National Guideline

Diagnosis and treatment of dementia and Mild Cognitive Impairment

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Scope and objective of the Guideline

The Guidelines for the diagnosis and treatment of dementia was included among the specific objectives of the Italian Fund for Alzheimer's and Other Dementias (IFAD), which also defined its scope.
The Strategic Committee of the National Guidelines System (Sistema Nazionale Linee Guida, SNLG), established within the Ministerial Decree 27.02.2018, identified dementia as a priority issue for the development of the Guidelines (GL). In Italy, around two million people have dementia or some type of mild cognitive decline (Mild Cognitive Impairment, MCI), with around four million of their family members caring for them. Considering the relevance of the topic, the Ministry of Health, as part of the IFAD, entrusted the National Institute of Health (Isituto Superiore di Sanità, ISS) with developing a GL on the diagnosis and treatment of dementia and MCI, within the National System Guidelines (SNLG), based on currently available evidence and both national and international best practices.
The primary objective of the present GL was to provide recommendations based on the best and most updated evidence aimed at facilitating and uniforming the timely diagnosis, and at ensuring the availability and appropriateness of a coordinated care process and of the best available treatments, minimizing the inappropriateness and variability of clinical practices. The GL had the specific objective of indicating the most adequate, appropriate, efective, efficient, and useful clinical practices for the management of dementia. GLs are, in fact, defined as documents providing an ideal care pathway based on both Evidence Based Medicine (EBM) and a structured cost-benefit analysis for the National Health System (NHS). This care pathway should be considered as a reference by regional and local healthcare services and policymakers, who, taking into account their peculiarities, should base the definition of their integrated care pathways (ICPs) on the indications provided by the GL and its care pathway.

Existing international guidelines

Based on the methodological indications provided by the Methodological Handbook developed by the SNLG (SNLG-ISS MH)[1], a preliminary scoping review was performed to identify available international guidelines or guidance documents.
As indicated by the SNLG-ISS MH, specific searches were carried out on the main international GLs databases and on the websites of the main international institutions producing GL.
A total of 28 international LGs has been identified on the database Guidelines International Network (GIN)[2], while 798 documents were found by searching the NICE Evidence[3] database.
Identified documents were selected based on scope and date of publication, and on the type of institution that developed it. Three GLs on the diagnosis and treatment of dementia were developed by public institutions within the last 10 years. Out of these, only one GL, NICE Guideline 97 (NG97) developed by the National Institute for Health and Care Excellence (NICE) was considered as comparable in terms of scope and objectives to the document requested by the Italian Fund for Alzheimer's and Other Dementias. Therefore, based on the methodology proposed by the SNLG-ISS MH, the working group (WG) agreed to the adaptation, update, and integration of the NG97 published by NICE in June 2018 (hereon referred to as NICE GL)[4].

[1] https://www.iss.it/documents/20126/7949265/Manuale+Metodologico+-+marzo+2023.pdf/01f4bc8e-f3e6-66ec-bbe1-e80186908c6c?t=1679921943422 (Last visited: 30/08/2023)
[2] https://guidelines.ebmportal.com/ (Last visited: 30/08/2023)
[3] https://www.evidence.nhs.uk/ (Last visited: 30/08/2023)
[4] http://www.nice.org.uk/guidance/ng97 (Last visited: 30/08/2023)

NICE Guideline

The NICE GL was developed as part of the activities coordinated by the Government of the United Kingdom within the Challenge on Dementia 2020 (CD 2020)[5], a continuation of the previous Challenge on Dementia 2012-2015. The CD 2020 established national strategies aimed at improving the care for people with dementia in the UK[6]. The objectives of the strategy included improving the diagnosis, assessment and care process for people with dementia, ensuring equal access to diagnosis for all people with dementia, providing healthcare staff with appropriate dementia training, and ensuring that each person diagnosed with dementia receives adequate assistance.

The NICE GL complements existing legislation on the management and organization of care for people with dementia and includes indications to guarantee the quality of care provided by health and social services and professionals.

The content of the guideline was also used as a basis to develop further documents aimed at care planning and appropriateness of interventions[7]. These documents are part of the CD 2020 implementation plan, whose main tools are the "Well Pathway"[8] and its related "Full implementation guidance"[9].

The Well Pathway, a care pathway produced by the National Collaborating Center for Mental Health (NCCMH) in collaboration with NICE, was developed based on the NICE GL and other guidance documents produced by NICE, and on existing experiences reported as effective and efficient by stakeholders or scientific literature. The primary objective of this tool is to provide professionals with training on the essential knowledge on dementia and its impact on families and care; provide information on available services and care models for people with dementia; describe the principles of the Well Pathway defined as an ideal care process for people with dementia and their caregivers starting from the diagnosis and post-diagnostic support until the end of life (diagnose well, support well, live well, die well); summarize the recommendations from the NICE GL and other guidance documents produced by NICE; provide information on useful tools for the implementation of local care pathways.

The Well Pathway, both in its original form and in the interactive version produced by the University of Manchester[10], was developed as a relatively brief visual tool to support clinicians in outlining the ideal care process that the person with dementia should follow to receive adequate and appropriate care. Therefore, this tool is an evidence-based indication of the ideal care pathway that allows to identify a framework of reference on which to base the definition local care pathways.

Adaptation of the NICE Guideline

Considering the context and the purposes for which the NICE GL, the Well Pathway, and the other resources for implementation were developed, the aim of the Italian Guideline Woking Group (WG) was to update and adapt this document and its care pathway. The adaptation process was based on the indications provided by the SNLG-ISS MM.

[5] https://www.gov.uk/government/publications/prime-ministers-challenge-on-dementia-2020 (Last visited: 30/08/2023)
[6] https://www.england.nhs.uk/mental-health/dementia/ (Last visited: 30/08/2023)
[7] https://www.england.nhs.uk/mental-health/resources/dementia/ (Last visited: 30/08/2023)
[8] https://www.england.nhs.uk/mentalhealth/wp-content/uploads/sites/29/2016/03/dementia-well-pathway.pdf (Last visited: 30/08/2023)
[9] https://www.rcpsych.ac.uk/docs/default-source/improving-care/nccmh/dementia/nccmh-dementia-care-pathway-fullimplementation-guidance.pdf?sfvrsn=cdef189d_8 (Last visited: 30/08/2023)
[10] https://www.cheshire-epaige.nhs.uk/wp-content/uploads/2019/02/dementia-interactive-care-toolkit_280217_linked.pdf (Last visited: 30/08/2023)

Scope

The SNLG Strategic Committee, as mentioned, included dementia among the priority topics for developing a guideline. Due to the relevance of the topic, the Ministry of Health, as part of the activities of the Italian Fund for Alzheimer's and Other Dementias, entrusted the ISS to develop a guideline on the diagnosis and treatment of dementia, within the SNLG, based on the evolving evidence in the areas of pathophysiology and intervention available from scientific literature and national and international best practices.
Symptoms of dementia, which are the consequence of the severe impairment of cognitive functions, are characterized by a progressive disability that requires an extremely complex management. Moreover, people with cognitive deficits can often have a clinical condition characterized by multimorbidity, which is a relevan risk factor for disability and consequent by medical, psychiatric, social, ethical and medico-legal issues.

Local services are often organized heterogeneously across Regions, and sometimes even within the same Region, thus causing a wide variability in the quality and quantity of services for the diagnosis and treatment of dementia. A lack of integration and collaboration is often reported between CCDDs, hospitals and local services, general practitioners and integrated home care, which can affect the quality and continuity of care. The quality of available services is widely variable, with areas of excellence alongside areas that require specific interventions to improve care quality. Healthcare providers who are in charge for clinical governance (Ministry of Health, Regions and Autonomous Provinces, local authorities) are required, based on their different prerogatives and responsibilities, to:

- identify objectives and strategies;
- define governance and control structures;
- monitor and evaluate functioning;
- measure and assess the achievement of predefined goals;
- provide management systems aimed at constant improvement and capable of be activated in progress to enhance specific performances.

In Italy there are several initiatives dedicated to dementia. However, despite the efforts of Administrations, Associations and health and social care professionals, this condition is still managed in different moments and following different paths.
Based on the results from a study on people over 60 years (Sachdev 2015), the prevalence of MCI is estimated to be 5.9% in this age class. A stratified analysis according to age groups reported a prevalence of 4.5% in people aged 60 to 69 years, 5.8% in people aged 70 to 79 years, and 7.1% in people aged 80 to 89 years.
MCI is considered as a relevant risk factor for dementia and therefore a potential target for pharmacological and non-pharmacological treatments. However, the nature of this condition is still unclear, and several aspects remain to be explored. People with MCI were reported to have an annual rate of progression to dementia ranging from 5% to 15% depending on the setting and the diagnostic criteria applied.

Population

- People aged 40 years or older with dementia, MCI, or suspected cognitive impairment.
- Formal or informal caregivers (including family members) of people aged 40 years or older with dementia, MCI or with suspected cognitive impairment.
- Health and social care professionals involved in the management of people aged 40 years or older with dementia, MCI, or suspected cognitive impairment.

Groups

- People in inpatient hospital settings.
- People in long-term care facilities.
- People in residential care facilities.

- People with comorbidities (e.g., cardio-cerebrovascular diseases, diabetes).
- People with mental disorders.
- People aged 40 to 65 years with early-onset dementia.

Groups that will not be covered

- People aged < 40 years with dementia.

Setting

All settings.

Key areas that will be covered

- Identification, diagnosis, and differential diagnosis of MCI and dementia either in primary and non-specialist settings or in specialist settings, including the identification of potential causes (e.g., drugs).
- Models of organization of health and social care services care for the management and coordination of care for people with MCI and dementia and their caregivers, including involvement and support of people and their caregivers and staff training.
- Identification of the specific needs of people aged 40 to 65 with early-onset dementia.
- Pharmacological treatments (including new biological drugs and drug repositioning), rehabilitative, psychoeducational, cognitive, and psychosocial interventions for cognitive symptoms in people with MCI or dementia.
- Pharmacological, rehabilitative, psychoeducational, cognitive, and psychosocial interventions for non-cognitive symptoms in people with MCI or dementia.
- Management and treatment of co-existing physical conditions and mental disorders in people with MCI or dementia.
- Identification and treatment of intercurrent illnesses in people with MCI or dementia.
- Palliative or end-of-life care interventions in people with dementia.

Outcomes

- Incidence of accurately identified dementia or MCI and diagnostic accuracy measures.
- Resources use and costs.
- List of commonly prescribed drugs that may cause dementia or MCI.
- Change in prevalence of appropriate polypharmacy.
- Inappropriate discharge rates and inadequate care planning rates.
- Clinical outcomes (cognitive, behavioral, and functional).
- Change in/resolution of non-cognitive symptoms.
- Access to health and social care support.
- Experience, wellbeing, satisfaction, and health-related quality of life of people with dementia or MCI and their caregivers.
- Equity.
- Process outcomes (e.g., adherence of staff to care protocols).
- Potentially avoidable adverse events and effects.

- Pain reduction.
- Clinical progression of dementia or MCI.
- Clinical progression of comorbidities and associated symptoms.
- Hospital admissions and potentially avoidable hospital admissions.
- Malpractice.
- Adherence.
- Intervention related outcomes (concordance, compliance, and satisfaction) in people with dementia or MCI and their caregivers.
- Caregiver burden and stress.
- Over-prescribing and under-prescribing.
- Time to institutionalization.
- Frequency of accurately identified intercurrent illness in people with dementia.
- Staff wellbeing, job satisfaction, and skill levels.

Figures and professionals involved

Social workers, biologists, formal and informal caregivers and family representatives, dietitians, educators, physiotherapists, geriatricians, nurses, speech and language therapists, general practitioners, neurologists, neuropsychologists, social workers, psychiatrists, psychologists, mental health rehabilitation technicians, occupational therapists.

Target users of the Guideline

The target users of this Guideline are all health and social care professionals involved in caring for people with dementia or MCI in any setting. The recommendations included in the document are also meant to be used by all decision makers and managers of services that are responsible for the organization and management of care for people with dementia or MCI referring to different care settings.

References

Sachdev PS, Lipnicki DM, Kochan NA, et al. The Prevalence of Mild Cognitive Impairment in Diverse Geographical and Ethnocultural Regions: The COSMIC Collaboration. PLoS One. 2015; 10(11): e0142388. Published 2015 Nov 5.

Review questions

The Working Group, during the first Panel meeting, agreed to adapt and update 34 review questions from the NICE Guideline and to add 13 new review questions. The review questions were numbered from 1 to 24 with some classified as sub-questions, for a total of 47 review questions.

The review questions were categorised into five areas: Identification, diagnosis and post-diagnostic support; Care models and coordination of care; Pharmacological interventions for cognitive symptoms; Non-pharmacological interventions for cognitive symptoms; Non-cognitive symptoms, intercurrent illnesses and palliative care.

IDENTIFICATION, DIAGNOSIS AND POST-DIAGNOSTIC SUPPORT	
Q1	(NICE RQ) What are the most effective methods of case finding for people at high risk of dementia?
Q2a	(NICE RQ) What are the most effective methods of primary assessment to decide whether a person with suspected dementia should be referred to a dementia service?
Q2b	(New RQ) What are the most effective methods of primary assessment to decide whether a person with suspected cognitive deficit should be referred to a dementia service?
Q2c	(NICE RQ) What are the most effective methods of diagnosing dementia and dementia subtypes in specialist dementia diagnostic services?
Q2d	(New RQ) What are the most effective methods of diagnosing Mild cognitive impairment (MCI) in specialist dementia diagnostic services?
Q3a	(NICE RQ) What drugs that may worsen cognitive decline are commonly prescribed in people diagnosed with dementia?
Q3b	(NICE RQ) What are the most effective tools to identify drugs that may be causing cognitive decline?
Q4	(NICE RQ) What are the most effective methods of differentiating dementia or dementia with delirium from delirium alone?
Q5	(NICE RQ) How effective are pre-, peri- and post-diagnostic counselling and support on outcomes for people living with dementia and their caregivers?
Q6	(NICE RQ) What are the specific needs of younger people living with dementia?
CARE MODELS AND COORDINATION OF CARE	
Q7a	(NICE RQ) What are the most effective methods of care planning, focusing upon improving outcomes for people with dementia and their carers?
Q7b	(New RQ) What are the most effective methods of care planning, focusing upon improving outcomes for people with Mild cognitive impairment (MCI) and their carers?
Q7c	(NICE RQ) How should health and social care be coordinated for people living with dementia?
Q7d	(New RQ) How should health and social care be coordinated for people living with Mild cognitive impairment (MCI)?

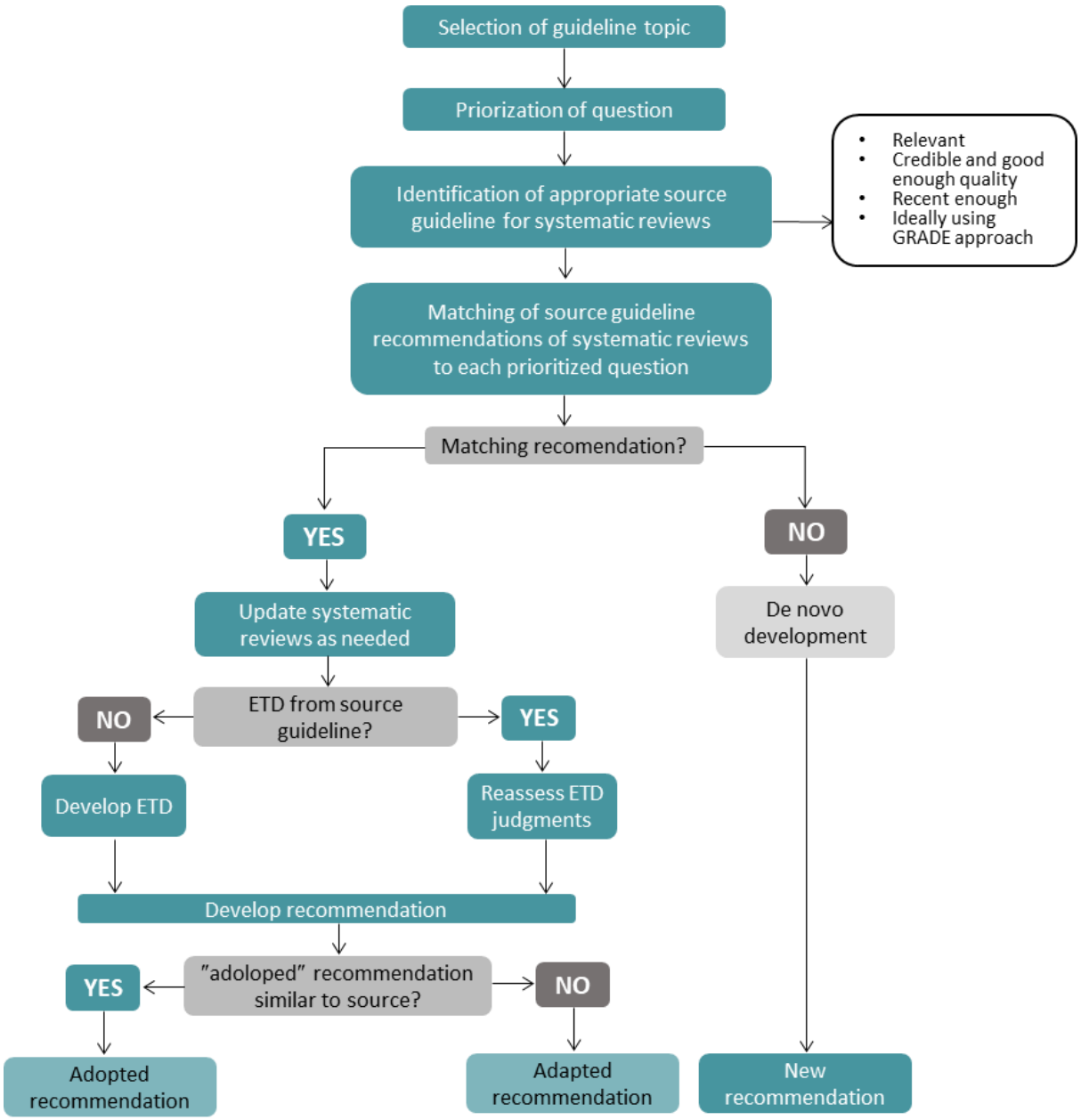
Q8a	(NICE RQ) How should people living with dementia be reviewed post diagnosis?
Q8b	(New RQ) How should people living with Mild cognitive impairment (MCI) be reviewed post diagnosis?
Q9	(NICE RQ) What effect does training for staff working with people living with dementia have upon the experiences of people living with dementia in their care?
Q10a	(NICE RQ) What barriers and facilitators have an impact on involving people living with dementia in decisions about their present and future care?
Q10b	(NICE RQ) What barriers and facilitators have an impact on how people living with dementia can make use of advance planning?
Q11a	(NICE RQ) What are the optimal management strategies (including treatments) for people living with dementia with co-existing physical long-term conditions?
Q11b	(New RQ) What are the optimal management strategies (including treatments) for people living with Mild cognitive impairment (MCI) with co-existing physical long-term conditions?
Q12a	(NICE RQ) What are the optimal management strategies (including treatments) for people with dementia and an enduring mental health condition?
Q12b	(New RQ) What are the optimal management strategies (including treatments) for people with Mild cognitive impairment (MCI) and an enduring mental health condition?
Q13	(NICE RQ) What are the most effective ways of managing the transition between different settings (home, care home, hospital, and respite) for people living with dementia?
Q14a	(NICE RQ) How effective are carers' assessments in identifying the needs of informal carers of people living with dementia?
Q14b	(New RQ) What interventions/services are most effective for supporting the wellbeing of informal carers of people living with dementia?
PHARMACOLOGICAL TREATMENTS FOR COGNITIVE SYMPTOMS	
Q15a	(New RQ) What is the safety and efficacy of acetylcholinesterase inhibitors and memantine for the treatment of cognitive symptoms in people with Alzheimer's dementia and how should they be monitored?
Q15b	(New RQ) What is the safety and efficacy of acetylcholinesterase inhibitors and memantine for the treatment of cognitive symptoms in people with Mild cognitive impairment (MCI) and how should they be monitored?
Q15c	(New RQ) What is the safety and efficacy of biological drugs (active and passive immunotherapy) for the treatment of cognitive symptoms in people with Alzheimer's dementia or Mild cognitive impairment (MCI) and how should they be monitored?
Q16a	(NICE RQ) What effect does modifying risk factors (repositioning drugs acting on possible etiological causes of dementia) have on slowing the progression of dementia?

Q16b	(New RQ) What effect does modifying risk factors (repositioning drugs acting on possible etiological causes of dementia) have on slowing the progression of Mild cognitive impairment (MCI)?
Q17a	(NICE RQ) How effective is the co-prescription of cholinesterase inhibitors and memantine for the treatment of Alzheimer's disease?
Q17b	(NICE RQ) When should treatment with donepezil, galantamine, rivastigmine, memantine be withdrawn for people with Alzheimer's disease?
Q18a	(NICE RQ) What is the comparative effectiveness of donepezil, galantamine, memantine and rivastigmine for cognitive enhancement in dementia associated with Parkinson's disease?
Q18b	(NICE RQ) What is the comparative effectiveness of donepezil, galantamine, memantine and rivastigmine for cognitive enhancement in dementia with Lewy bodies?
Q19	(NICE RQ) How effective are cholinesterase inhibitors and memantine for types of dementia other than typical Alzheimer's disease?
NON-PHARMACOLOGICAL INTERVENTIONS FOR COGNITIVE SYMPTOMS	
Q20a	(NICE RQ) What are the most effective non-pharmacological interventions for supporting cognitive functioning in people living with dementia?
Q20b	(NICE RQ) What are the most effective non-pharmacological interventions for supporting functional ability in people living with dementia?
Q20c	(NICE RQ) What are the most effective non-pharmacological interventions to support wellbeing in people living with dementia?
Q20d	(NICE RQ) What are the most effective methods of supporting people living with dementia to reduce harm and stay independent?
Q20e	(New RQ) What are the most effective non-pharmacological interventions for supporting cognitive functioning, functional ability and wellbeing in people with Mild Cognitive Impairment?
NON-COGNITIVE SYMPTOMS, INTERCURRENT ILLNESSES AND PALLIATIVE CARE	
Q21a	(NICE RQ) What are the most effective pharmacological interventions for managing illness emergent non-cognitive symptoms, such as psychosis, depression, behavioral changes in people living with dementia?
Q21b	(NICE RQ) What are the most effective non-pharmacological interventions for managing illness emergent non-cognitive symptoms, such as psychosis, depression, behavioral changes in people living with dementia?
Q22a	(NICE RQ) 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?
Q22b	(NICE RQ) 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?
Q23	(NICE RQ) How should people living with dementia be cared for when admitted to hospital?

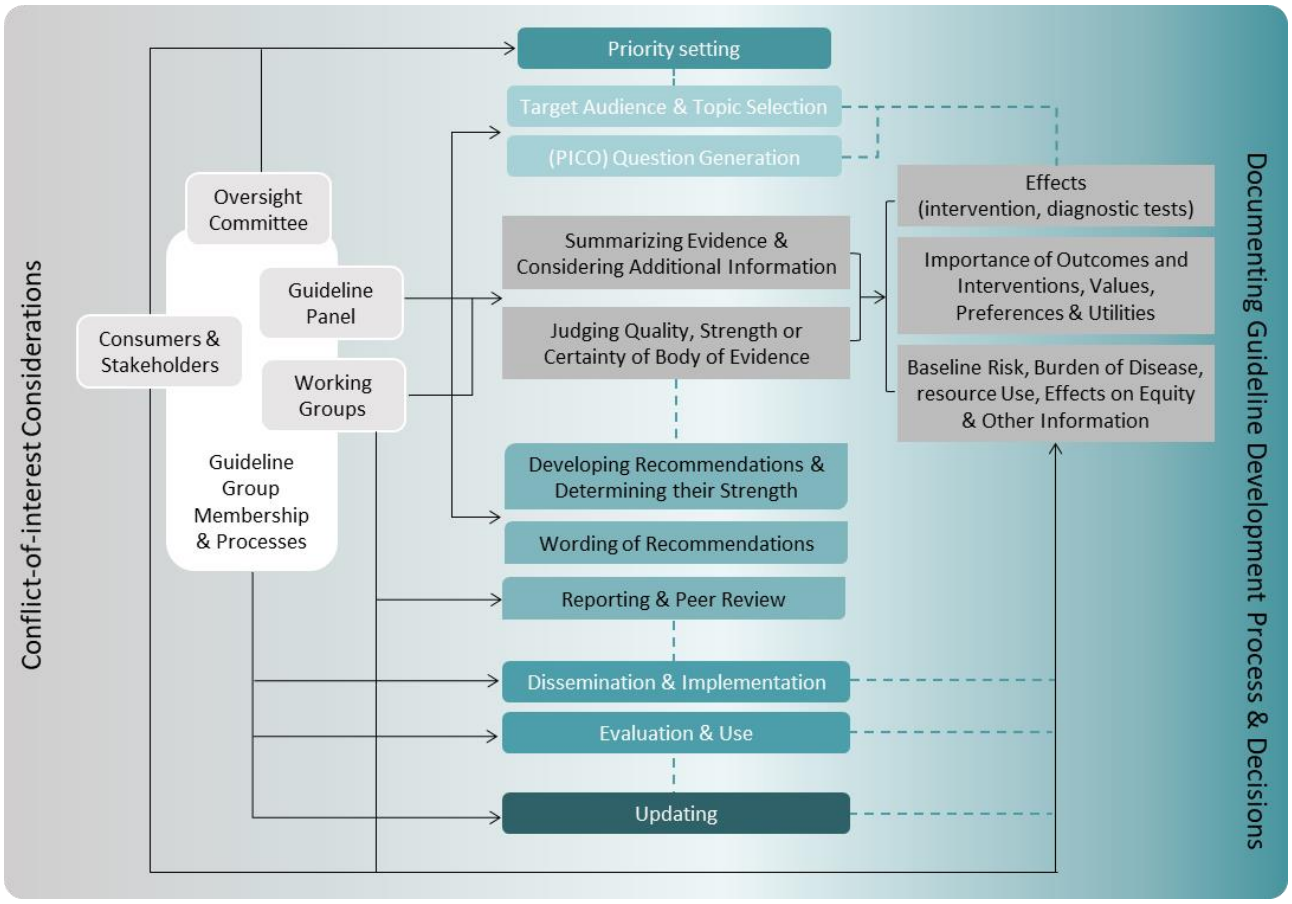
Q24	(NICE RQ) What models of palliative care are effective for people with dementia?

Methods

The adaptation and development of the guideline followed the SNLG-ISS Methodological Manual (MM SNLG-ISS) and was based on the following scheme:



The guideline development process was based on the GRADE-ADOLOPMENT (G-A) methodology defined by Schünemann (2017) for adopting, adapting or developing *ex novo* clinical recommendations.
The following diagram graphically summarises the developing process of a GL according to the GRADE methodology (GRADE 2013)[11] and the SNLG-ISS MM (CNEC 2023)[12].



[11] GRADE. Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. Updated October 2013. https://gdt.gradepro.org/app/handbook/handbook.html (Last access on August 30, 2023).
[12] CNEC. Manuale metodologico per la produzione di linee guida di pratica clinica. v. 1.3.3 marzo 2023. Available at: https://www.iss.it/documents/20126/7949265/Manuale+Metodologico+-+marzo+2023.pdf/01f4bc8e-f3e6-66ec-bbe1- e80186908c6c?t=1679921943422 (Last access on August 30, 2023).

Schedule of the activities

ACTIVITY	DATE/PERIOD
Designation of Guideline Committee, Chair and Methodological Co-Chair	January 15, 2022
Call for participants to establish the Multidisciplinary Panel	March 8, 2022
Consultation workshop with Scientific Societies on the draft scope	March 17, 2022
Establishment of the Multidisciplinary Panel	April 22, 2022
First meeting of the WG	May 5, 2022
Second meeting of the WG and definition of the review questions	May 11, 2022
Stakeholder consultation on the draft scope	May 27, 2022
Third meeting of the WG	October 27, 2022
Fourth meeting of the WG	December 2, 2022
Fifth meeting of the WG	February 28, 2023
Sixth meeting of the WG	April 20, 2023
Seventh meeting of the WG	May 29, 2023
Eighth meeting of the WG	June 26, 2023
Ninth meeting of the WG	July 5, 023
Last meeting of the WG	September 18, 2023
Stakeholder consultation on the draft guideline	October 6 – November 7, 2023
External review of the draft guideline	October 18 –November 7, 2023
Publication of the final draft of the Guideline	December 7, 2023

WG: Working Group

The Guideline Working Group

Guideline Committee (GC): The role of the GC included defining the roles of each member of the WG, selecting the panel members, stakeholders and patient representatives, by coordinating all activities, ensuring their transparency and traceability at any stage.

Multidisciplinary Panel: Each panel member was nominated following a public call. The applications were evaluated by the Committee, which then constituted the multidisciplinary Panel. Panel membersparticipated in the GL activities as individuals and not as representatives of specific organisations, associations or scientific societies. Panel members were involved in all stages of GL development from the definition of the scope and objectives to the formulation of each recommendation. Moreover, panel members contributed to the drafting of the final document. Among panel members, representatives of family members/caregivers were also included to ensure their views, perspectives, preferences and experiences are taken into consideration, along with those of people with dementia/MCI.

Methodological Chiar and Co-Chair: Chair and Co-Chair both took part in sharing the scope, objectives and questions of the GL. They also participated in the systematic review of the literature and definition of the recommendations, ensuring the involvement of all panel members in all the stages of the GL development.

Developers: They coordinated all the activities required to develop the GL, ensuring the continuity of the work, the uniform and standardised application of the GRADE methodology, and the transparency and traceability of all activities.

Evidence Review Team (ERT): The ERT included clinical experts and methodologists who assessed, summarized and presented to the Multidisciplinary Panel results from the systematic reviews performed for each question.

Team for the economic analysis and team of bioethicists: These teams had an essential role in analysing all the economic aspects and ethical implications deriving from the summary and interpretation of the results from the systematic literature review, and in the definition of recommendations.

Documentalists: This team includes staff from the Scientific Communication Service of the ISS with specific expertise in defining search strategies on biomedical databases. They:

- collaborate with the ERT in defining the protocols of the systematic literature reviews;
- search databases and export the reference lists to be submitted to the ERT;
- participate in defining the PICOs for each review questions;
- do not participate in voting recommendations.

External methodological groups can also be involved from collaborating entities selected by the General Directorate of the ISS through public procedures.

Quality Assurance Team: The team includes the Director and research staff of the National Centre for Clinical excellence, healthcare quality and safety (Centro nazionale per l'eccellenza clinica, qualità e sicurezza delle cure, CNEC) of the ISS. It guarantees that the development process of the GL meets the methodological standards adopted by CNEC. Specifically, the team participates in defining the scope, ensures that the evidence review and the economic evaluations are updated, reliable, robust, and relevant, and verifies that the connection between evidence and recommendations is valid. The Director of CNEC signs the preliminary and final drafts of both the scope and the GL.

To ensure the transparency and integrity of professional judgment, the SNLG-ISS MH requires all participants at any title in the development or assessment of the ISS GL to declare any circumstances where a secondary interest interferes or may interfere with their impartial participation in the WG. Therefore, each member of the WG, declared, using a standardised module, any financial, professional or other type of interest relevant to the topic of the GL, which could affect the impartiality of their judgment. The statement included all current or planned commercial, non-commercial, economic, intellectual, and institutional activities related to the potential scope of the GL. The presence of potential conflicts of interest related to the GL topic was assessed by the Guideline Committee (GC). In case of potential or significant conflict, based on the SNLG-ISS MH, these were managed as follows: a) partial exclusion from specific activities (e.g., exclusion from the parts of meetings or activities that were related to the declared interest, and from their decision-making processes); b) exclusion (exclusion from all meetings and the entire process).

All Conflict of Interest (CoI) forms are available as supplementary material to the GL on the SNLG-ISS website.

The Guideline development

Literature search and selection strategies

The literature searches were carried out hierarchically, including all studies already identified by the NICE GL and using the same search strategies to search for new literature starting from the date of their last update. The update of the systematic reviews was carried out using the Cochrane Library Databases, PubMed, and Embase. The update of the SR for the questions adapted from the NICE GL was performed using search strategies from the NICE GL, while new search strategies were defined for the new questions using the NICE strategies as a basis for uniformity. Only studies published in English or Italian in peer-*reviewed* journals were selected.

Search strategies generated a list of records for each question. From each list, only articles that were pertinent and relevant to the topic of the question were selected. Selected articles were retrieved in full text and were applied the predefined inclusion and exclusion criteria. For each included study qualitative assessment, data extraction, and summary of the results was performed according to the GRADE methodology.

For each question, only studies with the most appropriate design were selected. Specifically, only experimental studies with a placebo or usual care control group were selected for questions investigating the efficacy and safety of interventions, while studies comparing two experimental interventions were not selected as they do not allow to assess the absolute effect of each individual intervention. Similarly, studies investigating the effect of combinations of two or more interventions were not included (unles they also included other arms where participants were allocated to the individual interventions separately) as this design does not allow to assess the effect of each individual interventions and therefore the added value of combining the investigated interventions. For questions investigating the utility and accuracy of diagnostic tests, only cohort/cross-sectional studies were selected reporting data on sensitivity, specificity and positive and negative predictive values. The need for the studies to report enough data to calculate the sensitivity, specificity and predictive values was based on the GRADE methodology, which requires assessing for the implementability of results, thus assessing the appropriateness of implementing a test in a specific clinical context. Sensitivity and specificity allow to assess the intrinsic accuracy of the test, therefore the discriminatory ability of the index test, while predictive values allow to assess the performance of the index test in the setting in which it is ment to be applied, as they depend on the prevalence of the condition in the considered sample. Hence the need to exclude diagnostic case-control studies as they are based on prevalences that, due to the nature of the study design, are fictitious and not representative of clinical practice, and therefore do not allow to assess the performance and utility of the test in clinical practice. This information is essential in a GL to determine the utility and cost/utility profile of each test in order to provide public health recommendations. Qualitative studies were selected for questions specifically investigating the experiences and preferences of people with dementia, caregivers and/or healthcare professionals.

All interim documents are available as supplementary materials on the SNLG-ISS website.

Outcomes rated as important/relevant

According to the GRADE methodology, evidence from included studies was analysed based on the list of outcomes considered as relevant by the multidisciplinary panel. The list of outcomes to be considered for each question was defined based on the list of outcomes included in the NICE GL, and was discussed and approved by the multidisciplinary panel. For uniformity, the lists of outcomes considered as relevant for the new questions were also defined based the outcomes included in the NICE GL, and were then discussed and approved by the multidisciplinary panel.

Each outcome was assigned a score using a nine-point scale, and based on the median score, it was assigned to one of the three categories reported in Table 1.

Table 1. Importance categories for rating outcomes

Score	Importance
7, 8, 9	Critical
4, 5, 6	Important, but not critical
1, 2, 3	Limited importance

Quality of evidence

Based on the GRADE methodology, recommendations were formulated taking into account the overall certainty of the body of evidence supporting each question. The full texts of included studies were retrieved and submitted to the *Evidence Review Team* for data extraction and quality assessment.

For each question, quality assessment and data extraction were performed taking into account available evidence for each outcome, considering that the intrinsic quality of a study may vary depending on the outcome considered (see Table 2). After quality assessment and data extraction, structured tables were produced summarising available evidence for each outcome considered for each question of the GL (*Summary of Findings*, SoF). All quantitative and qualitative SoF tables were produced using the GRADE Pro3 tool and are available as supplementary material on the SNLG-ISS website.

Table 2. Quality of evidence according to GRADE

Grade	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

QUANTITATIVE EVIDENCE

The GRADE approach to the overall assessment of the certainty of evidence starts by defining the study design: experimental (*Randomised Controlled Trial*, RCT), which is the gold standard; observational, which is considered as having intrinsic methodological limitations.

On this basis, systematic reviews of RCTs are rated as having a high baseline level of certainty, whereas systematic reviews of observational studies are rated as having a low baseline level of certainty due to the inherent challenges of this study design in controlling especially selection bias and confounding factors.

The following steps of the assessment of certainty of evidence include considering seven factors. The first four factors can lead to lowering the level of certainty of the evidence supporting the recommendations.

Risk of bias. Possible limitations in the design, execution, and analyses of the study assessed by using the following methodological quality checklists specific for each study design: Revised Tool for Quality Assessment for Diagnostic Accuracy Studies II (QUADAS II) (Whiting 2011) for diagnostic studies, and the *Cochrane Collaboration's tool for assessing risk of bias in randomised trials* (RoB) (Higgins 2011) for experimental studies.

Inconsistency. Unexplained heterogeneity in the estimates reported by included studies. This can be caused by differences in the populations, interventions, outcomes, or methodologies used and may affect the reliability of results.

Indirectness. Results from the studies included by the systematic literature review cannot be generalised to the target context of the guideline. Problems in generalizability of results can be due to differences in the adopted populations, interventions, outcome measures, or comparisons.

Imprecision. The lack of reproducibility of results from included studies. Studies with small sample sizes or observing a limited number of events can be imprecise, providing estimates with wide confidence intervals (CIs), thus leading to uncertainty on the reproducibility of their results.

The remaining three factors, specifically a **large magnitude of an effect**, the presence of a **dose-response gradient**, and the potential effect of plausible **residual confounders** that may have led to an underestimation of the effect, may increase the certainty of evidence, especially in case of observational studies.

For the overall assessment of the evidence supporting each recommendation, the following model was used:

Risk of bias	High / Moderate / Low
Inconsistency	High / Moderate / Low
Indirectness	High / Moderate / Low
Imprecision	High / Moderate / Low
Magnitude of Effect	Large / Moderate / Small
Dose-response gradient	Present / Absent / Not applicable
Effect of plausible residual confounding	Present / Absent / Not applicable

The evidence supporting each outcome considered for each question is the basis of the discussion leading to formulating and *grading* recommendations.

The definition of the strength of a recommendation, being based on elements such as the certainty of evidence and the risk-benefit profile, reflects a *continuum.* The overall assessment of the certainty of evidence is not the sum of the certainty of each included study but reflects both the methodological quality of each study and the role and weight that each study has in determining the overall effect size. Some arbitrariness will thus be associated with assigning each recommendation its strength. However, the simplicity and transparency of this process outweigh these limitations.

QUALITATIVE EVIDENCE

The quality of qualitative studies was assessed using the CASP (Critical Appraisal Skills Programme) checklist for qualitative studies[13]. The checklist includes 10 items categorised into three sections identified by the following questions: «are the results of the study valid?", "what are the results?" and "will the results help locally". Based on the ratings expressed for each item, each individual study was classified as at low, moderate or high risk of bias.

Where multiple qualitative studies were identified for a single question, results from the studies were combined using a thematic analysis. By examining the results from each included study, descriptive themes were independently identified and coded. After reviewing and codeing all studies, the resulting themes and sub-themes were assessed 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. Identified themes and sub-themes were compared and possibly integrated to those identified by the NICE GL. The qualitative synthesis then proceeded by using these "descriptive themes" to develop "analytical themes," which were interpreted considering the overarching questions.

The CERQual method (Confidence in the Evidence from Reviews of Qualitative research) was used to assess the confidence in the findings of each of the identified themes, therefore, to assess the extent to which a finding is a reasonable representation of the phenomenon of interest (Lewin 2018). The CERQual includes four components: methodological limitations, relevance, coherence and adequacy of data (see Table 3). Based on the judgment expressed for each component, the overall level of certainty was scored as high, moderate, low or very low.

Qualitative evidence was initially rated as having a high level of certainty, and the level of certainty for each theme was then downgraded based on the criteria reported in Table 4.

Table 3. CERQual components

Component	Definition
Methodological limitations	The extent to which there are problems in the design or conduct of the primary studies that contributed evidence to a review finding.
Relevance	The extent to which the body of evidence from the primary studies supporting a review finding is applicable to the context (perspective or population, phenomenon of interest, setting) specified in the review question.
Coherence	The extent to which the review finding is well grounded in data from the contributing primary studies and provides a convincing explanation for the patterns found in these data
Adequacy of data	An overall determination of the degree of richness and quantity of data supporting a review finding

[13] CASP qualitative checklist, https://casp-uk.net/casp-tools-checklists/ (Last visited: 30/08/2023)

Table 4. Rationale for downgrading confidence in evidence for qualitative questions

Component	Reason
Methodological limitations	**Not serious**: If the theme was identified in studies at low risk of bias, the outcome was not downgraded **Serious:** If the theme was identified only in studies at moderate or high risk of bias, the outcome was downgraded one level. **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 **Moderate**: If the theme was identified only in relevant and partially relevant studies, the outcome was downgraded one level. **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: • **Between study** – does the theme consistently emerge from all relevant studies • **Theoretical** – does the theme provide a convincing theoretical explanation for the patterns found in the data 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.

From evidence to recommendations

According to the definition provided by GRADE, the strength of a recommendation reflects extent to which the GW is confident that the desirable effects of an intervention outweigh undesirable effects.
The recommendations provided in this document are classified as strong or weak and in favour or against an intervention. Certainty of evidence was considered as a relevant element in determining the strength of the recommendation. However, it was not the only considered element. Considerations on clinical and contextual aspects, such as challenges that are intrinsic to the question, low costs, absence of risks, higher acceptability and accessibility sometimes allowed to grade some recommendations as strong even when supported by evidence with a low level of certainty.
In some cases, research recommendations were produced to support the production of new evidence in specific areas considered as promising but for which available evidence is still limited.

Strong recommendations: Most the involved people would benefit from the recommended course of action. The benefits are clearly hiher than the risks.

Weak recommendations: Not all the involved people would benefit from the recommended course of action, people's circumstances, values, and preferences should be carefully considered to identify the best balance between risks and benefits.

Recommendations were graded as strong only when relevant evidence consistently supports a clear balance towards either the desirable effects of an intervention (to recommend an action) or undesirable effects (to recommend against an action).

Recommendations were graded as weak, based on the precautionary principle, when the balance between desirable and undesirable effects was unclear (in terms of both the magnitude of the effect and the certainty of evidence), or in case evidence suggested that desirable effects were higher only in a specific subgroup of people, or in case of limitations were present in terms of feasibility, acceptability, equity, use of resources.

According to the GRADE methodology[11], recommendations were graded based on the following elements:

1. balance between desirable and undesirable outcomes (trade-off) taking into account the best estimates of the magnitude of effects on desirable and undesirable outcomes, and the importance of outcomes (estimated typical values and preferences);
2. confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes);
3. confidence in values and preferences and their variability;
4. feasibility, acceptability, equity, resources use.

The above-mentioned elements were analysed according to the Evidence to decision (EtD) framework (see Table 5).

A first draft of the recommendations was defined by the WG and was presented and discussed with the multidisciplinary Panel until agreeing on a final version that was voted only by panel members. Any disagreements were noted and reported in the analysis of evidence.

Research recommendations were formulated, using the same procedure as for clinical practice recommendations, in case of topics considered by the WG as relevant but supported by insufficient or limited evidence suggesting a possible positive effect (strong rational, preliminary data of important desirable effect).

The EtD tables were produced using the GRADE Pro[14] tool e they are available as supplementary material on the SNLG-ISS website.

Table 5. Evidence to decision framework[11]

	Criteria
Problem	Is the problem a priority?
Benefits & harms	• What is the overall certainty of the evidence of effectiveness? • Is there important uncertainty about how much people value the main outcomes? • How substantial are the desirable anticipated effects? • How substantial are the undesirable anticipated effects? • Do the desirable effects outweigh the undesirable effects?
Equity	What would be the impact on health iniquities?
Acceptability	Is the option acceptable to key stakeholders?
Feasibility	Is the option feasible to implement?
Resource use	• How large are the resource requirements? • How large is the incremental cost relative to the net benefit?

[14] GRADE Pro: https://www.gradepro.org/ (Last visited: 08/30/2023)

Consultation with stakeholders and peer review

The final draft of the Guideline was uploaded on the SNLG-ISS website and made available for one month for consultation with the stakeholders[15]. All received observations and comments were collected and considered by the WG for inclusion in the document. Both the comments received from the stakeholders and the responses from the WG are reported as supplementary material on the SNLG-ISS website.

The final draft of the document was then submitted for peer review by two independent external reviewers who assessed both the contents of the GL and its methodology. The comments received from the reviewrs and responses from the WG are available as supplementary material on the SNLG-ISS website.

Guideline update and dissemination

Based on the constant evolution of biomedical knowledge, the document is scheduled to be updated within three years (January 2027).
Several dissemination strategies will be adopted, including the following approaches:

- disseminating the initiative through media and press;
- shipment to reference centres;
- publication on the SNLG-ISS website and on the websites of scientific societies, health and social care entities, etc.;
- scientific publications;
- presentations at national and international conferences.

Implementation resources

Care pathway

Considering the relevance of providing guidance for the management of people with dementia, the WG, throughout the entire development process of the GL, specifically focused on the adaptability of the recommendations to the clinical conrtext and to their feasibility in clinical practice. As mentioned, the GL also aimed at producing a care pathway based on the Well Pathway available in the UK. The care pathway was developed as a tool to facilitate the dissemination and implementation of the recommendations included in the GL and is available as supplementary material on the SNLG-ISS website.

The care pathway is a visual representation, in the form of a pathway, of the recommendations included in the GL aimed at facilitating their interpretation and implementation. The objective of a care pathway is to provide a method to organise the care process of a defined group of people over a defined period of time.

Based on the definition provided by the European Pathway Association (EPA)[16] the development of the care pathway included all the key elements considered as useful in providing evidence-based medicine (EBM), while taking into consideration the values and preferences of people and their family members/caregivers, potentially useful elements facilitating the communication between health professionals and people and their caregivers, and the coordination of the diagnostic and care process by defining roles and sequences of activities and the resources that are needed and appropriate to carry out each step.

Indicators

One of the specific objectives of the Italian Fund for Alzheimer's and Other Dementias was to carry out three national surveys in the main services dedicated to people with dementia and cognitive disorders (Centers for Cognitive Disorders and Dementias - CCDDs, Nursing Homes, Daycare Centers) in order to map and monitor

[15] https://www.iss.it/snlg (Last visited: 30/08/2023)
[16] http://e-p-a.org/care-pathways/ (Last visited 30/08/2023)

the levels of care coordination and management in Italy. Moreover, as part of the activities for this guideline, we analysed data on drugs prescriptions using the OSMED information system and performed a health economics evaluation using available national information systems. These activities were considered as the basis to define the outcome indicators to measure the impact of the implementation of the recommendations included in the GL.

The identified indicators will be monitored through available information systems and by updating the surveys carried out as part of the activities of the Italian Fund for Alzheimer's and Other Dementias. As for the initial diagnostic assessment, a proposed indicator is the increase in the proportion of people with a confirmed diagnosis who underwent a complete neuropsychological assessment. A further indicator is the increase in the opening hours and days of healthcare facilities and the increase in the proportion of facilities offering services such as promoting legal entities, supporting legal and protection policies and procedures, and providing contacts with family associations and charities.

As for access to non-pharmacological interventions and multidisciplinary care, proposed indicators are the increase in the proportion of people with confirmed diagnosis and their caregivers who received psychosocial, psychoeducational and rehabilitative interventions, and the increase in the proportion of facilities offering specific treatments, interventions, and services (e.g., counselling, information, remote monitoring) either directly or within the public health care system.

As for pharmacological treatments, a proposed indicator is a decrease in the proportion of people with a diagnosis of dementia who received one or more prescriptions of drugs with medium to high anticholinergic burden. When considering specific drugs for the treatment of non-cognitive symptoms, the proposed indicators are a decrease in the proportion of people with a confirmed diagnosis who received a prescription for psychotropic medication, and an increase in the proportion of people with a prescription for antipsychotics receiving a medication review every four weeks.

As for hospitalization, a proposed indicator is the decrease in the mean length of stay in people with a diagnosis of dementia.

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IDENTIFICATION, DIAGNOSIS AND POST-DIAGNOSTIC SUPPORT

Introduction

High-income countries are witnessing a progressive ageing of their population linked to an increase in average lifespan, due to both the increasing number of advanced and targeted treatments and awareness of the importance of prevention, and to the decreasing birth rate. Lower-income countries are also estimated to witness a similar trend in the future.

Epidemiological estimates report an exponential increase in conditions related to ageing, among which dementia is the most challenging in terms of diagnosis, treatment, and care.

The management of dementia is a complex challenge since diagnosis. People with dementia to access care and support need to receive a diagnosis.

A timely, accurate, and specific diagnosis allows planning targeted interventions and appropriate care and support paths, involving people with dementia and their family members/caregivers in all phases of the disease.

Dementia can be due to different clinical conditions, which are classified into different nosological entities based on specific diagnostic criteria. A common feature to all different dementia subtypes is the progressive decline of cognitive functions associated with a variety of psychobehavioral disorders. The progressive decline in cognitive functions can affect to various extents different domains such as memory, attention, visuospatial functions, executive functions, and language.

Dementia progressively interferes with a person's ability to critically thinking and judging, preventing them to perform the most common activities of their daily life, with a gradual loss of autonomy in all functions, even the simplest ones. Dementia involves not only people who have it but also their family members, affecting their emotional connections and social relationships. Those who directly care for people with dementia, as well as healthcare professionals, are the ones experiencing the greatest burden throughout all the phases of the disease.

