:<br>• Usual care | • Neuropsychiatric symptoms |
| Sandvik et al (2014), | Cluster RCT | 352 people with dementia (MMSE < 20) | Intervention:<br>• Stepwise protocol for treating pain<br>Comparator:<br>• Usual care | • Pain<br>• Adverse events |
| Delirium | | | | |
| Kolanowski et al (2011) | RCT | 16 people with delirium superimposed on dementia | Intervention:<br>• Standard nursing care and prescribed rehabilitation therapies, plus 30 minutes per day of cognitively stimulating recreational activities for 30 days.<br>Comparator:<br>• Standard nursing care and prescribed rehabilitation therapies | • Delirium symptoms<br>• Activities of daily living<br>• Cognition |
| **Hip fracture rehabilitation** | | | | |
| Smith et al (2015) | Systematic review | RCTs evaluating the effectiveness for people with dementia of enhanced care and rehabilitation following hip fracture surgery compared with usual care. | Intervention:<br>• Enhanced models of care and/or rehabilitation:<br>Comparator:<br>• Standard nursing, medical and therapy intervention | • Mortality<br>• Activities of daily living<br>• Adverse events<br>• Hospitalisation |

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| Study reference | Study design | Study population | Intervention & comparator (including study aim) | Relevant outcomes |
|---|---|---|---|---|
| Stenvall et al (2007) | Cluster RCT | 199 people post neck of femur fracture (including 64 people with dementia) | Intervention:<br>• Comprehensive geriatric assessments, management and rehabilitation<br>• Active prevention, detection and treatment of postoperative complications such as falls, delirium, pain and decubitus ulcers<br>Comparator:<br>• Specialist orthopaedic unit following conventional postoperative routines | • Falls |
| **Falls** | | | | |
| Chan et al (2015) | Systematic review | RCTs that compared the efficacy of physical exercise with routine medical care or other controlled activities in preventing falls in older people with cognitive impairment | Intervention:<br>• Group or home-based exercise<br>Comparator:<br>• Routine care or less intensive interventions | • Falls<br>• Fractures |
| Oliver et al (2006) | Systematic review | Trials, case-control or observational cohort studies of patients in hospitals or care homes that reported the number of rate of falls or fractures or people who fell. | Multiple intervention types:<br>• In hospital multifactorial interventions<br>• In care home multifactorial interventions<br>• Hip protectors in care homes<br>• Removal of physical restraint<br>• Fall alarm devices<br>• Exercise<br>• Changes or differences in physical environment<br>• Calcium and vitamin D in care homes<br>• Medication review | • Association of dementia prevalence in study with effect size |
| Pitkälä et al (2013) | RCT | 210 home-dwelling patients with Alzheimer's disease and their carers | Home-based exercise: | • Falls<br>• Hospital admissions |

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| Study reference | Study design | Study population | Intervention & comparator (including study aim) | Relevant outcomes |
|---|---|---|---|---|
| | | | • Physiotherapist led individually tailored training<br>Group-based exercise:<br>• Physiotherapist led group exercise consisting of endurance, balance and strength training, and exercise for improving executive functioning<br>Control group:<br>• Usual care provided by the Finnish healthcare system, plus oral and written advice on nutrition and exercise methods | • Cost |
| Shaw et al (2003) | RCT | 274 cognitively impaired older people presenting to the accident and emergency department after a fall | Intervention:<br>• Multifactorial assessment and intervention<br>Control:<br>• Usual care from all health professional who were involved in their management | • Falls<br>• Fractures<br>• A&E attendance<br>• Hospital attendance<br>• Mortality |
| Suttanon et al (2013) | RCT | 40 people with mild to moderate Alzheimer's disease | Home-based exercise programme:<br>• Six-month individualised home-based exercise programme supervised by a physiotherapist<br>• Based on the Otago home-exercise programme<br>Control (education) programme:<br>• Education and information programme delivered by an occupational therapist<br>• Designed to provide the same number of home visits and phone calls as the exercise programme | • Falls<br>• Quality of life<br>• Carer burden |

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| Study reference | Study design | Study population | Intervention & comparator (including study aim) | Relevant outcomes |
|---|---|---|---|---|
| Tchalla et al (2013) | RCT | 96 people with Alzheimer's disease | Intervention:<br>• Fall reduction program following an initial Comprehensive Gerontological Assessment. Participants were equipped with an HBTec-TS system<br>Control:<br>• Fall reduction program following an initial Comprehensive Gerontological Assessment. No HBTec-TS system was implemented | • Falls |
| Toulotte et al (2003) | RCT | 20 elderly dementia patients with a history of falling | Training group:<br>• Two supervised 1 hour exercise sessions per week for 16 weeks<br>• Exercises to develop muscular strength, proprioception, static and dynamic balance and flexibility<br>Control (education) programme:<br>• Usual care | • Falls |
| Wesson et al (2013) | RCT | 22 person living with dementia and carer dyads | Home-based exercise program:<br>• Strength and balance training exercises<br>Home hazard reduction:<br>• Six occupational therapist and five physiotherapist visits over 12 weeks<br>Control group:<br>• Usual care | • Falls<br>• Carer burden |

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### 18.1.3 Health economic evidence

A single search was undertaken for review questions 20 and 21. A total of 2,565 citations was returned. Following review of titles and abstracts, the full text of 1 study was retrieved for detailed consideration, but it did not meet inclusion criteria. Therefore, no relevant cost–utility analyses were identified for these questions.

### 18.1.4 Evidence statements

#### 18.1.4.1 Assessment

##### *18.1.4.1.1 Pain assessment*

Low- to moderate-quality evidence from 1 observational study with 600 participants found that rates of those assessed as having pain increased significantly for people with cognitive impairment when pain was assessed by an observational rating scale (PAINAD) compared with those who did not have cognitive impairment. When pain was assessed by a self-report scale (NRS), there were no significant differences between people with cognitive impairment and those who did not have cognitive impairment.

Low-quality evidence from 1 observational study with 40 participants found that pain intensity ratings from an observational rating scale (NOPPAIN) did not correlate with pain intensity ratings from self-report scales (VDS and NRS), for people with cognitive impairment; however, for people who did not have cognitive impairment, there was a significant positive correlation between pain intensity ratings from the observational rating and self-report scales.

The same study found there was a significant positive correlation between pain intensity ratings from an observational rating scale (NOPPAIN) and total number of pain indicators observed for both people with cognitive impairment and those who did not have cognitive impairment.

Very low-quality evidence from 1 observational study with 25 participants found a significant positive correlation between pain ratings on an observational rating scale (PAINAD) and self-report scale (NRS) for both people with cognitive impairment and those who did not have cognitive impairment.

Very low-quality evidence from 1 observational study with 174 participants found ratings from two observation scales (REPOS versus PAINAD) were significantly positively correlated but when self-report observations were obtained by a nurse, pain ratings were not positively correlated with an observational rating scale (REPOS) for people with cognitive impairment. Significant positive correlations were found for both the observational rating scale and nurse led self-report rating scale for people who did not have cognitive impairment. The same study also found that pain scores recorded on the observational rating scales were significantly higher for people with cognitive impairment compared with those who did not have cognitive impairment.

Moderate-quality evidence from 1 observational study with 108 participants found higher levels of agreement between the presence of self-reported pain and the presence of observer-rated pain in people without cognitive impairment compared with people with cognitive impairment.

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Moderate-quality evidence from 1 observational study with 108 participants found significant positive correlations between observational rating scales (PAINAD, NOPPAIN and Abbey pain scale) for people with cognitive impairment. The relationship between observational rating scales and self-report ratings was not significantly correlated for people who did not have cognitive impairment.

#### *18.1.4.1.2 Falls assessment*

Low-quality evidence from 1 observational study with 88 participants found people with cognitive impairment scored significantly lower on a balance assessment than those who did not have cognitive impairment. The same study also found there was a significant negative correlation between the number of falls recorded and scores on the balance scale for people with cognitive impairment and a significant positive correlation between the number of falls recorded and scores on the balance scale for those who did not have cognitive impairment.

#### *18.1.4.1.3 Delirium assessment*

Low-quality evidence from 1 observational study with 125 participants found the difference in scores assessed by the Delirium rating scale (DRS) compared with the ICD-10, DSM-II-R, DSMIV and DSM-5 were significantly higher for people who did not have cognitive impairment compared with those with cognitive impairment.

### 18.1.4.2 Management

#### *18.1.4.2.1 Pain management*

Low-quality evidence from 1 cluster-randomised RCT of 173 people followed up for 3 months showed that people monitored using the PACSLAC had a significantly higher increase in the amount of pain medications used than those assessed using an activity log.

Low-quality evidence from 1 cluster-randomised RCT of 173 people followed up for 3 months showed that nurses monitoring people using the PACSLAC reported lower levels of stress (as measured by the Nursing stress scale) than those monitoring people using an activity log.

Moderate-quality evidence from 1 cluster-randomised RCT of 327 people followed up for 8 weeks showed that people treated using a stepwise treatment protocol had significantly lower overall pain intensity scores, measured using the MOBID-2, than those receiving usual care. This included reductions in both musculoskeletal and internal organ, head and skin pain.

Moderate-quality evidence from 1 cluster-randomised RCT of 298 people followed up for 8 weeks showed that people treated using a stepwise treatment protocol had significantly fewer behavioural symptoms (as measured by the NPI-NH) than those receiving usual care. This included reductions in mood symptoms, depressive symptoms and apathy, but no significant differences in anxiety or irritability.

### 18.1.4.3 Delirium

Very low-quality evidence from 1 RCT of 16 people followed up for 30 days showed that people randomised to cognitively stimulating activities had significantly higher rates of improvement in activities of daily living (BI) and cognition (MMSE), but could not distinguish a difference in rates of improvement in delirium symptoms (CAM and DRS).