In recent years, the scientific community has placed great emphasis on the search for biomarkers that could allow for an early diagnosis of dementia, with the even more relevant objective of starting timely pharmacological treatments, which, when available, could modify the natural history of the disease. However, the actual impact of case-finding strategies, defined as active strategies to assess people at risk of developing the disease, on the health of people with dementia and their caregivers is still unclear.

The opportunity of a timely identification of cognitive decline linked to dementia, emphasized in recent years by the scientific community, requires the involvement of primary care as a first step of the diagnostic process. General practitioners (GP) are the first contact with people reporting cognitive and behavioural changes and their family members. Family and medical history, clinical interview, and some initial diagnostic tests can guide the GP in defining the initial suspect of dementia. This approach allows them to differentiate potential primary forms of dementia to be referred to specialist centres for cognitive disorders and dementia (CDCD) from conditions affecting cognitive functions and could be potentially reversible causes of cognitive decline. These secondary conditions, including normal-pressure hydrocephalus, medical conditions, toxic-metabolic disorders, brain tumors, and subdural hematoma, require different, appropriate settings and specialized diagnosis, treatment, and care. Specialist assessment is also needed for diagnosing cases where the neurocognitive disorder is associated with previous encephalitis, limbic encephalitis and other immune-mediated conditions, and paraneoplastic encephalitis. These conditions are characterized by a peculiar clinical onset of the associated cognitive disorder, generally subacute, associated with epileptic seizures. Moreover, people with dementia have a significantly higher risk of delirium and many older people with delirium have undiagnosed dementia. However, some older adults with delirium can fully recover from this

condition. Distinguishing isolated delirium, from dementia and delirium superimposed on dementia is essential, especially in cases of acute hospitalisations, where a correct diagnosis can affect decisions about treatments and post-discharge treatment plans.
Considering the available time in the different healthcare settings, it is necessary to identify tests combining diagnostic accuracy with short administration times that could be useful in primary care.
Detecting a suspect of dementia in a primary care setting allows for quickly referring to the subsequent, more complex diagnostic process within the CDCD aimed at confirming the diagnositc suspect and defining a differential diagnosis of the dementia subtype, which is essential for timely planning targeted interventions.
The diagnosis of primary dementia is currently essentially clinical, based on confirming the cognitive deficit identified by targeted neuropsychological tests, and it is guided by specific diagnostic criteria developed by Consensus and Working Groups.
In these contexts, diagnostic criteria for dementia and criteria supporting the identification of a condition defined as mild cognitive impairment (MCI) have been developed. MCI is characterized by mild involvement of one or more cognitive domains (attention, executive functions, learning and memory, language, perceptual and motor skills, and social cognition). The identification of MCI is based on 1) complaints from the patient, a reliable informant, or a clinician; 2) clear deficits of cognitive performance resulting from a standardized neuropsychological assessment.
The reported deficit should not exclusively occur in the context of delirium and should not be attributable to other mental disorders (e.g., major depressive disorder or schizophrenia).
The condition of MCI was not considered in the first criteria for diagnosis of *Alzheimer's disease* (AD) defined by the *National Institute of Neurological and Communicative Disorders and Stroke* (NINCDS) and *Alzheimer's Disease and Related Disorders Association* (ADRDA) *Workgroup* in 1984. It was initially described by Petersen (Petersen 1997) and by Winblad (Winblad 2004) and then defined in the diagnostic criteria of the *National Institute on Aging* (NIA) *Workgroup* in the 2011 revision. This initial definition of MCI specifies that the mild cognitive deficit is not associated with significant consequences on social relations and the autonomy of people, who, however, may take longer that before to perform tasks, be less efficient, and make more mistakes (Albert 2011).
Despite independence in functional abilities being preserved in people with MCI, they may show subtle deficits in instrumental activities of daily living (IADL) (Petersen 1999, Petersen 2004, Petersen 2018, Winblad 2004). A growing number of studies show that the IADLs that require a higher cognitive load and higher functional performance are the most affected. People with MCI and a deficit in IADLs appear to have a higher risk of converting to dementia than patients with MCI with no deficit in IADLs (Jekel 2015).
The estimated prevalence of MCI is 6.7% in people aged 60 to 64 years, 8.4% in people aged 65 to 69 ayears, 10.1% in people aged 70 to 74 years, 14.8% in people aged 75 to 79 years, and 25.2% in people aged 80 to 84 years (Petersen 2018).
It is important to note that people with MCI does not necessarily convert to dementia. People with MCI may remain stable, show a regression of symptoms and return to normal cognition, or may progress to dementia. The regression of subjects with MCI to normal cognition is estimated, in several case studies, to range from 14.4% to 55.6% (Canevelli, 2016; Petersen, 2018). However, these cases still have an increased risk to develop MCI again or to convert to dementia compared to people who never received a diagnosis of MCI (range 55% to 65%). Up to 37% of people with amnestic MCI (aMCI) (Perri 2007) remain stable with no progressive decline to dementia.
People with MCI have a higher risk of progressing to dementia compared to age-matched people without MCI. The cumulative incidence of dementia in people with MCI aged > 65 years in the two years following diagnosis is 14.9%. The relative risk (RR) of developing any type of dementia in people with MCI compared to age-matched people without MCI is 3.3, and the risk of developing AD is 3.0 (Petersen 2018).
Since 1980, several studies have analyzed the condition of subjective cognitive decline and its relationship with the subsequent risk of developing a measurable cognitive decline. In 2014, an international working

group defined as Subjective Cognitive Decline (SCD) or Subjective Cognitive Impairment (SCI) a condition where people report experiencing a cognitive disorder, such as difficulties with reasoning, memory, and attention, which does not interfere with their autonomy and is not clinically detectable (Jessen 2014).
The first clinical criteria for the diagnosis of AD defined by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and Alzheimer's Disease and Related Disorders Association (ADRDA) Workgroup 1984 (McKhann 1984) were largely based on the exclusion of other conditions that can cause dementia. These criteria defined AD as «an acquired and progressive cognitive, behavioral, and functional deterioration, in the absence of other obvious causes, in 2 or more cognitive functions» (Frisoni 2011). These criteria did not mention the degenerative etiology of AD, and no specific diagnostic criteria were available for other relevant forms of degenerative dementia, such as Dementia with Lewy Bodies (DLB), frontotemporal dementia (FTD), and subcortical vascular dementia, which were defined later.
The NINCDS-ADRDA criteria for diagnosing AD were updated in 2011 (*National Institute on Aging and Alzheimer's Association* criteria, NIA-AA) (Albert 2011, McKhann 2011, Sperling 2011), based on the growing knowledge on the pathophysiology and the relationship between molecular pathology and time to the onset of clinical symptoms. Four international workgroups defined the different phases of AD, agreeing on a semantic and conceptual distinction between the pathophysiological processes of AD (AD-P) and the various clinically observable syndromes resulting from it (AD-C). In particular, a distinction was made between syndromic definitions that define different qualitative and quantitative clinical expressions of the disease and the pathophysiology underlying them. In this context, the NIA workigroup examined, for the first time, evidence on biomarkers, epidemiology and neuropsychological aspects the could be the best predictors of the risk of converting from 'normal' cognition to MCI and dementia, thus defining the preclinical stages of the pathology. A three-level classification of AD was proposed: the first two levels intended for clinical use; the third level, defining 'probable AD' or 'possible AD' based on pathophysiological evidence, limited to research purposes (Sperling 2011).
It should be noted that the NIA developed two different sets of consensus criteria: 1) the core clinical criteria, which can be used in all specialist clinical and care settings and can be applied with no need for advanced tests and/or procedures; 2) the clinical research criteria, which can be used in academic and research settings, including clinical trials (eligibility criteria in clinical trials to reduce heterogeneity among enrolled participants, identifying people at higher risk of endpoint and having a higher probability of being responders). Therefore, the use of biomarkers is considered for research purposes, including the use of advanced diagnostic imaging techniques and measuring specific parameters through cerebrospinal fluid (CSF) tests. These recommendations, as specified in the document, are intended exclusively for research purposes and aim to allow for earlier interventions in a preclinical/prodromal phase of the disease, where any potentially disease-modifying treatment may be more effective. The document also underlines how a significant amount of work is required to validate biomarkers and the criteria adopting them before their use can be considered in clinical practice. This work is currently underway and has not yet been completed for any of the investigated biomarker. Therefore, the condition that the the NIA workgroup defines as MCI due to AD cannot currently be diagnosed through a laboratory test. MCI is a syndrome defined by clinical, cognitive, and functional criteria and requires, for its definition, the judgment of a specialist.
In 2018, NIA defined a Research Framework specifically for research purposes. Within this framework, AD is defined based on the underlying pathological processes that can be documented by post-mortem examination or in vivo by biomarkers and not according to the clinical consequences of the pathology (symptoms/signs) (Jack 2018). This changes the definition of AD in living people from a syndromic construct to a biological construct.
In 2007, the International Working Group (IWG) also proposed a review of the NIA and DSM IV criteria by proposing new criteria specifically for research purposes. These criteria were further reviewed in 2010, 2014 and 2021, highlighting the possible role of biomarkers in increasing diagnostic accuracy and defining AD as a clinical-biological entity. The last update of the IWG framework, characterized AD as a clinical-biological entity

defined by a specific clinical phenotype associated with in vivo evidence of AD pathology, which can be detected and defined in vivo by using biomarkers such as amyloid β (amyloid-β, Aβ) (low concentration of Aβ 42 or higher CSF Aβ 40 / Aβ 42 ratio; higher tracer uptake in amyloid-PET imaging) and biomarkers of Tau pathology (higher CSF levels of phosphorylated Tau; higher tracer uptake in tau-PET imaging). The same authors underlined that the definition of biomarker is not ready to be applied in clinical practice nor for the early diagnosis of people without cognitive impairment (Dubois 2007, 2010, 2014, 2021).

Several workgroups defined the neuropathological criteria of AD. The most used criteria are Khachaturian's criteria (Khachaturian, 1985), the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) criteria for the neuropathological assessment of Alzheimer's disease (Mirra 1991), and the NIA-Reagan Criteria Institute (Consensus Recommendations for the Postmortem Diagnosis of Alzheimer's Disease, Neurobiology of Aging, 1997).

The Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association DSM-5-TR) categorizes the diagnosis of Neurocognitive Disorder (NCD) in Minor Neurocognitive Disorder (Minor NCD) and Major Neurocognitive Disorder (Major NCD).

The diagnosis of Major NCD is supported by evidence of a significant cognitive decline compared to a previous level of performance in one or more cognitive domains. This is based on i) concerns reported by the person, an expert informant, or by the clinician who verified a significant decline in cognitive functions; ii) a substantial impairment of cognitive functions, preferably documented through standardized neuropsychological tests or another quantitative clinical assessment. Cognitive deficits should affect independence in daily life activities. The diagnosis of dementia subtypes is supported by specific diagnostics criteria for each subtype.

The diagnosis of Minor NCD is supported by evidence of a mild cognitive decline compared to a previous level of performance in one or more cognitive domains, based on concerns reported by the person, an expert informant, or the clinician. The disorder should preferably be documented by standardized neuropsychological tests or other quantitative clinical assessments. Cognitive deficits in Minor NCD do not affect the ability to be independent in daily life activities, which appear to be preserved, despite people may require more efforts and the use of compensation or adaptation strategies to perform them.

In both Major and Minor NCD, especially in case of new diagnoses, cognitive deficits should not occur only within a clinical picture of delirium and should not be explained by other psychiatric disorders.

It should be noted that since AD is a slow and progressive disease that is not characterized by specific determinants of its onset, its diagnosis is particularly challenging for physicians, as identifying with a certain degree of certainty the transition moments that mark its onset is impossible.

Over the last few years, the role of increasingly advanced techniques of structural and functional neuroimaging and of biological tests, especially CSF, to identify biomarkers that can support the differential diagnosis of dementia subtypes has gained growing relevance. The utility and validity of these diagnostic procedures are the object of a still ongoing debate. To be considered valid, a diagnostic procedure should be compared with the best available reference test, whose effectiveness is proven. In the diagnosis of dementia, neuropathology is currently considered the gold standard against which to assess the accuracy of any other clinical criteria or diagnostic tools. However, histopathological examination can be exclusively performed post-mortem, as best practices do not allow for performing biopsies in live people except for single cases of specific differential diagnoses. For this reason, the diagnostic tests used in studies are mostly compared with standard references such as clinical criteria.

Advanced neuroimaging techniques are available for structural and functional examinations.

Brain Magnetic Resonance Imaging (MRI) or, when unavailable or contraindicated, Brain Computed Tomography (CT), allow assessing brain morphology and volumetry. These procedures are used in clinical practice to identify structural alterations characterized by reduction in cortical and subcortical volume and ventricular dilation, which are indicative of parenchymal atrophy or presence of hydrocephalus, vascular lesions (ischemic, haemorrhagic, malformative), inflammatory, infectious, or space-occupying lesions.

Volumetric MRI allows for a targeted quantitative regional anatomical analysis, aimed at highlighting, in the diagnostic process for AD, a loss of tissue and reduced volume (atrophy), particularly in the hippocampus and other temporal structures, which are characteristic sites of degeneration. The evaluation of MRI scans can be supported by approved qualitative scales (e.g., Global Cortical Atrophy scale, GCA, and Scheltens Index for atrophy; Fazekas scale for cerebrovascular load).

The most recent functional neuroimaging techniques in nuclear medicine (PET, SPECT) allow the study of the metabolic activity and functional integrity of specific cerebral, cortical and subcortical regions by using radiopharmaceuticals, tracers, and radioligands. In particular, ^{18}F-fluoro-deoxyglucose PET (^{18}F-FDG PET), which allows to assess brain regional metabolism through infusion of a glucose marker, appears to be the most used procedure in suspected AD. As an alternative, Single-Photon Emission Computed Tomography (SPECT) allows, after tomographic reconstruction, to assess specific cerebral, cortical and subcortical regions of interest through infusion of specific radionuclides/radioisotopes. The most used tracers are ^{99m}Tc-HMPAO (^{99m}Tc-hexamethyl-propylene-amino-oxime) or ^{99m}Tc-hexamethazyme. Since cerebral blood flow is closely related to local metabolism and the energy used, the tracer ^{99m}Tc-HMPAO (as well as the similar ^{99m}Tc-ECD, 99mTc-ethyl-cysteine dimer) is used to assess brain metabolism of different regions.

In cases of suspected Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB), which are both synucleinopathies defined by a characteristic degeneration of the nigrostriatal pathway, the ^{123}I-FP-CIT (DaT scan) SPECT can support the diagnosis, allowing to assess the function of the presynaptic dopamine receptor (DAT) at the striatal level. The alteration that can be observed in these Parkinsonisms only allows to differentiate them from conditions that are not characterized by a nigrostriatal degeneration, while it does not allow for the differential diagnosis with primary atypical Parkinsonisms that are also characterized by this alteration. In this cases, myocardial MIBG scintigraphy radiolabeled with iodine 123 (123 iodine metaiodobenzylguanidine, ^{123}I-MIBG) can help in the diagnostic process, by noninvasively assessing the integrity of the postganglionic presynaptic cardiac sympathetic endings. This procedure, originally used to study heart diseases, was later proven to be able to show a reduction in the uptake in people with Lewy body diseases, such as PD and DLB, and is now considered as supporting clinical diagnosis in case of uncertainty in the differential diagnosis with other atypical parkinsonisms.

Neuropathology in AD is supported by a double proteinopathy characterized by the pathognomonic coexistence of extracellular aggregates of fibrils Aβ 42, which form the amyloid plaques, and intraneuronal aggregates of hyperphosphorylated Tau protein (p-Tau), defined as neurofibrillary tangles (NFTs). This is the basis of the most recent tests, which are aimed at identifying their diagnostic biomarkers.

PET imaging with ^{11}C-Pittsburgh compound B (^{11}C-PiB) and other fluorinated tracers (e.g., ^{18}F-florbetapir, ^{18}F-florbetaben, ^{18}Fflutemetamol), by specifically marking the binding to the fibrillar form of Aβ, allowed to highlight its higher deposition at a cortical level, and thus to quantify the cerebral amyloid load (amyloid PET). This nuclear medicine test is currently available and mainly used for specialized research purposes. Similarly, the more recently developed Tau-PET (^{18}F-flortaucipir Positron Emission Tomography) uses a specific tracer for phosphorylated Tau.

When considering biohumoral tests, a large part of diagnostic research focused on measuring CSF levels and, more recently, plasma levels, of Aβ 42, p-Tau, and t-Tau to identify biomarkers that could support to diagnose AD and differentiate it from other forms of dementia.

In particular, AD is described as being associated with lower CSF levels of Aβ 1-42 and a lower Aβ 1-42 / Aβ 1-40 ratio due to Aβ 1-42 sequestration in cerebral amyloid plaques, and with higher levels of Tau hyperphosphorylated (p-Tau) contributing to the formation of NFTs, and of total Tau (t-Tau), associated to neuronal damage and considered a marker of neurodegeneration. The higher levels of p-Tau are considered more specific in AD.

Overall, neuroimaging and CSF biomarkers can be classified as markers that specifically identify the presence of amyloid depositions (amyloid PET, CSF levels of Aβ 1-42) and markers of neurodegeneration (18F-FDG PET, SPECT and MRI, CSF levels of p-Tau and t-Tau).

The actual role of these biomarkers in supporting the early diagnosis of dementia has yet to be defined through a validation process (proving analytical validity, clinical validity, clinical utility) that is still ongoing and has not yet been completed for any of the available biomarkers.

Some cases of AD may have an early onset, even before the age of 40 years. These cases are sometimes linked to rare genetic forms due to mutations in the presenilin 1 and 2 genes (PSEN1, PSEN2), and in the amyloid precursor protein gene (Amyloid Precursor Protein, APP), which are responsible for autosomal dominant diseases. The ApoE ε4 genotype, instead, is the main genetic risk factor for sporadic AD but it does not cause the disease.

Overall, 15 to 20% of dementias are vascular dementias (VaD), while around 10% of dementias are considered as associated to mixed subtypes. Several criteria have been proposed to diagnose the different forms of vascular dementias, based on clinical and imaging data, linked to the distribution of brain lesions (NINDS-AIREN criteria, modified NINDS-AIREN criteria for SIVD-Subcortical Ischaemic Vascular Dementia, ADDTC criteria, DSM IV, ICD10).

A rare form of hereditary young-onset vascular dementia is CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy), which is considered as a model of subcortical ischemic vascular dementia (SIVD) due to a mutation in the Notch 3 gene. Its clinical course is characterized by migraine with aura, recurrent subcortical stroke, mood disorders, and progressive cognitive decline eventually leading to dementia.

Dementia associated with Lewy body disorders, such as DLB and PDD, is the second form of degenerative dementia. Specifically, the prevalence of DLB is estimated to range from 0.1% to 5% in the general elderly population, and from 1.7% to 30.5% among all cases of dementia. Data from brain banks report a frequency of presence of Lewy bodies in brain tissue in yp to 20% to 35% of all dementia cases. However, neuropathological examination of DLB cases can show the presence of fibrillar Aβ, which is a typical feature of AD (Zaccai 2005). The diagnosis of DLB in living people is based on recently updated Consensus clinical criteria (McKeith 2017). The diagnosis of PDD is based on the *Movement Disorders Society-MDS criteria for Parkinson's disease dementia* (Postuma 2015).

Frontotemporal Dementia (FTD) is the third most common degenerative dementia after AD and DLB and is the second most frequent form in presenile people (< 65 years). Around 40% of FTD cases have a family history of early onset, with 10% of them having an autosomal dominant hereditaty pattern. Several genetic factors have been identified, such as mutations in the genes coding for Tau protein (Microtubule Associated Protein Tau, MAPT), in the progranulin gene (Granulin Precursor, GRN), and the C9ORF72 gene. While several families have been identified with disease-causing mutations, many people with familial transmission do not carry any known mutation.

The term FTD refers to a family of degenerative diseases defined by clinical conditions with an insidious onset, characterized by progressively worsening changes in executive functions, language, behavior, and personality, which may mimic various mental disorders. This peculiar aspect can delay the diagnosis and can lead to underestimating the prevalence of this condition. One of these disease variants may occur in people with motor neuron disease and is associated with faster fatal progression.

The clinical diagnosis of the three main variants of FTD is based on the consensus criteria *International FTD criteria for frontotemporal dementia* for nonfluent primary progressive aphasia and semantic dementia (Rascovsky 2013) and on the *International Frontotemporal Dementia Consortium* criteria for the behavioral variant of frontotemporal dementia (bv-FTD) (Rascovsky 2011).

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Case finding for people at high risk of dementia

Review question 1	What are the most effective methods of case finding for people at high risk of dementia?

Literature review

Records identified from databases	2,422
Studies assessed for eligibility	11
Included studies	0
Studies included in the NICE GL	1
Total number of included studies	1

Eligibility criteria

Population	People aged ≥ 40 years at high risk of dementia including people aged > 60 at high vascular risk (previous stroke), people with neurodevelopmental disorders, and people with other neurological disorders.
Intervention	Standard cognitive tests.
Outcomes	• Incidence of dementia correctly identified in people classified as at risk. • Delay to diagnosis. • Sensitivity, specificity, predictive values. • Health-related quality of life. • Overtreatment. • Resource use and costs.
Setting	Primary, acute, residential care

Aim

The primary objective of the systematic literature review, as defined by NICE Guideline, was to establish the potential influence of case finding strategies on the incidence of correct diagnoses of dementia in people at high risk of cognitive decline and the possible consequences in terms of outcomes for people who receive a new diagnosis.
To this purpose, only prospective cohort studies and randomized clinical trials (RCT) were considered as eligible, investigating case finding approaches and including, along with data on the incidence of new cases, an intervention for people receiving a new diagnosis.

Summary of evidence

The systematic review performed for the NICE guideline identified only one study meeting the predefined eligibility criteria. No studies were identified after updating the systematic review.

The included RCT (van den Dungen 2016) investigated, in a first phase, the impact of a training intervention for general practitioners (GP), in a primary care setting, on the incidence of new diagnoses of MCI or dementia in a population of older people with a suspect of cognitive decline. The study also investigated, in a second phase, the impact of a functional and cognitive assessment made by professional nurses in a subgroup of participants from the first phase of the study.
The study enrolled a total of 647 participants with a suspect of cognitive decline referring to 15 primary care practices. When considering the primary outcome in the first phase of the study, participants who received a diagnosis of MCI or dementia were 42.3% of the 326 participants referring to the seven practices randomized to the interventions, and 30.5% of the participants referring to the eight practices randomized to the control group (RR 1.33, 95% CI 0.70 – 2.07, very low certainty). A total of 145 participants from the first phase of the study were included in the second phase. During this phase, an increase in the number of new diagnoses of MCI and dementia was observed (RR 1.07, 95% CI 0.60 – 1.62, very low certainty).
When considering the secondary outcomes, no differences between groups were observed in participants' mental health at six months (Mental Health Inventory-5, MH-5: MD 2.11, 95% CI -3.31 – 7.53, low certainty) and at 12 months of follow-up (MH-5: MD 0.21, 95% CI -6.35 – 6.77, very low certainty). No differences were observed also in the mental health of family members/caregivers at 6 months (General Health Questionnaire-12 items, GHQ-12: MD -0.30, 95% CI -1.19 – 0.59, very low certainty) and at 12 months of follow-up (GHQ-12: MD -0.33, 95% CI -1.30 – 0.64, very low certainty). No significant differences were observed in participants' quality of life at 6 months (QoL-AD: MD -0.61, 95% CI -2.31 – 1.09, low certainty) and at 12 months of follow-up (QoL-AD: MD -0.85, 95% CI -2.46 – 0.76, low certainty). For both outcomes, the certainty of evidence was classified as low due to the heterogeneity of the sample and the type of diagnosis.

Analysis of evidence

The timely diagnosis of dementia is increasingly considered as a public health priority. From a public health point of view, case finding approaches are considered as an active search for cases in groups of people at a higher risk of developing the considered condition. As for dementia, the risk groups could be identified based on the knowledge of clinical conditions/reports or family history of dementia, assessed by clinicians, and based on clinical judgement. The WG underlined that the methodological approach defining case finding strategies is specific and should not be mistaken for the one defining screening strategies[17]. Screening strategies are targeted to all people from a specific group, that is not considered at a higher risk or already experimenting the symptoms of a condition, who are offered a questionnaire or a test to identify said condition (e.g., cancer screening).
This distinction is essential when considering dementia, where performing screening strategies is considered inappropriate and is not recommended based on methodological and ethical considerations. The balance between potential benefits and harms derived from an active search for cases of dementia is a very debated and controversial issue, considering that no disease-modifying treatments are currently available, and a formal diagnosis could not benefit everyone.
When considering dementia, despite case-finding being based on a targeted identification of people at a high risk, the approaches should also include an intervention providing support to people after the diagnosis. An intervention limited to identifying people with a diagnosis and not including an intervention aimed at modifying their management is in fact unlikely to be effective. It could also be harmful, as it would introduce a highly destabilizing factor affecting how people and their families perceive their future without providing any adequate benefit.

[17] https://www.gov.uk/government/collections/uk-national-screening-committee-annual-reports UK National Screening Committee: annual reports. These reports summarise the work of the UK National Screening Committee (UK NSC).

No studies were found when updating the systematic review from the NICE guideline, which identified one study, a cluster RCT, where case finding was performed by a professional nurse and a GP who took part in a training program aimed at allowing performing a higher number of diagnoses of MCI/dementia. The secondary outcomes of the RCT used to assess, in participants and their caregivers, the potential benefits and harms from the case finding approach and the subsequent management of cases were considered as appropriate (van den Dungen 2016). Results reported no differences in the quality of life of participants and their family members/caregivers, suggesting that neither of them benefited from the strategy. It should also be considered that this type of case finding approaches, due to the inaccuracy of the diagnostic tests, could lead to a percentage of people being misdiagnosed with dementia (false positive). This would cause these people to suffer from unjustified stress and being administered inappropriate treatments. From a cost-benefit point of view, case finding approaches would have high costs in terms of impact on specialist centers (e.g., memory clinics), due to the subsequent increase in the number of rereferrals, which could be inappropriate and could increase the time to diagnosis for people with dementia. Moreover, as highlighted in the considered study, a considerable percentage of people at a higher risk of dementia might not agree to perform the further examinations needed for the diagnosis. This would not only prevent them from being appropriately followed up but would also cause an impact in terms of resource use that could be more conveniently used for other purposes. Therefore, considering the current lack of supporting evidence, the WG agreed to recommend further research through adequately designed studies including an intervention on people receiving a diagnosis of dementia. In particular, the current lack of evidence on the effectiveness of an active search of cases of dementia requires a research recommendation defining a structured case finding approach using defined criteria for the selection of people at high risk and including an intervention targeted to people who receive a diagnosis of dementia.

Recommendations

No clinical practice recommendations were made.

Research Recommendations

1R	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?

References

Van den Dungen P, van Charante EPM, van de Ven PM et al. Case Finding of Mild Cognitive Impairment and Dementia and Subsequent Care; Results of a Cluster RCT in Primary Care. PLoS One 2016; 11(6): e0156958.

Diagnosis and differential diagnosis of dementia and Mild Cognitive Impairment

Review question 2a	**What are the most effective methods of primary assessment to decide whether a person with suspected dementia should be referred to a dementia service?**
Review question 2b	**What are the most effective methods of primary assessment to decide whether a person with suspected cognitive deficit should be referred to a dementia service?**
Review question 2c	**What are the most effective methods of diagnosing dementia and dementia subtypes in specialist dementia diagnostic services?**
Review question 2d	**What are the most effective methods of diagnosing MCI and its subtypes in specialist dementia diagnostic services?**

Literature review

	2a	2b	2c	2d
Records identified from databases	11,905	11,030	11,905	11,030
Studies assessed for eligibility	19	11	82	94
Included studies	2	1	9	19
Studies included in the NICE GL	7	-	123	-
Total number of included studies	9	1	132	19

Eligibility criteria

Review question 2a and review question 2b

Population	People aged ≥ 40 years with a suspected diagnosis of dementia or cognitive deficit.
Diagnostic variables	Potential diagnostic variables include: • clinical history; • clinical cognitive assessment (e.g. MMSE); • neuropsychological tests; • physical examination; • medication review.
Outcomes	• Incidence of accurately identified dementia. • Diagnostic accuracy measures (e.g. sensitivity, specificity, predictive values). • Resource use and costs.
Setting	Primary care

Review question 2c and review question 2d

Population	People (aged ≥ 40 years) with a suspected diagnosis of dementia or MCI.
Diagnostic variables	Potential diagnostic variables include: • specific clinical criteria; • structural imaging (e.g., MRI, CT); • SPECT (e.g., blood flow, dopamine); • PET (e.g., ^{18}F-FDG, amyloid); • CSF examination; • electroencephalography (EEG); • brain biopsy; • neuropsychological assessment; • functional assessment; • genetic testing; • neurological examination.
Outcomes	• Incidence of accurately identified dementia or MCI. • Diagnostic accuracy measures (e.g. sensitivity, specificity, predictive values). • Resource use and costs.
Setting	Specialist care

Aim

Review question 2a and review question 2b

The objective of the systematic reviews performed to update question 2a and to elaborate new searches for question 2b was to identify, according to the strategy defined in the NICE guideline, all diagnostic studies assessing the accuracy of available test for the identification of a suspected dementia or cognitive deficit in a non-specialist, primary care setting.
Search strategies for both questions initially aimed at identifying recent, updated systematic reviews (RS), on different tools used for the diagnosis of dementia. RS were also analyzed to identify primary studies. Further structured searches were then performed to identify other relevant primary studies.
Only diagnostic studies were included, reporting enough data to allow for computing all diagnostic accuracy parameters, including sensitivity, specificity and predictive values. Diagnostic case-control studies were excluded.

Review question 2c

The objective of the systematic review, according to the strategy defined in the NICE guideline, was to identify all diagnostic studies assessing the accuracy of available test for the identification of people with dementia and in classifying dementia subtypes in a specialist care setting.
Search strategies for both questions initially aimed at identifying recent, updated systematic reviews (RS), on different tools used for the diagnosis of dementia. RS were also analyzed to identify primary studies. Further structured searches were then performed to identify other relevant primary studies.
Only diagnostic studies were included, reporting enough data to allow for computing all diagnostic accuracy parameters, including sensitivity, specificity and predictive values. Diagnostic case-control studies were excluded.

Review question 2d

The objective of the systematic review, according to the strategy defined in the NICE guideline, was to identify all diagnostic studies assessing the accuracy of available test for the identification of people with MCI and in classifying dementia subtypes in a specialist care setting.
Search strategies for both questions initially aimed at identifying recent, updated systematic reviews (RS), on different tools used for the diagnosis of MCI. RS were also analyzed to identify primary studies. Further structured searches were then performed to identify other relevant primary studies.
Only diagnostic studies were included, reporting enough data to allow for computing all diagnostic accuracy parameters, including sensitivity, specificity and predictive values. Diagnostic case-control studies were excluded.

Summary of evidence

Initial assessment in a non-specialist, primary care setting

Review question 2a and 2b

The systematic review preformed for the NICE guideline identified seven studies meeting the predefined eligibility criteria. Updating the SR allowed to identify two studies for both questions.
Studies were classified according to type of diagnostic tool, and data were reported according to type of test and its cut-offs, where considered.

6-item Cognitive Impairment Test (6-CIT)

One study (Abdel-Aziz 2015) reported data on the accuracy of the 6-CIT compared to clinical criteria in 245 participants. The study reported a sensitivity of 0.88 and a specificity of 0.78 in distinguishing people with dementia from people without dementia applying a cut off < 9 (high certainty). A second study (Creavin 2023) on 240 participants reported a sensitivity of 0.76 and a specificity of 0.70 in distinguishing people with dementia from people without dementia applying a cut off < 7 (moderate certainty).

6-item Screener (6-IS)

One study (Callahan 2002) reported data on the accuracy of the 6-IS compared to clinical criteria in 651 participants. When considering the accuracy of 6-IS in distinguishing people with dementia from people without dementia, the study reported a sensitivity of 1 and specificity of 0 applying a cut-off ≥ 0 (very low certainty), a sensitivity of 0.97 e specificity of 0.53 applying a cut-off ≥ 1 (low certainty). It reported a sensitivity of 0.90 and specificity of 0.79 applying a cut-off ≥ 2 (moderate certainty), a sensitivity of 0.81 and specificity of 0.91 applying a cut-off ≥ 3 (moderate certainty), a sensitivity of 0.68 and specificity of 0.96 applying a cut-off ≥ 4 (moderate certainty). It also reported a sensitivity of 0.49 and specificity of 0.99 applying a cut-off ≥ 5 (low certainty), and a sensitivity of 0.30 and specificity of 0.99 applying a cut-off ≥ 6 (moderate certainty).

10-point Cognitive Screener (10-CS)

One study (Apolinario 2015) reported data on the accuracy of the 10-CS test compared to clinical diagnosis in 230 participants. When considering the accuracy of the 10-CS test in distinguishing people with dementia from people without dementia, the study reported a sensitivity of 0.69 and specificity of 0.94 applying a cut-off ≤ 5 (low certainty). It also reported a sensitivity of 0.94 and specificity of 0.60 applying a cut-off ≤ 7 (very low certainty), and a sensitivity of 0.97 and specificity of 0.40 applying a cut-off ≤ 8 (low certainty).

Abbreviated Mental Test (AMT)

One study (Flicker 1997) reported data on the accuracy of the AMT compared to clinical diagnosis in 299 participants. When considering the accuracy of the AMT in distinguishing people with dementia from people without dementia, the study reported a sensitivity of 0.97 and specificity of 0.28 applying a cut-off < 10 (low certainty), a sensitivity of 0.88 and specificity of 0.53 applying a cut-off < 9 (very low certainty). It also reported a sensitivity of 0.73 and specificity of 0.71 applying a cut-off < 8 (very low certainty), a sensitivity of 0.58 and specificity of 0.87 applying a cut-off < 7 (very low certainty).

Functional Activities Questionnaire (FAQ)

One study (Cruz-Orduna 2012) reported data on the accuracy of the FAQ test compared to clinical diagnosis. The study enrolled 160 participants and reported a sensitivity of 0.87 and specificity of 0.82 in distinguishing people with dementia from people without dementia applying a cut-off < 9 (low certainty).

GP-Cog

One study (Brodaty 2016) reported data on the accuracy of the GP-Cog test compared to the CAMCOG scale. The study enrolled 1.717 participants and reported a sensitivity 0.79 and specificity of 0.92 in distinguishing people with dementia from people without dementia applying a cut-off < 11 (moderate certainty). A second study (Creavin 2023) on 240 participants reported a sensitivity of 0.93 and specificity of 0.52 in distinguishing people with dementia from people without dementia applying a cut-off < 8 (low certainty).

Informant Questionnaire on Cognitive Decline in the Elderly – 26 items (IQCODE26-item)

One study (Cruz-Orduña 2012) reported data on the accuracy of the IQCODE26-item test compared to clinical diagnosis on 160 participants. The study reported a sensitivity of 0.80 and specificity of 0.77 in distinguishing people with dementia from people without dementia applying a cut-off > 3,6 (low certainty).

Memory Impairment Screen (MIS)

One study (Carnero-Pardo 2011) reported data on the accuracy of the MIS test compared to clinical diagnosis on 117 participants. When considering the accuracy of the MIS test in distinguishing people with dementia from people without dementia, the study reported a sensitivity of 0.93 and specificity of 0.80 applying a cut-off < 4 (high certainty), a sensitivity of 0.97 and specificity of 0.71 applying a cut-off < 5 (high certainty).

Mini-Cog

One study (Carnero-Pardo 2013) reported data on the accuracy of the Mini-Cog test compared to clinical diagnosis on 142 participants. The study reported a sensitivity of 0.99 and specificity of 0.40 n in distinguishing people with dementia from people without dementia applying a cut-off ≤ 2 (moderate certainty). The second study (Creavin 2023) on 240 participants, reported a sensitivity of 0.70 and specificity of 0.73 in distinguishing people with dementia from people without dementia applying a cut-off < 3 (moderate certainty).

Mini Mental State Examination (MMSE)

Three studies reported data on the accuracy of the MMSE compared to clinical diagnosis (Brodaty 2016, Carnero-Pardo 2013, Cruz- Orduña 2012). When considering the accuracy of the MIS test in distinguishing people with dementia from people without dementia, one study on 360 participants (Carnero-Pardo 2013) reported a sensitivity of 0.70 and specificity of 0.93 applying a cut-off < 17 (moderate certainty), a sensitivity of 0.81 and specificity of 0.92 applying a cut-off < 18 (moderate certainty). It reported a sensitivity of 0.94 and specificity of 0.82 applying a cut-off < 20 (moderate certainty), a sensitivity of 0.95 and specificity of 0.73 applying a cut-off < 21 (moderate certainty), a sensitivity of 0.96 and specificity of 0.67 applying a cut-off <

22 (moderate certainty). It also reported a sensitivity of 0.99 and a specificity of 0.57 applying a cut-off < 23 (low certainty), a sensitivity of 0.1 and a specificity 0.38 applying a cut-off < 25 (moderate certainty). Two studies on a total of 520 participants (Carnero-Pardo 2013, Cruz- Orduña 2012) reported a sensitivity of 0.80 a 0.88 and specificity of 0.86 a 0.87 applying a cut-off < 19 (low certainty). Two studies on a total of 2.388 participants (Brodaty 2016, Carnero-Pardo 2013) reported a sensitivity ranging from 0.51 to 1 and a specificity ranging from 0.46 to 0.97 applying a cut-off < 24 (low certainty).

Phototest

One study (Carnero-Pardo 2011) reported data on the accuracy of Phototest compared to clinical diagnosis in 140 participants. The study reported a sensitivity of 0.81 and specificity of 0.89 in distinguishing people with dementia from people without dementia applying a cut-off > 9 (high certainty).

Diagnosis of dementia in a specialist care setting

Review question 2c

The systematic review performed for the NICE guideline identified 123 studies meeting the predefined eligibility criteria. Updating the SR allowed to identify 11 studies.
Studies were classified according to the target of the test, with a first category referring to diagnosis (distinguishing people with dementia from people without dementia) and the following categories referring to differential diagnosis. Studies within each category were classifies according to type of diagnostic tool, and data were reported according to type of test and its cut-off where considered.

DIAGNOSIS (dementia *versus* non-dementia)

COGNITIVE TESTS

AD8 Dementia Screening Interview (AD8)

One study on 212 participants (Larner 2015) investigated the accuracy of the AD8 tool compared to clinical criteria, reporting a sensitivity of 0.97 and specificity of 0.11 applying a cut-off ≥ 2 (moderate certainty).

Addenbrooke's Cognitive Examination (ACE), ACE-III, ACE-R e Mini-ACE

Seven studies reported data on the accuracy of the different versions of the ACE scale compared to clinical diagnosis or standard diagnostic criteria. When considering the accuracy of the ACE tool in distinguishing people with dementia from people without dementia, one study on 285 participants (Mathuranath 2000) reported a sensitivity of 0.85 and a specificity of 0.83 applying a cut-off < 75 (high certainty). Two studies on a total of 424 participants (Larner 2007, Mathuranath 2000) reported a sensitivity ranging from 0.82 to 0.96 and a specificity ranging from 0.63 to 0.96 applying a cut-off < 83 (very low certainty), and a sensitivity ranging from 0.93 to 1 and specificity ranging from 0.43 to 0.71 applying a cut-off < 88 (very low certainty).
When considering the accuracy of the ACE-III tool, one study on 59 participants (Jubb 2015) reported a sensitivity of 0.81 and a specificity of 0.97 applying a cut-off < 81 (low certainty), a sensitivity of 0.81 and a specificity of 0.70 applying a cut-off < 82 (low certainty). It also reported a sensitivity of 0.92 and a specificity of 0.61 applying a cut-off < 84 (very low certainty), and a sensitivity of 0.96 and a specificity of 0.50 applying a cut-off < 88 (low certainty).
When considering the accuracy of the ACE-R tool, one study on 140 participants (Hancock 2011) reported a sensitivity of 0.90 and a specificity of 0.93 applying a cut-off < 74 (moderate certainty). Two studies on a total of 442 participants (Bastide 2012, Terpening 2011) reported a sensitivity ranging from 0.79 to 0.92 and a specificity ranging from 0.69 to 0.80 applying a cut-off < 83 (moderate certainty). One study on 122

participants (Terpening 2011) reported a sensitivity ranging from 0.85 to 0.91 and a specificity ranging from 0.80 to 0.69 applying respectively a cut-off < 85 (moderate certainty) and a cut-off < 89 (moderate certainty).

When considering the accuracy of the Mini-ACE tool, two studies on a total of 859 participants (Larner 2007, Williamson 2018) reported a sensitivity ranging from 0.98 to 0.99 and a specificity ranging from 0.34 to 0.35 (moderate certainty).

Boston Naming Test (BNT)

Only one study (Beinhoff 2005) investigated the accuracy of the BNT tool compared to clinical criteria on a total of 232 participants reporting a sensitivity of 0.39 and a specificity of 0.93 applying a cut-off < 13 (moderate certainty). It also reported a sensitivity of 0.55 and a specificity of 0.84 applying a cut-off < 14 (low certainty), and a sensitivity of 0.71 and a specificity of 0.63 applying a cut-off < 15 (low certainty).

Brief Neuropsychological Test Battery (BNTB)

Only one study including 131 participants (Coutinho 2013) investigated the accuracy of the BNTB battery compared to clinical criteria and reported a sensitivity of 0.91 and specificity of 0.83 (high certainty).

Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Battery

Only one study on 100 participants (Hentschel 2005) investigated the accuracy of the CERAD battery reporting a sensitivity of 0.74 and specificity of 0.98 (low certainty).

Clock Drawing Test (CDT)

Four studies investigated the accuracy of the different systems used to calculate the CDT score compared to clinical criteria for the diagnosis of dementia. One study on 232 participants (Beinhoff 2005) reported sensitivity values of 0.86 and 0.71 and specificity values of 0.52 e 0.88 respectively for cut-off values > 0 (low certainty) e > 1 (moderate certainty) of the Shulman system. For the same system, two studies on a total of 734 participants (Beinhoff 2005, Milian 2012) reported a sensitivity ranging from 0.29 to 0.78 and a specificity ranging from 0.97 to 0.98 applying a cut-off > 2 (very low certainty). One study on 462 participants (Berger 2008) reported a sensitivity of 0.90 and a specificity of 0.56 applying a cut-off > 3 (low certainty). This last study also reported a sensitivity of 0.72 and a specificity of 0.64 applying a cut-off > 4 with the Watson system (low certainty), and a sensitivity of 0.88 and a specificity of 0.49 applying a cut-off < 3 with the Lin system (low certainty). The same study reported a sensitivity of 0.58 and a specificity of 0.81 applying a cut-off < 7 with the Wolf-Klain system (low certainty), and values of sensitivity of 0.81 and 0.93 and values of specificity of 0.60 and 0.37 applying cut-offs respectively < 8 (low certainty) and < 9 (low certainty) with the Manos and Wu system. One last study on 364 participants (Sager 2006) reported a sensitivity of 0.72 and a specificity of 0.83 applying a cut-off < 8 with an unspecified scoring system (moderate certainty).

Free recall score of 5-word test

Only one study on 145 participants (Mormont 2012) investigated the accuracy of the 5-word test compared to clinical diagnosis, reporting a sensitivity of 0.78 and a specificity of 0.90 applying a cut-off ≤ 6 of the free recall score (low certainty). It also reported values of sensitivity of 0.81 and 0.75, and values of specificity of 0.90 and 0.96 respectively for a cut-off ≤ 9 of total recall scores (low certainty) and a cut-off ≤ 15 of total weighted scores (low certainty).

Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) 16 e 26 item

Five studies investigated the accuracy of the different versions of the IQCODE tool compared to clinical diagnosis. When considering the accuracy of the 16-item version, two studies on a total 436 participants (Garcia 2002, Knaefelc 2003) reported values of sensitivity ranging from 0.92 to 0.94 and values of specificity

ranging from 0.47 to 0.83 applying a cut-off > 3,5 (moderate certainty). One study on 204 participants (Gonçalves 2011) reported a sensitivity of 0.72 and a specificity of 0.67 applying a cut-off > 4,1 (low certainty).

When considering the accuracy of the 26-item version, two studies on a total of 443 participants (Flicker 1997, Hancock 2009) reported values of sensitivity ranging from 0.86 to 0.87 and values of specificity ranging from 0.39 to 0.83applying a cut-off > 3,5 (very low certainty). For the same version, one study on 299 participants (Flicker 1997) reported, with very low certainty, values of sensitivity of 0.81 and 0.78, and values of specificity of 0.61 and 0.65 for cut-offs respectively > 3,6 and > 3,7. It also reported values of sensitivity of 0.75 and 0.70 and values of specificity of 0.71 and 0.75 for cut-offs respectively > 3,8 and > 3,9, and values of sensitivity of 0.65 and 0.58, and values of specificity of 0.80 and 0.83 for cut-offs respectively > 4 and > 4,1.

Letter Sorting Test (LST)

Only one study on 232 participants (Beinhoff 2005) investigated the accuracy of the LST test compared to clinical criteria, reporting values of sensitivity of 0.12, 0.44 and 0.80, and values of specificity of 0.99, 0.93 and 0.69 applying cut-offs respectively < 1 (moderate certainty), < 2 (low certainty) e < 3 (low certainty).

Mini-Cog (Scanlan & Borson)

One study on 502 participants (Milian 2012) investigated the accuracy of the Mini-Cog test compared to clinical criteria. The study reported a sensitivity of 0.87and a specificity of 0.99 for the Scanlan and Borson scoring system (moderate certainty).

Memory Impairment Screen (MIS)

One study on 232 participants (Beinhoff 2005) investigated the accuracy of the MIS test compared to clinical diagnosis reporting, with moderate certainty, values of sensitivity of 0.82, 0.88 and 0.98, and values of specificity of 0.81, 0.70 and 0.32 applying cut-offs respectively < 5, < 6 e < 8. It also reported, with low certainty, a sensitivity of 0.92 and a specificity of 0.53 applying a cut-off < 7.

Mini Mental State Examination (MMSE)

Overall, 18 studies investigated the accuracy of applying different cut-off scores of the MMSE tool compared to clinical criteria, clinical diagnosis and neuropathology for the diagnosis of dementia. One study on 299 participants (Flicker 1997) reported, with very low certainty, values of sensitivity of 0.50 and 0.56, and values of specificity of 0.90 and 0.97 applying cut-offs respectively < 18 e < 19, and values of sensitivity of 0.62 and 0.69, and values of specificity of 0.84 and 0.76 for the cut-offs < 20 and < 21. Four studies on a total of 1.214 participants (Callahan 2002, Flicker 1997, Kukull 1994, Torkpoor 2022) reported, with very low certainty, a sensitivity ranging from 0.56 and 0.75, and a specificity ranging from 0.71 and 1 for a cut-off < 22. Six studies on a total of 1.489 participants (Abdel-Aziz 2015, Callahan 2002, Flicker 1997, Kukull 1994, Nielsen 2013, Torkpoor 2022), reported, with very low certainty, a sensitivity ranging from 0.54 to 0.80, and a specificity ranging from 0.69 to 1 applying a cut-off < 23. Twelve studies on a total of 3.100 participants (Bastide 2012, Callahan 2002, Flicker 1997, Gonçalves 2011, Hancock 2011, Knaefelc 2003, Kukull 1994, Mathuranath 2000, Nielsen 2013, Postel-Vinay 2014, Sager 2006, Torkpoor 2022) reported, with low certainty, a sensitivity ranging from 0.39 and 0.88, and a specificity ranging from 0.60 to 0.99 applying a cut-off < 24. Eight studies on 2.145 participants (Callahan 2002, Flicker 1997, Kukull 1994, Larner 2007, Milian 2012, Nielsen 2013, Torkpoor 2022, Yeung 2014) reported, with very low certainty, a sensitivity ranging from 0.70 to 0.95 and a specificity ranging from 0.53 to 1 applying a cut-off < 25. Six studies on 1.934 participants (Callahan 2002, Flicker 1997, Milian 2012, Morris 2020, Nielsen 2013, Torkpoor 2022) reported, with very low certainty, a sensitivity ranging from 0.52 to 0.92, and a specificity ranging from 0.46 to 1 applying a cut-off < 26. Four studies on 1.241 participants (Bastide 2012, Callahan 2002, Mathuranath 2000, Nielsen 2013) reported, with low certainty, a sensitivity ranging from 0.74 to 0.94, and a specificity ranging from 0.63 to 0.96 applying a

cut-off < 27. Two studies on 796 participants (Callahan 2002, Mormont 2012) reported, with very low certainty, a sensitivity ranging from 0.93 to 0.98, and a specificity ranging from 0.65 to 0.78 applying a cut-off < 28.

Montreal Cognitive Assessment (MoCA)

Five studies investigated the accuracy of applying different cut-off scores of the MoCA scale compared to clinical criteria and clinical diagnosis for the diagnosis of dementia. Two studies on a total of 495 participants (Chen 2011, Yeung 2014) reported, with very low certainty, a sensitivity ranging from 0.92 to 0.94, and a specificity ranging from 0.66 to 0.92 applying a cut-off < 19. One study on 693 participants (Dautzenberg 2022) reported, with low certainty, a sensitivity of 0.90 and a specificity of 0.74 compared to clinical diagnosis applying a cut-off < 26. One study on 272 participants (Yeung 2014) reported, with moderate certainty, a sensitivity of 1 and a specificity of 0.37 applying a cut-off < 22. One study on 81 participants (Goldstein 2014) reported, with low certainty, values of sensitivity of 0.96 and 0.98 and values of specificity of 0.31 and 0.23 applying cut-offs respectively < 24 e < 25. Two studies on 953 participants (Dautzenberg 2022, Larner 2017) reported, with moderate certainty, values of sensitivity of 0.98 and 0.99 and values of specificity of 0.29 and 0.31, compared to clinical diagnosis and clinical criteria, applying a cut-off < 26.