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#### *18.1.4.3.1 Hip fracture rehabilitation*

Moderate-quality evidence from 1 cluster RCT of 199 could not distinguish the effectiveness of a neck of femur fracture rehabilitation programme on reducing the incidence of falls between people with and without dementia.

Very low- to low-quality evidence from 1 RCT of 47 people could not distinguish the odds of mortality or activities of daily living independence at 12 months between people offered enhanced or conventional inpatient care. There was very low-quality evidence from the same study of lower incidence of:

- urinary tract infections
- nutritional problems
- postoperative delirium
- recurrent falls

Very low-quality evidence from the same study could not distinguish:

- rates of pneumonia
- rates of decubital ulcers
- rates of postoperative fracture
- length of stay
- number of drugs prescribed on discharge

Very low-quality evidence from 2 RCTs of 177 people could not distinguish the odds of mortality at 12 months between people offered enhanced or conventional home and inpatient care.

Very low-quality evidence from 1 RCT of 47 people found higher activities of daily living scores for people offered enhanced rather than conventional home and inpatient care, but could not distinguish the odds of falls at 12 months.

Very low-quality evidence from the same study could not distinguish:

- Frequency of hospital admissions
- Attendance at accident and emergency

Very low-quality evidence from 1 RCT of 126 people could not distinguish the odds of delirium incidence between people offered geriatrician-led vs orthopaedic-led inpatient management.

#### *18.1.4.3.2 Falls*

Low- to moderate-quality evidence from 2 RCTs of 148 people found home-based exercise programmes reduced the proportion of people falling and the mean number of falls in a population of community-dwelling people with dementia, but could not differentiate levels of carer burden.

Moderate-quality evidence from 1 RCT of 123 people found group-based exercise programs reduced the proportion of people falling in a population of community-dwelling people with dementia, but could not differentiate the mean number of falls.

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Low- to moderate-quality evidence from a systematic review of 7 RCTs found exercise programmes reduced the proportion of people falling by a similar amount to equivalent interventions in a population without dementia, but could not differentiate the proportion of people with subsequent fractures.

#### 18.1.4.4 Health economic evidence

No health economic evidence was identified for this review question.

### 18.1.5 Evidence to recommendations

| | |
|---|---|
| **Relative value of different outcomes** | The committee noted that both the evidence presented and members' own experience pointed to the under-diagnosis of pain in people living with dementia, and therefore any evidence that showed either an increase in the number of people living with dementia correctly identified as being in pain, or evidence of effective treatment protocols for this group would be highly relevant. The committee recognised the relevance of the evidence associated with pain and agreed there was appropriate evidence to support a recommendation for the use of structured observational tools alongside self-reported pain. This was supported by the evidence presented, which demonstrated a lack of correlation between self-reported and observer-reported pain in people living with dementia, compared with people without dementia, and that whwn observational tools were used, a similar proportion of people with and without dementia were found to be in pain, which was not the case when self-report alone was used. The committee also agreed that specific mention should be made of people who are unable to self-report pain, where observational tools may present the only viable method of evaluating pain.<br>The committee noted that there were already published NICE guidelines in a number of the areas under consideration, such as falls and delirium, and these guidelines did not explicitly exclude people living with dementia from their scope. Therefore, evidence that merely confirmed what was already in those guidelines was considered but did not justify the need for specific recommendations. The committee agreed that further recommendations would only be relevant were the evidence pointed towards the need for differences in the management between people living with dementia and people without dementia. |
| **Trade-off between benefits and harms** | The committee noted that, for pain management, there was a key trade-off between the risk of overtreatment and what was believed to be the larger current problem of people being prescribed insufficient pain relief. The committee agreed there was appropriate evidence to support a recommendation for the use of structured observational tools alongside self-reported pain. This was supported by the evidence presented, which demonstrated a lack of correlation between self-reported and observer-reported pain in people living with dementia, compared with people without dementia. The committee also agreed that specific mention should be made of people who are unable to self-report pain, where observational tools may present the only viable method of evaluating pain. The committee observed that pain management was undertaken with a stepped approach which balances the need for analgesia alongside a change in a person's behaviour or any signs of distress attributed to pain. In practice, treating pain in all people should be done with a holistic approach, which takes into consideration a need to assess and intervene. The committee noted that RCT evidence indicated the effectiveness of a stepwise protocol to manage pain, |

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| | consistent with the way pain would be managed in people without dementia.<br>The committee agreed that it was appropriate to make a recommendation to use such a protocol, noting that it was unlikely that there would be major differences in the way pain was treated in people with and without dementia, once the pain had been correctly identified. It was also noted that pain assessment and management was an iterative process, and there is a need to repeat assessments both when people show signs of pain and display behaviours indicative of being in pain, and during treatment to ensure healthcare staff are following the appropriate step of the protocol.<br>The committee agreed that the principles of assessment and treatment of falls in people living with dementia should not necessarily differ to those applied to people without dementia, and the evidence presented was broadly supportive of this. It was agreed therefore that it would be appropriate to cross refer to the recommendations in the NICE guideline on Falls in Older People (CG161). However, it also noted that many of the trials of falls interventions in people living with dementia had specific modifications to ensure they worked appropriately in that group (e.g. involvement of carers in delivering or monitoring interventions). The committee therefore agreed that it would be appropriate to add a recommendation for healthcare professionals to consider the specific needs of people living with dementia when referring them for falls intervention programmes or to consider how interventions may need to be modified to ensure adequate participation.<br>The committee noted that there was a specific area where the evidence on falls management in people living with dementia did not align with that of people without dementia, which was the effectiveness of multi-factorial interventions. These interventions are recommended in the falls guideline (CG61) but the evidence presented did not show a significant effect in a population of people living with dementia. The committee noted that the population in this RCT contained a significant proportion of people identified as having severe dementia and this raised concerns that the interventions may be less effective in this group, and that this may be attributable to the intensity of the interventions and the large number of tests involved, which may cause additional distress to someone living with dementia and in particular severe dementia. These negative factors would outweigh any benefits of the intervention. The committee discussed the evidence noting that it was strong enough to recommend that such interventions should not be used in people with severe dementia without consideration, on a case-by-case basis, to ensure that the benefits of the intervention were expected to be greater than the possible harms. |
| **Trade-off between net health benefits and resource use** | No health economic evidence was identified for inclusion when addressing these review questions. The committee noted that the recommendations made for pain and falls were unlikely to be more intensive than managing the same intercurrent illnesses for people without dementia, as the recommended approaches for treating pain and falls were similar to those for people without dementia. Therefore, it would be unlikely to add a significant additional cost to the NHS. |
| **Quality of evidence** | The committee acknowledged that the lack of longitudinal evidence in the studies meant that it was difficult to provide specific recommendations on the frequency of pain assessment. All the included studies involved regular monitoring using a prescribed protocol, but this may not be either practical or appropriate for all people with dementia in routine practice. It was acknowledged that there was a need to balance harms and benefits and, for this reason, the committee agreed it would |

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| | not be appropriate to give specific recommendations about assessment frequency. Generally the committee agreed that reassessment would be appropriate where there was a concern that a person may continue to be in pain or to be experiencing a new episode of pain, as this would be the situation where a change of pain management could be relevant.<br>Due to the lack of relevant evidence related to intercurrent delirium or urinary tract infection, the committee agreed that it was unable to draft recommendations in these areas. |
| **Other considerations** | The committee recognised that, in general, there was a lack of evidence appropriate to address these review questions. However, it noted that there were several NIHR-funded trials currently in development that might help mitigate this lack of evidence in the future. It therefore agreed that it was not necessary to address the current evidence gap by making specific recommendations for future research above that already being undertaken and/or considered. An exception to this was in the area of long term recovery from delirium superimposed on dementia, where the committee agreed it was appropriate to recommend future research, as there is currently a lack of evidence on how best to help people with dementia to recover to their baseline cognitive status after an acute episode of delirium. |

### 18.1.6 Recommendations

**Pain**

**115. Consider using a structured observational pain assessment tool:**

- alongside self-reported pain and standard clinical assessment for people living with moderate to severe dementia
- alongside standard clinical assessment for people living with dementia who are unable to self-report pain.

**116. For people living with dementia who are in pain, consider using a stepwise treatment protocol that balances pain management and potential adverse events.**

**117. Repeat pain assessments for people living with dementia:**

- who seem to be in pain
- who show signs of behavioural changes that may be caused by pain
- after any pain management intervention.

**Falls**

**118. For guidance on managing the risk of falling for people living with dementia (in community and inpatient settings), see the NICE guideline on falls in older people. When using this guideline:**

- take account of the additional support people living with dementia may need to participate effectively
- be aware that multifactorial falls interventions may not be suitable for a person living with severe dementia.

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### 18.1.7 Research recommendations

**20. What are the most clinically and cost-effective non-pharmacological interventions for helping the long-term recovery of people with delirium superimposed on dementia?**

For more details on the research recommendation made, and the rationale behind it, see appendix L.

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# 18.2 Management strategies for people living with dementia and co-existing physical long term conditions

**Review question**

- What are the optimal management strategies (including treatments) for people living with dementia with co-existing physical long term conditions?

## 18.2.1 Introduction

The aim of this review question was to identify the most effective interventions/ strategies to manage medical comorbidities (for example diabetes, cardiovascular disease etc.) in people living with dementia and to consider if the most effective interventions and strategies used for treating medical comorbidities in people living with dementia are different from the interventions and strategies used for people with medical comorbidities who do not have dementia.