Orientation Test (OT)

Only one study on 232 participants (Beinhoff 2005) investigated the accuracy of the OT compared to clinical diagnosis for the diagnosis of dementia reporting, with moderate certainty, a sensitivity of 0.39 and a specificity of 0.99 applying a cut-off < 7 and, with low certainty, a sensitivity of 0.65 and a specificity of 0.90 applying a cut-off < 8.

Rowland Universal Dementia Assessment Scale (RUDAS)

Four studies investigated the accuracy of the RUDAS score for the diagnosis of dementia. One study on 116 participants (Daniel 2022) reported, with low certainty, values of sensitivity of 0.67 and 0.74 and values of specificity of 0.83 and 0.82 compared to clinical criteria applying cut-offs respectively ≤ 19 e ≤ 20. Two studies on 320 participants (Daniel 2022, Gonçalves 2011) reported, with moderate certainty, a sensitivity ranging from 0.66 to 0.85 and a specificity ranging from 0.82 to 0.90 compared to clinical diagnosis and clinical criteria applying a cut-off < 21. Three studies on a total of 376 participants (Daniel 2022, Nielsen 2013, Torkpoor 2022), comparing the scale to clinical criteria, reported, with low certainty, a sensitivity ranging from 0.49 to 0.92 and a specificity ranging from 0.75 to 0.91 applying a cut-off < 22. It also reported a sensitivity ranging from 0.61 to 0.97 and a specificity ranging from 0.62 to 0.83 applying a cut-off < 23, and a sensitivity ranging from 0.69 to 1,00 and a specificity ranging from 0.56 to 0.80 applying a cut-off < 24. Two studies on 260 participants (Nielsen 2013, Torkpoor 2022), comparing the scale to clinical criteria, reported, with very low certainty, a sensitivity ranging from 0.76 to 0.92 and a specificity ranging from 0.60 to 0.66 applying a cut-off < 25, and a sensitivity ranging from 0.82 to 0.90 and a specificity ranging from 0.50 to 0.65 applying a cut-off < 26.

Seven-Minute Screen (SMS)

Only one study on 95 participants (Skjerve 2008) investigated the accuracy of the SMS test compared to clinical diagnosis reporting, with low certainty, values of sensitivity of 0.72, 0.72 and 0.71 and values of specificity of 0.65, 0.69 and 0.73 applying cut-off values respectively < 0.6, < 0.7 and < 0.8.

Short Portable Mental Status Questionnaire (SPMSQ)

One study on 127 participants (Malhotra 2013) investigated the accuracy of the SPMSQ test compared to clinical diagnosis reporting, with very low certainty, values of sensitivity of 0.79, 0.78 e 0.72 and values of specificity of 0.75, 0.75 and 0.42 applying cut-off values respectively ≥ 4, ≥ 5 and ≥ 6.

Syndrom Kurztest (SK)

Only one study on 95 participants (Skjerve 2008) investigated the accuracy of the SK test compared to clinical diagnosis reporting, with low certainty, values of sensitivity of 0.71, 0.65 and 0.58 and values of specificity of 0.54, 0.65 and 0.69 applying cut-off values respectively of ≥ 7, ≥ 8 and ≥ 9.

Semantic fluency test

Two studies investigated the accuracy of testing semantic fluency for the diagnosis of dementia. One study on 364 participants (Sager 2006) reported, with moderate certainty, a sensitivity of 0.85 and a specificity of 0.60 applying a cut-off < 14 compared to diagnostic criteria. A second study on 232 participants (Beinhoff 2005), comparing the test to clinical diagnosis, reported, with low certainty, values of sensitivity of 0.85, 0.94, 0.94 and 0.95, and values of specificity of 0.63, 0.58, 0.52 and 0.46 applying cut-off values respectively of < 19, < 20, < 21 e < 22. It also reported, with moderate certainty, values of sensitivity of 0.97 and 0.98, and values of specificity of 0.39 and 0.31 applying cut-off values respectively of < 23 e < 24.

Test Your Memory (TYM)

Two studies investigated the accuracy of the TYM tool compared to clinical diagnosis. One study on 224 participants (Hancock 2011) reported, with moderate certainty, values of sensitivity of 0.73 and 0.95 and values of specificity of 0.88 and 0.45 applying cut-off values respectively of ≤ 30 e ≤ 42. A second study on 201 participants (Postel-Vinay 2014) reported, with moderate certainty, a sensitivity of 0.90 and a specificity of 0.70 applying a cut-off ≤ 39.

NEUROIMAGING

^{18}F-FDG PET

Three studies investigated the accuracy of ^{18}F-FDG PET compared to clinical diagnosis or neuropathology for the diagnosis of dementia. The 3 studies, on a total of 386 participants (Döbert 2005, Frisoni 2009, Silverman 2001), reported, with very low certainty, a sensitivity ranging from 0.54 to 1 and a specificity ranging from 0.76 to 0.83.

Brain Magnetic Resonance imaging (MRI)

Two studies, on a total of 234 participants (Frisoni 2009, Hentschel 2005) investigated the accuracy of RM compared to clinical diagnosis and reported, with very low certainty, a sensitivity ranging from 0.69 to 0.92 and a specificity ranging from 0.55 to 0.58.

^{99m}Tc-HMPAO SPECT

One study on 24 participants (Döbert 2005) investigated the accuracy of ^{99m}Tc-HMPAO SPECT compared to clinical diagnosis reporting, with low certainty, a sensitivity of 0.89 and a specificity of 0.33.

Brain Computerized Tomography (CT)

One study on 116 participants (O'Brien 2000) investigated the accuracy of TC compared to clinical criteria for the diagnosis of dementia reporting, with moderate certainty, a sensitivity of 0.54 and a specificity of 0.77.

CSF

β amyloid (Aβ) 1-42 and total Tau (t-Tau)

Only one study on 94 participants (Frisoni 2009) investigated the accuracy of testing for CSF levels of Aβ 1-42 e t-Tau compared to clinical criteria for the diagnosis of dementia reporting, with moderate certainty, a sensitivity of 0.42 and a specificity of 0.79.

OTHER TESTS

Applause sign (AS)

Only one study on 275 participants (Bonello 2016) investigated the accuracy of the AS test compared to clinical diagnosis reporting, with moderate certainty, a sensitivity of 0.54 and a specificity of 0.85.

Short Smell Test (SST) e riflesso palmo mentoniero (Palmomental Reflex, PMR)

One study on 154 participants (Streit 2015) investigated the accuracy of the SST and PMR tests, individually or combined, compared to clinical criteria, for the diagnosis of dementia. The study reported, with very low certainty, a sensitivity of 0.53 and a specificity of 0.75 for the SST test, and, with low certainty, a sensitivity of 0.41 and a specificity of 0.82 for the PMR test. When considering the combination of both tests, the study reported, with low certainty, a sensitivity of 0.71 and a specificity of 0.64 for at least one positive result, and a sensitivity of 0.24 and a specificity of 0.93 for both positive results.

DIFFERENTIAL DIAGNOSIS

Alzheimer's dementia (AD) *versus* dementia with Lewy's Bodies (DLB)

NEUROIMAGING

^{18}F-FDG PET

One study on 70 participants (Ossenkoppele 2013) investigated the accuracy of ^{18}F-FDG PET compared to clinical criteria in distinguishing people with AD from people with DLB reporting, with very low certainty, a sensitivity of 0.58 and a specificity of 0.20.

Brain Magnetic Resonance imaging (MRI)

One study on 315 participants (Koikkalainen 2016) investigated the accuracy of MRI compared to clinical criteria reporting, with moderate certainty, a sensitivity of 0.29 and a specificity of 0.77.

CSF

β amyloid (Aβ) 1-42

One study on 172 participants (Andreasen 2001) investigated the accuracy of testing for CSF levels of Aβ 1-42 compared to clinical criteria reporting, with moderate certainty, a sensitivity of 0.65 and a specificity of 0.67.

Alzheimer's dementia (AD) versus frontotemporal dementia (FTD)

NEUROIMAGING

^{18}F-FDG PET

One study on 83 participants (Ossenkoppele 2013) investigated the accuracy of ^{18}F-FDG PET compared to clinical criteria reporting, with very low certainty, a sensitivity of 0.58 and a specificity of 0.78.

Brain Magnetic Resonance imaging (MRI)

One study on 315 participants (Koikkalainen 2016) investigated the accuracy of MRI compared to clinical criteria reporting, with moderate certainty, a sensitivity of 0.29 and a specificity of 0.77.

^{99m}Tc-HMPAO SPECT

Three studies investigated the accuracy of single or multiple camera ^{99m}Tc-HMPAO SPECT compared to clinical diagnosis in distinguishing people with AD from people with FTD. When considering single camera 99mTc-HMPAO SPECT, two studies on a total of 59 participants (Launes 1991, Velakoulis 1998) reported, with low certainty, a sensitivity ranging from 0.64 to 0.89 and a specificity ranging from 0.67 to 0.80. When considering multiple camera ^{99m}Tc-HMPAO SPECT, one study on 29 participants (Boutoleau-Bretonnière 2012) reported, with low certainty, a sensitivity of 0.78 and a specificity of 0.73.

CSF

Phosphorylated Tau (p-Tau) 181

One study on 100 participants (Toledo 2012) investigated the accuracy of testing for CSF levels of p-Tau 181 compared to neuropathology for the differential diagnosis, reporting, with moderate certainty, a sensitivity of 0.90 and a specificity of 0.83.

Alzheimer's dementia (AD) versus no dementia

COGNITIVE TESTS

Free recall score of 5-word test

Only one study on 110 participants (Mormont 2012) investigated the accuracy of the 5-word test compared to clinical diagnosis, reporting, with low certainty, a sensitivity of 0.81 and a specificity of 0.99 applying a cut-off ≤ 5. It also reported values of sensitivity of 0.92 and 0.90, and values of specificity of 0.90 and 0.92 applying cut-off values respectively ≤ 9 for total recall scores and ≤ 15 for weighted scores.

Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) 16 and 26 items

One study on 269 participants (Sikkes 2010) investigated the accuracy of the 16-item version of the IQCODE tool compared to clinical criteria and reported, with very low certainty, values of sensitivity of 0.96 and 0.92 and values of specificity of 0.47 and 0.63 applying cut-off values respectively > 3.3 and > 3.4. It also reported, with low certainty, values of sensitivity of 0.96, 0.89 and 0.86 and values of specificity of 0.42, 0.69 and 0.74 applying cut-off values respectively > 3.2, > 3.5 e > 3.6.

Mini Mental State Examination (MMSE)

One study on 110 participants (Mormont 2012) investigated the accuracy of the MMSE compared to clinical diagnosis, reporting, with low certainty, a sensitivity of 0.98 and a specificity of 0.78 applying a cut-off < 28.

NEUROIMAGING

^{18}F-FDG PET

One study on 46 participants (Yakushev 2010) investigated the accuracy of ^{18}F-FDG PET compared to clinical criteria in distinguishing people with AD from people without dementia, reporting, with low certainty, a sensitivity of 0.79 and a specificity of 0.91.

CSF

β amyloid (Aβ) 1-42 and p-Tau 181

One study on 70 participants (Maddalena 2003) investigated the accuracy of testing for CSF levels of Aβ 1-42 e p-Tau 181 compared to clinical criteria in distinguishing people with AD from people without dementia. The study reported, with low certainty, a sensitivity of 0.84 and a specificity of 0.84 for Aβ 1-42, and a sensitivity of 0.67 and a specificity of 0.23 for p-Tau 181. The same study reported, with moderate certainty, a sensitivity of 0.80 and a specificity of 0.89 for the p-Tau/Aβ 1-42 ratio.

Total Tau (t-Tau)

One study on 46 participants (Yakushev 2010) investigated the accuracy of testing for CSF levels of t-Tau compared to clinical criteria, reporting, with low certainty, a sensitivity of 0.46 and a specificity of 0.95.

OTHER TESTS

Applause sign (AS)

One study on 275 participants (Bonello 2016) investigated the accuracy of the AS test compared to clinical criteria, reporting, with moderate certainty, a sensitivity of 0.54 and a specificity of 0.85.

Alzheimer's dementia (AD) versus no dementia or other dementias

NEUROIMAGING

^{18}F-FDG PET

Six studies on a total of 544 participants (Döbert 2005, Frisoni 2009, Ossenkoppele 2013, Panegyres 2009, Silverman 2001, Yakushev 2010) investigated the accuracy of ^{18}F-FDG PET compared to clinical criteria, clinical diagnosis and neuropathology, and reported, with very low certainty, a sensitivity ranging from 0.38 to 0.94 and a specificity ranging from 0.69 to 0.94.

Amyloid PET

Three studies on a total of 11.729 participants (Matsuda 2022, Rabinovici 2019, Zwan 2017) investigated the accuracy of amyloid PET compared to clinical criteria, reporting, with low certainty, a sensitivity ranging from 0.52 to 0.76 and a specificity ranging from 0.48 to 0.66.

Brain Magnetic Resonance (MRI)

Three studies investigated the accuracy of MRI for the differential diagnosis of AD.

Two studies on a total of 637 participants (Frisoni 2009, Koikkalainen 2016) investigated the accuracy of MRI compared to clinical diagnosis. The studies reported, with low certainty, a sensitivity ranging from 0.29 to 0.87 and a specificity ranging from 0.56 to 0.84. When considering the accuracy of the analysis of specific areas, one study on 100 participants (Suppa 2015) reported a sensitivity of 0.61 and a specificity of 0.86 for total hippocampal gray matter volume (cut-off 4.95 ml). The same study reported a sensitivity of 0.70 and a specificity of 0.71 for left hippocampal gray matter volume (cut-off 2.69 ml), a sensitivity of 0.80 and a specificity of 0.66 for the left hippocampal gray matter volume/total hippocampal gray matter volume ratio (cut-off 4,69 per mille). It also reported a sensitivity of 0.75 and a specificity of 0.77 for the right hippocampal gray matter volume (cut-off 2.70 ml), a sensitivity of 0.80 and a specificity of 0.80 for the right hippocampal gray matter volume/total hippocampal gray matter volume ratio (cut-off 4.54/1,000). It reported a sensitivity of 0.66 and a specificity of 0.88 for the total hippocampal gray matter volume/total gray matter volume ratio (cut-off 8.36/1000).

Mass spectrometry

One study on 86 participants (Jahn 2011) investigated the accuracy of CSF levels of synaptic peptides measured with mass spectrometry compared to clinical criteria reporting, with moderate certainty, a sensitivity of 0.87 and a specificity of 0.83.

^{99m}Tc-ECD SPECT

Two studies investigated the accuracy of ^{99m}Tc-ECD SPECT compared to clinical diagnosis for the differential diagnosis between people with AD and people without AD. The two studies, on a total of 206 participants (Kaneta 2016, Tripathi 2010), reported, with very low certainty, a sensitivity ranging from 0.33 to 0.93 and a specificity ranging from 0.73 to 0.95 for visual assessment. One study on 89 participants reported, with very moderate certainty, a sensitivity of 0.40 and a specificity of 0.83 for the automated assessment, and, with low certainty, a sensitivity of 0.71 and a specificity of 0.68 for any type of assessment.

^{99m}Tc-HMPAO SPECT

Two studies investigated the accuracy of ^{99m}Tc-HMPAO SPECT. Five studies on a total of 505 participants (Bergman 1997, Holman 1992, Launes 1991, Masterman 1997, McMurdo 1994) reported, with low certainty, a sensitivity ranging from 0.58 to 0.92 and a specificity ranging from 0.28 to 0.94 compared to clinical diagnosis for single camera ^{99m}Tc-HMPAO SPECT. Two studies on 72 participants (Döbert 2005, Rollin-Sillaire 2012) reported, with low certainty, a sensitivity ranging from 0.31 to 0.57 and a specificity ranging from 0.92 to 1 compared to clinical diagnosis and neuropathology for multiple camera ^{99m}Tc-HMPAO SPECT.

CSF

Amyloid β (Aβ) 1-42, Aβ 1-40, t-Tau, p-Tau

Overall, 13 studies investigated the accuracy of testing for CSF levels of Aβ 1-42, Aβ 1-40, t-Tau and p-Tau for the differential diagnosis of AD. Eight studies on 4,216 participants (Andreasen 2001, Brandt 2008, Duits 2014, Dumurgier 2015, Gabelle 2012, Knapskog 2016, Mulder 2010, Tariciotti 2018) reported, with low certainty, a sensitivity ranging from 0.43 to 0.90 and a specificity ranging from 0.45 to 0.83 compared to clinical diagnosis for Aβ 1-42. Seven studies on 3,979 participants (Brandt 2008, Duits 2014, Dumurgier 2015, Gabelle 2012, Knapskog 2016, Mulder 2010, Tariciotti 2018) reported, with very low certainty, a sensitivity ranging from 0.33 to 0.86 and a specificity ranging from 0.60 to 0.92 compared to clinical diagnosis for p-Tau. When considering the combination of biomarkers, one study on 1,149 participants (Duits 2014) reported, with high certainty, a sensitivity of 0.86 and a specificity of 0.72 compared to clinical criteria for at least two positive results for Aβ 1-42 and t-Tau or p-Tau, and a sensitivity of 0.74 and specificity of 0.86 for all three positive results. One study on 147 participants (Brandt 2008) reported, with high certainty, a sensitivity of 0.42 and a specificity of 0.90 compared to clinical criteria for two positive results out of three. Two studies on 225 participants (Brandt 2008, Jahn 2011) reported, with very low certainty, a sensitivity of 0.62 and a specificity of 0.93 compared to clinical diagnosis for all three positive results. One study on 94 participants (Frisoni 2009) reported a sensitivity of 0.71 and a specificity of 0.88 for positive Aβ 1-42 and e t-Tau. One study on 303 participants (Dumurgier 2015) reported, with low certainty, a sensitivity of 0.87 and a specificity of 0.91 for a positive result for both the Aβ 1-42/1-40 ratio and p-Tau.
When considering the ratios between considered biomarkers, one study on 1,200 participants (Gabelle 2012) reported, with moderate certainty, a sensitivity ranging from 0.81 to 0.85 and a specificity ranging from 0.80 to 0.84 compared to clinical diagnosis for the Aβ 1-42/p-Tau ratio. Two studies on 1,731 participants (Gabelle 2012, Tariciotti 2018), reported a sensitivity ranging from 0.84 to 0.97 and a specificity ranging from 0.43 to 0.79 compared to clinical criteria for the Aβ 1-42/t-Tau ratio. One study on 367 participants (Dumurgier 2015) reported a sensitivity ranging from 0.64 to 0.90 and a specificity ranging from 0.67 to 0.84 compared to clinical diagnosis for the Aβ 1-42/Aβ 1-40 ratio. Two studies on 1,434 participants (Duits 2014, Dumurgier

2015) reported a sensitivity ranging from 0.85 to 0.90 and a specificity ranging from 0.84 to 0.94 compared to clinical diagnosis for the p-Tau/Aβ 1-42 ratio.

Biomarker formulas

One study on 1,149 participants (Duits 2014) investigated the accuracy of different biomarker formulas compared to diagnostic criteria for the differential diagnosis of AD. The study reported, with high certainty, a sensitivity of 0.93 and specificity of 0.74 for Hulstaert's formula (240 + 1,18 x t-Tau = Aβ 42), a sensitivity of 0.80 and specificity of 0.85 Mattson's formula (3.694 + 0,0105 x Tau = Aβ 42/p-Tau). It also reported a sensitivity of 0.93 and specificity of 0.73 for Mulder's formula (373 + 0,82 x Tau =Aβ 42), and a sensitivity of 0.91 and specificity of 0.78 for Schoonenboom's formula (152 + 8,25 x p-Tau = Aβ 42).

OTHER TESTS

Electroencephalography (EEG)

Only one study investigated the accuracy of EEG on 372 participants (Engedal 2015) reporting, with moderate certainty, a sensitivity of 0.70 and a specificity of 0.40 compared to clinical diagnosis.

Urine AD7c-NTP

One study on 168 participants (Goodman 2007) investigated the accuracy of testing for urine levels of AD7c-NTP (Alzheimer-associated neuronal thread protein) compared to clinical criteria, reporting, with moderate certainty, a sensitivity of 0.59 and a specificity of 0.73.

Smell test

One study investigated the accuracy of the smell test compared to clinical diagnosis. The study (Christensen 2017), on 50 participants, reported, with moderate certainty, a sensitivity ranging from 0.79 to 0.50 and a specificity ranging from 0.46 to 0.73 applying cut-off values respectively ≥ 3 e ≥ 4. It also reported, with low certainty, a sensitivity of 0.21 and a specificity of 0.85 applying a cut-off ≥ 5.

Demenza di Alzheimer (AD) versus altre demenze

NEUROIMAGING

^{18}F-FDG PET

Six studies on 300 participants (Arslan 2015, Frisoni 2009, Hoffman 2000, Jagust 2007, Ossenkoppele 2013, Yakushev 2010) investigated the accuracy of ^{18}F-FDG PET compared to clinical diagnosis, clinical criteria and neuropathology reporting, with very low certainty, a sensitivity ranging from 0.58 to 0.93 and specificity ranging from 0.55 to 1.

Brain Magnetic Resonance Imaging (MRI)

Two studies on 471 participants (Frisoni 2009, Koikkalainen 2016) investigated the accuracy of MRI compared to clinical diagnosis reporting, with very low certainty, a sensitivity ranging from 0.29 to 0.87 and specificity ranging from 0.53 to 0.77.

^{99m}Tc-HMPAO SPECT

One study on 33 participants (Velakoulis 1998) reported, with very low certainty, a sensitivity of 0.89 and a specificity of 0.71 compared to clinical diagnosis for single camera ^{99m}Tc-HMPAO SPECT.

Brain Computerized Tomography (CT)

One study on 103 participants (O'Brien 2000) investigated the accuracy of CT compared to clinical criteria reporting, with low certainty, a sensitivity of 0.51 and a specificity of 0.38.

CSF

Amyloid β (Aβ) 1-42, protein 14-3-3, t-Tau, p-Tau 181

Overall, seven studies investigated the accuracy of testing for CSF levels of Aβ 1-42, 14-3-3 protein, t-Tau and p-Tau 181 for the differential diagnosis of AD.
Five studies on 1,099 participants (Boutoleau-Bretonnière 2012, Ibach 2006, Maddalena 2003, Mattsson-Carlgren 2022, Tariciotti 2018) reported, with low certainty, a sensitivity ranging from 0.71 to 1 and specificity ranging from 0.38 to 0.70 for Aβ 1-42 compared to clinical diagnosis and neuropathology. Five studies on 1,095 participants (Boutoleau-Bretonnière 2012, Ibach 2006, Maddalena 2003, Mattsson-Carlgren 2022, Tariciotti 2018) reported, with low certainty, a sensitivity ranging from 0.63 to 0.94 and specificity ranging from 0.20 to 0.86 compared to clinical diagnosis and neuropathology for p-Tau. Five studies on 1,055 participants (Boutoleau-Bretonnière 2012, Ibach 2006, Yakushev 2010, Mattsson-Carlgren 2022, Tariciotti 2018) reported, with low certainty, a sensitivity ranging from 0.54 to 0.89 and specificity ranging from 0.34 to 0.92 compared to clinical diagnosis and neuropathology for t-Tau.
When considering the ratios between considered biomarkers, three studies on 302 participants (Ibach 2006, Maddalena 2003, Mattsson-Carlgren 2022) reported, with low certainty, a sensitivity ranging from 0.78 to 1 and specificity ranging from 0.73 to 0.83 compared to clinical diagnosis and neuropathology for the p-Tau/Aβ 1-42 ratio. One study on 749 participants (Tariciotti 2018) reported, with moderate certainty, a sensitivity of 0.97 and specificity of 0.60 compared to clinical criteria for the Aβ 1-42/t-Tau ratio. One study on 124 participants (Ibach 2006) reported, with very low certainty, a sensitivity of 0.75 and specificity of 0.75 compared to clinical criteria for the t-Tau/Aβ 1-42 ratio.
When considering the combination between considered biomarkers, one study on 66 participants (Frisoni 2009) reported, with low certainty, a sensitivity of 0.71 and specificity of 0.96 compared to clinical criteria for a positive result of both Aβ 1-42 and t-Tau. One study on 44 participants (Boutoleau-Bretonnière 2012) reported, with very low certainty, a sensitivity of 0.97 and specificity of 0.69 for a positive result of 14-3-3 protein, t-Tau e p-Tau.

OTHER TESTS

Alzheimer's disease (AD) Scale

One study on 190 participants (Gustafson 2010) investigated the accuracy of the AD scale compared to neuropathology reporting, with high certainty, a sensitivity of 0.80 and specificity of 0.87 applying a cut-off ≥ 6.

Apolipoprotein E

One study on 2,188 participants (Mayeux 1998) investigated the accuracy of the genetic test for apolipoprotein E (allele ε4, ApoE ε4) compared to neuropathology reporting, with moderate certainty, a sensitivity of 0.65 and specificity of 0.68 for the presence of at least one ApoE ε4allele.

Demenza di Alzheimer (AD) versus demenza vascolare (VaD)

NEUROIMAGING

Brain Magnetic Resonance (MRI)

One study on 247 participants (Koikkalainen 2016) investigated the accuracy of MRI compared to clinical criteria reporting, with low certainty, a sensitivity of 0.29 and specificity of 0.88 in distinguishing AD from VaD.

^{99m}Tc-HMPAO SPECT

Three studies investigated the accuracy of single camera and multiple camera ^{99m}Tc-HMPAO SPECT. Two studies on 97 participants (Launes 1991, McMurdo 1994) reported, with low certainty, a sensitivity ranging from 0.58 to 0.64 and specificity ranging from 0.85 to 1 compared to clinical diagnosis for single camera ^{99m}Tc-HMPAO SPECT. One study on 26 participants (Boutoleau-Bretonnière 2012) reported, with very low certainty, a sensitivity of 0.78 and specificity of 0.50 for multiple camera ^{99m}Tc-HMPAO SPECT.

Brain Computerized Tomography (CT)

One study on 94 participants (O'Brien 2000) investigated the accuracy of CT compared to clinical criteria reporting, with low certainty, a sensitivity of 0.51 and specificity of 0.32 in distinguishing AD from VaD.

CSF

Amyloid β (Aβ) 1-42

One study on 186 participants (Andreasen 2001) reported, with moderate certainty, a sensitivity of 0.65 and specificity of 0.48 compared to clinical criteria for Aβ 1-42.

Behavioural variant (bv) of frontotemporal dementia (FTD) versus non-bv-FTD

NEUROIMAGING

^{18}F-FDG PET and brain MRI

One study on 111 participants (Vijverberg 2016b) investigated the accuracy of ^{18}F-FDG PET and MRI compared to clinical diagnosis. The study reported, with low certainty, a sensitivity of 0.89 and specificity of 0.68 for ^{18}F-FDG PET, a sensitivity of 0.70 and specificity of 0.93 for MRI, and a sensitivity of 0.96 and specificity of 0.73 for the combination of both tests.

CLINICAL CRITERIA

FTD Consortium Criteria (FTDCC)

Two studies investigated the accuracy of FTDCC criteria for the diagnosis of the behavioral variant of FTD. One study on 147 participants (Harris 2013) reported, with moderate certainty, a sensitivity of 0.79 and specificity of 0.96 compared to neuropathology. A second study on 116 participants (Vijverberg 2016a) reported a sensitivity of 0.85 and specificity of 0.27 compared to clinical diagnosis for the diagnosis of possible FTD based on FTCC criteria, and a sensitivity of 0.85 and specificity of 0.82 or the diagnosis of probable FTD.

CADASIL versus sindromi CADASIL-like

OTHER TESTS

Skin biopsy

One study on 90 participants (Ampuero 2009) investigated the accuracy of skin biopsy compared to clinical diagnosis. The study reported, with high certainty, a sensitivity of 0.96 and specificity of 0.68 in distinguishing

people with CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) from people with CADASIL-like syndromes.

Corticobasal Degeneration (CBD) versus non-CBD

CLINICAL CRITERIA

CBD Consensus Criteria (CBDCC)

One study on 33 participants (Alexander 2014) investigated the accuracy of CBDCC criteria compared to neuropathology for the differential diagnosis of CBD. The study reported, with low certainty, a sensitivity of 0.93 and specificity of 0.03.

Creutzfeldt-Jakob Disease (CJD) versus non-CJD

CLINICAL CRITERIA

Three studies investigated the accuracy of different clinical criteria for the diagnosis of CJD.

One study on 236 participants (Brandel 2000) reported, with moderate certainty, a sensitivity of 0.91 and specificity of 0.28 compared to neuropathology for the European Criteria for CJD, a sensitivity of 0.88 and specificity of 0.50 for the French Criteria for CJD, and a sensitivity of 0.98 and specificity of 0.10 for the Masters Criteria for CJD. One study on 74 participants (Zerr 2009) reported, with low certainty, a sensitivity of 0.98 and specificity of 0.71 compared to neuropathology and clinical diagnosis for the new proposed criteria for sporadic CJD. Two studies on 306 participants (Heath 2010, Zerr 2009) reported, with moderate certainty, a sensitivity ranging from 0.89 a 0,92 and specificity ranging from 0.71 to 0.71 compared to clinical criteria and neuropathology for the 1998 WHO criteria for CJD.

NEUROIMMAGINI

Brain Magnetic Resonance imaging (MRI)

Four studies on 564 participants (Schröter 2000, Tagliapietra 2013, Tschampa 2005, Van Everbroeck 2004) investigated the accuracy of MRI compared to clinical diagnosis and neuropathology reporting, with low certainty, a sensitivity ranging from 0.37 to 0.67 and specificity ranging from 0.80 to 0.98.

CSF

Amyloid β (Aβ) 1-42, t-Tau, p-Tau, 14-3-3 protein, S-100B protein

Overall, 23 studies investigated the accuracy of testing for CSF levels of Aβ 1-42, t-Tau, p-Tau, and 14-3-3 and S-100B proteins for diagnosis of CJD.

When considering the different methods for analyzing 14-3-3 protein, two studies on 292 participants (Kenney 2000, Leitão 2016) reported, with low certainty, a sensitivity ranging from 0.89 to 0.97 and specificity ranging from 0.95 to 0.98 for the analysis of 14-3-3 protein with ELISA. Eighteen studies on 6,266 participants (Bahl 2009, Beaudry 1999, Burkhard 2001, Chohan 2010, Coulthart 2011, Cuadrado-Corrales 2006, Fiorini 2020, Fourier 2017, Foutz 2017, Hamlin 2012, Kenney 2000, Lattanzio 2017, Lemstra 2000, Rohan 2015, Tagliapietra 2013, Van Everbroeck 2003, Zerr 1998, Zerr 2000) reported, with low certainty, a sensitivity ranging from 0.81 to 1 and specificity ranging from 0.28 to 1 for the analysis of 14-3-3 with immunoblotting. One study on 268 participants (Fourier 2017) reported, with high certainty, a sensitivity of 0.94 and specificity of 0.95 compared to clinical diagnosis for the analysis of 14-3-3 with Automated Capillary Western Assay.

One study on 174 participants (Tschampa 2005) reported, with moderate certainty, a sensitivity of 0.91 and specificity of 0.44 compared to neuropathology and clinical diagnosis for the analysis of 14-3-3 with multiple methods.

Three studies (Beaudry 1999, Coulthart 2011, Chohan 2010) investigated the accuracy of testing for CSF levels of S-100B protein. Of these, two studies on 1.053 participants (Beaudry 1999, Coulthart 2011) reported, with moderate certainty, a sensitivity ranging from 0.87 to 0.88 and specificity ranging from 0.85 to 0.87 compared to clinical diagnosis, applying a cut-off of 2,5 ng/ml. One study on 412 participants (Chohan 2010) reported, with moderate certainty, a sensitivity of 0.65 and specificity of 0.90 compared to neuropathology, applying a cut-off of 1 ng/ml. One last study on 924 participants (Coulthart 2011) reported, with moderate certainty, a sensitivity of 0.52 and specificity of 0.97 applying a cut-off of 4,2 ng/ml.

Twelve studies on 3.796 participants (Bahl 2009, Chohan 2010, Coulthart 2011, Fiorini 2020, Foutz 2017, Hamlin 2012, Lattanzio 2017, Leitão 2016, Rohan 2015, Tagliapietra 2013, Van Everbroeck 2003, Van Everbroeck 2004) investigated the accuracy of testing for CSF levels of t-Tau. These studies reported, with low certainty, a sensitivity ranging from 0.78 to 0.97 and specificity ranging from 0.67 to 0.98 compared to clinical criteria, clinical diagnosis and neuropathology.

When considering the ratios between considered biomarkers, two studies on 282 participants (Bahl 2009, Leitão 2016) reported, with moderate certainty, a sensitivity ranging from 0.86 to 0.97 and specificity ranging from 0.88 to 0.90 compared to clinical diagnosis and neuropathology for the p-Tau/t-Tau ratio.

When considering the combination of considered biomarkers, one study on 250 participants (Van Everbroeck 2003) reported, with high certainty, a sensitivity of 0.87 and specificity of 0.98 for positive results of Aβ 1-42 and t-Tau, and a sensitivity of 0.99 and specificity of 0.98 for positive 14-3-3 protein and Aβ 1-42. One study on 411 participants (Chohan 2010) reported, with moderate certainty, a sensitivity of 0.62 and specificity of 0.95 for positive 14-3-3 and S-100B. One study on 351 participants (Chohan 2010) reported, with moderate certainty, a sensitivity of 0.75 and specificity of 0.88 compared to neuropathology for positive 14-3-3 and t-Tau. It also reported a sensitivity of 0.59 and specificity of 0.95, with low certainty, for positive t-Tau and S-100B, and a sensitivity of 0.57 and specificity of 0.96, with low certainty, for positive 14-3-3, t-Tau and S-100B.

Neuron-specific enolase

Two studies on 295 participants (Bahl 2009, Beaudry 1999) investigated the accuracy of testing for neuron-specific enolase compared to clinical diagnosis, reporting, with moderate certainty, a sensitivity ranging from 0.73 to 0.80 and specificity ranging from 0.90 to 0.91.

Real-Time Quaking-Induced Conversion (RT-QuIC)

Three studies on 961 participants (Fiorini 2020, Foutz 2017, Lattanzio 2017) investigated the accuracy of RT-QuIC methodology compared to clinical criteria and neuropathology, reporting, with moderate certainty, a sensitivity ranging from 0.82 to 0.96 and specificity ranging from 0.99 to 1.

OTHER TESTS

Electroencephalography (EEG)

Two studies on 202 participants (Tagliapietra 2013, Tschampa 2005) investigated the accuracy of EEG compared to clinical diagnosis reporting, with very low certainty, a sensitivity ranging from 0.32 to 1 and specificity ranging from 0.04 to 0.94.

Dementia with Lewy bodies (DLB) versus Alzheimer's dementia (AD)

NEUROIMAGING

Brain Magnetic Resonance Imaging (MRI)

One study on 270 participants (Koikkalainen 2016) investigated the accuracy of MRI compared to clinical criteria for the differential diagnosis between DLB and AD, reporting, with low certainty, a sensitivity of 0.43 and specificity of 0.71.

OTHER TESTS

Lewy Body Composite Risk Score (LBCRS)

One study on 153 participants (Galvin 2015) investigated the accuracy of the Lewy Body Composite Risk Score compared to clinical criteria for the differential diagnosis between DLB and AD, reporting, with moderate certainty, a sensitivity of 0.94 and specificity of 0.78 applying a cut-off ≥ 3.

Dementia with Lewy bodies (DLB) versus frontotemporal dementia (FTD)

NEUROIMAGING

Brain Magnetic Resonance Imaging (MRI)

One study on 270 participants (Koikkalainen 2016) investigated the accuracy of MRI compared to clinical criteria for the differential diagnosis between DLB and FTD, reporting, with low certainty, a sensitivity of 0.43 and specificity of 0.86.

Dementia with Lewy bodies (DLB) versus non-DLB

NEUROIMAGING

^{18}F-FDG PET

Three studies on 387 participants (Caminiti 2019, Ossenkoppele 2013, Panegyres 2009) investigated the accuracy of 18F-FDG PET compared to clinical diagnosis and neuropathology for the differential diagnosis of DLB, reporting, with low certainty, a sensitivity ranging from 0.20 to 0.89 and specificity ranging from 0.95 to 0.99.

^{123}I-FP-CIT SPECT

Five studies investigated the accuracy of single camera and multiple camera ^{123}I-FP-CIT SPECT for the diagnosis of DLB. Four studies on 179 participants (Jung 2018, Kemp 2011, O'Brien 2009, Thomas 2017) reported, with low certainty, a sensitivity ranging from 0.63 to 0.92 and specificity ranging from 0.83 to 1 for multiple camera ^{123}I-FP-CIT SPECT. One studio on 23 participants (Walker 2009) reported, with low certainty, a sensitivity of 1 and specificity of 0.92 for single camera ^{123}I-FP-CIT SPECT.

^{123}I-IMP SPECT and ^{123}I-MIBG myocardial scintigraphy

Overall, six studies investigated the accuracy of ^{123}I-IMP SPECT and ^{123}I-MIBG myocardial scintigraphy as individual tests or in combination for the differential diagnosis of DLB.

Six studies on 663 participants (Estorch 2008, Manabe 2017, Matsubara 2022, Sakamoto 2014, Sakamoto 2017, Slaets 2015) investigated the accuracy of ^{123}I-MIBG myocardial scintigraphy compared to clinical

diagnosis and neuropathology for the differential diagnosis of DLB, reporting, with low certainty, a sensitivity ranging from 0.67 to 1 and specificity ranging from 0.75 to 1.

One study on 101 participants (Sakamoto 2014) investigated the accuracy of ^{123}I-IMP SPECT and ^{123}I-MIBG myocardial scintigraphy for the differential diagnosis of DLB. The study reported, with low certainty, a sensitivity of 0.62 and specificity of 0.75 compared to clinical criteria for ^{123}I-IMP SPECT and, with moderate certainty, a sensitivity of 0.88 and specificity of 0.86 compared to clinical diagnosis and neuropathology for the combination of ^{123}I-IMP SPECT and ^{123}I-MIBG myocardial scintigraphy.

Brain Magnetic Resonance Imaging (MRI)

One study on 504 participants (Koikkalainen 2016) investigated the accuracy of MRI compared to clinical criteria for the differential diagnosis of DLB, reporting, with moderate certainty, a sensitivity of 0.43 and specificity of 0.76.

OTHER TESTS

Electroencephalography (EEG)

One study on 387 participants (Engedal 2015) investigated the accuracy of the EEG compared to clinical diagnosis for the differential diagnosis of DLB, reporting, with moderate certainty, a sensitivity of 0.87 and specificity of 0.48.

Presence of Rapid-Eye-Movement Sleep Behavior Disorder (RBD), visual hallucinations, Parkinsonism, and fluctuations

One study on 234 participants (Ferman 2011) investigated the accuracy of the presence di RBD, visual hallucinations, Parkinsonism, and fluctuations, and the combination of these symptoms compared to clinical criteria for the differential diagnosis of DLB. The study reported, with high certainty, a sensitivity of 0.90 and specificity of 0.73 for presence of RBD and at least two of the remaining symptoms, and a sensitivity of 0.85 and specificity of 0.73 for the presence of at least two symptoms among visual hallucinations, Parkinsonism, and fluctuations. It also reported a sensitivity of 0.83 and specificity of 0.85 for the presence of at least two symptoms among visual hallucinations, Parkinsonism, and RDB, and sensitivity of 0.88 and specificity of 0.73 for the presence of at least two symptoms among visual hallucinations, Parkinsonism, fluctuations, and RDB.

Dementia with Lewy bodies (DLB) versus other dementias

NEUROIMAGING

^{18}F-FDG PET

One study on 98 participants (Ossenkoppele 2013) investigated the accuracy of the 18F-FDG PET compared to diagnostic criteria, reporting, with very low certainty, a sensitivity of 0.20 and specificity of 0.95.

^{123}I-FP-CIT SPECT

Two studies investigated the accuracy of single camera and multiple camera ^{123}I-FP-CIT SPECT for the differential diagnosis of DLB. One study on 31 participants (Treglia 2012) reported, with moderate certainty, a sensitivity of 0.90 and specificity of 0.91 compared to clinical criteria for single camera ^{123}I-FP-CIT SPECT. One study on 20 participants (Walker 2007) reported, with moderate certainty, a sensitivity of 0.88 and specificity of 1 compared to neuropathology for multiple camera ^{123}I-FP-CIT SPECT.

Brain Magnetic Resonance Imaging (MRI)

One study on 386 participants (Koikkalainen 2016) investigated the accuracy of MRI compared to clinical criteria, reporting, with low certainty, a sensitivity of 0.43 and specificity of 0.76.

CLINICAL CRITERIA

Consensus criteria

One study on 55 participants (Skogseth 2017) investigated the accuracy of the diagnostic consensus criteria for DLB compared to neuropathology, reporting, with low certainty, a sensitivity of 0.80 and specificity of 0.89.

OTHER TESTS

Lewy Body Composite Risk Score (LBCRS)

One study on 177 participants (Galvin 2015) investigated the accuracy of the Lewy Body Composite Risk Score compared to clinical criteria for the differential diagnosis of DLB, reporting, with moderate certainty, a sensitivity of 0.98 and specificity of 0.86 applying a cut-off ≥ 3.

^{123}I-MIBG myocardial scintigraphy

One study on 31 participants (Treglia 2012) investigated the accuracy of ^{123}I-MIBG myocardial scintigraphy compared to clinical diagnosis, reporting, with moderate certainty, a sensitivity of 0.90 and specificity of 0.91.

Dementia with Lewy bodies (DLB) versus vascular dementia (VaD)

NEUROIMAGING

Brain Magnetic Resonance Imaging (MRI)

One study on 71 participants (Koikkalainen 2016) investigated the accuracy of MRI compared to clinical criteria, reporting, with low certainty, a sensitivity of 0.43 and specificity of 0.88.

Demenza frontotemporale (FTD) versus demenza di Alzheimer (AD)

NEUROIMAGING

Brain Magnetic Resonance Imaging (MRI)

One study on 315 participants (Koikkalainen 2016) investigated the accuracy of MRI compared to clinical criteria, reporting, with low certainty, a sensitivity of 0.50 and specificity of 0.72.

^{99m}Tc-HMPAO SPECT

Overall, six studies investigated the accuracy of single camera and multiple camera ^{99m}Tc-HMPAO SPECT for the differential diagnosis between FTD and AD.

Four studies on 291 participants (Launes 1991, Read 1995, Talbot 1998, Velakoulis 1998) reported, with very low certainty, a sensitivity ranging from 0.40 to 1 and specificity ranging from 0.96 to 1 compared to clinical diagnosis and neuropathology for single camera ^{99m}Tc-HMPAO SPECT. Two studies on 64 participants (Boutoleau-Bretonnière 2012, Rollin-Sillaire 2012) reported, with very low certainty, a sensitivity ranging from 0.73 to 0.75 and specificity ranging from 0.96 to 1 compared to clinical diagnosis and neuropathology for multiple camera ^{99m}Tc-HMPAO SPECT.

Frontotemporal dementia (FTD) versus dementia with Lewy bodies (DLB)

NEUROIMAGING

^{18}F-FDG PET

One study on 23 participants (Ossenkoppele 2013) investigated the accuracy of ^{18}F-FDG PET compared to clinical criteria for the differential diagnosis between FTD and DLB, reporting, with very low certainty, a sensitivity of 0.34 and specificity of 0.92.

Brain Magnetic Resonance Imaging (MRI)

One study on 139 participants (Koikkalainen 2016) investigated the accuracy of brain MRI compared to clinical criteria for the differential diagnosis between FTD and FTD e DLB, reporting, with very low certainty, a sensitivity of 0.50 and specificity of 0.94.

Frontotemporal dementia (FTD) versus non-FTD

NEUROIMAGING

^{18}F-FDG PET

Two studies on 255 participants (Ossenkoppele 2013, Panegyres 2009) investigated the accuracy of ^{18}F-FDG PET compared to clinical diagnosis and neuropathology, reporting, with very low certainty, a sensitivity ranging from 0.33 to 0.53 and specificity ranging from 0.91 to 0.95.

Brain Magnetic Resonance Imaging (MRI)

Two studies on 638 participants (Koikkalainen 2016, Mendez 2007) investigated the accuracy of brain MRI compared to clinical diagnosis and neuropathology, reporting, with low certainty, a sensitivity ranging from 0.50 a 0,63 and specificity ranging from 0.70 to 0.84.

^{99m}Tc-ECD SPECT

One study on 117 participants (Tripathi 2010) investigated the accuracy of ^{99m}Tc-ECD SPECT with visual assessment compared to clinical criteria, reporting, with moderate certainty, a sensitivity of 0.96 and specificity of 0.99.

^{99m}Tc-HMPAO SPECT

Five studies investigated the accuracy of single camera and multiple camera ^{99m}Tc-HMPAO SPECT for the differential diagnosis of FTD.

Three studies on 501 participants (Launes 1991, Read 1995, Talbot 1998) reported, with very low certainty, a sensitivity ranging from 0.36 to 1 and specificity ranging from 0.92 to 1 compared to clinical diagnosis and neuropathology for single camera ^{99m}Tc-HMPAO SPECT. Two studies on 108 participants (Boutoleau Bretonnière 2012, Rollin-Sillaire 2012) reported, with very low certainty, a sensitivity ranging from 0.73 to 0.75 and specificity ranging from 0.80 to 0.97 compared to clinical diagnosis and neuropathology for multiple camera ^{99m}Tc-HMPAO SPECT.

CLINICAL CRITERIA

Frontotemporal dementia (FTD) Consensus Criteria

One study on 134 participants (Mendez 2007) investigated the accuracy of the consensus criteria for FTD compared to clinical diagnosis reporting, with high certainty, a sensitivity of 0.37 and specificity of 0.99.

Frontotemporal dementia (FTD) versus other dementias

NEUROIMAGING

^{18}F-FDG PET

Two studies on 146 participants (Arslan 2015, Ossenkoppele 2013) investigated the accuracy of ^{18}F-FDG PET compared to clinical diagnosis, reporting, with very low certainty, a sensitivity ranging from 0.33 to 0.47 and specificity ranging from 0.65 to 0.88.

Brain Magnetic Resonance Imaging (MRI)

One study on 386 participants (Koikkalainen 2016) investigated the accuracy of brain MRI compared to clinical criteria reporting, with low certainty, a sensitivity of 0.50 and specificity of 0.78.

^{99m}Tc-HMPAO SPECT

One study on 33 participants (Velakoulis 1998) investigated the accuracy of single camera ^{99m}Tc-HMPAO SPECT compared to clinical diagnosis, reporting, with very low certainty, a sensitivity of 0.56 and specificity of 0.96.

OTHER TESTS

FTD Scale

One study on 190 participants (Gustafson 2010) investigated the accuracy of the FTD compared to neuropathology for the differential diagnosis of frontotemporal dementia, reporting, with high certainty, a sensitivity of 0.92 and specificity of 0.92 applying a cut-off ≥ 6.

Frontotemporal dementia (FTD) versus vascular dementia (VaD)

NEUROIMAGING

Brain Magnetic Resonance Imaging (MRI)

One study on 116 participants (Koikkalainen 2016) investigated the accuracy of brain MRI compared to clinical criteria, reporting, with low certainty, a sensitivity of 0.50 and specificity of 0.96.

^{99m}Tc-HMPAO SPECT

Three studies investigated the accuracy of single camera and multiple camera ^{99m}Tc-HMPAO SPECT for the differential diagnosis between FTD and VaD.

Two studies on 196 participants (Launes 1991, Talbot 1998) reported, with very low certainty, a sensitivity ranging from 0.40 to 0.46 and specificity ranging from 0.73 to 0.94 compared to clinical diagnosis for single camera 99mTc-HMPAO SPECT. One study on 19 participants (Boutoleau-Bretonnière 2012) reported, with very low certainty, a sensitivity of 0.73 and specificity of 0.75 compared to clinical diagnosis for multiple camera 99mTc-HMPAO SPECT.

Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB) versus other dementias

OTHER TESTS

^{123}I-MIBG myocardial scintigraphy

One study on 96 participants (Hanyu 2006) investigated the accuracy of ^{123}I-MIBG myocardial scintigraphy compared to clinical criteria, reporting, with moderate certainty, a sensitivity of 0.95 and specificity of 0.87.

Parkinson's disease dementia (PDD) versus non-PDD

CLINICAL CRITERIA

Movement Disorders Society Criteri (MDS) for PDD

One study on 40 participants (Kiesmann 2013) investigated the accuracy of MDS criteria for PDD compared to clinical diagnosis, reporting, with low certainty, a sensitivity of 0.80 and specificity of 0.95 applying a cut-off ≤ 120, a sensitivity of 0.94 and specificity of 0.78 applying a cut-off ≤ 123, and a sensitivity of 0.98 and specificity of 0.45 applying a cut-off ≤ 132.

OTHER TESTS

Free and Cued Selective Reminding Test-Immediate Recall 3-FR (FCSRT-IR 3-FR)

One study on 40 participants (Kiesmann 2013) investigated the accuracy of the FCSRT-IR 3-FR tool for Parkinson's disease dementia compared to clinical diagnosis, reporting, with low certainty, a sensitivity of 0.84 and specificity of 0.78 applying a cut-off ≤ 22.

Primary Progressive Aphasia (PPA) versus non-PPA

NEUROIMAGING

^{18}F-FDG PET

One study on 102 participants (Panegyres 2009) investigated the accuracy of ^{18}F-FDG PET compared to clinical criteria, reporting, with low certainty, a sensitivity of 0.50 and specificity of 0.99 for the differential diagnosis of primary progressive aphasia.

Vascular dementia (VaD) and mixed dementia versus Alzheimer's dementia (AD)

OTHER TESTS

Hachinski Ischemic Score (HIS)

One study on 214 participants (Siritho 2006) investigated the accuracy of the HIS scale compared to clinical diagnosis for the differential diagnosis between vascular or mixed dementia and AD, reporting, with low certainty, a sensitivity of 0.86 and specificity of 0.73 applying a cut-off ≥ 5.

Vascular dementia (VaD) versus Alzheimer's dementia (AD) and mixed dementia

CLINICAL CRITERIA

Alzheimer's Disease Diagnostic and Treatment Centers Criteria (ADDTC)

Two studies investigated the accuracy of the ADDTC criteria compared to neuropathology for the differential diagnosis between vascular dementia and AD or mixed dementia. One study on 89 participants (Gold 2002) reported, with moderate certainty, values of sensitivity of 0.70 and 0.25, and values of specificity of 0.78 and 0.91 for the definition respectively of a possible and probable diagnosis. The second study, on 110 participants (Bacchetta 2007), reported, with low certainty, a sensitivity of 0.58 and specificity of 0.74.

Criteria of the National Institute of Neurological Disorders and Stroke (NINDS) and Association Internationale pour la Recherche et l'Enseignement en Neurosciences (AIREN) (NINDS-AIREN Criteria)

Two studies investigated the accuracy of NINDS-AIREN criteria compared to neuropathology for the differential diagnosis between vascular dementia and AD or mixed dementia. One study on 89 participants (Gold 2002) reported, with moderate certainty, values of sensitivity of 0.55 and 0.84, and values of specificity of 0.20 and 0.93 for the definition respectively of a possible and probable diagnosis. The second study, on 110 participants (Bacchetta 2007), reported, with low certainty, a sensitivity of 0.56 and specificity of 0.73.

OTHER TESTS

Hachinski Ischemic Score (HIS)

One study on 110 participants (Bacchetta 2007) investigated the accuracy of the HIS scale compared to clinical diagnosis for the differential diagnosis between vascular dementia and AD or mixed dementia, reporting, with low certainty, a sensitivity of 0.56 and specificity of 0.66 applying a cut-off ≥ 7.

Vascular dementia (VaD) versus Alzheimer's dementia (AD)

NEUROIMAGING

Brain Magnetic Resonance Imaging (MRI)

One study on 247 participants (Koikkalainen 2016) investigated the accuracy of brain MRI compared to clinical criteria for the differential diagnosis between VaD and AD, reporting, with low certainty, a sensitivity of 0.71 and specificity of 0.997.

^{99m}Tc-HMPAO SPECT

Two studies 97 participants (Launes 1991, McMurdo 1994) investigated the accuracy of single camera ^{99m}Tc-HMPAO SPECT compared to clinical criteria for the differential diagnosis between VaD and AD, reporting, with low certainty, a sensitivity ranging from 0.76 to 1 and specificity ranging from 0.72 to 0.785.

Vascular dementia (VaD) versus dementia with Lewy bodies (DLB)

NEUROIMAGING

Brain Magnetic Resonance Imaging (MRI)

One study on 71 participants (Koikkalainen 2016) investigated the accuracy of brain MRI compared to clinical criteria for the differential diagnosis between VaD and dementia with Lewy bodies, reporting, with low certainty, a sensitivity of 0.71 and specificity of 0.97.

Vascular dementia (VaD) versus frontotemporal dementia (FTD)

NEUROIMAGING

Brain Magnetic Resonance Imaging (MRI)

One study on 116 participants (Koikkalainen 2016) investigated the accuracy of brain MRI compared to clinical criteria for the differential diagnosis between VaD and frontotemporal dementia, reporting, with low certainty, a sensitivity of 0.71 and specificity of 0.96.

^{99m}Tc-HMPAO SPECT

One study on 38 participants (Launes 1991) investigated the accuracy of ^{99m}TcHMPAO SPECT compared to clinical criteria for the differential diagnosis between VaD and frontotemporal dementia, reporting, with low certainty, a sensitivity of 0.76 and specificity of 0.60.

Vascular dementia (VaD) versus non-VaD

NEUROIMAGING

Brain Magnetic Resonance Imaging (MRI)

One study on 504 participants (Koikkalainen 2016) investigated the accuracy of brain MRI compared to clinical criteria for the differential diagnosis of VaD, reporting, with moderate certainty, a sensitivity of 0.71 and specificity of 0.96.

^{99m}Tc-HMPAO SPECT

Two studies 204 participants (Launes 1991, McMurdo 1994) investigated the accuracy of ^{99m}Tc-HMPAO SPECT compared to clinical diagnosis for the differential diagnosis of VaD, reporting, with low certainty, a sensitivity ranging from 0.76 to 1 and specificity ranging from 0.53 to 0.76.

Vascular dementia (VaD) versus other dementias

NEUROIMAGING

Brain Magnetic Resonance Imaging (MRI)

One study on 386 participants (Koikkalainen 2016) investigated the accuracy of brain MRI compared to clinical criteria for the differential diagnosis of VaD, reporting, with low certainty, a sensitivity of 0.71 and specificity of 0.96.

OTHER TESTS

Hachinski Ischemic Score (HIS)

One study on 190 participants (Gustafson 2010) investigated the accuracy of the HIS scale compared to neuropathology for the differential diagnosis of VaD, reporting, with moderate certainty, a sensitivity of 0.69 and specificity of 0.92.

Diagnosis of Mild Cognitive Impairment (MCI) in a specialist care setting

Review question 2d

The systematic review of literature identified 19 studies meeting the predefined eligibility criteria. Studies were classified according to the type of diagnostic tool and data were reported according to type of test and its cut-off where considered.

COGNITIVE TESTS

AD8 Dementia Screening Interview (AD8)

Two studies on 200 participants (Larner 2015, Razavi 2014) investigated the accuracy of the AD8 tool compared to clinical diagnosis reporting, with low certainty, a sensitivity ranging from 0.97 to 1 and specificity ranging from 0.17 to 0.77 applying a cut-off ≥ 2.

Clinical Dementia Rating Scale (CDR)

Only one study on 697 participants (Woolf 2016) investigated the accuracy of the CDR scale compared to clinical diagnosis reporting, with moderate certainty, a sensitivity of 0.24 and specificity of 0.95 applying a cut-off score of 0,5.

Clock Drawing Test (CDT)

Five studies investigated the accuracy of the different systems used to calculate the CDT score compared to clinical diagnosis. When considering Sunderland's scoring system, two studies on 257 participants (Ravaglia 2005, Yamamoto 2004) reported, with low certainty, a sensitivity ranging from 0.06 to 0.40 and specificity ranging from 0.85 to 0.95 applying a cut-off score of 5. One study on 89 participants (Yanamoto 2004) reported, with low certainty, values of sensitivity of 0.60 and 0.67 and values of specificity of 0.95 and 0.90 for cut-off scores respectively of 7 and 8. The same study reported, with low certainty, values of sensitivity of 0.60, 0.75 and 0.83 and values of specificity of 0.93, 0.76 and 0.66 for cut-off scores respectively of 6, 7 and 8 for Cahn's system. When considering Rouleau's system, one study on 108 participants (Ramlall 2014) reported, with low certainty, a sensitivity of 0.43 and specificity of 0.92 for a cut-off score of 5. Two studies on 643 participants (Lee 2008, Yamamoto 2004) reported, with low certainty, a sensitivity ranging from 0.56 to 0.79 and specificity ranging from 0.66 to 0.93 for cut-off scores from 7 to 8. Only one study on 105 participants (Beinhoff 2005), on Shulman's system di, reported, with low certainty, a sensitivity of 0.40 and specificity of 0.60 compared to clinical criteria. One study on 168 participants (Ravaglia 2005) reported, with low certainty, a sensitivity of 0.23 and specificity of 0.89 for a cut-off score of 6 with Wolf-Klein's system. One last study on 465 participants (Lee 2008), reported, with moderate certainty, values of sensitivity of 0.44 and 0.41 and values of specificity of 0.81 and 0.83 for cut-off scores respectively from 6 to 6,5 with Todd's system and from 9 to 10 Freedman's system.

Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)

Only one study on 57 participants (Razavi 2014) investigated the accuracy of the IQCODE tool compared to clinical criteria, reporting, with low certainty, a sensitivity of 0.46 and specificity of 0.89 applying a cut-off ≥ 3,4.

Mini Addenbrooke's Cognitive Examination (Mini-ACE)

Two studies on 717 participants (Larner 2017, Williamson 2018) investigated the accuracy of the Mini-ACE tool compared to clinical diagnosis, reporting, with moderate certainty, a sensitivity ranging from 0.95 to 0.97 and specificity ranging from 0.49 to 0.51 applying a cut-off score of 25.

Mini Mental State Examination (MMSE)

Nine studies investigated the accuracy of different cut-off scores of the MMSE tool compared to clinical diagnosis or clinical criteria for the diagnosis of Mild Cognitive Impairment (MCI). Four studies on 574 participants (Dong 2013, Larner 2015, Luis 2009, Ravaglia 2005) reported, with low certainty, a sensitivity ranging from 0.17 to 0.76 and specificity ranging from 0.75 to 0.96 applying a cut-off score of 24-25. Six studies on 2.805 participants (Biundo 2013, Dong 2013, Mellor 2016, Saxton 2009, Smith 2007, Yu 2012) reported, with low certainty, a sensitivity ranging from 0.06 to 0.87 and specificity ranging from 0.74 to 1 applying a cut-off score of 25-26. One study on 89 participants (Biundo 2013) reported, with moderate certainty, a sensitivity of 0.53 and specificity of 0.78 applying a cut-off score of 26-27. Three studies on 701 participants (Biundo 2013, Luis 2009, Saxton 2009) reported, with low certainty, a sensitivity ranging from 0.29 to 0.85 and specificity ranging from 0.45 to 0.92 applying a cut-off score of 27-28.

Montreal Cognitive Assessment (MoCA)

Seven studies investigated the accuracy of different cut-off scores of the MoCA scale compared to clinical diagnosis or diagnostic criteria for the diagnosis of MCI. One study on 211 participants (Dong 2013) reported, with low certainty, a sensitivity of 0.80 and specificity of 0.92 applying a cut-off score of 19-20. One study on 693 participants (Dautzenberg 2022) reported, with very low certainty, a sensitivity of 0.37 and specificity of 0.78 compared to clinical diagnosis, applying a cut-off score of 21. One study on 980 participants (Yu 2012)

reported, with moderate certainty, a sensitivity of 0.69 and specificity of 0.64 applying a cut-off score of 21-22. Two studies on 1.064 participants (Luis 2009, Mellor 2016) reported, with low certainty, a sensitivity ranging from 0.87 to 0.96 and specificity ranging from 0.73 to 0.95 applying a cut-off score of 22-23. Six studies on 9.994 participants (Dautzenberg 2022, Larner 2017, Lu 2011, Luis 2009, Smith 2007, Yu 2012) reported, with low certainty, a sensitivity ranging from 0.80 to 1 and specificity ranging from 0.31 to 0.82 applying a cut-off score of 26.

Trail Making Test-A (TMT-A)

Two studies on 1.596 participants (Ramlall 2014, Wei 2018) investigated the accuracy of the TMT-A tool compared to clinical criteria reporting, with low certainty, a sensitivity ranging from 0.48 to 0.77 and specificity ranging from 0.,63 to 0.78 applying a cut-off score of 72 to 72,5.

Analysis of evidence

Initial assessment in a non-specialist, primary care setting

Review question 2a and 2b

The diagnostic process for dementia is very complex and should be performed on a consequential sequence. Diagnostic tools can vary according to different settings, such as primary care (e.g., general practitioners) and specialist structures (e.g., memory clinics), as each setting aims at identifying a different outcome. For this reason, evidence was analyzed separately for each different clinical setting.

Receiving a diagnosis of dementia is a traumatic and distressing experience both at the time on the actual communication, and during all the phases of the diagnostic process. Therefore, this process should be led with extreme care.

For this reason, the tool chosen to support the diagnosis should be accurate, but also easy to administer, and should require a small amount of time to reduce the impact on tested people in terms of physical and/or emotional stress, while ensuring the most appropriate diagnostic prescription. Providing information and explanations throughout the entire diagnostic process, to allow people with dementia and/or their caregivers/tutors to sign an informed consent to each proposed procedure, is also essential, mainly in case of particularly tasking procedures.

The systematic review of evidence on diagnostic tools in the primary care setting (e.g., general practices, hospital) was specifically aimed at defining the most accurate tests for identifying people with a suspect dementia/cognitive decline that have a higher probability of actually having a cognitive deficit and should therefore be referred to a specialist center to receive a formal diagnosis.

Identified tools were validated, informative cognitive tests that require a short amount of time to be administered, and that are supported by studies comparing their accuracy to clinical criteria or other reference tests with a proven accuracy in supporting the diagnosis of dementia.

The shorter amount of time for peoplein a primary care setting compared to a specialist setting allows them to access a faster evaluation of the suspect of dementia. Therefore, clinicians operating in the primary setting (e.g., general practitioners, hospital-based physicians) need to use validated cognitive tests that are at the same time fast to administer and accurate, in terms of sensitivity and specificity, in quickly determining whether the tested person might have a form of dementia or cognitive decline.

Based on these considerations, none of the invasive diagnostic tests was considered for this setting in the NICE guideline nor in this update.

The approach to people with a suspect of dementia should start with asking for an informative history guided by an accurate anamnesis on clinical history, activities of daily living, and family and social relationships, with particular attention to any change in interests and behaviors and in sleep quality. Specific attention should

be paid to cognitive and psycho-behavioral symptoms, but also to their impact on daily life and independence.
To this purpose, the NICE guideline recommends considering a structured tool, the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) or the Functional Activities Questionnaire (FAQ), which can be filled independently by an informant. Considering that these tools are not currently applied in clinical practice in Italy, the WG agreed to remove the recommendation to consider these tools.
The clinical interview involves both people with a suspect cognitive decline and their close family members/caregivers, who can provide valuable information. An appropriate initial assessment should include a physical examination where the general practitioner globally evaluates the person in relation to their basic clinical parameters (vital signs), nutritional status, motor functions, ability to stay focused during the examination, and ability to express themselves. Other conditions and diseases should also be considered that might affect cognitive assessment and support the suspect of dementia, such as sensory deficits (visual and hearing impairment), depressive disorders, delirium, and use of anticholinergic drugs or other psychotropic medications.
Within this initial diagnostic approach, using a validated test both accurate and requiring a short time to be administered is essential.
The initial assessment in the primary care setting is aimed at confirming the suspect of dementia or cognitive deficit, but also at excluding secondary and potentially reversible causes of cognitive decline that might be due to medical reasons or other neurological conditions. Therefore, along with blood and urine tests, as suggested by the NICE guideline, the WG discussed and agreed to include also basic neuroimaging tests (i.e., brain CT and/or brain MRI) within the initial diagnostic workup in the primary care setting. In the NICE guideline, this indication is included in the specialist setting based on the assumption that these tests, along with SPECT and PET imaging, and biomarkers, are not available in a primary care setting. However, the WG believes that basic structural imaging has a relevant role, allowing the potential identification of specific conditions, some of which are common, such as vascular issues (e.g., subdural hematoma), brain neoplasms, hydrocephalus, that may cause cognitive disorders, and require a timely intervention by a specialist team in a secondary care setting.
Particular attention should be payed to cases when symptoms of cognitive disorders or dementia have a quick progression in a short amount of time. These conditions require a timely neurological examination aimed at excluding, through specific tests, the potential presence of infective, inflammatory, vascular or toxic-metabolic disorders. This approach also includes the suspect of CJD (Creutzfeldt Jakob Disease) that requires a specific specialist diagnostic workup including neuroimaging, electrophysiology (EEG) and biomarkers.
Failing to identify a potential secondary cognitive decline significantly increases the time from symptom onset to diagnosis, mainly when people are inappropriately referred to a first neurological visit in a memory clinic instead of being referred to a neurological examination or, if necessary, a neurosurgical visit. An excessive deferral of the diagnosis causes both a delay in the initiation of any intervention for the condition, and an unmotivated stress for people and resource cost.
In line with the NICE guideline, and based on their clinical experience, the WG did not judge as appropriate considering the use of other tests such as SPECT, PET and CSF biomarkers in primary care setting to support the decision of referring people with a suspect of dementia to a clinician in a specialist setting. These tests are, in fact, not only unavailable in the primary care setting, but also expensive in terms of costs and resources. However, their informational value should be considered in a subsequent phase of the diagnostic process, in a specialist setting, as a tool to support the differential diagnosis and the classification of the subtype of dementia, that are both to be defined by an expert specialist.
The benefits of an early diagnosis of primary dementia are currently only theoretical, due to the unavailability of a disease-modifying pharmacological treatment. However, receiving a timely diagnosis can allow people with dementia and their families/caregivers to make important decisions on medical, legal and financial

issues, ensure the safety of their homes, define goals, and support healthcare professionals in planning a shared care path.
One of the critical issues of the initial diagnostic process is the possibility that people in this phase express the will not to receive feedback from the assessment or to know the diagnosis, thus preventing, to their detriment, the activation of a care plan.
Considering the primary setting and the use of tools for the initial assessment of a suspect of cognitive decline, the WG confirmed the recommendation not to rule out cognitive decline solely because the person has a normal score on a cognitive instrument.
The WG confirmed the indication from the NICE guideline to choose brief structured cognitive instrument, suitable for the primary setting, with adequate values of sensitivity (≥80%) and specificity (≥70%). It also agreed that available evidence did not support a specific test over the others, thus proposing a list of possible tests.
Based on new gathered evidence, the accuracy of analyzed tests was recalculated for each considered cut-off, including both the studies identified in the NICE guideline and those identified through the update, and both the tests analyzed in the NICE guideline and new tests identified by the update.
Some tests adopted in the studies identified through the update appeared too selective, as they were aimed at analyzing only one specific cognitive domain that might be impaired in one specific subtype of dementia, preventing the adequate assessment of a suspect of dementia within a primary care setting.
However, based on the update of the evidence considered for the NICE guideline, the WG included a recommendation to use, among the suggested brief structured cognitive instruments, the General Practitioner assessment of Cognition (GPCog), with a cut-off < 11, which showed a good accuracy in distinguishing people with dementia from people without dementia in a large moderate-quality study.
The WG confirmed the recommendations included in the NICE guideline to use the 10-point Cognitive Screener (10-CS), the 6-item Cognitive Impairment Test (6-CIT), the 6-item Screener (6-IS), the Memory Impairment Screen (MIS), the Mini-Cog, and the Test Your Memory (TYM) tool.
The analysis of evidence, in line with the NICE guideline, confirmed a low certainty of evidence for several tests, due to a high to very high risk of bias. Such risk was mainly due to a lack of reporting of blindness procedures (especially in relation to the use of an index test versus a reference standard), the use of optimized cut-offs, and subgroup analyses excluding large portions of participants (e.g., people with mild cognitive decline), lowering the quality of evidence.
The WG, in line with the NICE guideline, agreed that clinicians should be aware of the further challenges in diagnosis dementia in frail or vulnerable people, such as people with neurodevelopmental disorders or Down's syndrome, people with language and sensory impairment, or people with a lower level of education. Despite available evidence does not support a specific recommendation on how to organize a diagnostic process in these groups of people, the WG, in line with the NICE guideline, agreed on the importance of referring these patients, who require a more complex diagnosis, to a clinician with specific expertise, who should be able to adapt adequately the diagnostic procedure. A reference to the NICE Guideline NG54[18] was also included, referring to people with mental disorder or learning disabilities, providing indications on some specific tools that can be used to assess for dementia in these groups of people.
The WG, in line with the NICE guideline also highlighted the relevance of administering some tests (e.g., the MoCA) that provide less robust assessment in some subgroups due to cultural differences, levels of education, or language barriers, that could mistakenly lead to a diagnosis of dementia or a suspect of dementia.
Therefore, it is necessary to account for these issues, even in a specialist setting, while choosing which cognitive test to use, defining, if needed, the most appropriate and specific cut-offs. On this basis, the NICE

[18] NICE. Mental health problems in people with learning disabilities: prevention, assessment and management. NICE guideline [NG54]. Published: 14 September 2016. https://www.nice.org.uk/guidance/ng54

guideline underlines that specifying the cut-off to be adopted for each test is inappropriate, as these should always be adjusted for single persons and settings.
The WG observed that neuropsychological tests are not designed for diagnosing dementia in a primary setting. This assessment requires a specific expertise and a longer time for the administration and analysis or results. Moreover, these tests assess the performance for specific domains, or are included in batteries that assess several different aspects of complex constructs (e.g., memory).
Overall, the details obtained from an accurate neuropsychological assessment provide useful information both for the diagnostic process, and for the diagnosis of the different subtypes of dementia in a specialist setting.

Diagnosis of dementia in a specialist care setting

Review question 2c

The diagnostic process for dementia in a specialist setting, such as memory clinics (e.g., Centres for Cognitive disorders and dementias) needs to be planned as a sequence, and tailored to each person, based on the ability of the tests adopted in each phase to correctly define the diagnosis. The decision to include further tests in the diagnostic process should be programmed gradually when a further support is needed to clarify diagnostic uncertainties and perform a differential diagnosis to define a specific subtype of dementia. In cases where reaching a diagnosis is more difficult, clinicians can consider the use of all tests that can provide a relevant diagnostic support, along with the test that is considered as the best option to define the specific diagnosis.
The diagnosis of dementia remains mainly clinical, with the reference standard being the specific clinical criteria for each dementia subtype.
Clinical judgement from specialists throughout the diagnostic process should be guided by the recognized and updated clinical criteria of reference for each dementia subtype:

- International consensus criteria for dementia with Lewy bodies (McKeith 2017);
- International criteria for Creutzfeldt-Jakob disease (Watson 2022);
- International FTD criteria for frontotemporal dementia (primary progressive non-fluent aphasia and semantic dementia) (Gorno-Tempini 2011);
- International Frontotemporal Dementia Consortium criteria for behavioural variant frontotemporal dementia (Rascovsky 2011);
- NINDS-AIREN criteria for vascular dementia (Román 1993);
- NIA criteria for Alzheimer's disease (McKhann 2011);
- Movement Disorders Society criteria for Parkinson's disease dementia (Dubois 2007);
- WHO Global Surveillance, diagnosis, and therapy of human transmissible spongiform encephalopathies (1998).

Limited evidence is available on the diagnostic accuracy of clinical criteria compared to neuropathology, with variable certainty of evidence.
Literature from both the NICE guideline and this update did not identify studies assessing the diagnostic accuracy of clinical criteria for the diagnosis of AD (McKhann 2011) compared to neuropathological diagnosis, which is considered as the gold standard.
One low-quality study on the diagnostic performance of consensus criteria for DLB compared to neuropathology reported high sensitivity and specificity of these criteria in supporting the differential diagnosis of DLB versus other dementias.
Consensus criteria for frontotemporal dementia, in particular criteria referring to the behavioral variant (differential diagnosis bv-FTD versus non-bv FTD) compared to neuropathology, were reported to have a

good sensitivity and specificity for the diagnosis of overall FTD, irrespective of its subtypes, in a moderate-quality study.
A low-quality study on the Movement Disorders Society criteria for Parkinson's disease dementia reported a good accuracy of these criteria compared to clinical diagnosis (reference standard) for higher cut-offs.
Evidence on the NINDS-AIREN criteria compared to neuropathology reported a low sensitivity and good specificity of these criteria in distinguishing vascular dementia from AD and mixed dementia.
Several studies on the accuracy of different clinical criteria for the diagnosis of sporadic CJD reported a good sensitivity and specificity of the 1998 WHO criteria. However, the certainty of this evidence was very low. Evidence on the performance of the French criteria for CJD was instead of moderate certainty, despite reporting a lower overall accuracy.
One low-quality study on the Corticobasal degeneration Consensus Criteria (CBDCC) reported these criteria as having a good sensitivity and a very low specificity compared to neuropathology.
Most of the included studies used clinical criteria as a reference standard to assess the accuracy of investigated tests for the diagnosis of dementia subtypes. Clinical criteria can be considered as an appropriate *in vivo* reference standard, considering that neuropathology, the gold standard for diagnosis, is available, except for very rare cases, only *postmortem*.
Within the clinical framework leading to the initial diagnosis from the specialist, neuropsychological examination is crucial as it allows to confirm a cognitive deterioration (dementia versus non-dementia), and is also determinant, when using tests or batteries targeted to specific domains, in supporting the differential diagnosis of each dementia subtype.
The initial assessment from a specialist should include a neurological examination and the administration of cognitive tests capable to distinguish people with dementia from people without dementia.
In case the presence of cognitive decline is confirmed, the most reliable and updated clinical criteria should be used for the differential diagnosis.
The evidence reviewed identified data on several tests available for the diagnosis of dementia through a short but thorough evaluation of the cognitive performance.
Evidence from moderate-quality studies on the Addenbrooke's Cognitive Examination (ACE) and the Clock Drawing Test (CDT), both validated in the Italian population (Caffarra 2011, Pigliautile 2011) reported a good accuracy of some cut-offs of these tests. Evidence on the Boston Naming Test (< 13) reported a good accuracy of this test in confirming the presence of dementia but a low accuracy in excluding a cognitive decline.
One high-quality study reported a good accuracy of the Brief Neuropsychological Test Battery.
One moderate-quality study reported a very good performance of the Mini-Cog (Scanlan & Borson).
One high-quality study reported a good accuracy of the < 4 and < 5 cut-offs of the Memory Impairment Screen (MIS) test.
One moderate-quality study reported a good accuracy of cut-off up to < 22 of the Mini Mental State Examination (MMSE) in a primary care setting, while reporting a lower accuracy in the specialist setting.
Evidence on the MoCA, a tool validated in Italian population (Bosco 2017, Pirani 2022), reported, with low certainty, a good performance of the < 19 cut-off of this test.
Two moderate-quality studies on the Rowland Universal Dementia Assessment Scale (RUDAS) reported a good accuracy of this test in identifying true negatives.
One moderate-quality study reported a good performance of the < 14 cut-off of the semantic fluency test compared to clinical criteria.
Overall, the analysis of evidence on neuropsychological tests did not allow to recommend one specific test among the others.
Based on the relevance of the initial phase of the diagnostic process in a specialist setting, the WG agreed that a thorough assessment of cognitive functions through validated neuropsychological tests should an essential part of the diagnostic workup for dementia and its subtypes, thus modifying the strength of the recommendation from the NICE guideline from weak to strong. Clinicians should also consider that the

appropriate administration and interpretation of neuropsychological tests usually requires the involvement of a specialist in neuropsychology.
Considering that about two-thirds of all dementia diagnoses are Alzheimer's disease , the WG agreed that, in case of a suspect of AD, the initial assessment should also include a specific test for episodic verbal memory, as memory and verbal recall deficits are both peculiar to AD.
The WG also agreed, modifying the indications provided in the NICE guideline, that clinician should consider prescribing a CT and/or MRI in a primary care setting to confirm the suspect of dementia (see above), due to their accuracy in excluding secondary causes of cognitive decline that require a timely intervention in a different specialist setting from a memory clinic. However, clinician should consider that interpreting complex neuroradiological data requires the involvement of specialists even in the primary care setting.
However, in case these tests were not performed in a primary care setting, or in case specialists consider further tests are necessary (e.g., suspect of normal pressure hydrocephalus), structural imaging (CT and/or MRI) should be prescribed. In fact, it should help excluding potentially reversible causes of cognitive decline, and supporting the differential diagnosis of dementia subtypes, unless dementia is well established, and the subtype diagnosis is clear. Evidence on CT and MRI reported a low accuracy of these tests for the identification of dementia versus non-dementia. These data confirm the results from the NICE guideline reporting a good specificity but low sensitivity of MRI in distinguishing most of dementia subtypes. MRI was reported to have a better accuracy (good sensitivity and specificity, and moderate to high likelihood ratios), based on evidence of low to moderate certainty, in distinguishing vascular dementia and the behavioral variant of FTD (bv-FTD). The WG agreed to underline that a diagnosis of Alzheimer's disease should not be ruled out based on CT or MRI scan results alone. .
The WG underlined that even in a specialist setting, clinicians should aim for an accurate diagnosis based on the minimum number of essential tests in order to limit the potential distress of people undergoing the procedures, and to limit the high costs for the National Health System (NHS).
On this basis, the use of further diagnostic tests should only be considered if they help to reduce the uncertainty on the subtype of dementia, and if knowing more about the dementia subtype would change management. In such cases, the WG further discussed on the most appropriate tests for the differential diagnosis of dementia subtypes.
While underlining the undebatable benefit for people with dementia of a definite diagnosis of a specific subtype, the WG recommended prescribing tests such as functional neuroimaging (SPECT, PET) and CSF biomarkers in sequence rather than in parallel to minimize the burden on patients. Neuroimaging examinations, in fact, may not be well tolerated, especially when considering the condition of overall frailty of people with dementia, due to their length and their potential of triggering claustrophobia. Lumbar puncture is an invasive procedure that comes with possible complications.
Performing tests in parallel can, in some cases, allow a diagnosis to be made in less time , but clinician should be aware that in cases where this is not necessary, this approach could cause distress due to the length and invasive nature of some diagnostic procedures, which also come with potential complications. Therefore, the WG confirmed, based on evidence, the recommendation from the NICE guideline to perform these tests in sequence, and to consider further examinations in case of diagnostic uncertainty.
When considering further test for the specific diagnosis of AD, literature identified some neuroimaging and CSF biomarkers.
The use of biomarkers or more specialized neuroimaging examinations (^{18}F-FDG PET, perfusion SPECT – ^{99m}ECD SPECT, ^{99m}HMPAO SPECT) in people with a suspect of AD should be considered in case of persisting diagnostic uncertainty.
Evidence on the accuracy of ^{99m}ECD SPECT, ^{99m}HMPAO SPECT in distinguishing AD from non-AD is reported in studies of very low to moderate quality. Analyzed evidence reported a variable sensitivity from low to moderate and an overall adequate sensitivity of ^{18}F-FDG PET compared to clinical criteria and neuropathology.

Low quality studies reported good sensitivity, specificity, and likelihood ratios of ^{18}F-FDG PET to distinguish AD from other dementias, other dementias, and non-AD.
Low-certainty evidence reported a very variable, and overall lower, diagnostic accuracy of amyloid PET compared to clinical criteria. On this basis, the WG confirmed the research recommendation from the NICE guideline to further investigate the utility and cost-effectiveness of amyloid PET compared to standard diagnostic procedures and other imaging tests or biomarkers to support the diagnosis of AD and other dementia subtypes.
The WG, based on the heterogeneity of evidence, also confirmed the indication to consider the use of ^{18}F-FDG PET and, if unavailable, of perfusion SPECT, considering that the difference in their accuracy does not allow to recommend one test over the other. In both cases, evidence was of variable certainty (very low to moderate) and reported good sensitivity and specificity.
CSF biomarkers, specifically t-Tau and p-Tau along with Aβ 1-42 or Aβ 1-42/Aβ 1-40 ratio, can be considered as an alternative to neuroimaging for the differential diagnosis of AD.
Analyzed evidence overall reported that identifying CSF levels of these proteins and their ratios can be useful as a support for the differential diagnosis of some dementia subtypes, in particular AD and CJD. When considering the diagnosis of AD, based on the update of evidence, the WG agreed to recommend considering only the analysis of CSF t-Tau and p-Tau (and not t-Tau alone, without p-Tau) along with Aβ 1-42 or Aβ 1-42/Aβ 1-40 ratio.
When considering the diagnosis of CJD, evidence reported a good diagnostic accuracy for some proteins. One high-quality study reported a 99% sensitivity and 98% specificity for the combination of the 14-3-3 and Aβ 1-42 proteins in distinguishing people with CJD from people without CJD. Moreover, moderate-quality studies reported a good accuracy (sensitivity up to 96% e specificity up to 100%) of RT-QuIC compared to neuropathology in distinguishing people with CJD from people without CJD.
Despite the utility of CSF biomarkers, several issues should be considered, such as the difficulty of obtaining samples from patients due to the invasive nature of the procedure , and the lower reliability of some tests in older people. Results from these tests, in fact, can vary with age even in cognitively normal people, thus age should be accounted for before prescribing this type of tests due to the higher probability of obtaining a false positive result in older people. Therefore, mean age and age range should be taken into due consideration when interpreting evidence on the diagnostic accuracy of some tests such as CSF biomarkers.
The WG discussed the benefit for people suspected of having dementia of performing more specialist examinations in series and agreed to confirm the recommendation from the NICE guideline to consider PET/SPECT or CSF biomarkers alternatively if a diagnosis cannot be made after performing the other test . Therefore, if a diagnosis cannot be made after one of these tests, consider using the other one.
The WG also discussed that the use of these biomarkers should be limited due to lumbar puncture being an invasive procedure requiring hospitalization and expert staff, and due to the high costs and potential complications associated to CSF sampling procedures.
The possibility of performing these examinations on blood samples could be extremely useful to avoid these issues. However, currently available evidence does not allow for a recommendation. Therefore, plasmatic biomarkers are currently useful only for research purposes to investigate their potential to replace CSF biomarkers or to be a first step within a diagnostic process to identify who could benefit from a subsequent CSF test.
The WG confirmed the recommendation not to offer genetic testing for apolipoprotein E (ApoE). ApoE is, in fact, a risk factor for AD and cannot be considered as a diagnostic biomarker for dementia.
The WG also confirmed the recommendation not to offer EEG as high-quality studies reported that it does not provide significant diagnostic information relevant for the diagnosis of AD. The role of EEG remains crucial in clinical practice as a support to differentiate dementia from other specific condition such as secondary encephalopathies or encephalitis, including viral or limbic encephalitis and other immune-mediated

conditions, or epileptiform activities in people with paraneoplastic syndromes, or late-onset epilepsy, specific conditions of brain suffering associated to specific clinical pictures.
The WG underlines the need to always consider that young-onset Alzheimer's disease has a genetic cause in some people, which means that genetic testing may be used to confirm the diagnosis in these people .

Diagnosis of Dementia with Lewy Bodies (DLB)

Dementia with Lewy bodies is a synucleinopathy characterized by dementia and parkinsonism with a specific involvement of a degeneration of the nigrostriatal pathway and the posterior cortex. The analysis of evidence on neuroimaging tests as a support for the diagnosis of DLB supported the utility of ^{123}I-FP-CIT SPECT (DaTScan) that allows highlighting, through uptake of the radiopharmaceutical at a presynaptic dopamine transporter level in the striatum, to highlight its function. This test, in fact, allows to distinguish DLB from other dementias that are not characterized by the presence of Lewy bodies and basal ganglia involvement. On this basis, this test is not useful to differentiate DLB form PDD. The use of ^{123}I-FP-CIT SPECT for the diagnosis of DLB is recommended based on low (DLB versus non-DLB compared to neuropathology) to moderate (DLB versus other dementias) quality evidence reporting good sensitivity and specificity of this test.
Low quality evidence reported a lower accuracy of SPECT with N-isopropyl-(^{123}I)-p-iodoamphetamine (^{123}I-IMP SPECT) compared to ^{123}I-FP-CIT SPECT, therefore its use is not recommended for the diagnosis and differential diagnosis of DLB.
Myocardial scintigraphy with the radiopharmaceutical drug iodine-123 (^{123}I-MIBG) is a non-invasive examination to assess cardiac postganglionic presynaptic sympathetic nerve terminals. This test, originally used to assess heart disease, was subsequently found to be able to show a lower uptake in people with Lewy bodies disorders such as Parkinson's disease and DLB. This led to consider this test as a support for the clinical diagnosis of these conditions in case of diagnostic uncertainty with another atypical parkinsonism.
Five low-quality studies reported a good accuracy, along with high to very high likelihood ratios, for ^{123}I-MIBG in differentiating DLB from non-DLB. One other moderate-quality study reported similar accuracy of this test in differentiating DLB from other dementias.
This evidence led the WG to confirm the recommendation to consider ^{123}I-MIBG myocardial scintigraphy as a support for the diagnosis of DLB in case ^{123}I-FP-CIT SPECT is not available. The WG underlined that this examination is not useful to distinguish DLB from PDD, as ^{123}I-MIBG myocardial scintigraphy may show postganglionic sympathetic denervation in PD as in DLB. However, a diagnosis of DLB should not be ruled out based solely on normal results on ^{123}IFP-CIT SPECT or ^{123}I-MIBG cardiac scintigraphy due to their non-optimal accuracy.
One moderate-quality study reported a good sensitivity but low specificity of the EEG for the diagnosis of DLB. The highest accuracy has been reported in studies using EEG methodologies that require signal processing by quantitative EEG , which is not always feasible in the routine clinical practice on the National Health System, and that needs to be assessed in specialised centers. Polysomnography with EEG can be considered to confirm the presence of REM sleep Behavior Disorder (RBD), which is one of the core criteria for the diagnosis of DLB (McKeith 2017). On this basis, the WG modified the NICE guideline recommendation to include an indication, in case of diagnostic uncertainty and a suspect of DLB, to consider either ^{123}I-MIBG cardiac scintigraphy or polysomnography with EEG recording as an alternative when the ^{123}IFP-CIT SPECT is not available.
The Lewy Body Composite Risk Score (LBCRS) is a 10-item questionnaire identifying signs and symptoms commonly associated to DLB, thus it cannot be considered as a diagnostic test for dementia. On this basis, despite evidence reporting a good accuracy for this test, it was not recommended.

Diagnosis of Frontotemporal Dementia (FTD)

The WG discussed several issues in relation to the evidence on the use of ^{18}F-FDG PET and perfusion SPECT (ECD SPECT and HMPAO SPECT) for the diagnosis of FTD.
Evidence from low quality studies reported variable accuracy, with very low sensitivity and in some cases good specificity, of ^{18}F-FDG PET for distinguishing FTD from non-FTD, AD or other dementias and for the differential diagnosis of bv-FTD. The certainty of evidence on its accuracy for the diagnosis of primary progressive aphasia (PPA) versus non-PPA was also low. On this basis, the WG confirmed the indication to use this test in case of persisting diagnostic uncertainty, due to its good specificity.

Evidence on the use of multi-headed camera systems ^{99m}Tc-HMPAO SPECT for the differential diagnosis between FTD and other dementias compared to clinical diagnosis and neuropathology reported a higher sensitivity and similar specificity of this technique compared to the automated reading and the combination with data from its single camera version (no longer in use).
However, evidence from a single moderate-quality study reported a good sensitivity and specificity of ^{99m}Tc-HMPAO SPECT (visual assessment) in distinguishing FTD from non-FTD.
Considering the variable availability of these tools, the WG agreed not to specify the type of SPECT to be used in cases of diagnostic uncertainty and suspected FTD, and to recommend the use of perfusion SPECT with semi-quantitative reading as an alternative to ^{18}F-FDG PET**.**
Moreover, even though this test might show a clear involvement of the frontal and temporal lobes, this parameter cannot be assumed as a necessary condition for a diagnosis, considering the opportunity of inconclusive tests in people with a clinical diagnosis of FTD. Therefore, the WG confirmed the recommendation that a diagnosis of FTD should not be excluded based on the results of the recommended tests alone.
The clinician should always be aware and consider throughout the diagnostic process that FTD has a genetic cause in some people.

Diagnosis of Vascular dementia (VaD)

Vascular dementia (VaD) is the second most frequent type of dementia after AD, despite several aspects such as classification of the condition, diagnostic criteria, and the specific nature of the relationship between cerebrovascular pathology and cognitive decline are still debated.
The level of vascular pathology needed to affect cognitive functions is still unclear. Moreover, while the interpretation the effects of a high or low vascular burden as defined through imaging can be relatively easy, interpreting cases that are intermediate and moderate can be challenging. Evidence from low- to moderate-quality studies reported a good sensitivity and specificity of brain MRI in distinguishing VaD from AD, DLB and other dementias, and a moderate accuracy in distinguishing VaD from non-VaD. Therefore, in case of diagnostic uncertainty and a suspect of VaD, the WG confirmed the indication to perform brain MRI, and, in case MRI is unavailable or contraindicated (claustrophobia, presence of electronic devices or objects or devices made from magnetic metals), to perform brain TC as a viable alternative. Despite the unavailability of direct evidence on the accuracy of TC for the diagnosis of VaD, the WG agreed that the positive results found from evidence on MRI could indirectly imply a similar accuracy of other structural neuroimaging techniques. Brain MRI, however, should be considered as the first line tool, being supported by clear and reliable evidence.
One moderate-quality study on the use of the Hachinski Ischemic Score (HIS) for the differential diagnosis of VaD reported a good sensitivity and specificity of this tool compared to neuropathology. Given the overall diagnostic uncertainty of VaD, and the possibility of it being a case of mixed dementia with a degenerative component, the WG underlined that vascular dementia should not be diagnosed based on vascular lesion burden alone. Moreover, clinicians should always refer to available clinical criteria when diagnosing VaD, and, when necessary, should request consultation with an expert. Clinicians should be aware that young-onset VaD (e.g., CADASIL) can have a genetic cause in some people and this possibility should be taken into

account when defining the possibility of performing further diagnostic tests. When considering the use of neuroimaging in the diagnostic process for dementia, the WG agreed that the main cost for the NHS is the initial cost of acquiring the equipment, with the subsequent incremental cost of each performed examination being significantly lower, while a higher cost for the NHS is due to the acquisition of radiopharmaceuticals drugs for functional imaging.
The WG underlined that clinical judgement throughout the diagnostic process should be guided by validated criteria for each dementia subtype, along with the use of all the clinical and instrumental tests included in the criteria listed in the recommendation 11. In case of diagnostic uncertainty and as a support for the diagnosis of a specific dementia subtype further tests can be indicated, as reported in the recommendations 14 to 27.
The NICE guideline reported that the variability observed in the sensitivity and specificity reported by considered evidence on the same tests might be due to differences in the enrolled populations. The WG agreed that studies on some specific tests could be more vulnerable to this type of bias (e.g., studies on some cognitive tests). The WG also agreed with the NICE on considering available evidence on some rarer dementia subtypes (HIV-Associated Neurocognitive Disorder – HAND, neurosyphilis, CADASIL e corticobasal degeneration) as insufficient to support a recommendation. However, considering that these cases are probably treated by highly specialized structures, the decision not to include any recommendations in the guideline should not affect the quality of their care.

Diagnosis of Mild Cognitive Impairment (MCI) in a specialist care setting

Review question 2d

The diagnosis of MCI, in a specialist clinical setting, is currently supported only by clinical criteria (Albert 2011).
No validated biomarker is available for the differential diagnosis of MCI in this clinical setting. The use of CSF and neuroimaging biomarkers for the diagnosis of MCI is currently limited to research purposes, including clinical trials, as support of the eligibility criteria of the population to be included. The National Institute on Aging (NIA), which defines the diagnostic criteria for MCI “due to AD”, underlines that this condition cannot be currently diagnosed with a laboratory test. MCI is a condition defined by clinical, cognitive, and functional criteria and requires, for its definition, the clinical judgement of a specialist (see the introduction to the chapter “Identification, diagnosis, and post diagnostic support”).
On this basis, the WG, when deciding on recommendations, did not extend the discussion to tests other than neuropsychological examinations . The analysis of evidence on the identification of the most useful tests for the diagnosis of MCI in a specialist setting (e.g., memory clinics) was, therefore, based on identifying validated neuropsychological tests, along with their cut-offs, compared to clinical criteria or clinical diagnosis as a reference standard. The literature reviwed identified several tests (Mini Mental State Examination – MMSE, Montreal Cognitive Assessment – MoCA, Clinical Dementia Rating Scale – CDR, AD8 Dementia Screening Interview – AD8, Informant Questionnaire on Cognitive Decline in the Elderly – IQCODE, Mini Addenbrooke’s Cognitive Examination – Mini-ACE, Clock Drawing Test – CDT, Trail Making Test-A –TMT-A), with overall small effects and low to moderate certainty of evidence.
The MMSE was identified as one of the most widely used tests, and evidence reported widely varying levels of accuracy, in terms of sensitivity and specificity, for all analyzed cut-offs of this test for the diagnosis of MCI. Two studies reported an overall good accuracy of the cut-offs 19-20 and 22-23 of the MoCA scale. The WG agreed, in line with the approach adopted for the diagnosis of dementia, to recommend that an initial assessment be carried out in a specialist setting, using validated neuropsychological tests, including specific tests of episodic memory, as part of the diagnostic process for MCI and its subtypes, given the higher probability of MCI progressing to AD compared with other dementia subtypes. The WG also agreed to recommend a regular assessment of people diagnosed with MCI to monitor, in a standardized way, possible

changes in their cognitive functions, including a regression of symptoms, a stabilization of cognitive functions, or a progression to dementia.

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 cognitive decline and • if possible, from someone who knows the person well (such as a family member).	STRONG IN FAVOR
2	If cognitive decline 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 and • prescribe brain CT and/or MRI to exclude secondary causes of cognitive decline.	STRONG IN FAVOR
3	When using cognitive testing to assess people with dementia or someone who knows the person well (such as a family member), use a validated brief structured cognitive instrument such as: • 10-point cognitive screener (10-CS); • 6-item cognitive impairment test (6CIT); • 6-item screener (6-IS); • Memory Impairment Screen (MIS); • Mini-Cog; • Test Your Memory (TYM); • General Practitioner Assessment of Cognition (GPCOG).	STRONG IN FAVOR
4	Do not rule out cognitive decline solely because the person has a normal score on a cognitive instrument and plan a monitoring of cognitive functions in time.	STRONG AGAINST
5	Refer the person to a specialist dementia diagnostic service (Centre for Cognitive Disorders and Dementias) 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.	STRONG IN FAVOR
6	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.	STRONG IN FAVOR
7	For more guidance on assessing for dementia in people with learning disabilities, see Table 6.	STRONG IN FAVOR

Diagnosis of dementia in specialist settings

8	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.	WEAK IN FAVOR
9	If Alzheimer's disease is suspected, include a test of verbal episodic memory in the assessment.	STRONG IN FAVOR
10	Offer neuropsychological testing with validated neuropsychological tests as an essential part of the diagnostic process for dementia and dementia subtypes.	STRONG IN FAVOR
11	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 for vascular dementia; • NIA-AA criteria for Alzheimer's disease; • Movement Disorders Society criteria for Parkinson's disease dementia; • WHO and International criteria for Creutzfeldt-Jakob disease.	STRONG IN FAVOR
12	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.	STRONG IN FAVOR
13	Only consider further diagnostic tests if: • it would help to diagnose a dementia subtype and • knowing more about the dementia subtype would change management.	WEAK IN FAVOR

Further tests for Alzheimer's disease

14	If the diagnosis is uncertain (see recommendation 13) and Alzheimer's disease is suspected, consider either: • ^{18}F-FDG PET, or perfusion SPECT if ^{18}F-FDG PET is unavailable or • examining cerebrospinal fluid for: – total Tau and phosphorylated-Tau 181 and – amyloid β 1-42/amyloid β 1-40 ratio or amyloid β 1-42 If a diagnosis cannot be made after one of these tests, consider using the other one.	WEAK IN FAVOR
15	Be aware that the older a person is, more likely they are to get a false positive with cerebrospinal fluid examination.	WEAK IN FAVOR
16	Do not rule out Alzheimer's disease based solely on the results of CT or MRI scans.	STRONG AGAINST
17	Do not use *ApoE* ε4 genotyping or electroencephalography to diagnose Alzheimer's disease.	STRONG AGAINST
18	Be aware that young-onset Alzheimer's disease has a genetic cause in some people.	WEAK IN FAVOR

Further tests for dementia with Lewy bodies

19	If the diagnosis is uncertain (see recommendation 13) and dementia with Lewy bodies is suspected, use ^{123}I-FP-CIT SPECT.	STRONG IN FAVOR
20	If ^{123}I-FP-CIT SPECT is unavailable, consider as an alternative: • ^{123}I-MIBG cardiac scintigraphy or • polysomnography with EEG	WEAK IN FAVOR
21	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.	STRONG AGAINST

Further tests for frontotemporal dementia

22	If the diagnosis is uncertain (see recommendation 13) and frontotemporal dementia is suspected, use, with semi-quantitative reading, either: • ^{18}F-FDG PET or • perfusion SPECT.	STRONG IN FAVOR
23	Do not rule out frontotemporal dementia based solely on the results of structural, perfusion or metabolic imaging tests.	STRONG AGAINST
24	Be aware that frontotemporal dementia has a genetic cause in some people.	WEAK IN FAVOR

Further tests for vascular dementia

25	If the dementia subtype is uncertain (see recommendation 13) and vascular dementia is suspected, use MRI. If MRI is unavailable or contraindicated, use CT.	STRONG IN FAVOR
26	Do not diagnose vascular dementia based solely on vascular lesion burden.	STRONG AGAINST
27	Be aware that young-onset vascular dementia has a genetic cause in some people.	WEAK IN FAVOR

Diagnosis of Mild Cognitive Impairment in specialist settings

28	Offer a neuropsychological assessment using validated neuropsychological tests, including specific tests for episodic memory, as part of the diagnostic process for MCI and its subtypes.	STRONG IN FAVOR
29	Do not offer biomarkers for the diagnosis and differential diagnosis of MCI.	STRONG AGAINST
30	Offer people with a diagnosis of MCI regular neuropsychological assessments over time to monitor possible changes in cognitive functions.	STRONG IN FAVOR

Research Recommendations

2R	What is the utility and cost effectiveness of amyloid PET imaging as an additional test to support the diagnosis of Alzheimer's disease and other dementias when compared with standard diagnostic procedures and other imaging or biomarker tests?