The focus of the question was to consider strategies that reduce the progression of co-existing conditions and to specifically focus on people living with dementia and the following co-existing long term conditions:

- Continence
- Recurrent falls (rehabilitation)
- Hypertension
- Diabetes
- Risk of Cardiovascular disease (anticoagulation)
- Sensory impairment

The review identified studies that fulfilled the conditions specified in Table 101. For full details of the review protocols, see Appendix C.

**Table 101: Review summary: management of physical health comorbidities**

| | |
|---|---|
| **Population** | • Studies including people (aged 40 years and over) with a diagnosis of dementia and living with a co-existing long term condition |
| **Interventions** | • Pharmacological interventions/ self-care strategies/ observational or monitoring strategies specific to people living with dementia and a coexisting long term condition |
| **Comparator** | • Pharmacological interventions/ self- care strategies, monitoring or observational strategies for people living with a coexisting long term condition but not specific to people living with dementia<br>• Standard care |
| **Outcomes** | • Clinical progression of comorbidity and associated symptoms.<br>• Clinical outcomes including cognitive, functional and behavioural ability<br>• Change in prevalence of appropriate polypharmacy<br>• Intervention related problems such as potentially avoidable hospital admissions and re-admissions, errors, poor adherence and potentially avoidable adverse effects<br>• Intervention related outcomes including concordance, compliance satisfaction of person living with dementia and their carers |

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### 18.2.2 Evidence review

A systematic search identified 9,306 references filtered by randomised controlled trials. The references were screened on their titles and abstracts and 100 references were ordered for full text. The included studies and references of any eligible systematic reviews were also screened and full text copies of any appropriate studies were ordered, giving a total of 119 full-text studies. 112 papers were subsequently excluded because they did not fit the inclusion criteria (see Appendix F for a detailed list of excluded studies and reasons for their exclusion). Seven randomised controlled trials were included in the evidence review.

Four studies were included for strategies to treat risk of cardiovascular disease (2 studies focused upon strategies to treat hypertension, 1 of these trials compared pharmacological treatment with a PPAR-ɣ agonist (telmisartan) to pharmacological treatment with a CCB (amlodipine), the other compared the use of relative-measured blood pressure and automated blood pressure measurement). One study was included for cerebrovascular lesions (comparing a standardised protocol approach, involving both pharmacological and behavioural strategies with a standard care approach which was non-specific to vascular care) and 1 study for diabetes (comparing pharmacological treatment with a PPAR-ɣ agonist-pioglitazone to no treatment).

Three studies were included for treating incontinence. All 3 trials compared behavioural strategies.

One additional study was included from rerun searches conducted at the end of the guideline an was on sensory impairment, comparing active hearing aids to placebo hearing aids in people living with Alzheimer's disease and moderate age related hearing loss.

No studies were identified as relevant for falls rehabilitation.

A summary of the characteristics of the included studies is provided in Table 101. Data from the included studies were extracted into evidence tables. See Appendix E for the full evidence tables, and for the full GRADE profiles see Appendix G. References for the included studies are given in appendix I.

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### 18.2.2.11 Description of included studies

| Study reference | Study design | Study population | Intervention & comparator | Relevant outcomes | Comments |
|---|---|---|---|---|---|
| **Dementia and cardiovascular risk (hypertension, CV risk factors, diabetes)** | | | | | |
| **Hypertension** | | | | | |
| Kume (2011) | Randomised open-label trial | 20 patients with mild dementia (CDR=1) and hypertension (NINCDS-ADRDA criteria) | Participants received either telmisartan or amlodipine | • Mean difference in Blood pressure measurements | Location: Japan<br>Follow up: 6 months |
| Plichart (2013) | Randomised open comparative study | 66 outpatients diagnosed with dementia (based on DSM-IV criteria) and hypertension (BP ≥140/90mmHg at two or more occasions) | Participants received either relative measured home blood pressure measurement or automated blood pressure measurement | • Mean difference in Blood pressure measurements<br>• Correlation between ABPM or r-HBPM | Location: France<br>Follow up 3 days |
| **Vascular disease** | | | | | |
| Richard (2009) | Randomised multi centre controlled trial | 130 patients with probable Alzheimer's disease (according to CEMDE and white matter lesions of vascular origin | Intervention:<br>Multi component vascular care (for hypercholesterolemia and hypertension)<br>involving pharma treatment 8 to 100 mg acetylsalicylic acid;<br>50 mg pyridoxine; 0.5 mg folic acid per day and a stepped protocol of dietary, exercise and lifestyle changes<br>Control: Standard care | • Change in comorbidity outcome<br>• Clinical outcomes including cognitive, functional behavioural ability<br>• Adverse events | Location: Netherlands<br>2 year follow up |
| **Diabetes** | | | | | |
| Sato (2011) | Randomised open label controlled trial | 42 patients with mild Alzheimer's disease (CDR 0.5 or 1) and Type II Diabetes | Intervention: 15-30mg pioglitazone<br>Control: | • rCBF change from baseline<br>• Adverse events | Location Japan<br>6 month follow up |

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| Study reference | Study design | Study population | Intervention & comparator | Relevant outcomes | Comments |
|---|---|---|---|---|---|
| | | (diagnosis based on NINCDS-ADRDA criteria) | No treatment | | |
| **Continence** | | | | | |
| Ostaskiewicz (2010) | Systematic review | RCTs and quasi RCTs of timed voiding interventions for management of incontinence in people living with dementia | 3 (1 RCT, 1 mixed design and 1 controlled cross over study) | • Incontinence rates | Location: Multinational |
| Jirovec 2001 | Randomised controlled trial | Carers of 118 patients with cognitive impairment (based on SPMSQ) and urinary incontinence | Intervention:<br>Carers taught an individualised toileting schedule program<br>Control:<br>No precise details | • Mean change in number of incontinent episodes<br>• Correlation between baseline and follow up incontinence frequency | Follow up 6 months |
| Engberg (2002) | Randomised controlled cross-over study | 19 cognitively impaired older adults (MMSE<24) with urinary incontinence | Intervention:<br>Prompted voiding initially every 2 hours,<br>Control:<br>No precise details | • Change in daytime incontinent episodes<br>• Carer satisfaction with prompted voiding intervention | After 8 weeks participants in control group were crossed over to treatment group |
| **Age related hearing loss** | | | | | |
| Adrait (2017) | Randomised controlled semi-crossover study | 48 people living with probable Alzheimer's disease (NINCDS-ADRDA) and age-related hearing loss | Intervention: Active hearing aids<br>Control: Placebo hearing aids | • Clinical outcomes including cognitive, functional, behavioural ability | Location : France<br>After 6 months the participants in control group had hearing aids activated |

*Abbreviations NINCDS and ADRDA = National Institute of communicative disorders and Stroke and the Alzheimer's disease and related disorders association criteria; BS = Barthel Index score; DSM- IV Diagnostic & statistical manual 4th ed; MMSE= mini mental state examination; CDR= clinical dementia rating; CEMDA= Cambridge Examination for Mental Disorders in Elderly; SPMSQ= short portable mental status questionnaire*

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### 18.2.3 Health economic evidence

A total of 3,078 citations was returned from the search for this question. Following review of titles and abstracts, the full text of 1 study was retrieved for detailed consideration, but it did not meet the inclusion criteria. Therefore, no relevant cost–utility analyses were identified for this question. For full details of the literature review, please see Appendix D.

### 18.2.4 Evidence statements

#### 18.2.4.1 Hypertension

Very low-quality evidence from 1 RCT of 20 participants with Alzheimer's disease and hypertension found the mean difference in systolic blood pressure, diastolic blood pressure and pulse rate at 6 months was not significantly different for participants receiving telmisartan, compared with participants receiving amlodipine. The mean difference in cognitive and functional outcomes (MMSE scores, ADAS-Cog and WMS-R [logical memory scores]) at 6 months were also not significantly different for participants receiving telmisartan, compared with participants receiving amlodipine.

Low to moderate-quality evidence from 1 randomised comparative crossover study of 60 participants with cognitive impairment and hypertension found the mean systolic blood pressure readings were significantly higher when blood pressure readings were taken by a relative compared with 24 hour readings or daytime only readings taken from an ambulatory blood pressure measurement device. The mean diastolic blood pressure readings were not significantly different for readings taken by a relative compared with 24 hour or daytime readings taken from an ambulatory blood pressure measurement device.

#### 18.2.4.2 Cardiovascular risk

Moderate -to high-quality evidence from 1 RCT with 94 participants with Alzheimer's disease and cerebrovascular lesions found the mean difference in change over 2 years for systolic blood pressure readings, diastolic blood pressure readings, HBA1c, and HDL cholesterol did not differ significantly for participants receiving a multicomponent vascular care programme to participants receiving standard care. However, after 2 years, the total cholesterol readings and LDL cholesterol readings had significantly reduced for participants receiving the vascular care programme compared with those receiving standard care.

The change in cognitive outcomes (as measured by MMSE, IDDAD and revised MBPC) did not significantly differ after 2 years for participants receiving a multicomponent vascular care programme to participants receiving standard care.

#### 18.2.4.3 Diabetes

Low-quality evidence from 1 RCT with 42 participants with mild Alzheimer's disease and type II diabetes mellitus found no difference in fasting plasma glucose, HBA1c, or fasting insulin levels at 6 months between participants receiving pioglitazone compared with those who did not receive a drug therapy. The clinical outcomes (as measured by MMSE, ADAS-Cog and WMS-R logical memory) at 6 months did not differ for participants receiving pioglitazone compared with those who did not receive a drug therapy.