3R	What is the utility of plasma biomarkers as additional tests to support the diagnosis of Alzheimer's disease and other dementias when compared with standard diagnostic procedures and other imaging or biomarker tests?
4R	What is the utility of biomarkers within the diagnostic process, and for the differential diagnosis and prognosis of MCI?

Table 6. Reference documents for managing specific conditions.

Condition	Reference documents	Source
Multimorbidity	*Linea guida inter-societaria per la gestione della multimorbilità e polifarmacoterapia*	SNLG 2021
	Multimorbidity: clinical assessment and management	NICE-NG56
	Older people with social care needs and multiple long-term conditions	NICE-NG22
Delirium	Delirium: prevention, diagnosis and management in hospital and long-term care	NICE-CG103
Diabetes	*La terapia del diabete mellito di tipo 2*	SNLG 2022
	Type 2 diabetes in adults: management	NICE-NG28
	Type 2 diabetes in adults	NICE-QS209
Hypertension	Hypertension in adults: diagnosis and management	NICE-NG136
Cardiovascular/obesity problems	Cardiovascular disease: risk assessment and reduction, including lipid modification	NICE-CG181
	Terapia del sovrappeso e dell'obesità resistenti al trattamento comportamentale nella popolazione adulta con comorbilità metaboliche	SNLG 2022
Incontinence	Faecal incontinence in adults: management	NICE-CG49
	Urinary incontinence in neurological disease: assessment and management	NICE-CG148
Sensory disabilities	Hearing loss in adults: assessment and management	NICE-NG98
Falls/fractures	Diagnosi, stratificazione del rischio e continuità assistenziale delle fratture da fragilità	SNLG 2021
	Fratture del femore prossimale nell'anziano	SNLG 2021
	Falls in older people: assessing risk and prevention	NICE CG161
	Falls in older people	NICE-QS86
	Hip fracture: management	NICE-CG124
Oncological diseases	*Tumori dell'anziano (parte generale)*	SNLG 2022
Depression	Depression in adults: treatment and management	NICE-NG222
Parkinson's Disease	Parkinson's disease in adults	NICE-NG71
Specific Learning Disability	Mental health problems in people with learning disabilities: prevention, assessment and management	NICE-NG54

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Drugs that may worsen cognitive decline

Review question 3a	**What drugs that may worsen cognitive decline are commonly prescribed in people diagnosed with dementia?**
Review question 3b	**What are the most effective tools to identify drugs that may be causing cognitive decline?**

Literature review

Review question 3a

In line with the approach adopted by the NICE guideline, no systematic review was performed for this question, as its only possible objective would have been to gather data on the potential risks associated to well known drugs. The objective of the question was instead to identify which drugs associated with a higher risk of causing cognitive decline are currently commonly prescribed in general population. The reference territory in the analyses from the NICE guideline was UK, while the analyses for this guideline referred to the Italian territory. Evidence for question 3a in the NICE guideline was obtained from a survey performed by the o UK Prescribing Observatory for Mental Health (POMH), who analysed the prescription patterns within a cluster of mental health trusts. For this question, the WG involved the National Centre for Research, and Preclinical and Clinical Evaluation of Drugs (CNRVF) of the Italian National Institute of Health (ISS). Analyses were performed using the database of drug prescriptions provided by public and private pharmacies through the National Health Service (NHS). The database was instituted in accordance to the L. 448/1998, and is monitored by the Medicines Utilization Monitoring Centre (OsMed) of the Italian Medicines Agency (AIFA).

Review question 3b

Records identified from databases	1,711
Studies assessed for eligibility	20
Included studies	8
Studies included in the NICE GL	7
Total number of included studies	15

Eligibility criteria

Population	People aged ≥ 40 years with a suspected diagnosis of dementia.
Diagnostic variables	• Standardised tools assessments, instruments and protocols used to identify drugs that cause cognitive decline. • Clinical history.
Outcomes	• Incidence of accurately identified dementia. • Measures of diagnostic accuracy (e.g. sensitivity, specificity, predictive values). • Change in prevalence of appropriate polypharmacy. • Potentially avoidable hospital admissions. • Resource use and costs.
Setting	Primary, specialist, acute, residential care.

Aim

The primary objective of the systematic literature review, as defined by the NICE Guideline, was to identify diagnostic studies aimed at identifying drugs associated to a higher risk of causing cognitive decline. To this purpose, only cohort/cross-sectional diagnostic studies providing sufficient data to calculate the main diagnostic accuracy measures (e.g., sensitivity, specificity, predictive values) were included. Diagnostic case-control studies were not included.

Summary of evidence

Review question 3a

Analyses from the NICE guidelines were based on a population of 9,180 participants referring to 54 mental health trusts. Of these, in 2013, 1,600 participants received drug prescriptions with an overall anticholinergic burden ≥ 2 as assessed through the ACB (Anticholinergic Cognitive Burden) scale, while 115 participants received drug prescriptions with an overall ACB burden ≥ 3. In this subgroup, the most commonly prescribed drugs with an ACB = 3 were amitriptyline (20%), quetiapine (19%), olanzapine (13%), and solifenacin (11%). Analyses from the NICE guidelines conclude that drugs with a high anticholinergic burden (ACB = 3) are prescribed to a limited amount of people with dementia and the specific drugs responsible for most of this burden are a limited subgroup of medicines for which alternatives with a lower if not absent ACB are available.
The adaptation of these analyses was based on a cohort of 183,982 participants aged ≥ 65 years from the entire Italian territory who received at least one prescription of a drug for the treatment of dementia in 2020. Data showed that 49.2% of the cohort received medications with an overall ACB ≥ 3, while 13.4% received medications with an overall ACB = 2, and 17.9% received medications with an overall ACB = 1. The most commonly prescribed drugs with an ACB = 3 were quetiapine (19.4%), paroxetine (5.9%), and olanzapine (2.7%). Results showed that in Italy the cumulative anticholinergic burden is not always attributable to a specific subgroup of drugs with an ACB = 3, but also to the combination of different drugs with an ACB ≥ 1.

Review question 3b

The systematic review performed for the NICE guideline identified seven primary studies meeting the predefined eligibility criteria. Eight new primary studies were identified by updating the systematic review.
Studies were classified according to the type of considered tool and were reported according to the type of scale adopted.

Anticholinergic Cognitive Burden Scale (ACB)

Six studies reported data on the risk of dementia in populations exposed to different levels of ACB. Analyses on the cumulative risk of dementia did not show a significanlty higher risk of dementia in people with ACB = 1 (RR 0.99, 95% CI 0.78 – 1.26, I^2 0%, n = 1,360) (Brombo 2018, Chuang 2017) or ≥ 1 (RR 1.02, 95% CI 0.99 – 1.05, I^2 0%, n = 119,496) (Hafdi 2020, Hsu 2021). A slightly but significantly lower risk of dementia was observed in people with an ACB = 1-2 (RR 0.94, 95% CI 0.90 – 0.98, I^2 90%, n = 675,160) (Grossi 2019, Liu 2020). A significantly higher risk was observed in people with ACB ≥ 2 (RR 1.08, 95% CI 1.06 – 1.11, I^2 77%, n = 748,739) (Brombo 2018, Chuang 2017, Liu 2020), ACB = 3 (RR 1.88, 95% CI 1.24 – 2.84, I^2 NA, n = 3,045) (Grossi 2019) and ACB ≥ 3 compared to ACB ≤ 2 (RR 4.14, 95% CI 1.71 – 10.05, I^2 NA, n = 109) (Naharci 2017). Only one study (Sheu 2019) did not report a significantly higher risk of dementia in people with Parkinson's disease and ACB ≥ 2 (RR 0.91, 95% CI 0.72 – 1.15, I^2 NA, n = 1,232).

All evidence was considered as low-certainty mainly due to the statistical and methodological heterogeneity of included studies, and, in a specific case, of the imprecision of the estimates. All included studies considered

different populations, risk categories, and lengths of follow-up. Two studies, one including people discharged from hospital and one on healthy volunteers, reported a significantly higher risk at 12 and 11 years in people with an ACB ≥ 1 based on multivariable models (Brombo 2018, Chuang 2017). Two studies on community-based participants did not report an increase in the risk of dementia at 10 and 6 years in people with ACB = 1-2, ACB = 3 e ACB ≥ 3 (Grossi 2019, Hafdi 2020). One study on insurance data in people ≥ 65 years reported a significantly higher risk of dementia at 10 years in all age classes (65-74, 75-84, ≥ 85) for all considered ACB cut-offs (ACB = 1, ACB = 2, ACB = 3, ACB ≥ 4) (Hsu 2021), while another study on insurance data reported a significantly higher risk only for people with ACB ≥ 5 (Liu 2020).

Anticholinergic Risk Scale (ARS)

Two studies (Brombo 2018, Hsu 2021) reported a significantly higher cumulative risk of dementia in 117,166 participants (RR 1.28, 95% CI 1.25 – 1.32, I^2 98%). Evidence was considered as low-certainty mainly due to the statistical and methodological heterogeneity of the two included studies. The studies consider different populations, risk categories, and lengths of follow-up. The first study (Brombo 2018) reported a significantly higher incidence of dementia at 12 months after discharge from hospital in the subgroup of people treated with drugs with an ACB = 1. However, this increased risk is non-significant when analyzed in a multivariable model. The second study (Hsu 2021) used an insurance database of drug prescriptions in people ≥ 65 years and reported a significantly higher risk of dementia at 10 years in all age classes (65-74, 75-84, ≥ 85) for all considered ARS cut-offs (ARS = 1, ARS = 2, ARS = 3).

Serum Anticholinergic Activity (SAA)

Only two studies reported data on the incidence of dementia in people with an anticholinergic burden calculated using the SAA measure. One study on 327 participants (Ancelin 2006) reported an 80% incidence of MCI and a 16% incidence of dementia in people treated with drugs with SAA (present versus absent), compared to a 35% incidence of MCI and a 14% incidence of dementia in people who were not treated with drugs with SAA. Another study on 235 participants (Ehrt 2010) reported a 64.3% incidence of dementia at 8 years in people with PD treated with drugs with SAA compared to a 30% incidence of dementia in people with PD who were not treated with drugs with SAA.

Other scales

One study on 544 participants (Han 2008) reported an association between being exposed to drugs with an anticholinergic burden measured with the Clinician's rated Anticholinergic Scale and a worsening of cognitive performances. Another study on 1,112 participants (Sittironnarit 2011) did not report differences in the frequency of MCI or AD in people treated with drugs with an anticholinergic burden measured with the Anticholinergic Loading Scale (ACL) compared to people who were not treated with the same class of drugs.

Analysis of evidence

Clinical and neuropathological studies reported an association between some classes of drugs, in particular anticholinergic drugs, and an increased risk of dementia. These effects seem to be more evident in older people, who are often treated with polypharmacy for a condition of multimorbidity that is in itself a risk factor for functional decline, lower quality of life, higher need for healthcare, and higher mortality.
Anticholinergic drugs are widely prescribed in older people for urinary dysfunction (incontinence and bladder hyperactivity), peptic ulcer disease, and irritable bowel syndrome. Along with being used as muscle relaxant agents during surgeries or endoscopic examinations, they are also considered for the treatment of neurological conditions, such as Parkinson's disease, or psychiatric conditions.
Acetylcholine is a neurotransmitter involved in several relevant functions at both the Central Nervous System (CNS) and Peripheral Nervous System (PNS) level, through its interaction with two types of receptors,

nicotinic and muscarinic. Its action on the CNS supports attention, learning abilities, and memory. In the PNS, it modulates, among other functions, urination, intestinal transit, and heart rate.
Anticholinergic drugs act differently according to the different receptors they interact with, and, similarly, they can be responsible for different adverse events depending on their involvement of the CNS of PNS. Some of the adverse reactions involving the PNS include dry mouth, urinary retention, constipation, tachycardia, and blurred vision, while adverse reactions involving the CNS (anticholinergic spectrum disorders) include somnolence, cognitive dysfunctions, confusion, and psychomotor retardation.
The mechanism by which anticholinergic drugs increase the risk of dementia is still unclear. Recent studies (Risacher 2016) reported a correlation between a higher anticholinergic burden and changes in brain metabolism, reduction of cortical volume (in particular of the temporal cortex), and ventricular enlargement. The cholinergic downregulation is thought to concur, through a cascade action, in worsening the mechanisms that support neurodegeneration.
The negative pharmacological effect on cognitive functions might precipitate a pre-existing condition, including asymptomatic conditions, mainly in people with concomitant frailty. However, a high anticholinergic burden can cause a clinical condition mimicking a cognitive decline, thus leading, especially in older people, to misdiagnose dementia. It should also be considered that the combined use of acetylcholinesterase inhibitor and anticholinergic drugs is common in clinical practice for the treatment of different conditions.
Based on the chronic and progressive nature of dementia, considering acting on the burden of prescribed anticholinergic drugs might improve, even slightly, cognitive functions.
The use of one drug with a high cholinergic burden, or the concomitant use of several anticholinergic drugs, increases the cumulative risk of cognitive decline. The use of these drugs in older people, and especially in people with a cognitive decline, might be inappropriate. However, if treatment with these drugs is initiated or confirmed, close monitoring is required.
Analysed evidence specifically focused on anticholinergic drugs, despite their well-known negative action on cognitive functions. The objective of the systematic review was to increase awareness on the relevance of this issue, and provide indications, when possible, to consider limiting the prescription of these drugs in older people and in people with cognitive decline. Included studies provided evidence on the utility of tools supporting the identification of drugs affecting cognitive decline.
The systematic review included studies in all types of settings, including primary care, specialist care, acute and residential care. Some issues might be specific to the setting where the drugs are prescribed, or where prescription plans are reviewed and updated.
The indication is to assess the cognitive status in any setting before deciding upon a treatment with an anticholinergic drug. Throughout the initial diagnostic phase of evaluating a suspected dementia patient, clinicians should reduce or, when alternatives are available, discontinue any anticholinergic drug to limit potential misdiagnoses. Clinicians should be aware that the anticholinergic activity of some drugs is still undefined. Therefore, structured and validated tools are needed to assess the anticholinergic burden.
The analysis of evidence from the NICE guideline concluded that drugs with a high anticholinergic burden (ACB = 3) are prescribed to a small number of people with dementia, and that the drugs responsible for most of the anticholinergic burden are a limited subgroup for which alternatives with a lower, if not absent, anticholinergic burden are available.
A specific analysis throughout the Italian territory was performed, on a large cohort of people ≥ 65 years that in 2020 received at least one prescription of a drug specific for the treatment of dementia. Data showed that almost half of the considered population received prescriptions with a cumulative ACB ≥ 3 (specifically quetiapine, paroxetine, and olanzapine). The analysis of results showed that the cumulative ACB in the Italian population was not attributable to a limited subgroup of drugs with an ACB score = 3, but to the concomitant use of different drugs with ACB ≥ 1.

Included studies on scales for the assessment of the anticholinergic burden were generally carried out on samples of older people, and were widely heterogeneous, mainly in terms of risk categories and lengths of follow-up. Moreover, each scale categorized drugs in a different way based on its structural methodology.
The most widely used tool was the Anticholinergic Cognitive Burden Scale (ACB). However, this is not the only available tool. The overall certainty of evidence was low, thus confirming the conclusions from the NICE guideline that no evidence is available supporting the use of a scale over the others. Clinicians should be aware of the anticholinergic burden throughout all the phases of the clinical management of their patients, considering that several tools are available as a support when reviewing pharmacological treatments and looking for alternatives. When considering costs, the use of anticholinergic drugs can affect resource use, due to possible adverse events and misdiagnoses.
Considering the current lack of evidence on whether reducing the anticholinergic burden can improve cognitive functions in people with cognitive decline, the WG agreed on a research recommendation supporting further studies in this topic.

Recommendations

Drugs that may worsen cognitive decline

31	Be aware that some commonly prescribed medicines are associated with increased anticholinergic burden, and therefore cognitive impairment.	WEAK IN FAVOR
32	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.	WEAK IN FAVOR
33	Consider that there are validated tools for assessing anticholinergic burden (for example, the Anticholinergic Cognitive Burden Scale).	WEAK IN FAVOR
34	For guidance on carrying out medication reviews, see the indications reported in Table 7.	STRONG IN FAVOR

Table 7. Quality statements from NICE Quality standard 120, referring to NICE guideline 5 (NG5) [19]

Quality statement 1. People are given the opportunity to be involved in making decisions about their medicines.
Quality statement 2. People who are prescribed medicines are given an explanation on how to identify and report medicines-related patient safety incidents.
Quality statement 3. Local health and social care providers monitor medicines-related patient safety incidents to inform their learning in the use of medicines.
Quality statement 4. People who are inpatients in an acute setting have a reconciled list of their medicines within 24 hours of admission.
Quality statement 5. People discharged from a care setting have a reconciled list of their medicines in their GP record within 1 week of the GP practice receiving the information, and before a prescription or new supply of medicines is issued.
Quality statement 6. Local healthcare providers identify people taking medicines who would benefit from a structured medication review.

[19] Medicines optimisation: the safe and effective use of medicines to enable the best possible outcomes. [NG5] Published: 04 March 2015. https://www.nice.org.uk/guidance/ng5; Medicines optimisation. [QS120] Published: 24 March 2016. https://www.nice.org.uk/guidance/qs120

Research Recommendations

5R	Does actively reducing anticholinergic burden in people living with dementia or Mild Cognitive Impairment improve cognitive outcomes compared with usual care?

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Distinguishing dementia from delirium or delirium with dementia

Review question 4	**What are the most effective methods of differentiating dementia or dementia with delirium from delirium alone?**

Literature review

Records identified from databases	1,746
Studies assessed for eligibility	17
Included studies	2
Studies included in the NICE GL	6
Total number of included studies	8

Eligibility criteria

Population	People aged ≥ 40 years with cognitive impairment and no current diagnosis of dementia or delirium.
Diagnostic variables	Relevant diagnostic variables may include: • history data; • duration of delirium; • Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE).
Outcomes	• Incidence of accurately identified dementia. • Measures of diagnostic accuracy (e.g. sensitivity, specificity, predictive values). • Inappropriate discharge rates. • Inadequate care planning rates. • Resource use and costs.
Setting	Primary, specialist, acute, residential care.

Aim

The primary objective of the systematic literature review, as defined by the NICE Guideline, was to identify studies investigating the utility of different diagnostic tests used to distinguish dementia from delirium or delirium with dementia.
To this purpose, cohort and cross-sectional diagnostic studies were included, while case-control diagnostic studies were excluded.

Summary of evidence

The systematic review performed for the NICE guideline identified six primary studies, while two new primary studies were identified by updating the systematic review. Evidence was classified according to the type of considered tool and were reported according to the type of scale.

4 A's Test (4AT)

One study on 350 participants (O'Sullivan 2017) reported data on the accuracy of the 4AT compared to clinical diagnosis in consecutive patients referring to the emergency department. The study reported a sensitivity of 0.84 and specificity of 0.63 in distinguishing people with dementia from people without dementia, and a sensitivity of 0.93 and specificity of 0.91 in distinguishing people with delirium from people without delirium (moderate certainty).

6-item Cognitive Impairment Test (6-CIT)

One study on 378 participants (O'Sullivan 2017) reported data on the accuracy of the 6-CIT compared to clinical diagnosis in consecutive patients referring to the emergency department. When considering the accuracy of the tool in distinguishing people with dementia from people without dementia, the study reported a sensitivity of 0.84 and specificity of 0.76 applying a cut-off of 8-9, and a sensitivity of a sensitivity of 0.81 and specificity of 0.76 applying a cut-off of 9-10. When considering the accuracy of the tool in distinguishing people with delirium from people without delirium, the study reported a sensitivity of 0.89 and specificity of 0.74 applying a cut-off of 9-10, and a sensitivity of a sensitivity of 0.83 and specificity of 0.87 applying a cut-off of 13-14 (moderate certainty).

Cognitive Test for Delirium – Spatial Span Forward (CTD-SSF)

One study on 233 participants (Leonard 2016) reported data on the accuracy of the CTD-SSF scale compared to clinical diagnosis in hospitalized people with altered mental state. The study reported a sensitivity of 0.15 and specificity of 0.97 when applying a cut-off < 4 in distinguishing people with dementia from people without dementia, and a sensitivity of 0.65 and specificity of 0.97 in distinguishing people with delirium from people without delirium. Applying the same cut-off, the study also reported a sensitivity of 0.63 and specificity of 0.97 in distinguishing people with dementia with delirium from people without dementia with delirium (very low certainty).

Confusion Assessment Method (CAM)

One study on 168 participants (Cole 2002) reported data on the accuracy of the CAM scale compared to the IQCODE for dementia and the DSM-III-R for delirium in people referring to the emergency department. The study reported a sensitivity of 0.27 and specificity of 0.83 when applying a cut-off ≥ 7 in distinguishing people with dementia from people without dementia and without delirium, and a sensitivity of 0.95 and specificity of 0.83 in distinguishing people with delirium from people without dementia and without delirium. Applying the same cut-off, the study also reported a sensitivity of 0.98 and specificity of 0.83 in distinguishing people with delirium and dementia from people without dementia without delirium (low certainty).

Delirium Rating Scale Revised 98 (DRS-R98)

Overall, three studies investigated the accuracy of the DRS-R98. One study on 37 participants (Trzepacz 2001) reported data on the accuracy of the DRSR98 compared to DSM-5 criteria in people with dementia or delirium and other psychiatric conditions enrolled from different clinical settings. When considering the accuracy of the tool in distinguishing people with delirium from people with dementia, the study reported a sensitivity of 1 and specificity of 0.85 applying a cut-off = 17.75, a sensitivity of 0.92 and specificity of 0.85 applying a cut-off = 21.5, and a sensitivity of 0.92 and specificity of 1 applying a cut-off = 22.5. Two studies (Leonard

2016, Meagher 2010) reported an association between DRS-R98 scores and presence of symptoms of delirium (respectively mean score in people with: delirium 22.0 ± 8,4 and 26.9 ± 6,7, dementia 14.0 ± 6.8 and 13.9 ± 4.2; very low certainty).

Modified Richmond Agitation Sedation Scale (mRASS)

One study on 285 participants (Grossman 2017) investigated the use of the mRASS, currently adopted to assess for arousal, as a tool to identify delirium, reporting data on its accuracy compared to the DSM-IV-TR criteria in consecutive patients aged ≥ 65 years referring to the emergency department. The study reported a sensitivity of 0.27 and specificity of 0.91 in distinguishing people with dementia from people without dementia, and a sensitivity of 0.70 and specificity of 0.93 in distinguishing people with delirium from people without delirium (low certainty).

Observational Scale of Level of Arousal (OSLA) e Attention Test (AT)

One study on 114 participants (Richardson 2017) reported data on the accuracy of the OSLA and AT singularly or in combination compared to DSM-5 criteria for delirium and the IQCODE or MMSE for dementia in people hospitalized for acute conditions or for rehabilitation. As for the OSLA, the study reported a sensitivity of 0.85 and specificity of 0.82 when applying a cut-off = 3-4 in distinguishing people with delirium or dementia and delirium from people without delirium (regardless of dementia), and a sensitivity of 0.74 and specificity of 0.96 in distinguishing people with delirium and dementia from people with dementia without delirium. As for the AT, the study reported a sensitivity of 0.90 and specificity of 0.65 when applying a cut-off = 3-4 in distinguishing people with delirium or dementia and delirium from people without delirium (regardless of dementia), and a sensitivity of 0.84 and specificity of 0.73 in distinguishing people with delirium and dementia from people with dementia without delirium. As for their combination, the study reported a sensitivity of 0.85 and specificity of 0.97 when applying a cut-off = 9-10 in distinguishing people with delirium or dementia and delirium from people without delirium (regardless of dementia), and a sensitivity of 0.94 and specificity of 0.93 in distinguishing people with delirium and dementia from people with dementia without delirium. (very low certainty).

Short Portable Mental Status Questionnaire (SPMSQ)

One study on 233 participants (Erkinjuntti 1987) reported data on the accuracy of the SPMSQ compared to clinical diagnosis in people admitted to a medical department. The study reported a sensitivity of 0.67 and specificity of 1 when applying a cut-off < 5 in distinguishing people with dementia without delirium from people without any brain syndrome, a sensitivity of 0.17 and specificity of 1 in distinguishing people with delirium without dementia from people without any brain syndromes. The study also reported a sensitivity of 0.78 and specificity of 1 in distinguishing people with delirium and dementia from people without any brain syndromes (very low certainty).

Analysis of evidence

The DSM-5 defines delirium as a neuropsychiatric disorder with an acute onset mainly characterized by a "disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) accompanied by reduced awareness of the environment". These symptoms can be associated to alterations of memory, orientation, language, visuospatial abilities, and perception.
The severity of the clinical picture is fluctuating during the course of the day. Diagnostic criteria underline that cognitive deficits should not be "explained by another pre-existing, established, or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal".
The diagnosis of delirium is complex, and this condition has frequently multiple aetiologies. Delirium can be due to an underlying medical condition (e.g., toxic-metabolic) which may be suspected by anamnesis, clinical

examination, and blood tests. Delirium can be due to intoxication (e.g., alcohol, opioids, hypnotics, anxiolytics), substance withdrawal (e.g., alcohol, opioids, narcotics, hypnotics, anxiolytics), or exposure to toxins.

Some older people with delirium have an underlying undiagnosed dementia, while some other show an excellent recovery of symptoms, without any evidence of an underlying cognitive decline at a subsequent evaluation. However, people with dementia have a significantly higher risk of delirium, and people who experienced delirium at any time have higher risk of dementia.

Symptoms of delirium in older people admitted to an emergency department or urgent care are associated with a poor prognosis in terms of length of stay, mortality, and risk of persistent functional and cognitive decline. The diagnosis of delirium in an emergency setting is challenging, mainly due to the difficulty of establishing whether symptoms are isolated, part of a pre-existing dementia, or due to dementia alone. An adequate differential diagnosis is essential, as it affects treatment both during hospitalisation and at discharge. The appropriate differential diagnosis is also essential in primary care, where the opportunity of further diagnostic tests in a specialist setting should be considered. To this purpose, indications are needed, based on consistent evidence, on how general practitioners and hospital staff in emergency departments should approach cases of delirium.

Short and easy-to-use tools should be identified, both accurate and quick, considering the availability of healthcare professionals in non-specialist settings, which can be administered bedside in case of hospitalized or institutionalized people, also including specialist settings.

Diagnostic variables include clinical history and symptom duration. Studies included in the NICE guideline and the subsequent update identified several tests with different intrinsic characteristics. Some of these assess several domains that are compromised in both people with dementia and people with delirium. Other tests, such as those targeting attention and focus, support the diagnosis of delirium but does not necessarily show positive results in people with dementia. Analysed evidence shows that some tests seem to be more useful in distinguishing delirium from dementia.

One relevant issue is the time required to administer each test, which is essential when assessing for delirium, due to the nature of the condition.

Data on the accuracy of the Delirium Rating Scale Revised 98 (DRS-R98), despite showing a good sensitivity and specificity of this tool in distinguishing delirium from dementia, were based on evidence of very low certainty. This low certainty, along with the long time required to administer this tool, does not allow recommending the DRS-R98 in a non-specialist setting.

The Cognitive Test for Delirium – Spatial Span Forward (CTD-SSF) was also considered as having limitations, due to its length and mostly due to it including non-specific items that could be altered both in people with dementia and in people with delirium. These considerations, along with the very low certainty of evidence due to methodological limitations of include studies and imprecision of estimates, prevented the WG from recommending this test.

The WG, in line with the NICE guideline, agreed on supporting the use of the CAM tool for the differential diagnosis, due to its good accuracy, in particular at a cut-off ≥ 7, in distinguishing people with delirium from people without dementia and delirium, and in distinguishing people with delirium and dementia from people without dementia and delirium. The WG confirmed the weak recommendation from the NICE guideline to consider the use of this test, due to the low-moderate certainty of evidence supporting it. Further considerations can be made on the use of its long or short form. The additional information provided by the longer version may be reasonably useful in cases where the differential diagnosis is more complex, while the shorter form is more appropriate in less complex cases.

Evidence also supported the 4AT, showing a good accuracy of this test in distinguishing delirium from delirium with dementia and dementia. On this basis, the WG agreed to include the 4AT in the recommendation.

The Short Portable Mental Status Questionnaire (SPMSQ) also proved accurate in distinguishing people with delirium and dementia, but not people with delirium without dementia, from people without any other brain

syndrome. When considering costs, misdiagnoses of delirium or dementia would be both expensive and harmful for people.
Considering that none of the analysed tests was reported to be accurate in distinguishing delirium superimposed on dementia from delirium alone, the WG confirmed the recommendation from the NICE guideline that this diagnosis should not be based on standardised instruments alone. In case of diagnostic uncertainty and inability to distinguish between the two conditions, based on clinical judgement, people showing symptoms of altered mental state should be treated for delirium first. However, in people with altered mental state who are negative to a screening for delirium and responded to treatment for delirium, a further assessment for underlying dementia can be considered, in case of persistent cognitive decline.
Considering that uncertainties still exist on the most appropriate time required before administering further tests, the WG also confirmed the research recommendation from the NICE guideline.

Recommendations

Distinguishing dementia from dementia with delirium or delirium alone

35	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); • 4-A's Test (4AT).	WEAK IN FAVOR
36	Do not use standardised instruments (including cognitive instruments) alone to distinguish delirium from delirium superimposed on dementia.	STRONG AGAINST
37	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 the identification and treatment of delirium, see Table 6.	STRONG IN FAVOR

Research Recommendations

Distinguishing dementia from dementia with delirium or delirium alone

6R	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?
7R	What is the accuracy of 4-A's Test (4AT) and Confusion Assessment Method (CAM) in distinguishing people with delirium or delirium superimposed on dementia from dementia alone in a primary care setting or in a residential care setting?

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Pre-, peri- and post-diagnostic counselling

Review question 5	**How effective are pre-, peri- and post-diagnostic counselling and support on outcomes for people living with dementia and their caregivers?**

Literature review

Records identified from databases	1,965
Studies assessed for eligibility	5
Included studies	4
Studies included in the NICE GL	3
Total number of included studies	7

Eligibility criteria

Population	People aged ≥ 40 years living with dementia and having been diagnosed within the previous 12 months.
Interventions	Counselling and support interventions for people with dementia and their caregivers, which may include elements such as: • diagnostic counselling; • psychosocial support; • peer support groups; • information and advice; • signposting.
Comparator	• Standard care. • Other interventions.
Outcomes	• Clinical outcomes including cognitive, functional and behavioural ability. • Access to health and social care support. • Patient and carer experience and satisfaction. • Patient and carer health-related quality of life. • Resource use and costs.

Aim

The primary objective of the systematic literature review, as defined by NICE Guideline, was to identify studies investigating the effectiveness of pre-, peri- and post- diagnostic interventions in improving outcomes for people with dementia and their caregivers.
To this purpose, only Randomized Controlled Trial (RCT) reporting sufficient data to calculate RRs or MDs along with their dispersion measures (e.g., CI, SD) were included.

Summary of evidence

The systematic review performed for the NICE guideline identified three primary studies whose results were reported in four publications, while four new primary studies were identified by updating the systematic review.

Five studies reported data on outcomes for people with dementia. When considering cognitive outcomes, three RCTs on 609 participants (Koivisto 2016, Phung 2013, Villars 2021) did not report any significant improvement in MMSE scores (MD -0.47, 95% CI -1.31 – 0.37, I^2 0%, low certainty). Two studies on 372 participants (Koivisto 2016, Laakkonen 2016) did not report any significant improvement in Clinical Dementia Rating Scale - Sum of Boxes (CDR-SB) scores (MD 0.30, 95% CI -1.48 – 2.09, I^2 85%, very low certainty).

When considering behavioural outcomes, three studies on 631 participants (Koivisto 2016, Phung 2013, Villars 2021) did not report any significant improvement in Neuropsychiatric Inventory (NPI) scores (MD 0.27, 95% CI -0.94 – 1.47, I^2 55%, low certainty). When considering functional status, two RCTs on 436 participants (Koivisto 2016, Phung 2013) reported a significant worsening of Alzheimer's Disease Cooperative Study – Activities of Daily Living Scale (ADCS-ADL) scores (MD -5.09, 95% CI -8.92 – -1.27, I^2 0%, n = 436, low certainty). Two more RCTs on 257 participants (Kim 2017, Villars 2021) did not report any significant improvement in functional as measured with different tools (SMD -0.05, 95% CI -0.30 – 0.19, I^2 0%, low certainty). When considering mental health outcomes, one study on 62 participants (Kim 2017) reported an improvement in depressive symptoms measured with the Geriatric Depression Scale (GDS) (MD -2.55, 95% CI-3.91 – -1.19, I^2 n.a., moderate certainty). Two more RCTs did not report any improvement in depressive symptoms as measured with respectively the Beck Depression Inventory (BDI) (MD -1.37, 95% CI -3.10 – 0.35, I^2 n.a., n = 236, low certainty) (Kim 2017) and the Cornell Scale for Depression in Dementia (CSDD) (MD 0.55, 95% CI -0.78 – 1.88, I^2 n.a., n = 194, low certainty) (Phung 2013). When considering quality of life, three RCTs on 630 participants (Koivisto 2016, Phung 2013, Villars 2021) did not report any significant improvement in global quality of life as measured with the QoL-AD scale (MD 0.15, 95% CI -1.46 – 1.76, I^2 63%, low certainty). Another RCT on 136 participants (Laakkonen 2016) did not report any improvement in health-related quality of life as measured with the Health-Related Quality of Life (HR-QoL) (MD 0.01, 95% CI -0.00 – 0.02, I^2 n.a., low certainty). One study on 62 participants (Kim 2017) reported a significant improvement in suicidal ideation scores (Suicidal Ideation Scale: MD -2.35, 95% CI -3.46 – -1.24, I^2 n.a., low certainty) and in the perceived health status as measured with the Perceived Health Status (PHS) (MD 1.33, 95% CI 0.37 – 2.29, I^2 n.a., low certainty).

Six studies reported data on outcomes for caregivers of people with dementia. One study on 222 participants (Livingston 2020) reported a significant improvement of Hospital Anxiety and Depression Scale (HADS) total scores (MD -1.45, 95% CI -2.80 – -0.10, I^2 n.a., n = 222, moderate certainty) and depression scores (MD -0.93, 95% CI -1.63 – 0.24, I^2 n.a., n = 222, moderate certainty). Two studies reported no differences between groups in burden and stress measured with the Zarit Burden Interview (ZBI) (MD -0.49, 95% CI -4.54 – 3.57, I^2 n.a., n = 195, very low certainty) (Villars 2021), the Burden Scale for Family Caregivers (BSFC-short version) (MD -0.70, 95% CI -5.78 – 4.38, I^2 n.a., n = 61, very low certainty) (Metcalfe 2019), and the Caregiver Perceived Stress Scale (CPSS) (MD -3.30, 95% CI -7.95 – 1.35, I^2 n.a., n = 61, very low certainty) (Metcalfe 2019). When considering quality of life, four studies reported differences between groups in health-related quality of life measured with NHP (MD -7.12, 95% CI -35.48 – 21.23, I^2 n.a., n = 196, very low certainty) (Villars 2021), QoL-15D (MD 0.0, 95% CI -0.03 – 0.02, I^2 n.a., n = 236, low certainty) (Koivisto 2016), GHQ (MD -0.92, 95% CI -2.51 – 0.67, I^2 n.a., n = 236, low certainty) (Koivisto 2016), EQ-5D-5L (MD 0.03, 95% CI -0.09 – 0.15, I^2 n.a., n = 61, low certainty) (Metcalfe 2019), and HR-QoL (MD 1.70, IC 95% CI -0.38 – 3.78, I^2 n.a., n = 136, low certainty) (Laakkonen 2016). Certainty of evidence was classified as low to very low due to methodological limitations and imprecision of estimates. When considering mental health, only one study did not report any significant improvement in depressive symptoms measured with GDS (MD 0.67, 95% CI -0.64 – 1.98, I^2 n.a., n = 197, low certainty) (Phung 2013).

Analysis of evidence

Dementia is a progressive condition that is not only responsible for a strictly cognitive deficit, but also for several other psycho-behavioral symptoms including anxiety, depression, and personality disorders, primarily or secondarily. Dementia highly affects the quality of life of both people and their caregivers.
The three phases that characterize the diagnostic process include the phase immediately preceding diagnosis, the communication of the diagnosis, and the phase immediately after diagnosis. These phases are crucial steps to define supportive interventions.
The objective of the systematic review was to assess the effectiveness of some types of interventions, in particular counselling and support, in people who received a diagnosis of dementia (within 12 months) and their caregivers, measuring, when possible, their outcomes over time.
Two main types of interventions were identified, psychosocial and self-management interventions, including counseling, psychosocial support, information, and advice to people with dementia and their caregivers.
One of the included studies investigated a home-based supportive intervention focused on depressive symptoms and anxiety in people with dementia and their family members. Growing evidence identify early-stage dementia as the condition associated with the highest risk of suicide in older people. Older people with early-stage dementia, who are aware of their condition, have a higher suicidal ideation compared to cognitively healthy older adults. On this basis, one study investigated the effectiveness of a suicide prevention intervention. Another included study investigated the effectiveness of a multimedia web-based intervention, including information and skill training, aimed at improving care especially in people with early-onset dementia. One study investigated a complex training intervention for people with dementia and their caregivers focusing on understanding and comprehending the diagnosis, considering also the subsequent feelings and thoughts of both people and their caregivers.
Evidence on the long-term efficacy on cognitive and psychiatric symptoms, and quality of life would undeniably be more relevant in answering this review question. However, most of the included studies enrolled people in the first 12 months after diagnosis, with mild symptoms. Therefore, evidence on longer follow-ups is needed to prove the effectiveness of these interventions on long-term outcomes. Further evidence could be useful on other outcomes such as access to full-time care and mortality. However, studies enrolling people close to the diagnosis are unlikely to report data on this type of outcomes.
In line with results from the NICE guideline, studies did not report significant results for any of the considered post-diagnostic interventions (psychosocial support or self-management). Despite observing short-term improvements in cognitive and psycho-behavioral symptoms and quality of life, studies did not report any long-term effect, and results were not consistent when outcomes were measured with different tools. In particular, no improvement in quality of life was observed when using both the QoL-AD and the HR-QoL scales.
The small number of studies on pre- and peri-diagnostic counseling and support for people with dementia and their caregivers seems to confirm that this approach, despite being recognized as good practice, is not investigated in clinical studies.
Certainty of evidence was mostly low to very low, due to methodological limitations and imprecision of the estimates. In particular, the randomization process and the times of administration of the interventions (pre-existing interventions in some participants) were unclear. Only the certainty of evidence from two studies, one reporting data on GDS scores and one reporting data on HADS scores, was categorized as high.
The indication from the NICE guideline to consider the cut-off of 12 months from diagnosis among the inclusion criteria appears to be arbitrary. However, clearly defining the transition from the post-diagnostic phase to the phase requiring more general supportive services is unfeasible, considering how this trajectory can vary among people with dementia. Moreover, the NICE guideline discusses how the current ability to achieve an earlier diagnosis compared to the past could lead to consider study populations as less representative of the population that currently is in a post-diagnostic phase.

The NICE guideline reports that the lack of efficacy reported by included studies might suggest that the period close to the diagnosis should not be considered as a separate phase during dementia, thus requiring specific interventions, different from the other phases. The severity of dementia, and not the time from diagnosis, could instead be a more relevant factor to be considered to define the effectiveness of an intervention, considering that included studies were limited to studies enrolling people within 12 months from the diagnosis. As a consequence, the NICE guideline did not include any recommendation for this question, discussing that available evidence was insufficient. Moreover, the guideline underlined that indications for the reference population of this question are included in the sections relating to non-pharmacological interventions.

This issue was widely discussed by the WG. Despite the considered interventions did not prove to be effective, this was not considered as meaning that other interventions could not be effective. Despite the lack of evidence, the WG underlined the importance of supporting the issues characterizing the life of people with dementia and their caregivers in this crucial step of the diagnostic process. Therefore, the WG agreed to include a recommendation to consider peri- and post-diagnostic counseling in people that received a diagnosis of dementia and their caregivers, considering the relevance of care continuity when shifting from the peri-diagnostic phase to the subsequent phases of the disease, requiring more general supportive services.

Recommendations

Pre-, peri- and post-diagnostic counselling

38	Consider offering people with dementia and their caregivers peri- and post-diagnostic counselling targeted to the specific conditions of each patient (including symptom severity).	WEAK IN FAVOR
39	For the communication of diagnosis and post-diagnostic support see the section "Communication of the diagnosis of dementia" of the document "Recommendations for the governance and clinical management in dementia"[20] issued by the National Committee for dementia.	STRONG IN FAVOR

Research Recommendations

No research recommendations were made.

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Specific needs of people aged 40 to 65 years with early-onset dementia

Review question 6	What are the specific needs of people aged 40-65 years with early onset dementia?

Literature review

A single literature search was performed for all qualitative questions included in this Guideline (GL) referred to people with dementia (Review questions 6, 7c, 10a, 10b, 24).

Records identified from databases	21,475
Studies assessed for eligibility	33
Included studies	2
Studies included in the NICE GL	7
Total number of included studies	9

Eligibility criteria

Population	• People aged 40-65 years living with dementia. • Carers of people aged 40-65 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: • Being in work at time of diagnosis; • Having a partner who still works; • Dependent children; • Caring for older relatives; • Large financial commitments (e.g. mortgage).
Outcomes	• Experiences and satisfaction of people living with dementia • Experiences and satisfaction of carers of people living with dementia

Aim

The objective of the systematic review was to identify qualitative studies and qualitative synthesis exploring the specific needs of people with early-onset dementia, focusing on improving outcomes for people with dementia and their caregivers.
Studies were excluded if they did not include the opinions of people with dementia or their caregivers, and if they only included a quantitative analysis of gathered information.

Summary of evidence

The systematic review performed for the NICE guideline identified seven primary studies, while two new primary studies were identified by updating the systematic review.
The qualitative analysis of evidence identified three categories of themes: experiences and coping in employment, general experiences and coping, and supporting activities and services.

Experiences and coping in employment

The following themes were identified based on two studies carried out in UK on 13 participants with early-onset dementia (Chaplin 2016, Clemerson 2014). Data were gathered through interviews or semi-structured interviews.

The following themes were identified for this category for people with dementia:

- people needed information about their rights in the workplace, and employers also needed to be educated about the same (low certainty);
- people with dementia had an awareness of changes in their functioning in the workplace as they developed dementia (low certainty);
- people with dementia experienced a shock at losing their expected future (low certainty);
- a reluctance from people with dementia to acknowledge the signs of cognitive decline (low certainty);
- attempting to self-manage – developing coping strategies, and spending more time and effort in planning and organising tasks (low certainty);
- feeling under scrutiny by managers and colleagues (low certainty);
- a lack of consultation about management decisions – not feeling they were offered the reasonable adjustments they were entitled to (low certainty);
- feeling abandoned by the workplace and consequent feelings of resentment towards the workplace (low certainty);
- financial hardship and consequent worry (low certainty).

General experiences and coping

This category includes four studies carried out in UK on a sample of 58 participants with early-onset dementia and 15 caregivers (Clayton-Turner 2015, Clemerson 2014, Pipon-Young 2012, Rabanal 2018). Data were gathered through interviews, group discussions, or semi-structured interviews.

The following themes were identified for this category for people with dementia and their caregivers:

- feelings of shock and a sense of loss at receiving the diagnosis, but also relief at having the diagnosis confirmed (low certainty);
- experiences of feeling ‘too young’ – assuming dementia was something that only affected older people (high certainty);
- sense of pressure at still having responsibility for children, a mortgage or a business to run (low certainty);
- 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 certainty);
- 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 certainty);
- negative impact of other’s perceptions (low certainty);
- a reduced sense of self-worth (very low certainty);

- 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 certainty);
- a fear of disclosing the diagnosis and a desire to hide it from others (low certainty);
- the importance of remaining independent, active and involved (low certainty);
- the importance of knowing other people with dementia and being able to share understandings through similar experiences (low certainty);
- lack of age-appropriate services (very low certainty);
- the intention to regain control emerged as a common coping strategy in response to the experience of loss of agency (very low certainty);
- people may well still be driving, and this should be discussed (low certainty).

Supporting activities and services

Four studies investigated the experiences of people with early-onset dementia involved in different types of supporting activities and services on a total sample of 260 participants with dementia and 222 caregivers (Davies-Quarrel 2010, Hegarty 2014, Johnson 2008, Stamou 2020). Data were gathered through focus groups, questionnaires, interviews, written and verbal feedback.

The following themes were identified for this category:

- benefits of building supportive and positive relationships, and a social network (low certainty);
- acquired a sense of belonging, purpose and achievement (low certainty);
- improved self-confidence by being able to interact with a group of people similar to themselves (low certainty);
- improved the opportunity of receiving specific information to better plan for the future, have access to appropriate services for their age, interventions for mental and physical health, and interventions supporting the management of finances and family relationships (moderate certainty).

Analysis of evidence

The systematic review of literature was aimed at identifying possible specific needs unique to people with early-onset dementia and their caregivers. It therefore focused on specific needs that are different from those of older people with dementia, to ensure the availability of targeted structured and accessible diagnostic and care pathways.

Two studies reported that people receiving the diagnosis and their caregivers/family members should be offered written and verbal information on their rights and needs in the workplace. Some people with early-onset dementia continue being employed for several years. These cases should be notified to public structures whose role is to support the access to employment for people with disabilities. Healthcare professionals should provide face-to-face training and mentoring for all staff supporting and caring for people with dementia. This should include specific needs of people with early-onset dementia (where relevant to their role).

The WG discussed specific issues referring to people with early-onset dementia who might still have financial commitments such as mortgages. This underlines the importance of the recommendations to offer financial and legal advice to all people with dementia.

Some studies investigated the experiences of people with early-onset dementia participating in support groups, while other studies discussed the need for them. Results showed that this type of services could provide a comforting environment supporting this population, especially in re-establishing and maintaining a positive self-confidence despite the disease. However, people with early-onset dementia and their caregivers may find it difficult to access these services due to their being open during working hours. Services should therefore be designed to be accessible to as many people as possible, accounting for their specific needs.

Recommendations

Further indications on the specific needs of people with early-onset dementia were added to the sections on involving people with dementia in decisions about their care (Review question 10a and Review question 10b), staff training (Review question 9), and care models and care coordination (Review question 7a, Review question 7b, Review question 7c, and Review question 7d).

Research Recommendations

No research recommendations were made.

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CARE MODELS AND COORDINATION OF CARE

Introduction

Dementia is a public health challenge due to the complexity of its clinical picture, which includes cognitive and behavioural symptoms, losing the ability to manage the most common activities of daily living, and a progressive loss of autonomy in all functions, even the simplest ones.

Caring for people with dementia is challenging, starting from making a diagnosis and communicating it, which is a process directly involving the person and their family members, to all the subsequent phases characterizing the course of t he disease.

The clinical picture of people with dementia is, by its nature, caracterised by changes that can sometimes be unpredictable, and that require the timely adaptation of the care plan and an interdisciplinary approach.

It is important to consider that each person can have their own disease trajectory due to potential comorbidities and polypharmacy. Some either medical or psychiatric pre-existing clinical conditions can cause the person to be in a particular condition of frailty. People could also be taking some medications for a pre-existing condition that may be inappropriate in case of onset of cognitive decline.

People with dementia and their caregivers experience different contexts, environments, and meet different professionals, especially when transferring between care settings, such as moving from their own home to residential facilities or hospitals. During these transitions, continuity of care should be ensured in terms of treatments, communication between facilities, and adequate management of the consequences that these changes can have on the psychophysical wellbeing and quality of life of people with dementia and their caregivers.

There is a need for more appropriate and targeted care models and care coordination approaches, capable of detecting the individual needs, skills, and competences of people with dementia and their caregivers (e.g., how well caregivers can interact with technological devices) in the environment where they live, and of improving clinical conditions and quality of life. Moreover, these strategies should support the physical and mental wellbeing of caregivers, considering that these can affect the people they care for.

Care models should include scheduled and regular monitoring performed by the healthcare professionals who care for people throughout the course of the disease and should also consider the opportunity of ensuring further unplanned access to other health and social services, when necessary, thus allowing to identify any clinical and social change in people with dementia and their caregiver. One of the most delicate aspects is managing the involvement of peoplewith cognitive decline in decisions about their care, from choosing their treatment options to issues related to end-of-life care. This process requires the staff caring for people with dementia to be aware of the emotional and psychological impact of this process, and of its crucial importance for people and their caregivers.

This would allow an approach aimed at optimizing person-centered intervention and support services in line with the principles of the International Classification of Functioning, Disability, and Health (ICF)[21].

One last essential issue relating to the effectiveness of a care model requires underlining the importance of continuous specific training for health and social care professionals and caregivers to ensure that any model can be feasible, used and implemented over time.

[21] World Health Organization. International Classification of Functioning, Disability and Health (ICF). https://www.who.int/standards/classifications/international-classification-of-functioning-disability-and-health (Last visited 30/08/2023).

Care planning, review and coordination

Review question 7a	**What are the most effective methods of care planning, focussing upon improving outcomes for people with dementia and their carers?**
Review question 7b	**What are the most effective methods of care planning, focussing upon improving outcomes for people with Mild Cognitive Impairment (MCI) and their carers?**
Review question 7c	**How should health and social care be co-ordinated for people living with dementia?**
Review question 7d	**How should health and social care be co-ordinated for people with Mild Cognitive Impairment (MCI)?**

Literature review

Quantitative evidence

	7a	7b
Records identified from databases	5,371	1,763
Studies assessed for eligibility	13	0
Included studies	2	0
Studies included in the NICE GL	26	-
Total number of included studies	28	0

Qualitative evidence

A single literature search was conducted for all the qualitative questions referring to people with dementia included in this Guideline (GL) (Review questions 6, 7c, 10a, 10b, 24).

	7c	7d
Records identified by databases	21,475	10,292
Studies assessed for eligibility	33	3
Included studies	0	0
Studies included in the NICE GL	18	-
Total number of included studies	18	0

Eligibility criteria

Quantitative evidence

Population	• People aged ≥ 40 years living with dementia or MCI. • Carers of people (aged ≥ 40 years) living with dementia or MCI.
Interventions	Methods and models of care planning for people living with dementia/MCI

Comparison	Standard care
Outcomes	• Clinical outcomes including cognitive, functional and behavioural ability. • Access to health and social care support. • Patient and carer wellbeing, experience and satisfaction. • Patient and carer health-related quality of life. • Resource use and costs.

Qualitative evidence

Population	• People aged ≥40 years living with dementia/MCI. • Carers of people (aged ≥40 years) living with dementia/MCI.
Phenomena of interest	• Methods and models of care planning for people living with dementia. • Models of health and social care co-ordination, which may include features such as: – configuration and integration of services; – timing and delivery of services (e.g. transfers, referral pathways); – staff communication; – location of services.
Outcomes	• Experiences and satisfaction of people living with dementia/MCI. • Experiences and satisfaction of carers of people living with dementia/MCI.

Aim

The objective of the systematic literature review, in line with the strategy defined by the NICE Guideline, was to identify Randomised Controlled Trial (RCT) or qualitative studies investigating the utility and effectiveness of different methods and models of care planning and coordination in improving outcomes for people with dementia/Mild Cognitive Impairment (MCI) and their caregivers. For all review questions, only studies reporting data on people with dementia/MCI and their caregivers were included.

Throughout the GL, we defined as “care and support plan” a document developed by the health and social care professional who is responsible for the care process, in collaboration with other professionals, people with dementia, and their caregivers. The document is aimed at defining the type of care and support needed in each stage of the disease, ensuring, as much as possible, the independence of people with dementia and the involvement of their caregivers in making decisions.

Summary of evidence

For review question 7a, the systematic literature review performed for the NICE guideline identified 26 studies meeting the predefined eligibility criteria. After updating the systematic review, two new studies were identified.
For review question 7b, no studies meeting the predefined eligibility criteria were identified.
Studies were analyzed individually and classified according to country, frequency of follow-up, contact method for follow-up visits, and type of professional responsible for care management/coordination/planning.

QUANTITATIVE EVIDENCE

Care coordination/management using a protocol/action plan (including training for caregivers) and meetings every three months

One study (Jansen 2011) enrolling 99 patient-carer dyads investigated a case management intervention managed by geriatric nurses specialized in geriatric care, whose main role was coordinating the evaluation, information and advice, and planning, coordination and organization of the care process. The study reported no differences between groups in quality of life of people with dementia (Dem-QoL: MD 0.40, 95% CI -0.14 – 0.94, I^2 n.a., low certainty). No differences between groups were reported in the physical and mental quality of life of caregivers (SF-36, Short Form Mental Health Survey: MD -2.90, 95% CI -8.10 – 2.30, I^2 n.a., very low certainty; SF-36 physical: MD 1.90, 95% CI -4.06 – 7.86, I^2 n.a., very low certainty), and their depressive symptoms (CES-D: MD -0.30, 95% CI -4.12 – 3.52, I^2 n.a., very low certainty) and perceived burden (SPPIC, Self-Perceived Pressure by Informal Care: MD 0.30, 95% CI -1.14 – 1.74, I^2 n.a., low certainty).

Coordination/management of care with monthly follow-up telephone contacts and visits every three months

One study (Schoenmakers 2010) enrolling 46 dyads investigated a case counselling intervention managed by a primary-care healthcare professional with experience in home care for people with dementia, whose role was supporting families in organizing home care through in-person visits and phone calls. The study reported a decrease in the frequency of depressive symptoms in caregivers in the treated group compared to the control group (OR 0.16, 95% CI 0.03 – 0.86, I^2 n.a., very low certainty). However, it reported no differences between groups in caregivers' burden (OR 0.09, 95% CI 0.007 – 1.1, I^2 n.a., very low certainty).

Care coordination/management using a protocol/action plan (including training for caregivers) and monthly meetings

Seven studies investigated the effectiveness of care coordination including the identification of a care manager/care coordinator and attempts of interdisciplinary collaboration between specialist and/or primary care health professionals. All studies included protocol/action plans aimed at supporting caregivers in care management and access to services. All evidence was rated as having low to very low certainty. Only one study on 486 participants (Bass 2013) reported an improvement in the mean frequency of needs perceived as unmet by caregivers (MD -4.30, 95% CI -7.29 – -1.31, I^2 n.a., low certainty).

When considering the outcomes of people with dementia, two studies on a total of 481 dyads (Bass 2015, Callahan 2006) reported no differences between groups in cognitive symptoms (SMD 0.03, 95% CI -0.15 – 0.22, I^2 0%, very low certainty) and behavioural symptoms (SMD -0.11, 95% CI -0.29 – 0.07, I^2 n.a., very low certainty). One study (Callahan 2006) on 153 dyads reported no differences between groups in depressive symptoms (CSDD, Cornell Scale for Depression in Dementia: MD -0.20, 95% CI -2.36 – 1.96, I^2 n.a., very low certainty). Three studies (Callahan 2006, Eloniemi-Sulkava 2001, Fortinsky 2009) on a total of 337 dyads did not report difference between groups in institutionalization rate (RR 0.74, 95% CI 0.49 – 1.12, I^2 12%, low certainty). As for hospitalization and admission to emergency department (ED), two studies (Bass 2003, Bass 2015) on a total of 510 dyads reported no significant differences between groups in the mean number of hospitalizations and admissions to ED (hospital MD -0.05, 95% CI -0.20 – 0.10, I^2 0%, low certainty; ED MD -0.18, 95% CI -0.42 – 0.05, I^2 0%, low certainty). One study on 328 participants (Bass 2015) reported no differences in the percentage of hospitalizations and admissions to ED (hospital RR 1.25, 95% CI 0.91 – 1.72, I^2 n.a., low certainty; ED RR 0.94, 95% CI 0.77 – 1.15, I^2 n.a., very low certainty).

When considering caregivers outcomes, two studies (Bass 2003, Vickrey 2006) reported no differences between groups in satisfaction with quality of services (SMD 0.10, 95% CI -0.07 – 0.26, n = 590 dyads, I^2 0%,

very low certainty). Two studies (Bass 2003, Fortinsky 2009) reported no differences between groups in depressive symptoms (SMD -0.17, 95% CI -0.42 – 0.08, n = 266 dyads, I^2 0%, very low certainty). One study (Fortinsky 2009) reported no differences between groups in perceived burden (ZBI: MD 1.21, 95% CI -7.87 – 10.29, n = 84 dyads, I^2 n.a., very low certainty), and one study (Vickrey 2006) reported no differences in quality of life (EuroQol-5D: MD 0.01, 95% CI -0.05 – 0.07, n = 408, I^2 n.a., low certainty).

Care coordination/management using a protocol/action plan (including training for caregivers) and 10-14 meetings within four months

One study on 92 dyads (Lam 2010) investigated a case-management model led by an occupational therapist whose role was to develop a care plan and manage support activities for families. The study reported no differences between groups in cognitive (MMSE, Mini Mental State Examination: MD 0.50, 95% CI -2.94 – 3.94, I^2 n.a., very low certainty), depressive (CSDD: MD -0.50, 95% CI -3.49 – 2.49, I^2 n.a., very low certainty) and behavioural symptoms (NPI, Neuropsychiatric Inventory: MD 5.00, 95% CI -14.87 – 24.87, I^2 n.a., very low certainty) of people with dementia. It also reported no differences between groups in caregivers' burden (ZBI, Zarit Burden Interview: MD 1.50, 95% CI -18.06 – 21.06, I^2 n.a., very low certainty).

Care coordination/management using a protocol/action plan (including training for caregivers) and one monthly meeting and further meetings upon request

Two studies investigated multicomponent care-coordination interventions aimed at supporting people with dementia and their caregivers, including multidisciplinary groups and guidance to accessing support services. One study on 188 dyads (Samus 2014) reported no differences between groups in depressive symptoms (CSDD: MD 0.10, 95% CI -1.76 – 1.96, I^2 n.a., low certainty), behavioural symptoms (NPI: MD 0.90, 95% CI -1.25 to 3.05, I^2 n.a., low certainty) and quality of life (QoL-AD: MD 1.90, 95% CI -0.66 – 4.46, I^2 n.a., very low certainty) of people with dementia. On study on 289 dyads (Tanner 2015) reported no differences in the physical (SF-12-f: MD 1.54, 95% CI -2.58 – 5.66, I^2 n.a., very low certainty) and mental quality of life (SF-12-m: MD 0.66, 95% CI -3.37 – 4.69, I^2 n.a., very low certainty) of caregivers. It also reported no differences in their depressive symptoms (Caregiver Depression: MD -0.39, 95% CI -1.53 – 0.75, I^2 n.a., low certainty) and burden (ZBI: MD -1.91, 95% CI -5.18 – 1.36, I^2 n.a., very low certainty).

Care coordination/management using a protocol/action plan (including training for caregivers) and about two monthly meetings for six months

Two studies investigated case-management and care-management interventions aimed at training and supporting caregivers in managing care and access to services, alone and with support from multidisciplinary groups. One study (Chien 2008) on 88 dyads reported a decrease in the treated group compared to controls in the mean institutionalization rate (MD -3.10, CI 95% -3.90 – -2.30, I^2 n.a., moderate certainty) and in caregivers' burden (FCBI, Family Caregiver Burden Inventory: MD -17.90, 95% CI -26.65 – -9.15, I^2 n.a., moderate certainty). It also reported an improvement in the treated group in caregivers' quality of life (WHO-QoL: MD 18.40, 95% CI 9.19 – 27.61, I^2 n.a., low certainty). However, it reported no differences between groups in cognitive symptoms in people with dementia (MMSE: MD -0.30, 95% CI -3.34 – 2.74, I^2 n.a., very low certainty). The second study (Dias 2008), on 81 dyads, reported no differences between groups in caregivers' burden (ZBI: MD -5.50, 95% CI -13.17 – 2.17, I^2 n.a., very low certainty. Both studies reported no differences between groups in behavioural symptoms in people with dementia (SMD -0.74, 95% CI -1.70 – 0.22, I^2 89%, very low certainty).

Care coordination/management using a protocol/action plan (including caregiver training) and weekly meetings for one month, followed by one meeting every two weeks for five months

One study (Chien 2011) on 92 dyads investigated a case-management intervention aimed at supporting people with dementia and their family members in every aspect and phase of the care process, including personalized training and support plans. The study reported a decrease in the mean institutionalization rate (MD -3.00, 95% CI -4.21 – -1.79, I^2 n.a., moderate certainty), and an improvement in quality of life (WHO-QoL: MD 20.50, 95% CI 12.73 – 28.27, I^2 n.a., moderate certainty) and caregivers' burden (FCBI: MD -19.70, 95% CI -26.76 – -12.64, I^2 n.a., moderate certainty). The study also reported an improvement in behavioural symptoms (NPI: MD -6.80, 95% CI -12.23 – -1.37, I^2 n.a., low certainty), but not in cognitive symptoms (MMSE: MD -0.20, 95% CI -2.46 – 2.06, I^2 n.a., low certainty), in people with dementia.

Follow-up managed by memory clinic versus by GPs

One study on 175 participants (Meeuwsen 2012) investigated the effectiveness of maintaining care coordination within specialist services compared to transferring it in General Practitioners (GPs). The study reported a worsening in the intervention group compared to the control grop of depressive symptoms (CES-D, Center for Epidemiologic Studies Depression Scale: MD 2.09, 95% CI 0.16 – 4.02, I^2 n.a., low certainty) and anxiety in caregivers (STAI, State-Trait Anxiety Inventory: trait MD 2.14, 95% CI 0.25 – 4.03, I2 n.a.; state MD 2.35, 95% CI 0.34 – 4.36, I^2 n.a., low certainty), possibly due to the number of drop-outs. The study reported no differences between groups in caregivers' quality of life (QoL-AD: MD 0.17, 95% CI -070 – 1.04, I^2 n.a., low certainty). It also reported no differences in behavioural (NPI: MD 1.13, CI 95% -0.51 – 2.77, I^2 n.a., low certainty) and depressive symptoms (GDS, Geriatric Depression Scale: MD 0.25, 95% CI -0.36 – 0.86, I^2 n.a., low certainty), and quality of life (QoL-AD: MD 0.25, 95% CI -0.73 – 1.23, I^2 n.a., low certainty) in people with dementia.

Medicare Alzheimer's Disease Demonstration (care coordination/management with unspecified follow-up frequency)

One study (Newcomer 1999) on 5,303 dyads investigated a model of case management and economic support, including support services for people with dementia and their caregivers. The study reported an improvement in the intervention group compared to the control group in caregivers' depressive symptoms (GDS: MD -0.32, 95% CI -0.58 – -0.06, I^2 n.a., moderate certainty). However, it reported no differences between groups in caregivers' burden (CB, Caregiver Burden: MD -0.50, 95% CI -1.11 – 0.11, I^2 n.a., low certainty).

Personalised carer support for minority groups

One study (Xiao 2016) on 61 dyads investigated a case-management intervention managed by care coordinators specifically trained to provide personalized care and support, including culturally and linguistically, to people with dementia and their caregivers. The study reported an improvement in the intervention group copared to the control group in the mental quality of life (SF-36-m: MD 12.70, 95% CI 7.09 – 18.31, I^2 n.a., low certainty) of caregiver. However, it reported no differences between groups in caregivers' physical quality of life (SF-36-f: MD 2.20, 95% CI -3, 28 – 7.68, I^2 n.a., very low certainty) and their stress (CD, Caregiver Distress: MD -6.40, 95% CI -12.87 – 0.07, I^2 n.a., very low certainty). When considering the outcomes of people with dementia, the study reported an improvement in the intervention group in their psychological and behavioural symptoms (BPSD: MD -3.30, 95% CI -7.35 – 0.75, I^2 n.a., very low certainty).

Care coordination/management within the DEM-DISC model

One study (Van Mierlo 2015) on 49 dyads investigated an intervention of case management and caregiver support based on a digital tool, DEM-DISC (DEMentia Digital Interactive Social Chart), aimed at personalizing the management and support of people with dementia and their caregivers. The study reported no

differences between groups in the frequency of depressive symptoms in caregivers (GDS: RR 1.48, 95% CI 0.87 – 2.51, I^2 n.a., very low certainty).

Multidisciplinary group

One study (Chen 2019) on 129 dyads investigated the effectiveness of an interdisciplinary team including professionals specifically trained in the management of people with Alzheimer's Disease (AD). The study reported no differences between groups in cognitive (MMSE: MD -0.17, 95% CI -3.75 – 3.41, I^2 n.a., very low certainty) and behavioural symptoms (NPI: MD -2.65, 95% CI -7.75 – 2.45, I^2 n.a., very low certainty), and in quality of life (QoL: MD 0.68, 95% CI -1.97 – 3.33, I^2 n.a., low certainty) of people with dementia. It also reported no difference between groups in caregivers' burden (ZBI: MD -3.39, 95% CI -10.33 – 3.55, I^2 n.a., very low certainty).

Review and optimization of pharmacological treatments using the Care Ecosystem model

One study (Liu 2023) on 49 dyads investigated the effectiveness of the Care Ecosystem (CE) program, a collaborative care program including, along with interventions for the involvement and support of caregivers, the review and optimization of pharmacological treatments to monitor and decrease inappropriate prescriptions. The study reported a lower mean number of potentially inappropriate prescriptions (MD -0.35, 95% CI -0.49 – -0.20, I^2 n.a., low certainty) and drugs prescribed (MD -0.53, 95% CI -0.92 – -0.14, I^2 n.a., low certainty) in the intervention group compared to the control group. The study also reported a decrease in the intervention group in the number of people with at least one potentially inappropriate prescription (-1 person on CE versus +13 people on control, moderate certainty).

Case management: combined, by frequency of follow-up

When considering studies by follow-up frequency, the single study with a weekly follow up (Chien 2011) reported, in 92 dyads, an improvement in the intervention group in caregivers' quality of life (WHO-QoL: MD 20.50, 95% CI 12.73 – 28.27, I^2 n.a., moderate certainty) and burden (FCBI: MD -19.70, 95% CI -26.76 – -12.64, I^2 n.a., moderate certainty). It also reported an improvement in the behavioural symptoms (NPI: MD -6.80, 95% CI -12.23 – -1.37, I^2 n.a., low certainty), but not in the cognitive symptoms (MMSE: MD -0.20, 95% CI -2.46 – 2.06, I^2 n.a., very low certainty), of people with dementia. The study also reported a lower mena institutionalization rate in the intervention group compared to the control group (MD -3.00, 95% CI -4.21 – -1.79, I^2 n.a., moderate certainty).

Four out of the seven studies that had monthly follow-up reported data on outcomes of people with dementia. Two of these studies (Samus 2014, Vickrey 2006), on 711 participants, reported an improvement in the intervention group compared to controls in the QoL of people with dementia (SMD 0.16, 95% CI 0.01 – 0.31, I^2 0%, low certainty). Two studies on 456 participants (Callahan 2006, Samus 2014) reported no differences between groups in depressive symptoms (CSDD: MD -0.03, 95% CI -1.44 – 1.38, I^2 0%, very low certainty). Two studies on 481 participants (Bass 2015, Callahan 2006) reported no differences between groups in cognitive symptoms (SMD 0.03, 95% CI -0.15 – 0.22, I^2 0%, very low certainty). Three studies on 456 participants (Bass 2015, Callahan 2006, Samus 2014) reported no differences between groups in behavioral symptoms (SMD -0.04, 95% CI -0.20 – 0.13, I^2 18%, very low certainty). Two studies on 456 participants (Callahan 2006, Samus 2014) reported differences in institutionalization rates (RR 1.23, 95% CI 0.72 – 2.11, n I^2 0%, low certainty). Three out of the seven studies with a monthly follow up reported data on caregivers' outcomes. Two of these studies (Bass 2003, Tanner 2015), on 471 participants, reported no differences between groups in depressive symptoms (SMD -0.12, 95% CI -0.31 – 0.06, I^2 0%, very low certainty). One study on 408 participants (Vickrey 2006) reported no differences between groups in quality of life (Euro-QoL: MD 0.01, 95% CI -0.05 – 0.07, I^2 n.a., low certainty), and one study on 289 participants (Tanner 2015) reported no differences in burden (MD -1.91, 95% CI -5.18 – 1.36, I^2 n.a., very low certainty).

Three studies had a follow-up every two months. Of these, one study (Chien 2008) on 88 dyads reported an improvement in the intervention group compared to the control group in caregivers' quality of life (WHO-QoL: MD 18.40, 95% CI 9.19 – 27.61, I^2 n.a., low certainty) and burden (FCBI: MD -17.90, 95% CI -26.65 – -9.15, I^2 n.a., moderate certainty). One study on 81 dyads (Dias 2008) reported no differences between groups in the same outcome measured with a different tool (ZBI: MD -5.50, 95% CI -13.17 – 2.17, I^2 n.a., very low certainty). One study on 88 dyads (Chien 2008) reported a lower mean institutionalization rate (MD -3.10, 95% CI -3.90 – -2.30, I^2 n.a., moderate certainty) in the intervention group compared to the control group. One study on 125 dyads (Eloniemi-Sulkava 2001) reported no difference between groups in the risk of institutionalization (RR 0.82, 95% CI 0.46 – 1.48, I^2 n.a., very low certainty). When considering the outcomes of people with dementia, two studies (Chien 2008, Dias 2008) on 169 participants reported no differences between groups in behavioral symptoms (SMD -0.74, 95% CI -1.70 – 0.22, I^2 89%, very low certainty), and one study (Chien 2008) on 88 participants reported no differences in cognitive symptoms (MD -0.30, 95% CI -3.34 – 2.74, I^2 n.a., very low certainty).

One study on 92 dyads (Lam 2010) had 10/14 follow-ups over four months. It reported no differences between groups in cognitive (MMSE: MD 0.50, 95% CI -2.94 – 3.94, I^2 n.a., very low certainty), behavioral (NPI: MD -0.50, 95% CI -3.49 – 2.49, I^2 n.a., very low certainty) and depressive symptoms (CSDD: MD 5.00, 95% CI -14.87 – 24.87, I^2 n.a., very low certainty) in participants with dementia. It also reported no differences between groups in caregiver's burden (ZBI: MD 1.50, 95% CI -18.06 – 21.06, I^2 n.a., very low certainty).

Case management: combined, by contact method at follow-up

Two studies had follow-up visits in clinics (Callahan 2006, Dias 2008). One study (Callahan 2006) on 153 participants reported no differences between groups in cognitive symptoms (0-41 scales: MD -0.10, 95% CI -3.83 – 3.63, I^2 n.a., very low certainty) and depressive symptoms of people with dementia (CSDD: MD -0.20, 95% CI -2.36 – 1.96, I^2 n.a., low certainty). Both studies (Callahan 2006, Dias 2008), on 234 participants, reported no differences in behavioral symptoms of people with dementia (NPI: MD -2.37, 95% CI -5.37 – 0.64, n = 234, I^2 0%, low certainty). One study on 81 dyads (Dias 2008) reported no differences between groups in caregivers' burden (ZBI: MD -5.50, 95% CI -13.17 – 2.17, I^2 n.a., very low certainty).

Four studies had follow-up visits at home (Chien 2008, Chien 2011, Lam 2010, Newcomer 1999). One of these studies, on 5,307 dyads (Newcomer 1999), reported an improvement in the intervention group compared to the control group in caregivers' depressive symptoms (GDS: MD -0.32, CI 95% -0.58 – -0.06, I^2 n.a., very low certainty). Two studies on 180 dyads (Chien 2008, Chien 2011) reported a lower institutionalization rate in the intervention group compared to the control group (MD -3.07, 95% CI -3.73 – -2.41, I^2 0%, moderate certainty). The same two studies (Chien 2008, Chien 2011) reported an improvement in caregivers' burden measured with FCBI (MD -18.99, 95% CI -24.48 – -13.50, I^2 0%, low certainty). Two other studies on 5,396 dyads (Lam 2010, Newcomer 1999) reported no differences between groups in the same outcome measured with ZBI (MD -0.50, CI 95% -1.11 – 0.11, I^2 0%, low certainty). When considering the outcomes of people with dementia, two studies on 180 dyads (Chien 2008, Chien 2011) reported no differences between groups in cognitive symptoms (MMSE: MD -0.24, 95% CI -2.05 – 1.58, I^2 0%, very low certainty). One study on 92 dyads (Lam 2010) reported no differences between groups in depressive symptoms (CSDD: MD -0.50, 95% CI -3.49 – 2.49, I^2 0%, very low certainty). Three studies on 272 dyads (Chien 2008, Chien 2011, Lam 2010) reported no differences between groups in behavioral symptoms (NPI: MD -9.34, 95% CI -20.04 – 1.37, I^2 80%, very low certainty). When considering caregivers' outcomes, two studies on 180 dyads (Chien 2008, Chien 2011) reported a difference between groups in quality of life (WHO-QoL: MD 19.63, 95% CI 13.69 – 25.56, I^2 0%, low certainty).

Three studies had telephone follow-up (Bass 2003, Bass 2015, Vickrey 2006). One study on 328 participants (Bass 2015) reported no differences between groups in cognitive (0-14 scales: MD 0.03, 95% CI -1.13 – 1.19,

I^2 n.a., very low certainty) and behavioral symptoms (BPSD, Behavioral and Psychological Symptoms of Dementia: MD -0.22, 95% CI -1.01 – 0.57, I^2 0%, very low certainty) in participants with dementia. One study on 408 dyads (Vickrey 2006) reported no differences in the quality of life of people with dementia (HUIM-3, Health Utility Index Mark 3: MD 0.06, 95% CI -0.02 – 0.14, I^2 0%, low certainty) and their caregivers (EuroQoL-5D: MD 0.01, 95% CI -0.05 – 0.07, I^2 n.a., low certainty). One study on 182 dyads (Bass 2003) reported no differences in caregivers' depressive symptoms (CES-D: MD -0.11, 95% CI -0.29 – 0.07, I^2 n.a., low certainty).

Two studies had mixed-method follow-up (Samus 2014, Tanner 2015). One study on 303 participants (Samus 2014) reported no differences between groups in the depressive symptoms (CSDD: MD 0.10, 95% CI -1.76 – 1.96, I^2 n.a., low certainty), behavioral symptoms (BPSD: MD 0.90, 95% CI -1.25 – 3.05, I^2 n.a., very low certainty), and quality of life (QoL-AD: MD 1.90, 95% CI -0.66 – 4.46, I^2 n.a., very low certainty) of participants with dementia. The second study (Tanner 2015), on 289 participants, reported no differences in caregivers' burden (ZBI: MD -1.91, 95% CI -5.18 – 1.36, I^2 n.a., very low certainty) and depressive symptoms (GDS: MD -0.39, 95% CI -1.53 – 0.75, I^2 n.a., very low certainty).

QUALITATIVE EVIDENCE

No studies meeting the predefined eligibility criteria were identified for review question 7d.
The qualitative analysis of studies for review question 7c identified nine categories of themes: self-management interventions, outcome-focussed/needs-led care vs standard care, community-based case management, memory-clinic case management, Daisy Chain: a commercial person-centred dementia service that seems to have some elements of case management, non-specified case management style(s) in predominantly remote and rural areas in Scotland, case management in residential care homes, case planning – Adaptation-Coping Model e Rotherham Carers Resilience Service and care coordination for people with dementia and comorbidities.

Self-management intervention

Three studies carried out in the UK on a total sample of 19 participants with dementia and an unspecified number (> 11) of caregivers explored self-management interventions (Martin 2015, Moore 2011, Toms 2015). Data were collected via unstructured or semi-structured interviews. One study (Martin 2015) reported the experiences of people with dementia and their caregivers who participated in a specific training on the self-management of their condition. A second study (Toms 2015) reported the perceptions and opinions of people with dementia and their caregivers on self-management. The last study (Moore 2011) reported the experiences of participants who used a "self-directed support" system ("system that is used to give people control over how they use and shape the support that they need to meet their social care needs").

The following themes were identified for this category for people 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)

Outcome-focused/needs-led care vs standard care

Two studies investigated the usefulness of outcome-focused/needs-led care in improving subjective well-being experienced by caregivers of older adults with dementia and perceived differences in comparison to standard care (Gethin-Jones 2014, Rothera 2007). Caregivers reported that this intervention had resulted in an improvement in their family member's well-being with dementia (Gethin-Jones 2014). The total sample of the two studies included 38 caregivers and 27 people with dementia. The data was collected through semi-structured interviews.

The following themes were identified for this category for people living with dementia and their caregivers:

- Standard care: The most common concern of familial caregivers 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 caregivers felt that they were isolated as they had all the responsibility and, in their eyes, potentially all the blame when things went wrong (moderate confidence)
- Outcome-focused care: There was an improvement in the caregivers' self-reported subjective well-being, after the outcome-focused homecare intervention had been implemented (high confidence)
- Outcome-focused care: All the caregivers felt the subjective well-being of their relative had improved after the six months outcome-focused care intervention (moderate confidence)

Community-based case management

Two studies explored the perceptions of non-institutionalized people with dementia and their caregivers on case-management interventions (Gibson 2007, Iliffe 2014). One study (Gibson 2007) investigated the performance of two models for prescribing acetylcholinesterase inhibitors for AD, focusing on how services' location and organization affected the experiences and preferences of users and their caregivers. The second study (Iliffe 2014) investigated the feasibility and acceptability of a promising US case-management project adapted to UK general practices. Overall, the two studies included 16 participants with dementia and 20 caregivers. Data were collected through interviews.

The following themes were identified for this category for people living with dementia and their caregivers:

- 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)
- Caregivers expected case managers to provide information about dementia and services (moderate confidence)
- Case managers should be proactive in asking caregivers 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 caregivers 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 caregivers 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 caregivers 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 caregivers 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)

Memory-clinic case management

Five studies assessed the experiences of people with dementia and their caregivers on case-management services in memory clinics (Gibson 2007, Hean 2011, Kelly 2016, Sonola 2013, Willis 2011). One study (Hean 2011) did not report the exact number of enrolled participants. Overall, the remaining studies included 43 participants with dementia and 42 caregivers.

The following themes were identified for this category for people living with dementia and their caregivers:

- 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 caregivers 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)
- Caregivers frequently reported positively on the help received from the project workers with claiming benefits (moderate confidence)
- Caregivers 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 caregivers 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 be 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 caregivers 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 caregivers liked seeing the same person throughout treatment (high confidence)
- People living with dementia and their caregivers 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 caregivers 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)

Daisy Chain: a commercial person-centred dementia service that seems to have some elements of case management

One study assessed the experiences of people with dementia in relation to the Daisy Chain service. Part of this service is an assessment team including an occupational therapist, a psychiatric nurse, and a home-care manager, and a specifically trained team of professionals providing care for 235 hours per week (Gladman 2007). The study enrolled 15 caregivers of people with dementia. Data were collected using 'non-participant observation', semi-structured interviews and focus groups.

The following themes were identified:

- 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 caregivers, and familial carers (low confidence)

Non-specified case management style(s) in predominantly remote and rural areas in Scotland

Two studies investigated experiences and perceptions in relation to care-coordination services in Scotland (Górska 2013, Innes 2014). The studies included 18 participants with dementia and 31 caregivers. Data were collected through semi-structured interviews.

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. Caregivers 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 caregivers, and provide relevant information (very low confidence)

Case management in residential care homes

Only one study investigated care coordination in residential facilities (Popham 2012). The study enrolled of 25 institutionalized participants with dementia and 11 caregivers. Data were collected through interviews using open questions.

The following theme was identified for case management in residential facilities:

- Participants spoke about having the freedom to be able to carry out normal everyday activities and domestic chores (moderate confidence).

Case planning – Adaptation-Coping Model e Rotherham Carers Resilience Service

Two studies assessed the experiences of people with dementia and their caregivers who were referred to services based on specific care models. One study (Brooker 2017) investigated the Adaptation-Coping model, used as a basis to train UK staff for the Meeting Centre pilot study, a community approach to post-diagnostic psychosocial support for people with dementia and their caregivers. Two focus groups were performed with nine people with dementia and six of their caregivers who had attended one of the Meeting Centres. The second study (Dayson 2016) reported results form an independent evaluation of Rotherham Carers Resilience Service provided by the Centre for Regional Economy and Social Research (CRESR) at Sheffield Hallam University. This service aims at supporting caregivers of people with dementia by providing targeted information, counselling, and support to maximizing resilience, allowing caregivers to keep caring for people with dementia at home for as long as possible.

The two studies reported similar results. Participants appreciated the opportunity to receive more information about dementia, and the opportunity to meet other people in a similar situation. Participants valued the presence of welcoming and experienced staff and receiving practical and emotional support.

Care coordination for people with dementia and comorbidities

One study investigated care coordination for people with dementia and comorbidities (Bunn 2017). The study carried out focus groups and interviews involving 28 people with dementia, 33 caregivers and 56 healthcare professionals. Results underlined the importance of caregivers having an active role in facilitating continuity and access to care, in informing each service of potential changes in the health status of people with dementia, and in acting as a proxy. External support provided by health and social services was recognised as relevant but often inadequate.

Analysis of evidence

The objective of this question was to identify the most effective models for care planning, with a specific focus on improving the outcomes of people with dementia and their caregivers.
Evidence underlines the relevance of including people with dementia in a care and support plan starting immediately after diagnosis, to ensure that they have the opportunity to plan for future care. The WG therefore agreed to link the recommendation for this section to the recommendations for the diagnosis.
Results from quantitative and qualitative studies on case management highlighted the need to identify a care coordinator to overcome difficulties in the communication among health and social care professionals involved in the care process. Most of the included studies investigated interventions based on the presence of a single care coordinator and reported improvements in the quality of life of people with dementia and in the burden and depressive symptoms of their caregivers.
Included studies also highlighted the relevance of performing an initial in-person evaluation of the needs, where possible, which was also confirmed by the experience of the WG. This assessment should not necessarily be performed by the care coordinator. In some of the studies, in fact, while the care coordinator was a nurse, active care was mostly provided by the GPs.
The WG underlined the importance of including in the recommendations also elements supporting health and social care professionals in identifying problems even in a proactive way.
Providing families and caregivers with adequate information on available services and how to access them is crucial for people with dementia, and their family members or caregivers should be specifically addressed and supported in identifying where and from whom they can receive information throughout each stage of the disease.
Another crucial aspect is involving family members or caregivers and, where possible, people with dementia in supporting and in decision making, to share and review care and support plans, defining times and methods for update, and documentation on any changes in care goals and needs. This involvement resulted useful in reducing the burden of care and the rate of institutionalization, improving the quality of life of both people with dementia and their caregivers. The active involvement of family members and caregivers in decision making, however, can be a challenging process, especially when they do not share a structured and continuous relationship with health and social care professionals. A research recommendation was included to support further research on the most effective models of care planning in these cases.
The WG underlined the importance of service providers designing services to ensure that the maximum number of people living with dementia can access them. This could minimize the existing barriers to accessing services and care and support interventions, as reported by people with dementia and their caregivers, in particular for those subgroups and minorities who are at a higher risk of isolation, such as people with dementia who live alone, have a condition of frailty or multimorbidity, or belong to a minority group.

Recommendations

Care planning, review and coordination

40	Provide people living with dementia with a single named health or social care professional who is responsible for their Personalized care plan (PAI) within an integrated care pathway. For further indications on how to organize a PAI, see: • indication 6 from the document "National Guidance for the Clinical Governance of Dementia"[22] issued by the National Committee for Dementia; • the document "National Guidance for the definition of Integrated Care Pathways for dementia"[23] issued by the National Committee for Dementia.	STRONG IN FAVOR
41	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 document "National Guidance for the Clinical Governance of Dementia" issued by the National Committee for Dementia; • ensure that people are aware of their rights to and the availability of local advocacy services, in line with the document "National Guidance for the Clinical Governance of Dementia" issued by the National Committee for Dementia; • 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).	WEAK IN FAVOR
42	When developing care and support plans and advance care and support plans, request consent to transfer these to different care settings as needed.	STRONG IN FAVOR
43	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).	WEAK IN FAVOR

[22] Available at: https://www.iss.it/documents/20126/5783571/Raccomandazioni+per+la+governance+e+la+clinica+nel+settore+delle+demenze.pdf/dbf0d6d5-6360-41d9-aa51-74b18f62dad8?t=1626171914860 (Last visited: 30/08/2023)

[23] Available at: https://www.iss.it/documents/20126/5783571/Testo+Linee+di+indirizzo+Nazionali+sui+Percorsi+Diagnostico+Terapeutici+Assistenziali+%28PDTA%29+per+le+demenze.pdf/d5123f6a-2161-6c42-5377-8796cce29fe0?t=1626170681347 (Last visited: 30/08/2023)

44	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.	WEAK IN FAVOR
45	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 minorities*.	WEAK IN FAVOR

*minorities are hereby defined as indicated by the Italian Ministry of domestic affairs: https://www.interno.gov.it/it/temi/cittadinanza-e-altri-diritti-civili/minoranze (Last visited: 30/08/2023)

Research Recommendations

Care planning, review and coordination

8R	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?
9R	What are the most effective methods of care planning for people in residential care settings?
10R	What are the most effective methods of care planning for people who do not have regular contact with an informal carer?

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Post diagnosis review for people living with dementia

Review question 8a	**How should people living with dementia be reviewed post diagnosis?**
Review question 8b	**How should people with Mild Cognitive Impairment be reviewed post diagnosis?**

Literature review

	8a	8b
Records identified from databases	5,067	2,789
Studies assessed for eligibility	15	0
Included studies	3	0
Studies included in the NICE GL	5	-
Total number of included studies	8	0

Eligibility criteria

Population	People aged ≥40 years living with dementia/MCI.
Interventions	Models of post diagnosis review for people living with dementia, which may include features such as: • review of mental health (memory, mood, challenging behaviours); • review of physical health (including co-morbidities); • review of functional ability; • nutrition and hydration (swallowing); • lifestyle advice; • medication review (including co-prescribing); • information needs; • driving safety review; • financial advice; • future care planning needs; • carer support and assessment.
Comparator	Usual care.
Outcomes	• Clinical outcomes including cognitive, functional and behavioural ability. • Process outcomes (e.g. adherence of staff to review protocols). • Access to health and social care support. • Experiences and satisfaction of people living with dementia/MCI and their carers. • Health-related quality of life of people living with dementia/MCI and their carers. • Equity of access to services. • Adverse events (medication). • Resource use and costs.

Aim

The objective of the systematic literature review, in line with the strategy defined by the NICE Guideline, was to identify all comparative experimental studies (e.g. Randomized Controlled Trial – RCTs, non-randomized trials) investigating the effectiveness and appropriateness of methods, models and settings for the monitoring of people with dementia and Mild Cognitive Impairment (MCI).

Summary of evidence

For review question 8a, the systematic literature review performed for the NICE guideline identified five studies meeting the predefined eligibility criteria. After updating the systematic review, three new studies were identified.

For review question 8b, no studies meeting the predefined eligibility criteria were identified.
Studies were analyzed individually and classified according to the type of considered intervention.
One study investigated the combination of a flexible, multicomponent telephone intervention of care consultation provided with the support of the Alzheimer Association (AA). The intervention was aimed at providing tailored support to people with dementia and their caregivers (Bass 2003). The study, on 157 dyads, reported an increase in the intervention group compared to the control group of the mean use of care consultation services (MD -0.16, 95% CI -0.29 – -0.03, I^2 n.a., moderate certainty). However, it reported no differences between groups in the use of the local (MD 0,02, IC 95% -0,47 – 0,51, I^2 n.a., low certainty) and information and support services that were not managed by the AA (MD -0.10, IC 95% -0.50 – 0.30, I^2 n.a., low certainty). It also reported no differences between groups in the mean number of accesses to ER (MD -0.17, IC 95% -0.51 – 0.17, I^2 n.a., low certainty), hospitalizations (MD -0.08, IC 95% -0.26 – 0.10, I^2 n.a., low certainty) and medical visits (MD -0.01, IC 95% -1.36 – 1.38, I^2 n.a., low certainty).

One study on 104 dyads investigated the efficacy of a case conferencing intervention carried out by a multidisciplinary group with the involvement of General Practitioners (GPs) in improving the appropriateness of the management of institutionalized people with dementia (Crotty 2004). The study reported an improvement in the intervention group compared to the control group in the Medication Appropriateness Index (MAI) (MD 3,69, 95% CI 1,53 – 5,85, I^2 n.a., low certainty). However, it reported no differences between groups in the number of prescribed medications (MD 0,39, IC 95% -0,55 – 1,33, I^2 n.a., low certainty) and the frequency of behavioral (NHBPS, Nursing Home Behaviour Problem Scale: MD -2,70, IC 95% -14,97 – 9,57, I^2 n.a., very low certainty) symptoms in people with dementia.

One study on 203 investigated the efficacy of a multidisciplinary network involving different health and social care professionals, including GPs and professionals from different care settings on the appropriateness of care (Köhler 2014). The study reported no differences between groups in the cognitive symptoms (MMSE, Mini Mental State Examination: MD 0.70, 95% CI -1.70 – 3.10, I^2 n.a., low certainty), functional symptoms (IADL, Instrumental Activities of Daily Living: MD 0.10, 95% CI -0.72 –0.92, I^2 n.a., low certainty) and quality of life (QoL-AD: MD -0.40, 95% CI -2.43 – 1.63, I^2 n.a., low certainty) of people with dementia. It also reported no differences between groups in the physical (SF-36: MD 2.60, 95% CI -0.81 – 6.01, I^2 n.a., low certainty) and mental quality of life of caregivers (SF-36: MD 0.10, 95% CI -2.67 – 2.87, I^2 n.a., low certainty).

One study on 175 dyads investigated the efficacy of a care-coordination intervention for people with dementia and their caregiver managed by specialist services in one group, and by GPs in the other group (Meeuwsen 2012). The study reported an improvement in the intervention group compared by the control group in caregivers' anxiety (STAI, State-Trait Anxiety Inventory: state MD 2.35, 95% CI 0.35 v 4.36, I^2 n.a., low certainty; trait MD 2.14, 95% CI 0.24 – 4.03, I^2 n.a., low certainty) e and depressive symptoms (CES-D, Center for Epidemiologic Studies Depression Scale: MD 2.09, 95% CI 0.15 – 4.02, I^2 n.a., low certainty). However, it reported no differences between groups in the depressive (GDS, Geriatric Depression Scale: MD

0.25, 95% CI -0.36 – 0.86, I^2 n.a., low certainty) e and behavioral symptoms (NPI, Neuropsychiatric Inventory: MD 1.13, 95% CI -0.51 – 2.77, I^2 n.a., low certainty) of people with dementia, and in their quality of life (QoL-AD: MD 0.25, 95% CI -0.76 – 1.23, I^2 n.a., low certainty).

One study on 1.131 dyads investigated the efficacy of a standardized comprehensive assessment intervention for people with dementia and their caregivers, including interventions based on standardized best practices for the management of the potential issued identified after the first assessment (Nourhashemi 2010). The study reported a higher mortality rate in the intervention group compared to the control group (RR 1,65, 95% CI 1,09 – 2,49, I^2 n.a., low certainty). However, it reported no differences between groups in the risk of institutionalization (RR 0,52, 95% CI 0,22 – 1,21, I^2 n.a., low certainty) and the frequency of lost to follow up (RR 1,08, 95% CI 0,90 – 1,26, I^2 n.a., low certainty), and in the functional abilities of people with dementia (ADCS-ADL, Alzheimer's Disease Cooperative Study Activity of Daily Living: MD -0,50, 95% CI -2,28 – 1,28, I^2 n.a., low certainty).

One study investigated the efficacy of the UCLA (University of California, Los Angeles) ADC (Alzheimer and Dementia Care) program, an integrated-management intervention for people with dementia provided by specialist services and GPs, based on a structured assessment of people with dementia and their caregivers and the implementation of personalized interventions followed by continuous monitoring (Jennings 2020). The study, on 3,995 participants, reported a higher frequency in the intervention group of admissions to hospice during the last 6 months of life (RR 1.35, IC 95% CI 1.10 – 1.65, I^2 n.a., n = 602, moderate certainty). However, it reported no differences between groups in the mortality rate at 7 days after hospice admission (RR 0.53, IC 95% CI 0.28 – 1.00, I^2 n.a., n = 602, low certainty). The study also reported no differences between groups in the mean number of hospitalizations (MD -8.50, IC 95% CI -17.50 – 0.50, I^2 n.a., n = 3,995, very low certainty) and accesses to ER (MD -9,40, IC 95% CI -18,97 – 0,17, I^2 n.a., n = 3,995, very low certainty). However, it reported a shorter mean length of stay in intensive care in the intervention group (MD -8,8, IC 95% CI -16,30 – -1,30, I^2 n.a., n = 3,995, low certainty) and a lower mean number of days of hospitalization (MD -160.10, IC 95% CI -215.74 – -104.46, I^2 n.a., n = 3,995, low certainty).

One study on 407 dyads investigated the efficacy of a collaborative integrated care intervention defined as a complex intervention aimed at the best treatment of people with dementia and the support of their caregivers through personalized interventions (Thyrian 2017). The study reported a higher frequency in the intervention group compared to the control groups of prescriptions of anti-dementia medications (RR 1.47, 95% CI 1.05 – 2.05, I^2 n.a., moderate certainty) and of potentially inappropriate medications (RR 2.31, 95% CI 1.45 – 3.68, I^2 n.a., moderate certainty). When considering the outcomes of people with dementia, the study reported an improvement of behavioral symptoms in the intervention group compared to the control group (NPI: MD -7.4, 95% CI -11.60 – -3.20, I^2 n.a., moderate certainty). However, it reported no differences between groups in cognitive symptoms (MMSE: MD -0.80, 95% CI -2.45 – 0.85, I^2 n.a., very low certainty), quality of life (QoL-AD: MD 0.10, 95% CI -0.01 – 0.21, I^2 n.a., low certainty), and functional abilities (Bayer-ADL: MD -0.1, 95% CI -0.92 – 0.72, I^2 n.a., low certainty). When considering caregivers, the study reported no differences between groups in burden (BIZA-D, Berlin Inventory of Caregivers' Burden with Dementia Patients: MD -0.46, 95% CI -1.25 – 0.33, I^2 n.a., low certainty).

One study on 237 dyads investigated the efficacy of a multicomponent training intervention, with specific attention to the monitoring and optimization of the pharmacological treatment with psychoactive drugs in cooperation with general practitioners (GPs) (Gedde 2022). The study reported an improvement in the intervention group compared to the control group of the quality of communication with the GP measured with the Clinical Global Impression of Change (CGI-C) tool (MD 0.54, 95% CI 0.09 – 0.99, I^2 n.a., moderate certainty). However, it reported no differences between groups in the mean number of prescribed drugs (MD 0.03, 95% CI -0.57 – -0.63, I^2 n.a., low certainty) and psychoactive medications (MD -0.04, 95% CI -0.26 – 0.18, I^2 n.a., low certainty), and in psychological and behavioral symptoms (MD -0.07, 95% CI -5.18 – 5.04, I^2 n.a., low certainty) and depressive symptoms (MD 1.22, 95% CI -0.46 – 2.90, I^2 n.a., low certainty).

Analysis of evidence

The use of specific strategies (methods, models, and settings) aimed at monitoring people with a diagnosis of cognitive deficit (MCI or dementia), could help people with dementia and their family members or caregivers in preserving or improving cognitive functions, functional abilities, and quality of life, which are the same outcomes considered to measure the efficacy of drug treatments. This consideration is based on the hypothesis that effective and appropriate review strategies, which can timely and accurately identify each person's needs, could lead to a more efficient and effective use of intervention and support services. On this basis, the analysis of evidence also assessed outcomes related to the appropriate and timely access to services and to the reduction of inappropriate prescriptions and service use.

The most frequent way of managing post-diagnosis reviews, which is based on scheduled control visits and standardized structured assessment, may not be sufficient to meet the real-life needs of people with dementia, whose needs can be subject to unpredictable changes throughout the course of the disease. It is essential to consider that disease trajectories can be specific to each person, thus implying specific individual care needs. A plan for the review and optimization of care and support intervention including only regularly scheduled visits could therefore fail to identify and respond to potential changes in the global clinical picture in a timely manner.

Considering that people with dementia often have complex clinical pictures, with either comorbidities or multimorbidity, which affect the course of the disease, is crucial. These conditions should always be taken in due consideration when planning care, as they can require adjustments to both the pharmacological and non-pharmacological treatment plan. Therefore, planning and implementing a more flexible clinical monitoring is essential, to optimize the management of the specific needs of people with dementia and their caregivers.

Proposing a model for the organization of monitoring and review should also include an appropriate assessment of how healthcare is organized in each national and regional structure. The NICE guideline discussed the variability in the organization of memory clinics in UK, thus agreeing not to recommend a single specific service model for the assessment of people with dementia. However, in general, the monitoring of people with dementia should be part of a care-coordination model referring to all settings involved in their review. Specifically, the monitoring includes not only the re-assessment of cognitive and functional abilities over time, which is part of the activities of the specialist centres, but also the treatment and stabilization of all clinical conditions and nutritional status. This also includes an appropriate review not only of pharmacological and non-pharmacological treatments for people with dementia, but also of their living conditions. Moreover, the WG underlined that people with early-onset dementia have specific needs, which include different social needs, such as monitoring their ability to work or drive a car. This assessment of the monitoring strategies also includes the need to plan future care and support to caregivers.

This question was aimed at assessing the most effective models for post diagnosis review and the clinical settings in which these models can be planned, with the objective of preventing people with dementia and their family members and caregiver from losing their way in a complex healthcare system. The WG discussed the opportunity to consider each contact with the different health professionals as an opportunity to review people with dementia. The primary care setting is likely the setting that most frequently has contact with people with dementia and their family members or caregivers, considering that GPs assess them for all comorbidities and treatment prescriptions. The opportunity for people and their caregivers to access multidisciplinary territorial services, involving healthcare, social and volunteer services would be ideal to timely identify emerging issues.