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#### 18.2.4.4 Incontinence

Low-quality evidence from 1 RCT of 74 participants living at home with cognitive impairment and incontinence found the number of participants showing decreased incontinence at 6 months did not differ significantly for those that received an individual scheduled toileting programme compared with those who did not receive the individualised programme. After 6 months, there was no significant difference in mean incontinence frequency for those participants that received an individual scheduled toileting programme compared with those who did not receive the individualised programme. There was no difference in cognitive ability (as measured by MMSE) or mobility (as measured by a composite mobility score) at 6 months for those that received an individual scheduled toileting programme compared with those who did not receive the individualised programme.

Very low-quality from 1 RCT of 19 participants living at home with cognitive impairment and incontinence found no significant difference in the reduction of incontinent episodes, reduction in daytime incontinent episodes per day after 8 weeks for participants receiving prompted voiding compared with a control group who did not receive prompted voiding. The mean percentage reduction in daytime wet and day and night time wet after 8 weeks was not significantly different for participants receiving prompted voiding compared with a control group who did not receive prompted voiding.

Very low- to moderate-quality evidence from 1 RCT of 174 participants with urinary incontinence and dementia found that after 2 months, the number of participants showing reductions in incidence of daytime incontinence did not differ significantly for participants receiving timed voiding compared with those receiving usual care. The number of participants with reductions in incidence of night time incontinence was significantly greater for participants receiving timed voiding compared with usual care. After 2 months the number of participants whose pad test indicated reductions in the volume of incontinence did not significantly differ for participants receiving timed voiding compared with usual care.

#### 18.2.4.5 Age related hearing loss

Low- to moderate-quality evidence from 1 RCT of 36 participants with age related hearing loss and Alzheimer's disease could not differentiate activities of daily living (ADCS-ADL); behavioural and neuropsychological symptoms (NPI); Quality of life (ADRQL) or carer burden (ZBI) at 6 months follow up for people using an active hearing aid, compared with those using a placebo hearing aid, but did find an improvement in quality of life at 12 months.

#### 18.2.4.6 Health economic evidence

No health economic evidence was identified for this review question.

### 18.2.5 Evidence to recommendations

| | |
|---|---|
| **Relative value of different outcomes** | The committee agreed that the evaluation of any intervention for this question relied on 2 key outcomes. First, how well the intervention manages the comorbidity itself (where the primary outcome measures would be the same as for evaluations of that condition in people without dementia), and secondly whether this treatment leads to any improvement or worsening of the person's dementia.<br>It was noted that there was a considerable body of evidence about the impact of managing cardiovascular risk factors on the progression of dementia (which is covered elsewhere in this guideline through a |

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| | question on modifying risk factors), but most of this evidence was not eligible for inclusion here, as only outcomes relating to the person's dementia were reported, without any data on the impact on the co-morbidity itself. |
| **Trade-off between benefits and harms** | **Diabetes**<br>The committee agreed that intensive interventions to improve diabetic control may not always be appropriate in people with severe dementia, as the benefits may not be sufficient to justify the distress/other harms these interventions can cause. It was noted that the diabetes guideline has a recommendation that it may be appropriate to relax the target HbA1c level for people with significant comorbidities in whom intensive management would not be appropriate. The committee agreed that severe dementia was a condition which would often meet this threshold, and therefore it was felt appropriate to cross-refer to this recommendation.<br>It was agreed, however, that whilst this recommendation established the principle that it is appropriate to reduce the intensity of treatment in some individuals, there was no evidence to establish which individuals were likely to benefit from the withdrawal of treatment, and what the most appropriate point in the person's dementia trajectory to withdraw treatment would be. Therefore, the committee agreed there would be value in additional research specifically looking at what the impact of the withdrawal of intensive treatments for diabetic control would be in people with severe dementia, and this would include attempting to identify subgroups of people in whom withdrawal is or is not beneficial.<br>**Cardiovascular disease**<br>The committee agreed that none of the evidence identified was sufficient on which to make recommendations. However, as with diabetes above, it was felt to be likely there were people with severe dementia in whom it was appropriate to withdraw treatments as the potential benefits would not be sufficient to justify the distress/other harms cause. In the absence of evidence no recommendations were made on this topic, but a research recommendation was made that trials should be conducted looking at the impact of the withdrawal of preventative vascular interventions for people with severe dementia.<br>**Falls**<br>No evidence was identified looking at the most appropriate interventions for rehabilitation following recurrent falls. Therefore, the committee decided not to add to the recommendations around falls made in the review question around the management of intercurrent illness.<br>**Incontinence**<br>The committee discussed the NICE guideline on urinary incontinence in neurological disease. This guideline recommends the use of antimuscarinic drugs to treat overactive bladder, but also mention they may be associated with confusion. The committee agreed it was important to highlight this is a particular concern in people with dementia, and that therefore antimuscarinic drugs should be avoided if possible in this population.<br>There is additionally a NICE technology approval on mirabegron, which says it is an appropriate treatment for overactive bladder in people for whom the side effects of antimuscarinics would be unacceptable. The committee highlighted that people with dementia would fulfil this criteria, and therefore should be eligible for mirabegron treatment.<br>Finally, the NICE guideline on faecal incontinence contains a specific recommendation around management in people with cognitive issues, and again it was felt appropriate to cross-refer to this recommendation. |

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| | In the absence of any high-quality evidence around interventions to reduce incontinence levels in people living with dementia, the committee felt it appropriate to make a research recommendation around this topic.<br>**Sensory impairment**<br>No evidence was identified looking at the most appropriate interventions for managing sensory impairment in people living with dementia. The committee noted the NICE guideline on hearing loss contained recommendations on assessments for hearing loss in people with suspected or diagnosed dementia, and agreed it was appropriate to cross-refer to these recommendations. The committee also agreed it was appropriate to include an equivalent recommendation around eye tests for people living with dementia, as this was also an important issue where the presences of visual impairment is higher in people living with dementia than those without.. |
| **Trade-off between net health benefits and resource use** | No health economic evidence was identified for this review question and it was not prioritised for economic modelling. The committee agreed that since the recommendations made either referred to recommendations from technology appraisals and other NICE guidance (and therefore any economic considerations should have been considered during those earlier evaluations) or were around potential reductions in the intensity of treatment (and therefore likely to be cost-saving) and that it was thus unlikely any of the recommendations made would lead to a substantial increase in resource use. |
| **Quality of evidence** | The committee agreed that the evidence presented was of a generally low quality, and did not provide sufficiently robust evidence to make recommendations. It was noted that the evidence search for this question was limited to trials in a population of people with dementia, and that another source of evidence was in published guidelines looking at populations with comorbidities of interest, where people with dementia/cognitive impairment may have been considered as a subgroup. Specific consideration was given to NICE guidance around diabetes and incontinence, and potentially relevant recommendations from these guidelines which could be cross-referred to were identified. The recommendations arising from these considerations are discussed in the trade-off between benefits and harms section above. |
| **Other considerations** | The committee noted there was often concern that people living with dementia were often not offered equitable access to treatment for comorbidities they may have, and agreed it was important to make a statement that people with dementia should be offered equivalent access to treatments for comorbidities. As part of this, it agreed that it was appropriate to cross-refer to the NICE guidance on manging multimorbidity, and on older people with social care needs and multiple long-term conditions. |

### 18.2.6 Recommendations

**119. Ensure that people living with dementia have equivalent access to diagnosis, treatment and care services for comorbidities to people who do not have dementia. For more guidance on assessing and managing multimorbidity, see the NICE guidelines on multimorbidity and older people with social care needs and multiple long-term conditions.**

**120. For more guidance on providing support for older adults with learning disabilities, see the NICE guideline on care and support of people growing older with learning disabilities.**

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**121. For guidance on setting HbA1c targets for people living with severe dementia who have type 2 diabetes, see recommendation 1.6.9 in the NICE guideline on type 2 diabetes in adults.**

**122. For guidance on pharmacological treatment of overactive bladder, see the NICE technology appraisal on mirabegron for treating symptoms of overactive bladder.**

**123. For guidance on treating faecal incontinence, see recommendations 1.7.2 and 1.7.8 in the NICE guideline on faecal incontinence.**

**Sensory impairment (such as sight loss, hearing loss, or both)**

**124. For guidance on hearing assessments for people with suspected or diagnosed dementia, see adults with suspected dementia in the NICE guideline on hearing loss**

**125. Encourage people living with dementia to have eye tests every 2 years. Consider referring people who cannot organise appointments themselves.**

### 18.2.7 Research recommendations

**21. What is the effectiveness of interventions to improve faecal and urinary continence in people living with dementia?**

**22. What is the impact on cognition, quality of life and mortality of withdrawing treatments for the primary and secondary prevention of vascular outcomes in people with severe dementia?**

**23. What is the impact on cognition, quality of life and mortality of withdrawing intensive treatments for diabetic control in people with severe dementia?**

For more details on the research recommendations made, and the rationale behind them, see appendix L.

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# 18.3 Managing mental health conditions alongside dementia

**Review question**

- What are the optimal management strategies (including treatments) for people with dementia and an enduring mental health condition?

## 18.3.1 Introduction

The aim of these review questions was to identify the most effective methods for managing pre-existing mental health comorbidities in people with dementia. This is distinct from the question of managing dementia-emergent mental health problems, which is addressed elsewhere in this guideline. All mental health conditions were eligible for inclusion but particular emphasis was placed on the following:

- Anxiety
- Depression
- Psychotic disorders
- Substance use disorders
- Personality disorder

The review identified studies that fulfilled the conditions specified in Table 102. For full details of the review protocol, see Appendix C.

**Table 102: Review summary: management of mental health comorbidities**

| | |
|---|---|
| **Population** | • People (aged 40 years and over) with a diagnosis of dementia and living with a psychiatric comorbidity/multimorbidity |
| **Interventions** | • Pharmacological interventions/non pharmacological interventions/self-care strategies/observational or monitoring strategies specific to people living with dementia and a comorbid psychiatric illness. |
| **Comparator** | • Pharmacological interventions/ non pharmacological/self- care strategies/monitoring or observational strategies for people living with a comorbid psychiatric illness but not specific to people living with dementia<br>• Standard care |
| **Outcomes** | • Clinical progression of mental health condition and associated symptoms.<br>• Clinical outcomes including cognitive, functional and behavioural ability<br>• Change in prevalence of appropriate polypharmacy<br>• Intervention related problems such as potentially avoidable hospital admissions and re-admissions, errors, poor adherence and potentially avoidable adverse effects<br>• Intervention related outcomes including concordance, compliance satisfaction of person living with dementia and their carers<br>• Health related quality of life of person living with dementia and their informal carers<br>• Resource use and costs |

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### 18.3.2 Evidence review

A systematic search identified 7,599 references. The references were screened on their titles and abstracts and 80 references were ordered for full text review, with an additional 5 papers identified through reference screening of included articles. All 85 papers were subsequently excluded because they did not fit the inclusion criteria (see Appendix F for a detailed list of excluded studies and reasons for their exclusion). In particular, 21 papers did provide information on people with dementia and one or more of depression, anxiety and psychosis, but in all these papers the onset of these symptoms came after the diagnosis of dementia, and therefore these papers were included in the section on illness-emergent non-cognitive symptoms.

#### 18.3.2.1 Description of included studies

No relevant studies were identified for this review question.

### 18.3.3 Health economic evidence

No health economic evidence was identified for this review question.

### 18.3.4 Evidence statements

No evidence was identified for this review question.

#### 18.3.4.1 Health economic evidence

No health economic evidence was identified for this review question.

### 18.3.5 Evidence to recommendations

| | |
|---|---|
| **Relative value of different outcomes** | The committee agreed that the evaluation of any intervention for this question relied on 2 key outcomes. First, how well the intervention manages the mental health comorbidity itself (where the primary outcome measures would be the same as for evaluations of that condition in people without dementia), and secondly whether this treatment leads to any improvement or worsening of the person's dementia. Some of the treatments for specified mental health comorbidities (e.g. antipsychotics) are known to cause harms in people with dementia, and therefore identified trials of the effectiveness of these medicines in managing mental health comorbidities in people with dementia would be valuable, as they would enable to trade-offs between these benefits and harms to be appropriately quantified. |
| **Trade-off between benefits and harms** | The committee agreed that the people in this group were likely to be complex to manage, because of the two way interaction between the two conditions. First, the presence of many mental health comorbidities has the potential to make dementia more difficult both to identify and manage and, conversely, the development/progression of dementia is likely to make management of the underlying mental health comorbidity more difficult.<br>The committee discussed whether, in the absence of evidence, there were any useful consensus recommendations that could be made for this group. However, it agreed that any such recommendations would either need to be vague (to capture the entire spectrum) and therefore |

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| | not provide useful guidance, or to be very specific and risk being inappropriate for many individuals within that group. The committee therefore agreed that no recommendations about management of people with dementia and long-term mental health comorbidities could be made.<br>The committee agreed however, that future research in this area would be valuable. It has been recognised for a long time that this is a complex patient group to manage, and yet there are still no randomised controlled trials in this population. It therefore recommended that trials should be conducted, looking at the optimum management strategies for people with an enduring mental health problem who go on to develop dementia. |
| **Trade-off between net health benefits and resource use** | No health economic evidence was identified for this review question and it was not prioritised for economic modelling. The committee agreed that the people specified in this review question were likely to be complex and therefore potentially expensive to manage. This meant that randomised controlled trials in this area are likely to be valuable, as they have the potential not only to improve patient care, but also to provide cost savings if more efficient and co-ordinated ways can be found to manage care for these individuals. |
| **Quality of evidence** | No evidence was identified for this review question. The committee agreed this is likely to be because of the relatively small numbers of people available for such trials (whilst a considerable number of people do have dementia and a mental health comorbidity, the number of different mental health comorbidities means there is not a large number in any individual group), and the complexity in conducting such trials. It also agreed that the population of people who develop a mental health comorbidity after a diagnosis of dementia is a larger group, but this is covered in a separate question in this guideline. |
| **Other considerations** | The committee noted that the prevalence of mental health problems is higher in people with learning disabilities than in the general population, and that there are particular challenges associated with managing mental health problems in people with learning disabilities and mental health issues who develop dementia. It was agreed that it would be highly desirable to be able to provide advice on how to manage dementia in this population, but the lack of relevant evidence did not make this possible. It was reinforced that this was an important subgroup for consideration throughout the guideline, and any evidence found in other questions relating to this population should be given a high priority for consideration. |

### 18.3.6 Recommendations

No recommendations were made

### 18.3.7 Research recommendations

**24. What are the optimal management strategies for people with enduring mental health problems (including schizophrenia) who subsequently develop dementia?**

For more details on the research recommendation made, and the rationale behind it, see appendix L.

# 19 Palliative care: care towards and at the end of life

The aim of palliative care is to achieve 'the best quality of life for patients and their families' (WHO 1990). Dementia is a life limiting illness that will often exist alongside other chronic conditions, and therefore most people with dementia will benefit from palliative care. The number of people who die with dementia is high and likely to substantially increase in the future. Dementia care is therefore an increasingly important strategic consideration for palliative and end of life care providers, and policies at national and international level recognise this (DoH End of life Strategy 2008)

Palliative care for people with dementia is compassionate, person centred and holistic; encompassing physical and psychological issues and social and spiritual aspects of their life. It requires attention to mental capacity and advance care planning to help people plan for the future, in order that they can live well and die in their usual place of residence. It recognises the central role of informal carers; also attending to their needs to enable them to play the vital role of supporting the person living with dementia. Care is coordinated and draws on support from professionals and carers who are well trained and highly skilled (Hospice enabled dementia care 2015).

Quality of care and access to palliative care for people with dementia is variable. This may in part be due to the challenges around recognition of end of life and knowing when to adopt a palliative approach. The GMC defines End of life care as "Patients are 'approaching the end of life' when they are likely to die within the next 12 months". One of the difficulties caring for people with a diagnosis of dementia is identifying the last 12 months of life. This means conversations about end of life do not always happen early enough.

The previous NICE dementia guidance 2006 highlighted the lack of evidence to support arguments concerning what constitutes good quality palliative care in dementia and highlighted the need for further research (Bayer 2006). In 2008, the NHS End of Life Strategy became the building blocks for the development of palliative care in the UK. It identified that we needed to prepare for larger numbers of people dying and that not everybody received high quality care. The NICE Quality Standards for End of Life Care in Adults (published 2011 and modified in 2013) set clear standards for quality of care.

Variation in quality of care across care settings and for different diagnoses remained a point of national debate and led to further reports and guidance including: The Leadership Alliances "One Chance to get it right" report (2014), Ambitions for End of life care Document (2015), Choice in End Of Life Care (2015), Health Select committee inquiry into end of life care (2015). These documents were a response to the variations and an attempt to build upon the national strategy by introducing frameworks for service development at a local level.

The European Association for Palliative Care (EAPC) aimed to produce the first definition of palliative care in dementia based on evidence and consensus from a range of experts (EAPC White Paper 2013). It proposed the differing trajectory of dementia from other life limiting illnesses created the need for a dementia specific definition and model of palliative care.

# 19.1 Palliative care

**Review question**

- What models of palliative care are effective for people with dementia?

## 19.1.1 Introduction

This question considered both quantitative and qualitative evidence on effective models of palliative care for people with dementia. The quantitative part of this review was undertaken as a collaboration between the NICE Internal Clinical Guidelines Team and the Cochrane Dementia and Cognitive Impairment Group.

**Table 103: Review summary: qualitative evidence**

| | |
|---|---|
| **Population** | • People (aged 40 years and over) living with dementia<br>• Carers of people (aged 40 years and over) living with dementia |
| **Phenomena of interest** | Aspects of palliative care approaches impacting on people living with dementia, which may include:<br>• Meeting physical care needs<br>• Psychological, social and spiritual care needs<br>• Planning<br>• Communication |
| **Outcomes** | • Experiences and satisfaction of people living with dementia<br>• Experiences and satisfaction of carers of people living with dementia |

**Table 104: Review summary: quantitative evidence**

| | |
|---|---|
| **Population** | People (aged 40 years and over) living with dementia |
| **Interventions** | • Defined models of palliative care<br>• Enteral tube feeding interventions |
| **Comparator** | • Alternative models of palliative care<br>• No enteral tube feeding<br>• Standard care |
| **Outcomes** | • Improvements in care<br>• Nutritional status<br>• Pain<br>• Patient satisfaction and quality of life<br>• Carer burden, satisfaction and quality of life<br>• Adverse events<br>• Resource use and costs |

Randomised and non-randomised controlled trials, controlled before-and-after studies, interrupted time series, qualitative studies and systematic review of either randomised controlled trials or qualitative studies were included if they explored the effectiveness of different models of palliative care for people living with dementia. Qualitative studies needed to report the views of either people living with dementia or their carers, and match the criteria given in Table 104. For full details of the review protocol, see Appendix C.

Quantitative studies needed to match the criteria given in Table 103. Papers were excluded if they:

- did not include the views people living with dementia or their carers
- were not in English language

- were abstracts, conference proceedings and other unpublished studies.

### 19.1.2 Evidence review

#### 19.1.2.1 Qualitative evidence

A single search was conducted for all the qualitative questions included in this guideline, which returned a total of 10,085 references. References were screened based on their titles and abstracts, and the full texts of 34 references that were potentially relevant to the review question were requested. Eight qualitative studies exploring the preferences of people living with dementia and their carers about palliative care were included in the review. The included studies are summarised in Table 105. For the full evidence tables and full CERQual profiles please see Appendix E and Appendix G. The 26 excluded papers, with reasons for exclusion, are presented in Appendix F. References for the included studies are given in appendix I.