Overall, evidence from included studies did not investigate the issues related to the post diagnosis review of people with dementia.

Some of the included studies compared, assessing clinical and process outcomes, monitoring by professionals in different clinical settings. However, evidence should be considered accounting for differences in the health and social care models adopted in the different countries where the studies were carried out.

One study investigated a care-coordination intervention for people with dementia and their caregiver led by specialist services compared to GPs, reporting a positive effect on some of the psychological and behavioural outcomes of caregivers, but reported no effect on people with dementia. The use of a multidisciplinary integrated network aimed at assessing the appropriateness of care, involving different health professionals, including GPs and other professionals from various clinical settings, did not report any relevant effects on the cognitive and functional abilities in people with dementia and on the physical and mental quality of life of their caregivers. A flexible, multicomponent, care-coordination intervention managed via phone calls by a volunteer organization and designed to provide tailored support in case of access to the ER, hospitalization, or the need for medical visits, did not show any effect on the considered outcomes of people with dementia and their caregivers.

Studies investigating the effectiveness of an integrated management intervention provided by specialists and GPs, based on a structured assessment of people with dementia and their caregivers and the implementation of personalized interventions and monitoring, reported no positive effects on the considered primary outcomes, access to hospice and mortality rate, but reported a decrease in the length of hospital stay.

The WG, based on the overall analysis of evidence, confirmed that the most effective care model that Centers for Cognitive Disorders and Dementias (CCDDs) could offer should be organized based on a flexible, coordinated and multidisciplinary monitoring, which should be accessible to all people with dementia. As post diagnosis review of people with dementia has an impact on caregivers, all recommendation were considered as relevant for both people with dementia and their caregivers, in line with the approach adopted by the NICE guideline.

The WG also discussed the need to assess the effectiveness of telemedicine interventions allowing the remote monitoring of people with dementia. These could help overcoming the difficulties and stress of transferring and be useful in optimizing the use of available resources. The WG also discussed the need to perform studies investigating the effect of interdisciplinary monitoring strategies led by GPs in collaboration with other healthcare professionals. To this purpose, two specific research recommendations were included.

For question 8b on the post diagnosis review of people with MCI, which was not included in the NICE guideline, no studies were identified meeting the predefined eligibility criteria.

The WG, after discussion, agreed to extend the recommendations for post diagnosis monitoring of people with dementia to include people with MCI, underlining the importance of monitoring being carried out in dedicated multidisciplinary specialist services, such as CCDDs, allowing for a flexible access. The recommendation to GPs to always assess any emergent specific need for targeted support was also extended to people with MCI.

Recommendations

Post diagnosis review for people living with dementia

46	After a person is diagnosed with dementia or Mild Cognitive Impairment, ensure they and their carers have access to specialist multidisciplinary dementia services (Centres for Cognitive Disorders and Dementias, CCDDs).	STRONG IN FAVOR

47	Specialist multidisciplinary dementia services (Centres for Cognitive Disorders and Dementias, CCDDs) should offer a choice of flexible access or prescheduled monitoring appointments.	WEAK IN FAVOR
48	General practitioners, when visiting people living with dementia or Mild Cognitive Impairment, or their carers, should assess for any emerging dementia-related needs and ask them if they need any more support.	WEAK IN FAVOR

Research Recommendations

Post diagnosis review for people living with dementia

11R	What is the effectiveness of telemedicine interventions for the post diagnosis review of people with dementia?
12R	What is the effectiveness of an interdisciplinary review from general practitioners in collaboration with other healthcare professionals in assessing for interventions for any emerging dementia-related needs?

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Staff training

Review question 9	**What effect does training for staff working with people living with dementia have upon the experiences of people living with dementia in their care?**

Literature review

Records identified from databases	3,809
Studies assessed for eligibility	22
Included studies	4
Studies included in the NICE GL	24
Total number of included studies	28

Eligibility criteria

Population	People aged ≥40 years living with dementia.
Interventions	Training interventions for formal, paid staff working with people living with dementia.
Comparison	No specific training intervention.
Outcomes	• Appropriate use of procedures/medicines. • Experience and satisfaction of people with dementia and their carers • Health-related quality of life of people with dementia and their carers. • Resource use and costs.

Aim

The objective of the systematic literature review, in line with the strategy defined by the NICE Guideline, was to identify all Randomized Controlled Trials (RCTs) investigating the effectiveness of training interventions for health and social care professionals in improving the outcomes of people with dementia and their caregivers. Only studies reporting data on the outcomes of people with dementia and their caregivers were included.

For the purposes of this question, a "care provider" is defined as any type of organisation that delivers health and/or social care.

Summary of evidence

The systematic literature review performed for the NICE guideline identified 24 studies meeting the predefined eligibility criteria. After updating the systematic review, four new studies were identified.

Studies were analysed individually and classified according to the type of considered intervention.

One study on 351 participants (Beer 2011) investigated the effectiveness of a training intervention for general practitioners (GPs) or nursing home staff aimed at improving communication, management of pain and

psychological and behavioural symptoms, and cooperation among staff from different structures. When considering nursing home staff, the study reported a higher frequency in the intervention group compared to the control group of documented pain assessments (aOR 3.75, IC 95% CI 1.26 – 11.14, I^2 n.a., very low certainty), but not of structured pain scales (aOR 1.98, 95% CI 0.81 – 4.83, I^2 n.a., very low certainty), at six months of follow up. It also reported a higher frequency in the intervention group of case conferencing (care coordination method involving the sharing of information among team members to optimize care) at four weeks (aOR 4.08, 95% CI 1.42 – 11.67, I^2 n.a., very low certainty), but not at six months of follow up (aOR 3.23, 95% CI 0.95 – 11.01, I^2 n.a., very low certainty). The study reported no differences between groups in the quality of life of people with dementia at six months (QoL-AD: aMD 0.97, 95% CI -1.55 – 3.50, I^2 n.a., very low certainty). It also reported no differences in the frequency of observed (aOR 1.06, 95% CI 0.39 – 2.94, I^2 n.a., very low certainty) and documented (aOR 1.53, 95% CI 0.33 – 7.14, I^2 n.a., very low certainty) restraints at six months of follow up. When considering GP training, the study reported a lower frequency of documented pain assessments (aOR 0.36, 95% CI 0.14 – 0.89, I^2 n.a., very low certainty), but not of structured pain scales (aOR 0.60, 95% CI 0.25 – 1.47, I^2 n.a., very low certainty) at six months of follow up. The study reported no differences between group in the frequency of case conferencing at 4 weeks (aOR 1.59, 95% CI 0.64 – 3.95, I^2 n.a., very low certainty) and at six months of follow up (aOR 1.02, 95% CI 0.34 – 3.02, I^2 n.a., very low certainty). The study reported a lower frequency of documented (aOR 0.13, 95% CI 0.03 – 0.47, I^2 n.a., very low certainty), but not of observed (aOR 0.44, 95% CI 0.17 – 1.11, I^2n.a., very low certainty) restraints at six months of follow up. It reported no differences between groups in the quality of life of people with dementia (QoL-AD: aMD -0.61, 95% CI -3.07 – 1.85, I^2 n.a., very low certainty).

One study on 210 investigated the effectiveness of an intervention program led by specifically trained occupational therapists targeted to nursing home staff to optimize the physical environment and improve communication thus allowing staff to motivate residents in participating in the proposed activities (Wenborn 2013). The study reported no differences between groups in cognitive (MMSE: aMD -0,36, IC 95% -2,22 – 1,51, I^2 n.a., very low certainty), behavioural (CBS, Challenging Behaviour Scale: aMD 4.13, 95% CI -21.10 – 29.36, I^2 n.a., very low certainty), and depressive symptoms (CSDD: aMD -0.09, 95% CI -1.33 – 1.16, I^2 n.a., low certainty). It also reported no differences between groups in the anxiety level (RAID: aMD 0.57, 95% CI -1.52 – 2.66, I^2 n.a., low certainty) and quality of life if people with dementia (QoL-AD: aMD 0.26, 95% CI -3.04 – 3.56, I^2 n.a., very low certainty).

One study on 117 investigated the effectiveness of a training intervention for nursing home staff on the snoezelen method (sensory camera or controlled multisensory environment) as an integrated approach in the daily management to provide a person-centered care and improve the attitude and non-verbal communication between residents and staff (van Weert 2005). The study reported a higher mean frequency of non-verbal reactions through smiles from residents with dementia (MD 2.87, IC 95% 0.81 – 4.93, I^2 n.a., moderate certainty) and an increased mean length of morning care routine (MD 3.98, IC 95% 1.27 – 6.69, I^2 n.a., moderate certainty) in the intervention group compared to the control group. The study reported no differences between groups in the non-verbal positive (MD 7.19, IC 95% -5.21 – 19.59, I^2 n.a., very low certainty) and negative (MD-5.36, IC 95% -9.39 – 1.33, I^2 n.a., very low certainty) affective communication of residents with dementia. It also reported no differences in the positive (MD 5.04, IC 95% -1.67 – 11.75, I^2 n.a., very low certainty) and negative (MD -0.46, IC 95% -1.61 – 0.69, I^2 n.a., very low certainty) instrumental communication of residents with dementia.

One study on 79 investigated the effectiveness of a training intervention for nursing home staff aimed at improving their skills in managing behavioral symptoms (Burgio 2002). The study reported no differences between groups in resident agitation during care interactions (MD 3.61, IC 95% -8.89 – 16.11, I^2 n.a., very low certainty) and maintained at follow yp (MD 0.60, IC 95% -6.85 – 8.05, I^2 n.a., very low certainty).

One study on 67 participants investigated the effectiveness of a training program for nursing home staff targeted at providing nutritional skills to improve the staff's attitude and behavior towards nutritional

disorders in people with dementia (Chang 2005). The study reported a decrease in the mean quantity of consumed food (MD -0.21, 95% CI -0.38 – -0.04, I^2 n.a., very low certainty), and an increase of the feeding difficulties in people with dementia (EdFED, Edinburgh Feeding Evaluation in Dementia: MD 2.70, 95% CI 1.06 – 4.34, I^2 n.a., very low certainty) in the intervention group compared to the control group. However, the study reported no differences between groups in the total time dedicated to eating (MD 2.90, 95% CI -0.01 – 5.81, I^2 n.a., very low certainty).

One study on 65 participants investigated the effectiveness of a training program for nursing home staff based on education, group supervision, and individual support, which was aimed at improving the communication between staff and residents with dementia, especially those at a late stage of the disease (Clare 2013). The study reported no differences between groups in the cognitive (GADS: MD -1.27, 95% CI -4.79 – 2.25, I^2 n.a., very low certainty), motor (BASOLL-M, The Behavioural Assessment Scale of Later Life: MD -0.09, 95% CI -0.77 – 0.59, I^2 n.a., very low certainty), and sensory functions (BASOLL-S: MD -0.02, 95% CI -0.69 – 0.65, I^2 n.a., very low certainty) of residents with dementia. It also reported no differences between groups in the wellbeing (PRS, Positive Response Schedule: MD 2.42, 95% CI -4.92 – 9.76, I^2 n.a., very low certainty) and quality of life of residents with dementia (QUALID: MD -3.25, 95% CI -7.94 – 1.44, I^2 n.a., very low certainty).

Three studies investigated the effectiveness of structured training programs for nursing home staff targeted at providing specific knowledge on the management of behavioural symptoms of dementia. Two studies (Davison 2007, Deudon 2009) on 384 participants reported an improvement in anxiety in residents with dementia (MD -5,55, IC 95% -9,34 – -1,76, I^2 0%, moderate certainty). Two studies (Deudon 2009, Visser 2008) on 359 participants reported no differences between groups in the mean frequency of physically (PAB, Phisically Aggressive Behaviour: MD -0,08, IC 95% -0,37 – 0,21, I^2 0%, low certainty) and verbally aggressive behaviors (VAB, Verbally Aggressive Behaviour: MD 0,19, IC 95% -1,10 – 1,49, I^2 44%, low certainty). One study (Visser 2008) on 53 participants reported no differences between groups in quality of life (ADR-QoL: MD 2,22, IC 95% -11,51 – 15,95, I^2 n.a., very low certainty), and one study (Deudon 2009) on 306 participants reported no differences between groups in the mean number of prescriptions of psychotropic drugs (MD -0,14, IC 95% -0,61 – 0,33, I^2 n.a., low certainty).

One study on 105 participants investigated the effectiveness of a personalized individual- and group-training program for specialized nursing home staff aimed at improving their knowledge and skills on dementia, verbal and non-verbal communication with people with dementia, and use of strategies for the management of memory and behavioral problems (McCallion 1999). The study reported an improvement in depressive symptoms in residents with dementia (CSDD: MD -1.41, 95% CI -2.47 – -0.35, I^2 n.a., moderate certainty). However, it reported no differences between groups in aggression (CMAI: MD -1.72, 95% CI -6.03 – 2.59, I^2 n.a., low certainty) and frequency of physical (MD 0.75, 95% CI -0.07 – 1.57, I^2 n.a., low certainty) and pharmacological restrain (MD 0.37, 95% CI -0.56 – 1.30, I^2 n.a., low certainty) in residents with dementia.

One study on 146 participants investigated the effectiveness of a combined training intervention for nursing home staff specifically aimed at the implementation of personalized care plans provided by a multidisciplinary group and an integrated, emotion-oriented care model (Finnema 2005). The study reported no differences between groups in depressive symptoms (CSDD: MD 0.72, 95% CI -1.35 – 2.79, I^2 n.a., low certainty), mean frequency of physically (CMAI: MD 0.10, 95% CI -1.20 – 1.40, I^2 n.a., low certainty) and verbally aggressive behaviors (CMAI: MD -0.16, 95% CI -2.14 – 1.82, I^2 n.a., low certainty).

Two studies on 383 participants investigated the effectiveness of training programs for nursing home staff to provide multicomponent person-centered interventions of care mapping for people with dementia (Chenoweth 2009, van de Ven 2013). Both studies reported a worsening of behavioural symptoms in the intervention group compared to the control group (NPI: MD 2.58, 95% CI 0.79 – 4.36, I^2 0%, low certainty). However, they reported no differences between groups in anxiety (CMAI: MD -4.97, 95% CI -15.54 – 5.59, I^2 86%, very low certainty) and quality of life (SMD -0.04, IC 95% -0.25 – 0.16, I^2 0%, very low certainty).

Three studies investigated the effectiveness of training programs for nursing home staff based on a person-centered approach and aimed at implementing person-centered care for people with dementia to improve the management of behavioural disorders in residents with dementia. One study (Fossey 2006) on 338 participants reported a decrease in the proportion of residents with dementia treated with neuroleptic drugs (RR 0.55, 95% CI 0.39 – 0.76, I^2 n.a., moderate certainty). However, it reported no differences between groups in the proportion of residents treated with other psychotropic drugs (RR 1.10, 95% CI 0.92 – 1.32, I^2 n.a., low certainty) and in the number of residents who fell at least one in the 12 months of follow up (RR 0.95, IC 95% 0.78 – 1.16, I^2 n.a., low certainty). It also reported no differences in anxiety (CMAI: MD -0.3, 95% CI -1.81 – 1.01, I^2 n.a., low certainty). Two studies (Chenoweth 2009, Chenoweth 2014) on 477 participants reported an improvement in the intervention group compared to the control group in anxiety (CMAI: MD -17.68, 95% CI -20.87 – -14.48, I^2 0%, moderate certainty). One study (Chenoweth 2009) on 180 participants reported and improvement in the intervention group of behavioural symptoms (NPI: MD -7.10, 95% CI -9.58 – -4.62, I^2 n.a., moderate certainty) and quality of life (QUALID: MD -3.10, 95% CI -3.90 – -2.30, I^2n.a., moderate certainty) in residents with dementia.

One study on 230 participants investigated the effectiveness of a training intervention for nursing home staff specifically focusing on the management of apathy and depression, and more generally on the management of behavioural symptoms in residents with dementia (Leone 2013). The study reported no differences between groups in apathy (NPI-A MD 0.11, 95% CI -1.57 – 1.79, I^2 n.a., low certainty), hyperactivity (NPI-H MD 0.40, 95% CI -2.97 – 3.77, I^2 n.a., very low certainty), and psychosis (NPI-P MD 0.60, 95% CI -1.17 – 2.37, I^2 n.a., low certainty) in residents with dementia.

One study on 57 participants investigated the effectiveness of a training intervention for nursing home staff specifically focusing on non-verbal communication and expressing emotions (Magai 2002). The study reported an overall improvement of symptoms measured with a composite score including behavioural symptoms, anxiety, depression, and expressiveness (MD -39.20, 95% CI -63.22 – -15.18, I^2 n.a., very low certainty) in the intervention group compared to the control group.

Three studies investigated training interventions for nursing home staff specifically focusing on the management of behavioral symptoms to decrease the use of restraints and promote the use non-pharmacological strategies. Two studies (Huizing 2006, Pellfolk 2010) on 432 participants reported a lower frequency of physical restraint in the intervention group compared to the control group (RR 0,65, IC 95% 0,45 – 0,94, I^2 62%, low certainty). One study (Pellfolk 2010) on 288 participants reported no differences between groups in the frequency of prescriptions of benzodiazepines (RR 1,40, IC 95% 0,94 – 2,08, I^2 n.a., very low certainty) and neuroleptic drugs (RR 1,24, IC 95% 0,94 – 1,64, I^2 n.a., very low certainty), and in the frequency of falls (RR 1.17, 95% CI 0.57 – 2.40, I^2 n.a., very low certainty). One last study (Testad 2005) on 142 participants reported an improvement in agitation in residents with dementia (BARS: MD 4.30, 95% CI 0.72 – 7.88, I^2 n.a., low certainty). However, it reported no differences between groups in the use of physical restraint (MD -2.40, 95% CI -5.20 – 0.40, I^2 n.a., very low certainty).

One study on 97 participants investigated the effectiveness of a specific training intervention for nursing home staff aimed at the implementation of guidelines for the management of depressive and behavioural symptoms in residents with dementia to increase their participation in pleasant activities and decreasing the frequency of unpleasant events (Verkaik 2011). The study reported no differences between groups in depressive symptoms in residents with dementia (CSDD: MD 0.09, 95% CI -3.21 – 3.39, I^2 n.a., very low certainty).

One study on 73 participants investigated the effectiveness of a training intervention for nursing home staff on a person-centered approach for the management of hygiene (towel-bath, showering) in residents with dementia through structured techniques targeted to the severity, preferences, and possible difficulties of each resident (Sloane 2004). The study reported no differences between groups in aggression, verbal and physical aggressive behaviors, and agitation towel bathing (agitation/aggression MD -11.22, 95% CI -27.80 –

5.36, I^2 n.a., very low certainty; physical agitation/aggression MD -0,59, 95% CI -1,36 – 0,18, I^2 n.a., very low certainty; verbal agitation MD -0.31, 95% CI -1.00 – 0.38, I^2 n.a., very low certainty). It also reported no differences between groups in shower bathing (agitation/aggression MD -8,89, 95% CI -25.83 – 8.05, I^2 n.a., very low certainty; physical agitation/aggression MD -0.39, 95% CI -1.19 – 0.41, I^2 n.a., very low certainty; verbal agitation MD -0.09, 95% CI -0.79 – 0.61, I^2 n.a., very low certainty).

One study on 33 occupational therapists (OTs) investigated the effectiveness of a training intervention for OTs aimed at the implementation of an OT program for people with dementia and their caregivers (COTiD, Community Occupational Therapy in Dementia), along with a specific training on an interdisciplinary training with clinicians and managers (Döpp 2015). The study reported no differences between groups in the occupational performance (COPM, Canadian Occupational Performance Measure: MD -0.30, IC 95% -1.79 – 1.19, I^2 n.a., very low certainty) and quality of life (DemQoL: MD -0.40, IC 95% -1.17 – 0.37, I^2 n.a., very low certainty) of residents with dementia.

One study on 130 participants investigated the effectiveness of the implementation of the digital version of a training program for nursing home staff aimed at promoting person-centered interventions, personalized activities and interaction, and the optimization of antipsychotics prescriptions (McDermid 2022). The study reported an improvement in the intervention group compared to the control group in the wellbeing of residents with dementia (wellbeing score: MD 0.32, IC 95% 0.10 – 0.54, I^2 n.a., moderate certainty), and the percentage of time engaged in positive activities (MD 10.37, 95% CI 1.71 – 19.03, I^2 n.a., low certainty).

One study on 197 participants investigated the effectiveness of a training intervention for nursing home staff, based on Relation Related Care (RRC) and specifically aimed at reducing the use of restraints (Testad 2016). The study reported no differences between groups in the frequency of restraints use (RR 2.06, 95% CI 0.97 – 4.36, I^2 n.a., very low certainty), and in the severity of behavioural symptoms (NPI: MD 4.00, 95% CI -2.86 – 10.86, I^2 n.a., very low certainty) and anxiety (CMAI: MD 0.50, 95% CI -4.67 – 5.67, I^2 n.a., very low certainty) in residents with dementia.

One study on 96 participants investigated the effectiveness of a training protocol for nursing home staff aimed at the implementation of psychosocial interventions and personalized activities, and at the optimization of antipsychotics prescriptions (Torres-Castro 2022). The study reported no differences between groups in the behavioural symptoms (NPI: MD 5.20, 95% CI -4.31 – 14.71, I^2 n.a., very low certainty) and quality of life (QoL-AD: MD 0.20, 95% CI -3.49 – 3.89, I^2 n.a., very low certainty) of people with dementia.

One study on 123 participants investigated the effectiveness of a training intervention for nursing home staff aimed at implementing guidelines for the review and optimization of medicines in people with severe dementia (Kroger 2023). The study reported no differences between groups in pain levels (PACSLAC: MD -0.90, IC 95% -2.54 – 0.74, I^2 n.a., low certainty) and agitation (MD -2.70, 95% CI -8.37 – 2.97, I^2 n.a., low certainty). It also reported no differences between groups in the overall number of drug prescriptions (MD 1.17, 95% CI -2.17 – 4.51, I^2 n.a., low certainty), mean number of regular prescriptions (MD 1.33, 95% CI -0.33 – 2.99, I^2 n.a., low certainty), and mean number of regular prescriptions of antipsychotics (MD 0.03, 95% CI-0.27– 0.33, I^2 n.a., low certainty).

Analysis of evidence

Therefore, training can be a need for both the staff and the organisation where they work. Healthcare professionals are required to update and acquire skills to perform their activities while ensuring the best standard of care, in line with the most updated available evidence. The organisation need to maintain their personnel as effective and efficient while guaranteeing high levels of safety in providing services. In this framework, people with dementia and their caregivers can receive the best possible care, based on their needs, and the availability of the organisations.

The studies included in the systematic review investigated training interventions for health and social care professionals caring for people with dementia. However, a wide heterogeneity was observed across studies in the type of considered interventions, tools, and outcome measures. Therefore, recommendations were more general, encompassing key aspects of the interventions, rather than focusing on specific types of training and ways of implementing them.

The WG agreed to specify within the recommendation to train healthcare professionals, the recurrent components of the interventions reported in the body of evidence, including general training on dementia, assessment and treatment of specific symptoms and needs, and management of non-cognitive symptoms such as agitation, aggression, and pain. The studies also included follow-up sessions aimed at providing feedback to the staff and advice on specific complex cases. The included recommendation also refers to people with early-onset dementia, based on evidence from question 6.

Almost all studies targeted their training interventions to nursing home staff. This highlights the level of difficulty encountered by the staff when carrying out their activities, and could in some way be considered the reason for the lack of significant results. People resident in these structures are usually older and have moderate to severe dementia. This, along with the structural limitations of this setting, could lead to underestimate the effect of the investigated interventions, despite the improvement in skills. Moreover, included studies are not representative of the impact of staff training on professionals caring for people with mild to moderate dementia.

Several studies mainly focused on the management of agitation and/or aggression, with the objective of decreasing the number of prescriptions of antipsychotic medications and the use of physical restraint. Results reported that some targeted interventions were able to decrease the use of antipsychotic medications and physical restraint without causing a significant increase in behavioural disorders or other symptoms. Therefore, the WG agreed that staff training should include this aspect. The use of physical and pharmacological restraint is only justified in case of documented necessity and should be enacted only after appropriately informing both people with dementia and/or their caregivers.

Considered evidence supported the use of multisensory stimulation in people with moderate to severe dementia. However, these results are based on evidence from one single study. Therefore, the WG agreed to grade the recommendation as weak and limit it to this specific population even though this intervention is usually provided to heterogeneous groups of people.

The body of evidence also included several, more specific, interventions. These were usually presented as person-centred care. However, they were focused only on a specific area of care instead of being based on a holistic approach to people. The WG agreed that this evidence was not as strong as the evidence supporting more inclusive training programs, and it was impossible to establish whether these interventions were less effective, or the number of studies was too low. Therefore, the WG agreed not to include any recommendations on this evidence.

Recommendations

Staff training

49	Care and support providers should provide all staff with appropriate 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;	WEAK IN FAVOR

	• respecting the person's individual identity, sexuality, and culture; • understanding the needs of the person and their family members or carers.	
50	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; • 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; • the specific needs of younger people living with dementia and people who are working or looking for work.	WEAK IN FAVOR
51	Consider giving carers and/or family members the opportunity to attend and take part in staff dementia training sessions.	WEAK IN FAVOR
52	Consider training staff to provide multi-sensory stimulation for people with moderate to severe dementia and communication difficulties.	WEAK IN FAVOR

Research Recommendations

Staff training

13R	What is the cost effectiveness of implementing a dementia-specific addition to training for community staff, including dementia-specific elements on managing anxiety, communication, nutritional status, personal care, and environment adaptation?
14R	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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Involving people living with dementia in decisions about care

Review question 10a	**What barriers and facilitators have an impact on involving people living with dementia in decisions about their present and future care?**
Review question 10b	**What barriers and facilitators have an impact on how people living with dementia can make use of advance planning?**

Literature review

A single literature search was conducted for all qualitative questions included in this Guideline (GL) referred to people with dementia (Review questions 6, 7c, 10a, 10b, 24).

Records identified from databases	21,475
Studies assessed for eligibility	17
Included studies	11
Studies included in the NICE GL	9
Total number of included studies	20

Eligibility criteria

Population	• People aged ≥40 years living with dementia. • Carers of people (aged ≥40 years) living with dementia.
Phenomena of interest	• Equity of access (financial, physical or geographic restrictions). • Behaviours and attitudes of professionals. • Communication. • Loss of autonomy. • Information needs.
Outcomes	• Experiences and satisfaction of people with dementia. • Experiences and satisfaction of carers of people with dementia. • Experiences of health and social care professionals.

Aim

The objective of the systematic review was to identify qualitative studies and qualitative evidence syntheses that explored barriers and facilitators to the involvement of people with dementia in decisions about their present and future assistance, and to their access to advance care planning.

Studies were excluded if they did not report the opinions of people with dementia or their caregivers and whether they included only a quantitative analysis of the collected information.

Summary of evidence

The qualitative analysis of studies identified two categories of themes: barriers to the involvement of people with dementia in decisions about their care and facilitators to the involvement of people with dementia in decisions about their care.

Barriers to the involvement of people with dementia in decision-making

Eighteen primary studies and one systematic review had the objective of identifying the perceived obstacles to the involvement of people with dementia in decision making. The systematic review included 20 qualitative studies on a total of 533 caregivers of people with dementia, using the following methods for data collection: unstructured or semi-structured interviews, focus groups, and observations (Lord 2015). Two studies did not report the exact number of participants enrolled (Mackenzie 2006, Tilburgs 2018). The remaining studies enrolled 223 participants with dementia and 306 caregivers. Data were gathered through interviews, semi-structured interviews, and focus groups (Ali 2021, Davies 2021, Dening 2017, Fried 2021, Goodman 2013, Ingravallo 2018, Lemos Dekker 2022, Livingston 2010, Poppe 2013, Samsi 2013, Sinclair 2018, Sinclair 2019, Sussman 2021, Tetrault 2022, Van Rickstal 2019, Van Rickstal 2022).

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).
- Focusing on the present. People will often focus on the present situation and did not consider as necessary focusing on problems beforehand, or they did not want to discuss their death (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).
- Individuals with dementia reported tending to delegate decision about their future care to their caregivers (high 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 had 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).
- Individuals reported that the subjective perceptions of physical health, psychological wellbeing, and capacity often affected the times and ways some decisions were made, including the evaluation of available options (high confidence).
- Individuals reported perceiving general practitioners (GPs) as distant and not very accommodating (low confidence).
- Caregivers reported that the hospitalization or institutionalization of the person with dementia changed the usual decision-making process, due to the regulations of each facility limiting the contacts and access to information (low confidence).

Facilitators to the involvement of people with dementia in decision-making

Six primary studies (Livingston 2010, Murphy 2013, Poppe 2013, Sinclair 2019, Sussman 2021, Tilburgs 2018) and one systematic review (Lord 2015) explored the elements facilitating the involvement of people with dementia in decision-making. One study did not report the number of enrolled participants (Tilburgs 2018). The remaining five studies included 65 participants with dementia and 155 caregivers. The studies gathered information through interviews, focus groups, and narrative interviews.

The following facilitators were identified to involving people living with dementia in decision about their current and future care:

- Caregiver reported as useful the reconceptualization and adjustment to altered circumstances, and presentation of decision-making as trying to maximise independence - allowing services to develop slowly (high confidence).
- Caregiver reported as useful the 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).

Analysis of evidence

Available evidence for these questions reported a summary of the elements that can be considered as obstacles or facilitators to the involvement of people with dementia in decision-making. The WG agreed that facilitators had a higher probability of being included in a recommendation.
In line with the approach adopted by the NICE guidelines, the WG agreed to maintain the reference to the other NICE guidelines on patient experience in adult NHS services (CG138)[24] and social care services (NG86)[25], and on the management of shared decision-making (NG197)[26].
Evidence reported that most people with dementia and their caregivers would rather receiving information in advance, preferably immediately after diagnosis. The WG agreed that the preferences and wishes of people with dementia and/or their caregivers should be respected, ensuring them support and information both on an ongoing basis and when requested. Moreover, people with dementia and their caregivers might need time to process information, thus the need for a recommendation aimed at ensuring they are offered information and provided the opportunity to discuss it regularly. Moreover, the WG agreed to specify that provided information should be adequate to the specific circumstances and all subgroups of people with dementia, such as younger people, and should not be too generic and non-specific to dementia.
Some people, following a diagnosis, may not initially want follow-up appointments or referrals to other services. However, since these people may change their minds, healthcare professionals should provide them the opportunity to access services at a later date, to prevent them to be left without and appropriate support.
Available evidence reported that the way some professionals currently interpret patient confidentiality guidance may have the unintended consequence of reducing perceived standards of care. Not sharing appropriate information on the health of people with dementia with their caregivers can hinder carers in

[24] NICE. Patient experience in adult NHS services: improving the experience of care for people using adult NHS services. Clinical guideline CG138. Last updated: June 2021. Available at: https://www.nice.org.uk/guidance/cg138 (Last visited: 30/08/2023).
[25] NICE. People's experience in adult social care services: improving the experience of care and support for people using adult social care services. NICE guideline NG86. Last updated: February 2018. Available at: https://www.nice.org.uk/guidance/ng86 (Last visited: 30/08/2023).
[26] NICE. Shared decision making. NICE guideline NG197. Last updated: June 2021. Available at: https://www.nice.org.uk/guidance/ng197 (Last visited: 30/08/2023).

providing the necessary support to people with dementia. Therefore, the WG agreed to underline that when a person is diagnosed with dementia, their consent should be sought for information sharing with them or their family members or caregivers. This conversation should happen at diagnosis because the person living with dementia is more likely at that time to have the capacity to decide who they would like their information to be shared with. The WG underlined the importance of reporting this consent, when obtained, in the medical record to help achieve the best standard of care.

The WG also underlined the importance of providing information and support to people with dementia and their caregivers to help them access social, advocacy and voluntary support services. Therefore, the WG agreed to confirm the recommendations from the NICE guideline to provide these services (informing people on available services). Moreover, since evidence reported that people with dementia and their caregivers benefited from accessing financial and legal services, these services were included in the list of services to inform people about.

The WG underlined the importance of discussing both advance statements and advance directives with people living with dementia as long as they have the capacity to be involved in decision-making. Some people living with dementia might feel discouraged from making decisions on their future care, as they might be concerned about not being able to change these decisions in the future. Therefore, the WG agreed to recommend offering people with dementia regular opportunities to make changes to their decisions. The WG also agreed that people with dementia should be informed in advance that they will be able to change their advance statements and advance directives in the future, to ensure that fears that they cannot be changed do not act as a barrier to advance planning.

The WG agreed that access to advanced care planning and advanced statements and directives should be transparent and standardised as far as possible, to maximise their level of transferability. This is to ensure that the wishes of people with dementia can be understood by everyone who needs to take them into consideration in the various care processes.

Included studies reported that training staff in managing difficult and emotional conversations should enable them to have the confidence to initiate and support discussions on the opportunity to access advance care planning. Evidence suggested that many people with dementia and their carers would prefer staff to initiate such conversations. However, evidence also reported that staff frequently lack confidence in their ability to discuss advance planning because they feel that it involves difficult and emotional conversations. The WG agreed that this type of training would also be important for people involved in the diagnosis of dementia, especially when communicating the diagnosis, as this was another time where emotionally challenging conversations would take place.

The evidence suggests that people with dementia can have a lack of confidence in the value of their own opinions and in their ability to express them, and that this is a significant barrier for them to make decisions on their care, as healthcare professionals may not be able to recognise the problems people have and their need for support. Therefore, the WG agreed on the importance that carers and staff are aware of this so they can try to overcome this barrier, and that people with dementia should be encouraged and enabled to express their opinions. Evidence also suggests that alternative communications strategies can facilitate involving people with dementia in decision-making. Therefore, the WG agreed to recommend considering their use by healthcare professionals.

The sections of recommendations referring to people who are working or are seeking occupation are also based on evidence from the specific needs of people with early-onset dementia (Review Question 6).

Recommendations

Involving people living with dementia in decisions about care

53	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.	STRONG IN FAVOR
54	Be aware of the obligation to provide accessible information. For more guidance on providing information and discussing people's preferences with them, see the document "National Guidance for the Clinical Governance of Dementia" issued by the National Committee for Dementia.	STRONG IN FAVOR
55	Throughout the diagnostic process, 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 health and social are professionals will be involved in their care and how to contact them; • if appropriate, how dementia affects driving, and that they need to tell the general practitioner and healthcare staff involved in renewing their licence about their dementia diagnosis; • their legal rights and responsibilities, see the document "National Guidance for the Clinical Governance of Dementia" issued by the National Committee for Dementia; • their right to reasonable adjustments (law 68/99[27] with modifications according to the Legislative Decree 151/2015[28]) 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.	STRONG IN FAVOR
56	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.	STRONG IN FAVOR
57	After diagnosis, direct people and their family members or carers (as appropriate) to relevant services for information and support (see recommendations 40 and 41 on care coordination).	STRONG IN FAVOR
58	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.	STRONG IN FAVOR

[27] Law, March 12, 1999, n. 68 (https://www.gazzettaufficiale.it/eli/id/1999/03/23/099G0123/sg) (Last visited: 30/08/2023).
[28] Legislative Decree, September 14, 2015, n. 151 (https://www.gazzettaufficiale.it/eli/id/2015/09/23/15G00164/sg) (Last visited: 30/08/2023).

59	Ensure that people living with dementia and their carers know how to get more information and who from if their needs change.	STRONG IN FAVOR
60	Tell people living with dementia (at all stages of the condition) about research studies they could participate in.	STRONG IN FAVOR
61	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.	STRONG IN FAVOR
62	Explain that they will be given chances to review and change any advance statements and decisions they have made.	STRONG IN FAVOR
63	At each care review, offer people the chance to review and change any advance statements and decisions they have made.	STRONG IN FAVOR
64	Encourage and enable people living with dementia to give their own views and opinions about their care.	STRONG IN FAVOR
65	If needed, use additional or modified ways of communicating (for example visual aids or simplified text).	STRONG IN FAVOR
66	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 41).	STRONG IN FAVOR
67	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.	WEAK IN FAVOR

Research Recommendations

No research recommendations were made.

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Management strategies for people living with dementia/Mild Cognitive Impairment and co-existing physical long-term conditions

Review question 11a	**What are the optimal management strategies (including treatments) for people living with dementia with co-existing physical long-term conditions?**
Review question 11b	**What are the optimal management strategies (including treatments) for people with MCI with co-existing physical long-term conditions?**

Literature review

	11a	11b
Records identified from databases	13,409	5,101
Studies assessed for eligibility	20	7
Included studies	1	4
Studies included in the NICE GL	9	-
Total number of included studies	10	4

Eligibility criteria

Population	People (aged ≥40 years) with a diagnosis of dementia/MCI and living with a co-existing long-term condition.
Interventions	Pharmacological interventions, self-care strategies, observational or monitoring strategies specific to people with dementia/MCI and a coexisting long-term condition.
Comparator	• Other interventions. • Standard care.
Outcomes	• Clinical progression of comorbidity and associated symptoms. • Clinical outcomes including cognitive, functional, and behavioural ability. • Change in prevalence of appropriate polypharmacy. • Intervention related problems such as potentially avoidable hospital admissions and re-admissions, errors, poor adherence, and potentially avoidable adverse effects. • Intervention related outcomes including concordance, compliance, satisfaction of people with dementia/MCI and their caregivers.

Aim

The objective of the systematic literature review for both questions, in line with the strategy defined by the NICE Guideline, was to identify Randomized Controlled Trial (RCT) and comparative studies investigating the effectiveness of interventions and strategies aimed at slowing the progression of comorbidities, especially in

people with dementia/MCI and at least one of the following coexisting conditions: incontinence, recurrent falls, hypertension, diabetes, risk of cardiovascular diseases, sensory impairments.

Summary of evidence

Review question 11a

For question 11a the systematic literature review performed for the NICE guideline identified nine studies meeting the predefined eligibility criteria. After updating the systematic review, one new study was identified.

Studies were classified according to the type of target comorbidity and, within each subgroup, according to the type of considered intervention.

HYPERTENSION

Thiazides

One study on 62 participants (Kocyigit 2019) investigated the efficacy of using thyazides compared to not using them in people with dementia and hypertension. The study reported an improvement in people treated with thyazides in cognitive symptoms when measured with MoCa (MoCA: MD 2.37, 95% CI 0.78 – 3.96, I^2 n.a., very low certainty) but not when measured with MMSE (MD -0.15, 95% CI -2.15 – 1.85, I^2 n.a., low certainty). The study reported no differences between groups in functional abilities (IADL: MD -0.03, 95% CI -1.21 – 1.15, I^2 n.a., very low certainty).

Home blood pressure measurement (HBPM) versus 24-hour or daily ambulatory blood pressure monitoring (ABPM)

One comparative study on 60 participants (Plichart 2013) investigated the efficacy of home blood pressure measurement by people with dementia or their caregivers (HBPM) compared to 24-hour (24h-ABPM) or daily ambulatory blood pressure monitoring (d-ABPM). The study reported higher systolic blood pressure values in the HBPM group compared to the 24h-ABPM (MD 11.30, 95% CI 4.61 – 17.99, I^2 n.a., moderate certainty) and the d-ABPM (MD 9.70, 95% CI 3.08 – 16.32, I^2 n.a., moderate certainty) groups. However, it reported no differences between groups in diastolic blood pressure values (24-ABPM MD 1.00, 95% CI -2.76 – 4.76, I^2 n.a., very low certainty; d-ABPM MD 0.00, 95% CI -3.76 – 3.76, I^2 n.a., very low certainty).

Telmisartan versus amlodipine

One study on 20 participants (Kume 2012) investigated the efficacy of the angiotensin II receptor antagonist telmisartan compared to the Dihydropyridine calcium channel blocker amlodipine for the treatment of hypertension in people with dementia. The reported no differences between groups in cognitive functions measured with MMSE (MD 1.30, 95% CI -2.27 – 4.87, I^2 n.a., very low certainty) and ADASCog (MD -4.20, 95% CI -10.14 – 1.74, I^2 n.a., very low certainty). It also reported no differences between groups in in systolic blood pressure (MD 5.00, 95% CI -6.61 – 16.61, I^2 n.a., very low certainty), diastolic blood pressure (MD -1.00, 95% CI -9.47 – 7.47, I^2 n.a., very low certainty), and heart rate (MD -1.00, 95% CI -5.36 – 3.36, I^2 n.a., very low certainty) at six months of follow up.

CARDIOVASCULAR RISK

One study on 94 participants (Richard 2009) investigated the effectiveness of a multicomponent intervention for the management of hypertension and hypercholesterolemia including the daily pharmacological treatment with acetylsalicylic acid (8 to 100 mg), pyridoxine (50 mg) e folic acid (0,5 mg) and a step protocol to improve diet, physical exercise, and lifestyle. The study reported a reduction in the intervention group

compared to the control group of blood levels of total cholesterol (MD -0.94, 95% CI -1.43 – -0.45, I^2 n.a., low certainty) and LDL (MD -0.90, 95% CI -1.44 – -0.36, I^2 n.a., low certainty) at 2 years of follow up. However, it reported no differences between groups in blood levels of HDL (MD -0.02, 95% CI -0.17 – 0.13, I^2 n.a., low certainty) at 2 years of follow up. It also reported no differences in cognitive functions (MMSE: MD -0.55, 95% CI -3.12 – 2.02, I^2 n.a., very low certainty), systolic (MD -4.12, 95% CI -14.75 – 6.16, I^2 n.a., very low certainty) and diastolic blood pressure (MD -1.97, 95% CI -8.21 – 4.26, I^2 n.a., very low certainty), and glycated haemoglobin (MD 0.20, 95% CI -0.08 – 0.48, I^2 n.a., low certainty).

DIABETES

Pioglitazone

One study on 42 participants (Sato 2011) investigated the effectiveness of thiazolidinedione, pioglitazone, in combination with standard treatment (sulfonylurea, biguanide, and α-glucosidase inhibitors) for the treatment of diabetes mellitus type 2 in people with mild Alzheimer's dementia. The study reported no differences between groups in cognitive functions measured with MMSE (MD 1.30, 95% CI -1.53 – 4.14, I^2 n.a., very low certainty) and ADAS-Cog (MD -3.50, 95% CI -8.02 – 1.02, I^2 n.a., very low certainty). It also reported no differences in fasting levels of insulin (MD -1.60, 95% CI -4.41 – 1.21, I^2 n.a., low certainty), glucose (MD 1.00, 95% CI -26.99 – 28.99, I^2 n.a., very low certainty), and glycated haemoglobin (MD 0.00, 95% CI -0.84 – 0.84, I^2 n.a., low certainty) at six months of follow up.

INCONTINENCY

Personalized programme

One study on 74 participants (Jirovec 2001) investigated the effectiveness of a personalized procedure of timed voiding planned in collaboration with the caregiver for the management of incontinence in people with dementia. The study reported no differences between groups in cognitive functions (SPMSQ: MD -0.37, 95% CI -1.81 – 1.07, I^2 n.a., low certainty) and functional abilities (composite mobility score: MD 1.18, 95% CI -1.24 – 3.60, I^2 n.a., low certainty). It also reported no differences between groups né in the mean frequency of incontinence (MD -0.08, 95% CI -0.27 – 0.11, I^2 n.a., low certainty) and in the proportion of participants with an improvement in urinary incontinence (RR 1.27, 95% CI 0.83 – 1.94, I^2 n.a., low certainty) at six months of follow up.

Behavioural therapy

One study on 19 participants (Engberg 2002) investigated the effectiveness of a behavioural intervention of prompted voiding (PV) based on vocal instruction and positive reinforcements, implemented in collaboration with caregivers, aimed at improving bladder control. The study reported no differences between groups in the mean reduction of incontinent episodes per day (MD 19.8, 95% CI -10.49 – 50.09, I^2 n.a., very low certainty) and in daytime (MD 12.8, 95% CI -21.55 – 47.15, I^2 n.a., very low certainty). It also reported no differences in the mean reduction of urinary incontinence episodes in daytime (MD 8.5, 95% CI -28.35 – 45.35, I^2 n.a., very low certainty) and per day (MD 17.60, 95% CI -14.58 – 49.78, I^2 n.a., very low certainty). The study reported no differences between groups in the number of self-initiated toilets per day (MD 1.20, 95% CI -2.20 – 4.60, I^2 n.a., very low certainty).

One study on 191 participants (Tobin 1986) investigated the effectiveness of an intervention based on timed voiding (TV) in people with dementia. The study reported a higher frequency of reduction in the number of night-time (RR 1.80, 95% CI 1.12 – 2.89, I^2 n.a., very low certainty), but not of daytime (RR 1.34, 95% CI 0.90 – 2.01, I^2 n.a., very low certainty) incontinent episodes in the TV group compared to the control group. However, the study reported no differences between groups in the number of people with a lower volume of incontinence (RR 1.01, 95% CI 0.52 – 1.96, I^2 n.a., very low certainty).

HEARING LOSS

Hearing aids

One study on 47 participants (reported in two publications, Nguyen 2017 and Adrait 2017) investigated the effectiveness of using hearing aids for the treatment of hearing loss in people with dementia. The study reported no differences between groups in cognitive functions measured with MMSE (MD -0.40, 95% CI -3.05 – 2.25, I^2 n.a., very low certainty) and ADAS-Cog (MD 1.50, 95% CI -5.71 – 8.71, I^2 n.a., very low certainty). It also reported no differences between groups in behavioural symptoms (NPI: MD -6.00, 95% CI -20.93 – 8.93, I^2 n.a., very low certainty), functional abilities (IADL: MD -0.5, 95% CI -2.21 – 1.21, I^2 n.a., very low certainty), and quality of life (ADRQL: MD 21.10, 95% CI -39.85 – 82.05, I^2 n.a., very low certainty).

Summary of evidence

Review question 11b

For Question 11b the systematic literature review identified four studies meeting the predefined eligibility criteria.

Studies were classified according to the type of target comorbidity and, within each subgroup, according to the type of considered intervention.

HYPERTENSION

Candesartan versus lisinopril

One study on 176 participants (Hajjar 2020) investigated the comparative efficacy of the angiotensin receptor blocker candesartan, and of the angiotensin-converting enzyme (ACE) inhibitor lisinopril, in people with Mild Cognitive Impairment (MCI) and hypertension. The study reported an improvement in the performance at the TMT B (aMD -12.0, 95% CI -21.7 – -2.3, I^2 n.a., moderate certainty) and TMT B-A (aMD -13.6, 95% CI -23.6 – -3.7, I^2 n.a., moderate certainty) tests in the group treated with candesartan compared to the group treated with lisinopril.

Nilvadipine versus amlodipine

One study on 12 participants (Hanyu 2007) investigated the comparative efficacy of the two calcium channel blockers nilvadipine e amlodipine in people with MCI and hypertension. The study reported no significant differences in cognitive functions measured with MMSE (MD 0.7, 95% CI -1.73 – 3.13, I^2 n.a., very low certainty) and ADAS-Cog (MD 0.00, 95% CI -2.86 – 2.86, I^2 n.a., very low certainty). It also reported no differences in systolic (MD -3.00, 95% CI -10.19 – 4.19, I^2 n.a., low certainty) and diastolic blood pressure (MD 2.00, 95% CI -4.46 – 8.46, I^2 n.a., low certainty).

DIABETES

Dapagliflozin and cognitive behavioural training

One study on 96 participants (Zhao 2022) investigated the effectiveness of a combined intervention with sodium-glucose co-transporter 2 (SGLT-2) inhibitor dapagliflozin and a cognitive behavioural training program for the management of diabetes in people with MCI. The study reported an improvement in the intervention group compared to the control group in cognitive functions (MMSE MD 2.72, IC 95% 1.58 – 3.86, I^2 n.a., moderate certainty) and quality of life (QoL-AD MD 9.74, IC 95% 7.18 – 12.30, I^2 n.a., moderate certainty). It also reported a higher reduction of blood levels of glycated haemoglobin (MD -1.78, IC 95% -2.47 – -1.09, I^2 n.a., moderate certainty), but not of fasting glucose (MD -0.93, IC 95% -2.24 – 0.38, I^2 n.a., low certainty), in the intervention group compared to the control group.

Behavioural intervention versus self-management training

One study on 87 participants (Rovner 2017) investigated the effectiveness of a behavioural intervention provided by an occupational therapist (OT) compared to a training intervention (TE) provided by health professionals aimed at supporting the self-management of diabetes in people with MCI. The study reported a reduction in both the intervention groups in blood levels of glycated haemoglobin at six months of follow up (TO -0.78, IC 95% -1.23 – -0.33; IE -0.44, IC 95% -0.87 – -0.004) and at 12 months of follow up (TO –0.91, IC 95% -1.45 – -0.37; IE -0.54, IC 95% -1.04 – -0.036). However, it reported no differences between groups in the effect size (MD -0.37, IC 95% -1.11 – 0.37, I^2 n.a., low certainty).