##### *19.1.2.1.1 Description of included studies*

**Table 105: Summary of included studies – qualitiative evidence**

| Study details | Study population | Topic/methods | Outcomes |
|---|---|---|---|
| Crowther (2013) | Bereaved carers | Unstructured interviews | Exploration of the experiences of bereaved carers of people living with dementia in the last year of life and time surrounding death and how the presence and lack of compassion, kindness and humanity influenced the experience of care. |
| Davies (2014) | Professionals involved in delivering palliative care | Semi-structured interviews | This study explored perceived barriers to the delivery of high-quality palliative care for people living with dementia. |
| Dening (2012) | Informal carers and staff | Semi-structured interviews and focus groups | Perceived and real barriers that prevent people living with dementia and their carers receiving end-of-life care of acceptable quality |
| Grisaffi (2010) | GPs | Semi-structured interviews | GP's views and experiences of end-of-life care for their patients living with dementia. |
| Lamahewa (2017) | Carers of people living with dementia | Topic: decision making at the end of life for people with dementia<br>Method of data collection: focus groups and semi-structured interviews | The opinions of carers of people living with dementia |
| Lawrence (2011) | Care professionals, bereaved family carers. | Structured interviews | An exploration of how effective good-quality end-of-life care might be delivered for people living with dementia across care settings |
| Moore (2017) | Family carers of people living with dementia | Topic: end-of-life care<br>Method of data collection: interviews | The opinions of familial carers of people living with dementia |

| Study details | Study population | Topic/methods | Outcomes |
|---|---|---|---|
| Trelar (2009) | Bereaved carers | Mixed methodology | Retrospective evaluation of palliative care given to the person living with dementia |

#### 19.1.2.2 Quantitative evidence (palliative care interventions)

The studies included in this review were identified through a collaboration with a Cochrane review on palliative care in people living with advanced dementia. A total of 1,535 unique citations were identified through a systematic search, of which 21 were retrieved for full-text appraisal. Two of these studies ultimately met the criteria for inclusion, with the remaining 19 studies excluded, with reasons for exclusion given in Appendix F. An additional RCT was identified after the final search date of the Cochrane review which was also included in the analysis, giving 3 included RCTs in total. The included studies are summarised in Table 106. For the full evidence tables and full GRADE profiles please see Appendix E and Appendix G. References for the included studies are given in appendix I.

**Table 106: Summary of included studies – RCT evidence**

| Study details | Study population | Interventions | Outcomes |
|---|---|---|---|
| Ahronheim (2000) | 99 participants with advanced dementia, staged as FAST 6d or greater, hospitalised for an acute illness | Specialist palliative care team versus usual care | Palliative care plans, deaths in hospital, hospital admissions, use of procedures, decisions to forgo procedures |
| Hanson (2011) | 256 dyads of a resident with advanced dementia and feeding problems and their surrogate | Decision aid on feeding options versus no decision aid | Decisional conflict, frequency of feeding discussions, assisted feeding treatments |
| Hanson (2017) | 302 dyads of a resident with advanced dementia and feeding problems and their family decision maker | Goals of Care palliative care intervention versus usual care | Quality of communication, concordance of decision making, satisfaction with care |

#### 19.1.2.3 Quantitative evidence (enteral tube feeding)

A total of 452 unique citations were identified through a systematic search, of which 16 were retrieved for full-text appraisal. Seven of these studies ultimately met the criteria for inclusion, with the remaining 9 studies excluded, with reasons for exclusion given in Appendix F. The seven included studies were all non-randomised observational studies that compared outcomes between people who did and did not receive enteral tube feeding.

### 19.1.3 Health economic evidence

**Goldfeld et al. (2013)** compared the cost-effectiveness of no do-not-hospitalise (DNH) order (meaning that patients can be hospitalised, as per current practice) with a DNH order. This analysis also compared hospitalisation for suspected pneumonia with no hospitalisation for suspected pneumonia in patients with advanced dementia who were nursing home (NH) residents. The authors conducted a cost–utility analysis alongside the Choices, Attitudes, and Strategies for Care of Advanced Dementia at the End of Life (CASCADE) study (n=268), a prospective cohort study conducted between 2003 and 2006, and collected Medicare expenditure and Health Utility Index Mark 2 (HUI2) data. Primary outcome measures were

quality-adjusted life days (QALD) and Medicare expenditures over 15 months. For further details, please see the economic evidence profile in Appendix M.

Service-use data included direct costs associated with hospital admissions, emergency department visits, physician and other professional visits in the NH, hospice enrolment, and skilled nursing facility admissions after hospitalisation. To estimate QALYs, the study authors developed and validated a method that mapped the Symptom Management at the End-of-Life in Dementia Scale and Comfort Assessment in Dying with Dementia Scale to the Health Utility Index Mark 2 (HUI2). The authors employed bootstrap methods to explore the uncertainty of the incremental expenditure and quality-adjusted survival estimates. The mean results with informal care costs excluded are presented in Table 107.

**Table 107: Base-case cost–utility results – Goldfeld et al (2013)**

| Treatment | Incremental | | |
|---|---|---|---|
| | Costs | Effects | ICER |
| Usual hospitalisation practice vs DNH Order | $5,972 | +3.7 QALD | $1,614 /QALD<br>$589,130 /QALY |
| Hospitalisation for Suspected Pneumonia vs No Hospitalisation for Suspected Pneumonia | $3,697 | -9.7 QALD | Dominated |

| Strategy | Absolute | | Incremental | | |
|---|---|---|---|---|---|
| | Cost | Effect | Cost | Effect | ICER |
| **Do-not-hospitalise -v- usual practice** | | | | | |
| DNH order | NR | NR | | | |
| Usual practice (no DNH order) | NR | NR | $5,972 | 0.010 QALYs | $589,130 /QALY |
| **Do-not-hospitalise for pneumonia –v- usual practice** | | | | | |
| No hospitalisation for suspected pneumonia | NR | NR | | | |
| Usual practice (hospitalisation) | NR | NR | $3,697 | 0.027 QALYs | Dominated |

Current hospitalisation practice, compared with a DNH order resulted in additional average costs of $5,972 and 3.7 quality-adjusted life-days per patient, with a resulting ICER of $589,130 per QALY. Probabilistic analysis showed that, if QALYs are valued at less than $300,000 each, the proportion of incremental net benefits that are positive – indicating usual hospitalisation practice would be the preferred option – is no more than 20%.

Hospitalisation for suspected pneumonia compared with no hospitalisation for suspected pneumonia resulted in an additional average cost of $3,697 and a loss of 9.7 quality-adjusted life-days per patient, meaning hospitalisation was dominated. Probabilistic analysis showed that, at all assumed QALY values up to $300,000, the proportion of incremental net benefits that are positive – indicating hospitalisation would be the preferred option – was less than 10%.

## 19.1.4 Evidence statements

### 19.1.4.1 Qualitative evidence

#### *19.1.4.1.1 Carer identified issues*

The following issues around palliative care for people living with dementia were identified by bereaved carers:

- Meeting physical care needs
  - Ensuring adequate food and fluid intake was considered paramount, but care homes were occasionally evaluated negatively in this respect (moderate confidence)
- Going beyond task-focused care
  - End-of-life care was evaluated positively if it was felt that the professionals cared about their dying relative (moderate confidence)
  - Getting to know individual's interests, sensitivities and preferences (including food preferences) was considered important (moderate confidence)
  - Knowing the person well and having a sense of their personal and social identity was said to enable carers and health-care professionals to make better informed best interests decisions on behalf of a person living with dementia (high confidence)
  - When healthcare professionals do not communicate with carers because of poor communication or lack of time to involve the family, this can complicate decision making (high confidence)
  - Family carers reported often having to retell the same narrative to different health-care professionals (high confidence)
  - Carers sometimes have doubts making decisions, particularly if there was not an up-to-date living will (high confidence)
  - Carers valued continuity and receiving regular feedback about their relative's health condition and the progression of dementia. (moderate confidence)
  - Carers were rarely informed about the dementia from diagnosis onwards through to the palliative stages (moderate confidence)
  - The unpredictable course of dementia made it very challenging for carers to prepare for the end of life (moderate confidence)
  - Carers valued timely and sensitive information provided by a knowledgeable professional and that was reinforced in writing (moderate confidence)
  - End of life (EOL) plans were not started early enough (moderate confidence)
  - Some carers were satisfied with EOL care if they felt adequately informed and involved, even when EOL care was not in accordance with advance care plans (moderate confidence)
  - Carers often grieve for their relative before the person dies (moderate confidence)
  - Participants discussed the failure of services to acknowledge their grief or to provide information about obtaining support (moderate confidence)
  - Despite high levels of grief, many carers felt they did not need formal support or counselling and did not seek it. (moderate confidence)
  - Carers who felt well informed about how dementia progressed, were regularly updated on their relative's health condition and felt involved appeared more satisfied with EOL care. (moderate confidence)
- Planning
  - The importance of advance directives and advance statements (moderate confidence)
  - The importance of discussing treatment planning with families and the wider care team (moderate confidence)

  - Family carers described how little happened routinely; they had to initiate and then "push" for services to be provided, these were unpredictable and fragmented (moderate confidence)
- Impact of hospitalisation
  - Not liking the hospital environment, and finding it an uncomfortable experience and place to be (moderate confidence)
  - Carers described how acute hospital staff struggled to provide basic care. Carers perceived a lack of understanding, little compassion and low staffing levels (moderate confidence)
  - Lack of dignity associated with dying on an open ward (moderate confidence)

#### 19.1.4.2 Professional identified issues

The following issues around palliative care for people living with dementia were identified by professionals working with these people:

- Meeting physical care needs
  - Identifying and responding to the physical care needs of the person living with dementia – often these needs were not complex, but basic needs were still not being met (moderate confidence)
  - Difficulties of pain management (moderate confidence)
  - Palliative care nurses were considered skilled in identifying and managing pain in patients with complex needs and were also sensitive to nausea and hallucinations in people with dementia at the end of life (moderate confidence)
- Complex pathways of care
  - People with advanced dementia had complex medical and social needs requiring input from a number of agencies, but the coordination was poor (moderate confidence)
  - Out of hours staff often felt unsupported and lacking in access to key information (moderate confidence)
- Going beyond task-focused care
  - Risk of becoming entirely task-focused with little empathy (moderate confidence)
  - Difficulties in getting to know individual's interests, sensitivities and preferences (moderate confidence)
- Planning
  - People with dementia should be given the opportunity to plan for the future (moderate confidence)
  - Whether individuals should be transferred to hospital during the final stages of their life. Hospitalisation was a frequent occurrence despite agreement among care professionals that this was often inappropriate (moderate confidence)
  - Palliative care staff noted that professionals across care settings could be reluctant to withdraw active treatment in the absence of explicit planning or a clear consensus among the care team (moderate confidence)
  - Problems with discontinuity of care (low confidence)
- Flexibility
  - The growing number of guidelines, standards, rules and regulations placed upon professionals in health and social care makes palliative care standardised leaving no room for flexibility (moderate confidence)
  - GP's prior knowledge of the person living with dementia is important in informing decisions. To help the person overcome the communication and capacity issues, relatives and carers are seen as an expert source of information regarding the person's wishes (low confidence)

  - NHS Primary Care Trusts have no duty of care for people who are self-funding their care home (moderate confidence)
- Systemisation
  - Some routines are useful, such as certain meetings, pain assessment, when to stop pursuing certain treatments (moderate confidence)
- Staff training to reduce the need to call for specialist help
  - Need for training on appropriate interventions (moderate confidence)
  - Many, particularly hospice, ambulance staff and district nurses acknowledged they had received little or no training in dementia, in particular concerning communication and managing behavioural problems (moderate confidence)
- Roles of generalists and specialists
  - Some district nurses and GPs feel that palliative care should be left to specialists (moderate confidence)
- Lack of trust, fear of litigation, fear of blame and threats to speciality
  - Managing both real and perceived risks can be a difficult challenge (moderate confidence)
- Difficulties in deciding when to start end-of-life care
  - The typically slow erratic decline and the indicators for starting the pathway could lead to either a person being on it for a long time or 'yo-yoing' on and off as their state fluctuated (low confidence)

#### 19.1.4.3 Quantitative evidence

##### *19.1.4.3.1 Specialist palliative care team versus usual care*

Low- to moderate-quality evidence from 1 RCT of 99 people found that people living with dementia and hospitalised for an acute illness who were offered support by a specialist palliative care team were more likely to have palliative care plans developed at any time and on discharge than people offered usual care, but could not differentiate proportions with palliative care plans during hospitalisation.

Low-quality evidence from 1 RCT of 99 people could not differentiate deaths in hospital, hospital admissions, use of procedures or decisions to forgo procedures between people living with dementia and hospitalised for an acute illness who were offered support by a specialist palliative care team compared with people offered usual care.

#### 19.1.4.4 Use of decision aid on feeding options

Low- to moderate quality evidence from 1 RCT of 90 people could not differentiate decisional conflict, frequency of feeding discussions and assisted feeding treatments between people living with dementia in nursing homes using a structured decision aid on feeding options and people in nursing homes providing usual care.

#### 19.1.4.5 Goals of care intervention versus usual care

Low- to moderate-quality evidence from 1 cluster RCT of 299 people found improved levels of quality of communication (end of life), concordance on primary care goals, and number of palliative care plans addressed in people offered a palliative care intervention (Goals of Care) versus usual care, but could not differentiate levels of quality of communication (overall), quality of communication (general), advanced care planning problems, symptom management and satisfaction with care.

#### *19.1.4.5.1 Enteral tube feeding*

A high-quality systematic review identified low-quality evidence from seven observational studies containing 1,813 people, and could not detect any differences in mortality, nutritional status or the prevalence of pressure ulcers between people given and not given enteral tube feeding.

### 19.1.4.6 Health economic evidence

One partially applicable cost–utility analysis with potentially serious limitations, based on an observational study, found that, compared with approaches that avoid hospitalisation, more aggressive treatment strategies leading to hospitalisation are not cost effective – and, in the case of hospitalisation for suspected pneumonia, do more harm than good – for nursing home residents with advanced dementia.

## 19.1.5 Evidence to recommendations

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| **Relative value of different outcomes** | The committee agreed that, in order to recommend specific palliative care interventions, data from quantitative studies (particularly randomised controlled trials) would be necessary. Data from qualitative studies would be likely to lead to more general recommendations around important principles of care.<br>The committee also discussed the existing NICE guidelines on palliative care and the last days of life, to assess their applicability for people living with dementia. |
| **Trade-off between benefits and harms** | The committee agreed that the general principles recommendations contained in the NICE guidelines on palliative care and the last days of life were relevant, and agreed it would be appropriate to cross-refer to both these pieces of guidance. It agreed that all further recommendations should then focus on areas of palliative care particularly relevant to people living with dementia, over and above standard palliative care. The main distinct features of people who live with advanced dementia were identified as being:<br>• the difficulty in assessing pain and distress<br>• the extreme unpredictability of when death will occur<br>• people lacking capacity to make palliative and end-of-life care decisions for themselves.<br>As a consequence of the extreme unpredictability of when death will occur and associated difficulty in recognising when end-of-life care is appropriate, the committee agreed that it was common for palliative care and end-of-life care to be applied and then unapplied and then re-applied for people who live with advanced dementia. As a consequence, the commonly used definition of palliative care being something that should be in the last year of life is often not applicable to people who live with dementia. Instead, a definition is needed that is more flexible and takes into account the needs of people who live with dementia. The committee therefore made a recommendation that palliative care should be both flexible and needs-based rather than time based, taking in to account the disease trajectory, and in principle be available from the point of diagnosis.<br>It was further noted that the person living with dementia may also have comorbidities, and that dementia may mean that these comorbidities can be exacerbated in an unpredictable way.<br>The committee noted that the Gold Standards Framework can be very helpful as an aid to palliative care, but agreed that in the absence of evidence it was not possible to make a direct reference to it. The committee also agreed that a palliative care approach is the responsibility of every health and social care professional working |

with people living with dementia, and therefore the terms 'non-specialist palliative care' or 'specialist palliative care' were avoided.

The committee agreed that anticipatory healthcare planning is important because for people who live with dementia, their 'voice' with regards to knowing their preferences is lost much earlier. Proactive planning can make the transition much easier, with the principles of best interest decision making becoming important when it is no longer possible for the person living with dementia to be involved in decision making. It was also agreed to be appropriate to include a recommendation on when it is appropriate to hold a best interested discussion, and in particular the need for capacity assessments to be conducted in all but emergency situations.

The committee agreed that one of the distinguishing features of dementia is the increasing difficulty in communication and 'trying to find the person inside'. The committee agreed that structured observational tools may help to continue person centred care. They agreed it was important to personalise care despite any communication issues, and therefore these tools should be used to assess people's "likes and dislikes, routines and personal history".

The committee also agreed that alternative methods of communication may be necessary to engage people. The most common example of this would be visual communication tools, but other methods may also be valuable (e.g. some people use touch as a way to augment communication). The recommendations stress the importance of "two-way communication", as the aim should be to involve the person rather than simply communicate to them.

The committee reflected on examples of available structured observational tools (e.g. the 'This is me' tool, which is published by the Alzheimer's Society). However in the absence of any evidence meeting the criteria for this review, the committee agreed that it was not appropriate to recommend any one specific tool above the others.

**Eating and drinking**

The committee agreed that the evidence available on enteral feeding did not show any benefits in people living with severe dementia, and there was also a lack of evidence on the potential harms of these interventions. The committee agreed it was therefore appropriate to make a recommendation that enteral feeding should not routinely be initiated in people living with severe dementia (though it may be used in situations where enteral feeding is necessary for a pre-existing condition and has been working satisfactorily). An important caveat to this recommendation was agreed to be in people where the enteral feeding is indicated for a potentially reversible co-morbidity. This is particularly relevant for the rarer types of dementia, including for younger patients who might otherwise be denied treatment (e.g. people with frontotemporal dementia who develop bulbar problems and consequently have difficulties with swallowing). In these examples, the cognitive aspects of dementia are generally mild when bulbar problems occur. In contrast, in cases of Alzheimer's or vascular dementia, by the time bulbar problems occur, the cognitive aspects of dementia are usually very severe.

The committee agreed this recommendation should be restricted to people with severe dementia as enteral feeding may well be appropriate for people living with mild or moderate dementia if they had a good quality of life.

The committee agreed it was important to make a positive counterpart to this recommendation, about supporting and encouraging oral eating and drinking for as long as possible. The committee also noted that in situations where there are concerns around the safety of eating and drinking, it is appropriate to consider involving a speech and language therapist as part of this process, in

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| | a similar way to how they would be involved if these concerns existed in a person without dementia.<br>**Hospitalisation**<br>The committee agreed that there are clear benefits in maintaining a familiar environment for a person living with dementia and acknowledged the possible harms from hospitalisation. The committee agreed it was therefore important, when considering hospitalisation for a person living with dementia to conduct a risk assessment that takes into account the specific difficulties people living with dementia may experience in a hospital environment. This assessment should ensure that people living with dementia are only hospitalised when there are clear benefits which justify the harms that may be caused.<br>The committee agreed this recommendation was necessary because acute hospitals are not set up to accommodate behavioural and other needs of people living with advanced dementia. In addition, people who live with advanced dementia, once hospitalised, are more likely to stay longer in hospital, become stuck in hospital and are more likely to die there. People who live with dementia could be admitted into hospital for treatment of an acute illness but maybe discharged with a significantly worse health status, e.g. their infection may be treated but they may no longer be able to walk. |
| **Consideration of health benefits and resource use** | The committee noted that there were often high costs associated with not providing appropriate palliative care and support (in particular, inappropriate and expensive hospitalisations). The committee agreed the potential increased costs associated with a palliative care approach initiated at the point of diagnosis should be offset by a reduction in the number of unnecessary hospital admissions.<br>The committee did not use the terms ‘non-specialist palliative care’ or ‘specialist palliative care’ in any recommendations. This was because there are large cost implications to the use of specialist palliative care teams and for which there was not strong enough evidence to support. Further, the committee agreed a palliative care approach is the responsibility of all health and social care professionals working with people living with dementia.<br>Goldfeld (2013) provided economic evidence that hospitalising people living with dementia who had pneumonia resulted in a reduction of QALYs compared with no hospitalisation. The study was from the USA and therefore not directly applicable, but was agreed to add weight to the suggestion that hospitalisation should be avoided where possible. |
| **Quality of evidence** | The committee agreed that none of the RCTs on specific palliative care interventions provided strong enough evidence to make recommendations. However, they noted that a number of larger RCTs on palliative care in dementia are currently underway, and therefore it is likely a higher quality evidence base will be available to support these decision in the future.<br>Confidence in the quality of the qualitative evidence was moderate overall. The amount of studies and participants was fairly small, but the themes identified all matched with the professional experience of members of the committee. |
| **Other considerations** | The committee agreed that staff training can be an important component in the delivery of good quality palliative care, but noted that these issues are covered in the separate question on staff training in this guideline.<br>The committee agreed there was a lack of quantitative evidence on specific palliative care interventions for people living with dementia, and therefore agreed it was appropriate to make research |

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| | recommendations around the most effective models and of palliative care, and specific palliative care interventions at the end of life. |

### 19.1.6 Recommendations

**126. From diagnosis, offer people living with dementia flexible, needs-based palliative care that takes into account how unpredictable dementia progression can be.**

**127. For people living with dementia who are approaching the end of life, use an anticipatory healthcare planning process (see recommendation 41 on advance care planning). Involve the person and their family members or carers (as appropriate) as far as possible, and use the principles of best-interest decision-making if the person cannot make decisions about their own care.**

**128. For standards and measures on palliative care, see the NICE quality standard on end of life care for adults.**

**129. For guidance on care for people in the last days of life, see the NICE guideline on care of dying adults.**

**130. For guidance, on best interests decision-making, see the NICE guideline on decision-making and mental capacity.**

**131. Encourage and support people living with dementia to eat and drink, taking into account their nutritional needs.**

**132. Consider involving a speech and language therapist if there are concerns about a person's safety when eating and drinking.**

**133. Do not routinely use enteral feeding in people living with severe dementia, unless indicated for a potentially reversible comorbidity.**

**134. When thinking about admission to hospital for a person living with severe dementia, carry out an assessment that balances their current medical needs with the additional harms they may face in hospital, for example:**

- disorientation
- a longer length of stay
- increased mortality
- increased morbidity on discharge
- delirium
- the effects of being in an impersonal or institutional environment.

**135. When thinking about admission to hospital for a person living with dementia, take into account:**

- any advance care and support plans
- the value of keeping them in a familiar environment.

**136. Consider using a structured tool to assess the likes and dislikes, routines and personal history of a person living with dementia..**

### 19.1.7 Research recommendations

**25. What are the most effective models of general and specialist palliative care support to meet the needs of people with advanced dementia?**

**26. What are the most effective interventions to support staff to recognise advanced dementia and develop appropriate escalation/end of life plans to facilitate care to remain at home?**

For more details on the research recommendations made, and the rationale behind them, see appendix L.

# 20 Glossary

| Abbreviations used in this guideline | |
|---|---|
| AAS | Anticholinergic Activity Scale |
| ABC | Anticholinergic Burden Classification |
| ACE | Angiotensin converting enzyme |
| ACER | Addenbrooke's Cognitive Exam-Revised |
| AChE | Acetyl(cholinesterase) inhibitor |
| ACL | Anticholinergic Loading Scale |
| AD | Alzheimer's disease |
| ADAS-cog | Alzheimer's Disease Assessment Cognitive Subscale |
| ADCS-ADL | Alzheimer's Diseases Cooperative Study – Activities Of Daily Living |
| ADCS-CGIC | Alzheimer's Disease Cooperative Study- Clinician's Global Impression Of Change |
| ADL | Activities Of daily living |
| Apo E | Apolipoprotein E |
| BBS | Berg Balance Scale |
| BNT | Boston Naming Test |
| BS | Barthel Index Score |
| BTA | Brief Test Of Attention |
| CADASIL | Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy |
| CAM | Confusion Assessment Method |
| CBD | Corticobasal degeneration |
| CDR | Clinical Dementia Rating Scale |
| CEMDA | Cambridge Examination for Mental Disorders In Elderly |
| CERAD | Consortium to Establish a Registry for Alzheimer's Disease |
| CIBIC+ | Clinician's Interview Based Impression of Change Plus Caregivers Assessment |
| CJD | Creutzfeldt-Jakob disease |
| CLP | Contrastophore-linker-pharmacophore |
| CrAS | Clinician's Rated Anticholinergic |
| CSF | Cerebrospinal fluid |
| CT | Computed tomography |
| CTD | Cognitive Test for Delirium |
| CVLT | California Verbal Learning Test |
| DAD | Disability Assessment for Dementia |
| DAD | Disability Assessment Daily |
| DEMQOL | Dementia-Specific Quality of Life |
| DI | Delirium Index |
| D-KEFS | Delis-Kaplan Executive Functions System Verbal Fluency Test |
| DLB | Dementia With Lewy bodies |
| DNAR | Do not attempt resuscitation |
| DRS | Delirium Rating Scale |
| DSM | Diagnostic and Statistical Manual of Mental Disorders |
| EDSSS | Expanded Disability Status Scale |

| Abbreviations used in this guideline | |
|---|---|
| EEG | Electroencephalography |
| FAQ | Functional Activities Questionnaire |
| FBI | Frontal Behavioural Inventory |
| FDG-PET | Fluorodeoxyglucose positron emission tomography |
| FST | Faces Symbol Test |
| FTD | Frontotemporal dementia |
| GDS | Global Deterioration Scale |
| GHQ | General Health Questionnaire |
| GMC | General Medical Council |
| GPCOG | General Practitioner Assessment of Cognition |
| HAND | HIV-associated neurocognitive disorder |
| HDL | High-density lipoprotein |
| HIS | Hachinski Ischemic Scale |
| ICD-10 | International Statistical Classification of Disease and Related Health Problems |
| ICER | Incremental cost-effectiveness ratio |
| IQCODE | Informant Questionnaire on Cognitive Decline in the Elderly |
| LBCR | Lewy Body Composite Risk Score |
| MAI | Medication Appropriateness Index |
| MCI | Mild cognitive impairment |
| MDRS | Mattis Dementia Rating Scale |
| MIBG | Metaiodobenzylguanidine |
| Mini-ACE | Mini-Addenbrooke's Cognitive Exam |
| MMSE | Mini-Mental State Examination |
| MoCA | Montreal Cognitive Assessment |
| MRI | Magnetic resonance imaging |
| MUSIC | Multiple Sclerosis Inventarium Cognition Score |
| NMB | Net monetary benefit |
| NOPPAIN | Non Communicative Patients Pain Assessment |
| NRS | Numerical Rating Scale |
| NPV | Negative predictive values |
| NSAIDs | Nonsteroidal anti-inflammatory drugs |
| NPI | Neuropsychiatric Inventory |
| OSLA | Observational Scale of Level of Arousal |
| PACSLAC | Pain Assessment Checklist for Seniors with Limited Ability to Communicate |
| PAINAD | Pain Assessment in Advanced Dementia |
| PASAT | Paced Auditory Serial Addition Test |
| PDD | Parkinson's disease dementia |
| PET | Positron emission tomography |
| PIB | Pittsburgh compound B |
| PPA | Primary progressive aphasia |
| PPV | Positive Predictive Values |
| QALY | Quality-adjusted life-year |
| QoL | Quality of life |

| Abbreviations used in this guideline | |
|---|---|
| RBANS | Repeatable Battery for The Assessment of Neuropsychological Status |
| REPOS | Rotterdam Elderly Pain Observation Scale |
| RFFT | Ruff Figure & Fluency Test |
| RUDAS | Rowland Universal Dementia Assessment Scale |
| SAA | Serum Anticholinergic Activity |
| SCEAM | Sheffield Care Environment Assessment Matrix |
| SDMT | Symbol Digit Modalities Test |
| SMC | Subjective Memory Complaints |
| SMMSE | Standardised Mini-Mental State Examination |
| SPECT | Single-photon emission computed tomography |
| SPMSQ | Short Portable Mental Status Questionnaire |
| SRT | Spatial Recall Test |
| TFLS | Texas Functional Living Scale |
| TOL | Tower of London Test of Learning and Memory |
| TYM | Test Your Memory |
| UPDRS | Unified Parkinson's Disease Rating Scale |
| WMS | Wechsler Memory Scale |
| VaD | Vascular dementia |
| ZBI | Zarit Burden Interview |