Analysis of evidence

Dementia mainly affects older people, who are also commonly affected by multimorbidity, defined as the presence in a single person of two or more long-term health conditions.
The NICE guideline extended the definition of long-term health conditions to include specific ongoing physical and mental conditions, symptoms, and sensory deficits (NICE NG56)[29].
The management of comorbidities in dementia is complex and should be considered from different points of view.
Physical conditions can be risk factors, or co-factors, for dementia, and can affect its progression or worsen its symptoms. Moreover, since multimorbidity is associated with polypharmacy, all different treatments should be reviewed and harmonized. Multimorbidity, per se, is associated with a lower quality of life, an increased risk of falls, more frequent use of healthcare services and access to emergency departments, and a higher risk of death. The systematic review (SR) for this question included studies investigating the management of comorbidities in people with dementia. The SR for review question 22 included evidence on intercurrent conditions, defined as conditions that occur after the diagnosis of dementia, including falls and fractures, urinary tract conditions, pain, and delirium.
The most reported chronic conditions in people with dementia include diabetes, hypertension, cardiovascular diseases, and musculoskeletal disorders linked to older age. The higher frequency of multimorbidity associated with an older age increases the clinical complexity of the management of older people, mainly when the healthcare system and healthcare services are organised towards disease-specific management.
Even from a research point of view, clinical trials on (pharmacological and non-pharmacological) treatments and care strategies for people with dementia and their caregivers rarely consider the fact that the general population generally has different comorbid conditions and pharmacological treatments.
A crucial aspect of multimorbidity in dementia is that each comorbidity individually modifies the clinical trajectory of each person, and this is even more evident when considering the comorbidity with dementia. Therefore, the appropriate management of concomitant conditions can directly affect the symptoms and the quality of life of people with dementia.
The objective of this SR was to identify the most effective interventions and strategies to manage physical comorbidities in people with MCI/dementia, and to assess whether these are different from those adopted in people without MCI/dementia.
Included studies mainly focused on two outcomes. Some studies assessed the efficacy of the investigated intervention on the management of the considered conditions, considering as primary outcomes the same measures they would consider in people without MCI/dementia. Some studies also considered the effect of the investigated treatment on MCI/dementia in terms of cognitive, functional and behavioural symptoms, or

[29] NICE. Multimorbidity: clinical assessment and management. NICE guideline NG56. Last updated: September 2016. Available at: https://www.nice.org.uk/guidance/ng56 (Last visited: 30/08/2023).

possible changes in polypharmacy. Considered outcomes included adverse events, hospitalizations, and potentially avoidable interventions. Studies also considered treatment satisfaction and compliance in both people with dementia and their caregivers.
Identified comorbidities included the most frequent conditions in older people, such as incontinence, recurrent falls, hypertension, diabetes, cardiovascular risk, and sensory deficits.
The SR identified a large body of evidence on the effect of the management of cardiovascular risk in the progression of dementia. These studies were analysed for question 16a which analysed the repositioning of drugs acting on possible etiological factors for dementia.
When considering the global risk of cardiovascular diseases, especially hypertension, hypercholesterolemia, and diabetes, none of the identified studies reported sufficient evidence to support a recommendation.
One study comparing the efficacy of an angiotensin II receptor antagonist to the effect of a calcium channel blocker reported no differences between treatments on both hypertension and cognitive functions. Another study comparing the effect of different strategies to measure blood pressure, either at-home or (24-hour or daily) outpatient monitoring, reported higher blood pressure levels with at-home monitoring compared to outpatient monitoring. A study investigating using thiazides in people with dementia and hypertension compared to not using them reported no differences between groups in cognitive symptoms apart from a small difference in MoCA scores. When considering the overall cardiovascular risk, a study investigating the effectiveness of a multicomponent treatment including drugs for the treatment of hypertension and hypercholesterolemia, acetylsalicylic acid, vitamins, in combination with diet, physical exercise and lifestyle changes only reported a decrease in blood cholesterol levels and no improvement in cognitive functions or hypertension.
However, clinicians should always base their clinical practice on best practices. Any established approach to people with dementia should be reassessed regularly at any stage of the disease. In case of malnourished people with severe dementia, the use of antidiabetic agents should be carefully considered due to their potentially being more harmful than useful and necessary. This raises the question on whether to comply with the strict target levels of HbA1c. The difficulty of people with dementia to comply to treatments and lifestyle habits, and their unpredictable behaviours, especially towards feeding and the quality and quantity of consumed food should always be considered. Similarly, medical judgement should carefully consider treating hypertension, always considering the best option, with lower risks, for each person. However, no studies are available on the impact of discontinuing preventive vascular treatments in people with severe dementia, to potentially identify further subgroups of people that could benefit or not from this option. To this purpose, the WG included the indication to refer to guidelines from the SNLG and further guidance from NICE.
The SR on cardiovascular risk in people with MCI identified one study investigating the use of an angiotensin receptor blocker compared to an angiotensin-converting enzyme (ACE) inhibitor reporting an improvement of the performance at the TMT tests.
When considering the management of diabetes, one study on a behavioural intervention delivered by an occupational therapist compared to a training intervention from healthcare professionals on the self-management of diabetes reported no differences between groups in blood levels of glycated haemoglobin. Another study on the use of dapagliflozin, a drug indicated for the treatment of diabetes, symptomatic chronic heart failure, and chronic kidney disease, in combination with cognitive-behavioural training reported an improvement in the intervention group in cognitive symptoms and quality of life.
When considering the risk of falls, no evidence was available on the effectiveness of rehabilitation after recurrent falls. Question 22a included all evidence referring to the management of falls as intercurrent conditions in people with a diagnosis of dementia.
Incontinence is an extremely relevant issue for people with dementia. This condition has a different impact on the clinical and social life of people with dementia at different stages of the disease. The three studies identified in the SR from the NICE guideline, with low to very low certainty, investigated behavioural

strategies of toileting and prompted voiding, assessing their effectiveness on the frequency of daytime and night-time incontinence episodes.

Some anticholinergic drugs are usually used, even in older people, within the management of some bladder disorders, to treat detrusor hyperactivity with subsequent urgency and urinary incontinence. Questions 3a and 3b analysed the undesired effects of these classes of drugs on cognitive functions. The NICE guideline for this topic refers to the GL on the treatment of urinary incontinence in people with neurological conditions (see Table 6). However, the NICE GL underlines that that specific GL recommends the use of antimuscarinic agents for the treatment of hyperactive bladder, whose undesired effects on cognitive functions should be carefully considered. As discussed in the analysis of Question 3, antimuscarinic drugs should be avoided in people with dementia, and, when treatment is necessary, any available alternative should be considered.
The NICE GL, in a specific technical assessment of mirabegron, a β3 adrenergic receptor agonist, states that this drug can be considered as an appropriate treatment in people who would suffer unacceptable side effects from any treatment with antimuscarinic agents.
The NICE GL also refers to its GL on faecal incontinence (see Table 6), including a specific recommendation in the management of people with cognitive disorders.
When considering sensory impairment, available evidence was insufficient to support any recommendation. Only one study was included investigating the use of hearing aids for the treatment of hearing loss in people with dementia and reporting, with low certainty, no differences in cognitive and behavioural outcomes, and in quality of life. The NICE GL for this topic refers to its GL on hearing loss (see Table 6), including a recommendation on hearing tests for people with suspected or diagnosed dementia.
No studies were identified on sensory deprivation for visual deficits. The NICE GL included a recommendation to encourage people with dementia to undergo eye examinations every two years, considering the possibility of supporting people who are not able to manage visits themselves.
The WG, after discussing the complexity of comorbidities in people with dementia, confirmed the recommendation to ensure that people living with dementia have equivalent access to diagnosis, treatment, and care services for comorbidities to people who do not have dementia.
Based on the analysis of evidence, that reported no indication to specific treatments for comorbidities in people with cognitive deficits, and based on good clinical practice, the WG agreed to include a recommendation to refer, when managing comorbidities in people with dementia or Mild Cognitive Impairment and at least one chronic physical comorbidity, to the best practices for each condition, considering each person's specific clinical conditions and except in case the administration of standard care could cause more harm than benefit (see Table 6).

Recommendations

Management strategies for people living with dementia/Mild Cognitive Impairment and co-existing physical long-term conditions

68	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 Table 6.	STRONG IN FAVOR
69	For people with dementia or Mild Cognitive Impairment and at least one chronic physical comorbidity, when managing comorbidities (e.g., hypertension, cardiovascular diseases, type 2 diabetes, sensory deficits, urinary tract conditions) refer to the best practices for each condition, considering each person's specific clinical conditions and except in case the	STRONG IN FAVOR

administration of standard care could cause more harm that benefit (see Table 6).

Research Recommendations

No research recommendations were made.

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Managing mental health conditions alongside dementia/Mild Cognitive Impairment

Review question 12a	**What are the optimal management strategies (including treatments) for people with dementia and an enduring mental health condition?**
Review question 12b	**What are the optimal management strategies (including treatments) for people with Mild Cognitive Impairment and an enduring mental health condition?**

Literature review

	12a	12b
Records identified from databases	10,430	5,452
Studies assessed for eligibility	0	0
Included studies	0	0
Studies included in the NICE GL	0	-
Total number of included studies	0	0

Eligibility criteria

Population	People (aged ≥40 years) with a diagnosis of dementia/MCI and living with a psychiatric comorbidity.
Interventions	Pharmacological/non-pharmacological interventions/self-care strategies/observational or monitoring strategies specific to people living with dementia/MCI and a comorbid psychiatric illness.
Comparator	• Other interventions. • Standard care.
Outcomes	• Clinical progression of mental health condition and associated symptoms. • Clinical outcomes including cognitive, functional, and behavioural ability. • Change in prevalence of appropriate polypharmacy. • Intervention related problems such as potentially avoidable hospital admissions and re-admissions, errors, poor adherence, and potentially avoidable adverse effects. • Intervention related outcomes including concordance, compliance, satisfaction of people with dementia/MCI and their carers. • Resource use and costs.

Aim

The objective of the systematic literature review for both questions, in line with the strategy defined by the NICE Guideline (NICE GL), was to identify Randomized Controlled Trials (RCT) and comparative studies investigating the effectiveness of interventions and strategies aimed at managing pre-existing psychiatric

disorders. Specifically, the question is distinguished from the management of disorders psychiatric disorders resulting from dementia/Mild Cognitive Impairment (MCI) as it refers to disorders with a diagnosis preceding the diagnosis of dementia/MCI.

Summary of evidence

Research question 12a

The systematic literature review performed for the NICE guideline did not identify any study meeting the predefined eligibility criteria. After updating the systematic review no further studies were identified.

Research question 12b

The systematic literature review performed for this question did not identify any study meeting the predefined eligibility criteria.

Analysis of evidence

The relationship between dementia and mental disorders is extremely complex and should be analysed from different points of view. Mental disorders are a risk factor for dementia. Mental disorders with onset in young adulthood have been associated with a higher risk of developing dementia at an earlier age. On the other hand, some types of dementia are associated with behavioural disorders, schizophrenia spectrum and other psychotic disorders. The presence of mental disorders in the earlier stages of the disease can sometimes fall within the diagnostic criteria for a specific subtype of dementia.

The Working Group (WG) discussed how the management of people with pre-existing mental disorders is more complex due to the two-way interaction between the two conditions. The presence of pre-existing mental disorders can make dementia more difficult both to identify and manage, while the onset and progression of dementia can make managing the underlying mental disorders more difficult.

These questions are specifically aimed at investigating the most effective ways of treating underlying psychiatric disorders in people with dementia or MCI. Therefore, they did not include the analysis of the efficacy of interventions for psychiatric disorders emerging after the diagnosis of dementia, which are considered in questions 21a and 21b.

In line with the approach to other comorbidities, the assessment of the effectiveness of any intervention for the questions is based on two main outcomes. The effectiveness of any intervention on the management of the specific condition, in this case, the mental disorder. To this purpose, the main outcome measures are the same adopted in case of people without dementia. Moreover, the analysis of evidence should assess whether treatments lead to an improvement or a worsening of dementia.

The fact that some pharmacological treatments for specific psychiatric comorbidities (such as antipsychotics) can affect cognitive performance and are considered a long-term risk factor for dementia, is a topic of wide debate. Studies investigating the complexity of managing psychiatric comorbidities in people with dementia would allow clarifying the outcome in terms of harms and benefits and would provide indications on treatments and care.

The SR for this question was aimed at identifying evidence on all possible psychiatric disorders, with specific attention to anxiety, depressive disorders, schizophrenia and other psychotic disorders, substance use disorders, and personality disorders. This included evidence on pharmacological and non-pharmacological interventions, self-management strategies, observation, or monitoring strategies specific for people with dementia and a coexisting psychiatric condition, compared to those for people with psychiatric conditions but without a diagnosis of dementia. To this purpose, in line with the analysis for other comorbidities, studies were considered eligible if including cognitive and functional outcomes, changes in polypharmacy, need for

healthcare and hospitalizations, avoidable adverse events, and compliance and satisfaction of people with dementia and their caregivers.
Dementia in people with psychiatric disorders is relatively under-investigated in terms of scientific research. No randomized studies are available in this population, probably due to the complexity of performing this type of studies.
No evidence was identified for this question in both the NICE GL and this update.
After discussion on the opportunity of including consensus recommendations on such a critical issue, and considering the wide spectrum of mental disorders, the WG agreed, in line with the NICE GL, not to make any recommendation.
Considering the lack of studies on this topic, the WG confirmed the research recommendation to support further studies on the best strategies to manage people with a pre-existing mental disorder receiving a diagnosis of dementia.

Recommendations

No recommendations were made.

Research Recommendations

Managing mental health conditions alongside dementia/Mild Cognitive Impairment

15R	What are the optimal management strategies for people with enduring mental health problems (including schizophrenia and other psychotic disorders) who subsequently develop dementia or Mild Cognitive Impairment?

Care setting transitions

Review question 13	**What are the most effective ways of managing the transition between different settings (home, care home, hospital, and respite) for people living with dementia?**

Literature review

Records identified from databases	4,978
Studies assessed for eligibility	3
Included studies	0
Studies included in the NICE GL	4
Total number of included studies	4

Eligibility criteria

Population	People (aged ≥40 years) living with dementia.
Interventions	Policies or systems for managing transfers between settings for people living with dementia, which may include elements such as: • assessment of person's needs and living environment (destination environment); • systems for monitoring and adjusting plans as needs change; • person-centred assessments; • ways of confirming required services are in place pre-transfer; • information for caregivers, access and involvement in care; • type of departments; • environment design; • multidimensional assessment; • reconciliation and optimization of pharmacological treatments.
Comparator	Standard care.
Outcomes	• Clinical outcomes including cognitive, functional and behavioural ability. • Rates of delayed discharge. • Access to health and social care support. • Experience and satisfaction of people with dementia and their carers. • Carer health-related quality of life. • Adverse events. • Resource use and costs.

Aim

The objective of the systematic review (SR), in line with the strategy defined by the NICE Guideline, was to identify Randomized Controlled Trial (RCT) comparing different methods of managing transitions between care settings. Literature on the management of hospitalization and discharge was analysed in question 23. When considering literature on the transitions to and from mental health facilities and the reconciliation and

optimization of pharmacological treatments during transitions between care settings the NICE guideline considered the SRs performed in 2016 on transition between care setting (NG53)[30] and on medicine optimization (NG5)[31], while this literature was gathered and analysed for this update.

Summary of evidence

The systematic literature review performed for the NICE guideline identified four studies meeting the predefined eligibility criteria. After updating the systematic review, no new studies were identified.
Studies were classified according to the type of target recipient of the intervention (people with dementia or their caregivers) and according to the type of considered intervention.

Intervention for people living with dementia

Only one study investigated an intervention targeted to people with dementia to improve spatial orientation when moving into a new care environment (McGilton 2003). The study, on 32 participants with dementia, reported no differences between groups in agitation (PAS, Pittsburgh Agitation Scale: MD 0.28, 95% CI -0.86 – 1.42, I^2 n.a., low certainty) and spatial orientation (SOS: MD 0.90, 95% CI -1.15 – 2.95, I^2 n.a., low certainty).

Intervention for caregivers

One study investigated a psychosocial intervention aimed at the psychological and emotional support of people with dementia and their caregivers when moving to a care home (Residential Care Transition Module, RCTM) (Gaugler 2015). The study, on 36 caregivers of people with dementia, reported no differences between groups in caregiver depressive symptoms (CES-D: MD -5.00, 95% CI -14.38 – 4.38, I^2 n.a., very low certainty) stress (PSS: MD -5.08, 95% CI -11.96 – 1.80, I^2 n.a., very low certainty), and perceived burden (ZBI: MD -2.85, 95% CI -7.93 – 2.23, I^2 n.a., very low certainty).

A second study investigated a social support intervention for caregivers of people with dementia (New York University Caregiver Intervention, NYUCI) based on family counselling sessions aimed at supporting caregivers of people with dementia who recently moved to a care home (Gaugler 2011). The study, on 406 dyads, reported no differences between groups in caregiver perceived burden (ZBI: MD -0.77, 95% CI -2.81 – 1.27, I^2 n.a., very low certainty). However, it reported an improvement in the intervention group compared to the control group in caregivers' depressive symptoms (GDS, Geriatric Depression Scale: MD -1.71, 95% CI -3.02 – -0.40, I^2 n.a., low certainty).

One study investigated a psychosocial telephone intervention aimed at supporting caregivers of people with dementia who recently moved to a care home (Davis 2011). The study, on 46 dyads, reported no differences between groups caregivers' depressive symptoms (CES-D: MD 0.29, 95% CI -8.27 – 8.85, I^2 n.a., very low certainty), perceived burden (ZBI: MD -5.07, 95% CI -15.39 – 5.25, I^2 n.a., very low certainty), and facility satisfaction (FS, Facility Satisfaction: MD 0.31, 95% CI -0.18 – 0.80, I^2 n.a., very low certainty).

Analysis of evidence

Dementia is a complex condition with a natural history characterized by the progressive involvement, at different stages of the disease, of cognitive functions, behaviour, and physical abilities and functions. Therefore, appropriate adjustments should be offered to care, planning programmable care and considering

[30] NICE. Transition between inpatient mental health setting and community or care home settings. NICE guideline NG53. Last updated: August 2016. Available at: https://www.nice.org.uk/guidance/ng53 (Last visited: 30/08/2023)
[31] NICE. Medicines optimisation: the safe and effective use of medicines to enable the best possible outcomes. NICE guideline NG5. Last updated: March 2015. Available at: https://www.nice.org.uk/guidance/ng5 (Last visited 30/08/2023)

the possibility of having to manage unpredictable situations, such as the onset of acute conditions. In these cases, people with dementia and their caregivers transfer between different care settings, encountering different facilities and professionals. In a healthcare system whose organization is fragmented and where care continuity and coordination are not planned, people with dementia can experience severe stress, due to their cognitive and physical frailty.

The WG discussed the main issues related to inadequate communication of the necessary changes in environment and care, including the lack of appropriate communication with health professionals and the lack of shared care plans among health professionals. People with dementia are highly vulnerable and at risk of complications, especially due to potential inadequacies in the transfer of information on pharmacological and non-pharmacological treatments during care setting transitions. The lack of a definition and programming of treatment reconciliation procedures can lead to mistakes potentially causing adverse events that could severely affect people's safety and quality of care. This can affect different care setting transitions (home, residential structures, rehabilitative structures, hospitals, nursing homes) and changes in the levels of care within the same structure, based on the different needs arising from different stages of the disease.

Evidence on the specific needs of people with dementia in case of admission and discharge from hospital was analysed for question 23. The NICE guideline (GL) for this topic refers to the GL on transition between inpatient hospital settings and community or care home settings for adults with social care needs (NG27)[32] and to the section of the GL on medicines optimization referring to care setting transition (NG5)[33].

Unlike the NICE GL, which referred for the transition to and from mental health structures to the guidelines NG53[34] and NG5, this update also analysed evidence on medicines optimisation during transitions in this care setting.

Identified interventions focused on providing information to caregivers, especially on accessing care and involvement in care processes, and on assessing the needs of people with dementia and the characteristics of the environment of the receiving structure. Monitoring strategies, multidimensional assessment interventions for medicines reconciliation and the optimisation of pharmacological and non-pharmacological treatment were also considered. A further element to be considered during care setting transition is the difficulty of ensuring the review of needs and wishes.

Evidence was assessed for both the outcomes of people with dementia and their caregivers. Outcomes included cognitive, functional, and behavioural symptoms, adverse events, delays in transition, access to health and social care support, quality of life, and satisfaction.

The analysis of evidence, including only the studies included in the NICE GL, as no new studies were identified, reported no significant effect of any specific system or strategy. Overall, the certainty of evidence was low to very low, due to methodological limitations.

The only study including data on the outcomes of people with dementia investigated an intervention based on the use of localization maps and cognitive training to support spatial orientation and manage psychomotor agitation during transfers between different building within a geriatric centre. The study reported no differences between the intervention group and the control group.

[32] NICE. Transition between inpatient hospital settings and community or care home settings for adults with social care needs. NICE guideline NG27. Last updated: December 2015. Available at: https://www.nice.org.uk/guidance/ng27 (Last visited: 30/08/23)

[33] NICE. Medicines optimisation: the safe and effective use of medicines to enable the best possible outcomes. NICE guideline NG5. Last updated: March 2015. Available at: https://www.nice.org.uk/guidance/ng5 (Last visited: 30/08/23)

[34] NICE. Transition between inpatient mental health settings and community or care home settings. NICE guideline NG53. Last updated: August 2016. Available at: https://www.nice.org.uk/guidance/ng53 (Last visited: 30/08/23)

No specific evidence was identified on transfers between community structures. On this topic, the NICE GL agreed that the evidence identified on hospital transitions, which led to the recommendations included in the NG 27, could be generalised to the community setting. The WG, after further discussion, agreed to recommend performing, on admission to hospital, a comprehensive geriatric assessment of people with dementia and to share any care plan among the admitting team. Moreover, at discharge, continuity of care should be ensured, accounting for the differences in territorial services.

When considering care setting transitions of people with dementia admitted to mental health services, the WG underlined the need to ensure them appropriate social and legal protection, and to guarantee that they are monitored by territorial services throughout the course of the disease. The WG agreed to include a specific recommendation on this topic.

Interventions on caregivers included direct or telephone psychosocial interventions, or family counselling, to provide psychological and emotional support to caregivers during the transition of people with dementia to a nursing home. Outcomes were assessed using standardised scales and included stress, emotional burden, depressive symptoms and satisfaction. The certainty of evidence was very low, and no significant results were reported.

In absence of evidence supporting a specific model or strategy over the others, the WG discussed the importance of the principles of person-centred planning, communication, collaboration, and support for people moving from one environment/setting to another. The WG underlined that a collaborative environment increases positive outcomes, ensuring that everyone is aware of the needed support and where to find it. The main crucial objectives remain the need to adequately review and reconcile treatments, and to consider individual needs in every step of the care process.

Recommendations

Care setting transitions

70	When managing transition between care settings consider that: • In case of hospitalisation, a comprehensive geriatric assessment should be performed on people with dementia on admission to hospital, and any care plan should be shared with the admitting team, while, at discharge, continuity of care should be ensured; • the NICE guideline on transition between inpatient mental health settings and community or care home settings.	STRONG IN FAVOR
71	For guidance on medicine optimisation and reconciliation, see Table 8. Follow the principles in these guidelines for transitions between other settings (for example from home to a care home or respite care).	STRONG IN FAVOR
72	Review the needs and wishes of people with dementia and their caregivers (including any care and support plans referring to current and future care) after every transition.	STRONG IN FAVOR

Table 8. NICE Guideline "Medicine optimisation" (NG5)[35] recommendations.

Organisations should ensure that robust and transparent processes are in place, so that when a person is transferred from one care setting to another: • the current care provider shares4 complete and accurate information about the person's medicines with the new care provider and • the new care provider receives and documents this information, and acts on it. Organisational and individual roles and responsibilities should be clearly defined. Regularly review and monitor the effectiveness of these processes. See Quality statements 4 and 5 in Table 7 on medicine optimisation. When sharing information consider the DPA regulations (Regulation UE 2016/679, General Data Protection Regulation).
For all care settings, health and social care practitioners should proactively share complete and accurate information about medicines: • ideally within 24 hours of the person being transferred, to ensure that patient safety is not compromised and • in the most effective and secure way, such as by secure electronic communication, recognising that more than one approach may be needed.
Health and social care practitioners should share relevant information about the person and their medicines when a person transfers from one care setting to another. This should include, but is not limited to, all of the following: • contact details of the person and their GP; • details of other relevant contacts identified by the person and their family members or carers where appropriate – for example, their nominated community pharmacy; • known drug allergies and reactions to medicines or their ingredients, and the type of reaction experienced (see the NICE guideline on drug allergy); • details of the medicines the person is currently taking (including prescribed, over-the-counter, and complementary medicines) – name, strength, form, dose, timing, frequency and duration, how the medicines are taken and what they are being taken for; • changes to medicines, including medicines started or stopped, or dosage changes, and reason for the change; • date and time of the last dose, such as for weekly or monthly medicines, including injections; • what information has been given to the person, and their family members or carers where appropriate; • any other information needed – for example, when the medicines should be reviewed, ongoing monitoring needs and any support the person needs to carry on taking the medicines. Additional information may be needed for specific groups of people, such as children*.
Health and social care practitioners should discuss relevant information about medicines with the person, and their family members or carers where appropriate, at the time of transfer. They should give the person, and their family members or carers where appropriate, a complete and accurate list of their medicines in a format that is suitable for them. This should include all current medicines and any changes to medicines made during their stay.
Consider sending a person's medicines discharge information to their nominated community pharmacy, when possible and in agreement with the person.
Organisations should consider arranging additional support for some groups of people when they have been discharged from hospital, such as pharmacist counselling, telephone follow-up, and GP or nurse follow-up home visits. These groups* may include: • adults, children and young people taking multiple medicines (polypharmacy); • adults, children and young people with chronic or long-term conditions;

[35] https://www.nice.org.uk/guidance/ng5

- older people.

* Statements are taken from Guidelines that refer to populations that also include pediatric and young adult patients.

Research Recommendations

No research recommendations were made.

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Supporting caregivers of people with dementia

Review question 14a	**How effective are caregivers' assessments in identifying the needs of caregivers of people with dementia?**
Review question 14b	**What interventions/services are most effective for supporting the wellbeing of informal caregivers of people with dementia?**

Literature review	14a	14b
Records identified from databases	6,690	6,690
Studies assessed for eligibility	0	92
Included studies	0	29
Studies included in the NICE GL	0	93
Total number of included studies	0	122

Eligibility criteria

Review question 14a

Population	Caregivers of people aged ≥40 years with dementia.
Interventions	Formal assessments of the needs of caregivers of people with dementia.
Comparator	• Alternative assessment methods; • No formal assessment.
Outcomes	• Access to health and social care support; • Caregiver burden and stress; • Caregiver experience and satisfaction; • Caregiver health-related quality of life; • Resource use and costs.

Review question 14b

Population	Caregivers of people aged ≥40 years with dementia.
Interventions	Interventions or services designed to improve the wellbeing of informal caregivers of people with dementia, which may include: • Peer support groups; • Training/information courses; • Information; • Psychosocial support; • Cognitive behavioural therapy; • Respite breaks.
Comparator	• Standard care.

Outcomes	• Caregiver burden and stress; • Caregiver experience and satisfaction; • Caregiver health-related quality of life; • Resource use and costs.

Aim

The aim of the systematic review of the literature was to identify quantitative comparative studies investigating the utility of different methods for assessing the needs of caregivers, and randomised controlled trials (RCT) investigating the effectiveness of interventions and services for supporting informal caregivers of people with dementia.

Summary of evidence

For review question 14a, the systematic review performed for the NICE guideline did not identify studies meeting the predefined eligibility criteria. No studies were identified after updating the systematic review.

For review question 14b, the systematic review performed for the NICE guideline identified 93 studies that met predefined eligibility criteria, while 29 new studies were identified after updating the systematic review. Studies were classified according to the type of considered intervention and the way they were delivered (e.g., group, individual, etc.).

Psychoeducational interventions

Twenty-one studies investigated the effectiveness of psychoeducational interventions to support caregivers of people with dementia.

Of these, nine investigated the effectiveness of group-based interventions. Five studies (Hébert 2003, Hepburn 2005, Seike 2021, Tawfik 2021, Yazdanmanesh 2023) on 421 participants reported a significant improvement of caregiver burden (ZBI: MD -6.53, 95% CI -11.35 – -1.70, I^2 74%, low certainty). When considering depressive symptoms, two studies (Seike 2021, Sepe-Monti 2016) on 218 participants (CES-D: MD -6.18, 95%CI -18.64 – 6.27, I^2 96%, very low certainty) and one study on 221 participants (Kurtz 2010) (MADRS: MD -0.80, 95%CI -2.72 – 1.12, I^2 n.a., N=221, low certainty) did not report differences between groups after the intervention. One study on 50 participants (Ghaffari 2019) reported an improvement of depressive symptoms in the treatment group compared to controls (GHQ: MD -4.38, 95% CI -6.62 – -2.14, I^2 n.a., low certainty). One study on 50 participants (Ghaffari 2019) reported a significant improvement of anxiety in the treated group compared to controls (GHQ: MD -8.66, 95%CI -10.54 – -6.78, I^2 n.a., very low certainty). However, one study on 116 participants (Hébert 2003) did not report differences between groups in the same outcome measured with STAI (MD 0.37, 95%CI -5.27 – 6.01, I^2 n.a., N=116, very low certainty), and on caregiver self-efficacy (MD -3.14, IC95% -10.88 – 4.60, I^2 n.a., N=116, very low certainty). Two studies on 41 (Done 2001) and 131 participants (Hepburn 2005) did not report differences between groups in symptoms of stress (MD -0.40, 95%CI -7.17 – 6.37, I^2 n.a., very low certainty) and distress symptoms (MD -1.99, 95%CI -7.17 – 3.19, I^2 n.a., very low certainty), respectively.

Three studies investigated the effectiveness of individual interventions (Caparrol 2021, Gitlin 2001, Stirling 2012). Two studies on 68 participants (Caparrol 2021, Stirling 2012) reported no differences between groups in caregiver stress (SMD -0.22, 95%CI -0.70 – 0.26, I^2 0%, very low certainty). One study on 37 participants (Caparrol 2021) reported no differences between groups in anxiety (BAI: MD -3.00, 95%CI -9.12 – 3.12, I^2 n.a., very low certainty), depressive symptoms (BDI: MD -3.60, 95%CI -9.47 – 2.27, I^2 n.a., very low certainty), and burden (ZBI: MD -2.60, 95%CI -14.42 – 9.22, I^2 n.a., very low certainty). One study on 171 participants (Gitlin

2001) reported no differences between groups in caregiver self-efficacy (MD 0.01, 95%CI -0.10 – 0.12, I^2 n.a., low certainty).

Seven studies investigated the effectiveness of technology-based psychoeducational interventions. Three studies on 256 participants (Hepburn 2022, Kales 2018, Salehinejad 2022) reported an improvement in caregiver burden in the treated group compared to controls (ZBI: MD -4.12, 95%CI -7.50 – -0.73, I^2 49%, low certainty). However, one study on 46 participants (Hattink 2015) reported no differences between groups in the same outcome measured with a specifically designed scale (MD 0.04, 95%CI -0.77 – 0.85, I^2 n.a., low certainty). Four studies on 353 participants (Brennan 1995, Eisdorfer 2003, Hepburn 2022, Kales 2018) reported a significant improvement in depressive symptoms in the treated group compared to controls (CES-D: MD -3.10, 95%CI -4.83 – -1.37, I^2 0%, moderate certainty). However, one study on 19 participants (Steffen 2000) reported no differences between groups in depressive symptoms measured with BDI (MD -4.66, 95%CI -9.40 – 0.08, I^2 n.a., very low certainty). One study on 160 participants (Hepburn 2022) reported a significant improvement in anxiety in the treated group compared to controls (STAI: MD 4.65, 95%CI 0.90 – 8.40, I^2 n.a., low certainty). Two studies on 206 participants (Hepburn 2022, Kales 2018) reported no differences between groups in caregiver stress (MD: 0.37, 95%CI -0.37 – 1.10, I^2 82%, very low certainty), and two studies on 65 participants (Hattink 2015, Steffen 2000) reported no differences in caregivers' sense of competence (SMD -0.43, 95%CI -0.06 – 0.93, I^2 0%, very low certainty).

Two studies on 165 participants (Au 2015, Sarabia-Cobo 2021) investigated the effectiveness of telephone-based interventions. Only one of these studies (Sarabia-Cobo 2021), on 106 participants, reported a significant improvement in caregivers' sense of competence (CSES: MD 4.40, 95%CI 4.08 – 4.72, I^2 n.a., moderate certainty), while reporting no differences between groups in caregiver stress (PSS: MD 2.30, 95%CI -1.56 – 6.16, I^2 n.a., very low certainty). Overall, the two studies reported no differences between groups in caregivers' depressive symptoms (CES-D: MD 1.66, 95%CI -11.10 – 14.42, I^2 90%, N=165, very low certainty).

Skill-training interventions

Twelve studies investigated the effectiveness of specific interventions for caregivers of people with dementia aimed at providing them with training and information on specific practical aspects of care (skill training).
Four studies investigated the effectiveness of group-based interventions. Three of these (Gonzalez 2014, Hepburn 2001, Oken 2010), on 217 participants, reported no differences between groups in caregivers' depressive symptoms (CES-D: MD -2.25, 95%CI -4.59 – 0.08, I^2 0%, low certainty). One study on 21 participants (Zarit 1982) reported no differences between groups in the same outcome measured with ZDS (MD 5.16, 95%CI -3.52 – 13.84, I^2 n.a., very low certainty). One study on 21 participants (Oken 2010) reported no differences between groups in caregiver stress (PSS: MD 1.43, 95%CI -4.68 – 7.54, I^2 n.a., very low certainty) and in their sense of competence (GPSE: MD -1.00, 95%CI -6.35 – 4.35, I^2 n.a., very low certainty). Two studies on 115 participants (Hepburn 2001, Zarit 1982) reported no differences between groups in caregiver burden (ZBI: MD -4.32, 95%CI -11.37 – 2.74, I^2 17%, very low certainty), and one study on 102 participants (Gonzalez 2014) reported no differences between groups in caregiver anxiety (STAI: MD 2.37, 95%CI -3.93 – 8.67, I^2 n.a., very low certainty).

Five studies investigated the effectiveness of individual interventions. Only one study on 82 participants (Martín-Carrasco 2009) reported an improvement in caregiver burden (ZBI: MD -10.20, 95%CI -17.52 – -2.88, I^2 n.a., low certainty). One study on 108 participants (Hovarth 2013) reported no differences between groups in caregiver strain (MD -1.01, 95%CI -2.36 – 0.34, I^2 n.a., low certainty) and their sense of competence (RSCSE: MD 44.65, 95%CI -31.50 – 120.80, I^2 n.a., very low certainty). One study on 44 participants (Quayhagen 2000) reported no differences between groups in depressive symptoms (BSI: MD 0.06, 95%CI -0.31 – 0.43, I^2 n.a., low certainty) and caregiver stress (MD -1.33, 95%CI -14.55 – 11.89, I^2 n.a., N=44, very low certainty). Two studies on 137 participants (Burgio 2003, Losada 2004) reported no differences between groups in depressive

symptoms (CES-D: MD -2.50, 95%CI -6.88 – 1.88, I^2 0%, very low certainty), and one study on 118 participants (Burgio 2003) reported no differences between groups in anxiety (STAI: MD -0.39, 95%CI -3.85 – 3.07, I^2 n.a., very low certainty).

Two studies investigated the effectiveness of technology-based interventions. One study on 65 participants (Chang 1999) reported no differences between groups in caregivers' depressive symptoms (specific score MD -0.08, 95%CI -0.48 – 0.32, I^2 n.a., very low certainty), anxiety (specific score MD -0.05, 95%CI -0.43 – 0.32, I^2 n.a., very low certainty) and sense of competence (specific score MD 3.04, 95%CI -0.71 – 6.79, I^2 n.a., very low certainty). The second study (Liddle 2012), on 29 participants, reported no differences between groups in caregiver burden (ZBI: MD -3.66, 95%CI -10.41 – 3.09, I^2 n.a., very low certainty).

One study on 26 participants (Davis 2004) investigated the effectiveness of a telephone-based intervention and reported no differences between groups in caregiver burden (MD -5.10, 95%CI -12.71 – 2.51, I^2 n.a., very low certainty).

Psychoeducational and skill-training interventions

Twenty-four studies investigated the effectiveness of psychoeducational for caregivers of people with dementia aimed at providing them with training on specific practical aspects of care.
Six studies investigated group-based interventions. One study on 85 participants (Coon 2003) reported an improvement in depressive symptoms in the treated group compared to controls (MAACL: MD -3.30, 95%CI -4.06 – -2.54, I^2 n.a., moderate certainty). Two studies on 199 participants (Losada 2011, Ostwald 1999) and one study on 141 participants (De Rotrou 2011) reported no differences between groups in the same outcome measured with CES-D (MD -2.86, 95%CI -6.75 – 1.03, I^2 0%, very low certainty) and MADRS (MD -1.41, 95%CI -5.45 – 2.63, I^2 n.a., very low certainty), respectively. Two studies on 221 participants (De Rotrou 2011, Ostwald 1999) reported no differences between groups in caregiver burden (ZBI: MD -3.42, 95%CI -9.03 – 2.20, I^2 0%, very low certainty). Two studies on 226 participants (Coon 2003, De Rotrou 2011) reported no differences between groups in caregivers' coping skills (SMD 1.04, 95%CI -0.37 – 2.44, I^2 95%, very low certainty), and two studies on 221 participants (Senanarong 2004, Ulstein 2007) reported no differences between groups in caregiver stress (SMD -0.17, 95%CI -0.44 – 0.09, I^2 0%, low certainty).

Ten studies investigated the effectiveness of individual interventions. Two studies on 111 participants (Gavrilova 2009, Guerra 2011) reported an improvement in caregiver burden in the treated group compared to controls (ZBI: MD -4.18, 95%CI -5.96 – -2.39, I^2 0%, moderate certainty). One study on 518 participants (Belle 2006) reported no differences between groups in the frequency of caregivers reporting a significant burden (RR 1.14, 95%CI 0.90 – 1.44, I^2 n.a., N=518, low certainty). The same study on 518 participants reported a higher frequency of depressive symptoms in caregivers in the control group compared to the treated group (RR 1.38, 95%CI 1.11 – 1.35, I^2 n.a., moderate certainty). Three studies on 306 participants (Bourgeois 2002, Burns 2003, Joling 2012) reported no differences between groups in depressive symptoms (CES-D MD -1.12, 95%CI -3.59 – 2.63, I^2 n.a., low certainty). One study on 118 participants (Judge 2013) (CES-D short: MD -0.78, 95%CI -2.47 – 0.91, I^2 n.a., very low certainty), and one study on 259 participants (Livingston 2013) (HADS: MD -0.80, 95%CI -2.24 – 0.64, I^2 n.a., low certainty) also reported no differences between groups in the same outcome measured with different tools. Two studies on 451 participants (Joling 2012, Livingston 2013) reported no differences between groups in caregiver anxiety (HADS: MD -0.35, 95%CI -1.30 – 0.61, I^2 n.a., low certainty). One study on 118 participants (Judge 2013) (MD -1.47, 95%CI -4.17 – 1.23, I^2 n.a., very low certainty), and one study on 39 participants (Bourgeois 2002) (STAI: MD 4.20, 95%CI -5.99 – 14.39, I^2 n.a., very low certainty) also reported no differences between groups in the same outcome measured with different tools. Two studies on 77 participants (Bourgeois 2002, Nobili 2004) reported no differences between groups in caregiver stress (SMD -0.11, 95%CI -0.56 – 0.34, I^2 n.a., very low certainty). Three studies on 256 participants (Bourgeois 2002, Ducharme 2011, Judge 2013) reported no differences

between groups in caregivers' sense of competence (SMD 0.16, 95%CI -0.10 – 0.43, I^2 n.a., low certainty). Four studies on 433 participants (Burns 2003, Gavrilova 2009, Joling 2012, Judge 2013) reported no differences between groups in caregivers' quality of life (SMD -0.04, 95%CI -0.15 – 0.23, I^2 n.a., low certainty), and one study on 33 participants (Bourgeois 2002) reported no differences in caregiver burden (CSS: MD -11.50, 95%CI -27.88 – 4.88, I^2 n.a., very low certainty).

Five studies investigated the effectiveness of technology-based interventions. Four studies on 717 participants (Beauchamp 2005, Blom 2015, Gallagher-Thompson 2010, Kajiyama 2013) reported an improvement in caregivers' depressive symptoms in the treated group compared to controls (CES-D: MD -2.45, 95%CI -4.01 – -0.88, I^2 n.a., moderate certainty). However, one study on 49 participants (Cristancho-Lacroix 2015) reported no differences between groups in the same outcome measured with BDI (MD 1.40, 95%CI -5.54 – 8.34, I^2 n.a., very low certainty). One study on 245 participants (Blom 2015) reported an improvement in caregivers' anxiety in the treated group (HADS-A: MD 2.16, 95%CI 1.30 – 3.02, I^2 n.a., moderate certainty), while another study on 299 participants (Beauchamp 2005) reported differences between groups in the same outcome measured with the STAI (MD -1.80, 95%CI -3.72 – 0.12, I^2 n.a., low certainty). One study on 299 participants (Beauchamp 2005) reported an improvement in caregiver stress in the treated group (MD -2.70, 95%CI -4.87 – -0.53, I^2 n.a., moderate certainty), while two studies on 152 participants (Cristancho-Lacroix 2015, Kajiyama 2013) reported no differences between groups in the same outcome measured with PSS (MD -1.49, 95%CI -5.40 – 2.41, I^2 n.a., very low certainty). Two studies on 348 participants (Beauchamp 2005, Cristancho-Lacroix 2015) reported no differences between groups in caregivers' sense of competence (SMD 0.12, 95%CI -0.09 – 0.33, I^2 n.a., low certainty), and one study on 103 participants (Kajiyama 2013) reported no differences between groups in caregivers' quality of life (MD 0.43, 95%CI -0.52 – 1.38, I^2 n.a., low certainty). One study on 49 participants (Cristancho-Lacroix 2015) (ZBI: MD 1.80, 95%CI -9.69 - 13.29, I^2 n.a., very low certainty) and one study on 299 participants (Beauchamp 2005) (Caregiver Strain: MD -2.20, 95%CI -5.31 - 0.91, I^2 n.a., very low certainty) reported no differences between groups in caregiver burden.

Three studies investigated the effectiveness of telephone-based interventions. Two studies on 361 participants (Au 2019, Tremont 2015) reported a significant improvement in depressive symptoms in the treated group compared to controls (CES-D: MD -4.37, 95%CI -7.19 – -1.54, I^2 0%, moderate certainty). However, one study on 33 participants (Tremont 2008) reported no differences between groups in the same outcome measured with the GDS (MD -2.44, 95%CI -7.95 – 3.07, I^2 n.a., very low certainty). Overall, the three studies (Au 2019, Tremont 2008, Tremont 2015), on 394 participants, reported no differences between groups in caregiver burden (ZBI: MD -9.64, 95%CI -21.78 – 2.49, I^2 n.a., very low certainty). One study on 250 participants (Tremont 2015) reported no differences between groups in caregivers' quality of life (Euro-QoL: MD -0.66, 95%CI -6.28 – 4.96, I^2 n.a., very low certainty) and sense of competence (SEQSM: MD 2.29, 95%CI -1.41 – 5.99, I^2 n.a., very low certainty).

Supportive interventions

Seven studies investigated the effectiveness of supportive interventions for caregivers of people with dementia.

Three studies investigated group-based interventions. One study on 60 participants (Chu 2011) reported no differences between groups in caregiver burden (CBI: MD -2.71, 95%CI -15.29 – 9.87, I^2 n.a., very low certainty). One study on 52 participants (Fung 2002) reported an improvement in quality of life in the treated group compared to controls (WHO-QoL: MD 31.87, 95%CI 23.66 – 40.08, I^2 n.a., moderate certainty), but reported no differences between groups in distress (NPI-D: MD -5.02, 95%CI -13.48 – 3.44, I^2 n.a., very low certainty). One study on 44 participants (Quayhagen 2000) reported no differences between groups in caregivers' depressive symptoms (BSI: MD 0.20, 95%CI -0.17 – 0.57, I^2 n.a., very low certainty) and anxiety (BSI: MD 0.00, 95%CI -0.37 – 0.37, I^2 n.a., very low certainty).

Only one study on 231 participants (Charlesworth 2008) investigated an individual intervention and reported no differences between groups in depressive symptoms (HADS-D: MD 0.10, 95%CI -1.37 – 1.57, I^2 n.a., low certainty), anxiety (HADS-A: MD -0.02, 95%CI -1.65 – 1.61, I^2 n.a., low certainty) and quality of life (EQ-5D: MD 3.50, 95%CI -3.15 – 10.15, I^2 n.a., very low certainty).

One study on 55 participants (Baruah 2021) investigated a technology-based intervention reporting no differences between groups in depressive symptoms (CES-D: MD 0.46, 95%CI -3.53 – 4.45, I^2 n.a., very low certainty), burden (ZBI: MD -3.02, 95%CI -12.56 – 6.50, I^2 n.a., very low certainty), and quality of life (EuroQoL-VAS: MD -8.13, 95%CI -20.64 – 4.39, I^2 n.a., very low certainty).

Three studies investigated telephone-based interventions. Two studies on 169 participants (Goodman 1990, Winter 2006) reported no differences between groups in caregiver burden (ZBI: MD 1.76, 95%CI -4.43 – 7.95, I^2 n.a., very low certainty). Two studies on 203 participants (Mahoney 2003, Winter 2006) reported no differences between groups in caregivers' depressive symptoms (CES-D: MD -3.37, 95%CI -7.18 – 0.45, I^2 n.a., low certainty), and one study on 100 participants (Mahoney 2003) reported no differences between groups in anxiety (STAI: MD -1.70, 95%CI -5.42 – 2.02, I^2 n.a., low certainty).

Cognitive-behavioural therapy

Twelve studies investigated the effectiveness of cognitive-behavioural therapy for caregivers of people with dementia.
Six studies investigated group-based interventions. Four studies on 375 participants (Au 2010, Gallagher-Thompson 2008, Losada 2015, Márquez-González 2007) and one study on 40 participants (Marriott 2000) reported an improvement in the treated group compared to controls in depressive symptoms measured with CES-D (CES-D: MD -4.02, 95%CI -7.09 – -0.94, I^2 0%, moderate certainty) and BDI (MD -6.40, 95%CI -12.15 – -0.65, I^2 n.a., low certainty). Two studies on 125 participants (Akkerman 2004, Losada 2015) reported no differences between groups in anxiety (SMD -0.43, 95%CI -0.97 – 0.12, I^2 49%, very low certainty). On study on 27 participants (Au 2010) and one study on 184 participants (Gallagher-Thompson 2008) reported no differences between groups in caregivers' sense of competence (RSCSE: MD 104.42, 95%CI -8.65 – 217.49, I^2 n.a., very low certainty) and stress (PSS: MD -1.87, 95%CI -4.65 – 0.91, I^2 n.a., low certainty), respectively.

Two studies on 61 participants (Gallagher-Thompson 2007, Losada 2004) investigated individual interventions and reported an improvement in depressive symptoms in the treated group compared to controls (CES-D: MD -6.88, 95%CI -13.40 – -0.37, I^2 0%, N=61, low certainty). However, one of the studies (Gallagher-Thompson 2007), on 45 participants, reported no differences between groups in caregiver stress (PSS: MD -1.25, 95%CI -4.70 – 2.20, I^2 n.a., low certainty).

Two studies investigated the effectiveness of technology-based interventions. One study on 38 participants (Kwok 2014) reported an improvement in caregiver burden in the treated group compared to controls (ZBI: MD -4.08, 95%C -8.02 – -0.14, I^2 n.a., low certainty), but reported no differences between groups in caregivers' sense of competence (CSE: MD 3.59, 95%CI -2.58 – 9.76, I^2 n.a., very low certainty). The second study (Meichsner 2019), on 37 participants, reported no differences between groups in caregivers' depressive symptoms (CES-D: MD 5.69, 95%CI -2.43 – 13.81, I^2 n.a., very low certainty) and burden (VAS, Visual Analogue Scale: MD 11.83, 95%CI -5.98 – 29.64, I^2 n.a., low certainty).

Two studies investigated the effectiveness of telephone-based interventions. Overall, the two studies (Töpfer 2021, Wilz 2018), on 324 participants, reported no differences between groups in caregivers' depressive symptoms (CES-D: MD 0.12, 95%CI -2.89 – 3.13, I^2 n.a., low certainty) and burden (VAS: MD -6.02, 95%CI -18.69 – 6.65, I^2 n.a., very low certainty). One of the studies (Töpfer 2021), on 51 participants, reported no differences between groups in caregivers' quality of life (WHO-QoL: MD -2.27, 95%CI -16.19 – 10.75, I^2 n.a., very low certainty).

Case management

Three studies investigated the effectiveness of case management interventions specifically aimed at supporting caregivers of people with dementia.
One study on 34 participants (Fortinsky 2009) investigated the efficacy of involving a case consultant in care management, and reported no differences between groups in depressive symptoms (CES-D: MD -2.23, 95%CI -9.57 – 5.11, I^2 n.a., very low certainty) and caregiver burden (ZBI: MD 1.21, 95%CI -7.87 – 10.29, I^2 n.a., very low certainty). One study on 99 participants (Jansen 2011) investigated the effectiveness of a case management intervention carried out by district nurses. The study reported no differences between groups in caregivers' depressive symptoms (CES-D: MD 0.60, 95%CI -3.22 – 4.42, I^2 n.a., low certainty), burden (SPPIC: MD 0.30, 95%CI -1.14 – 1.74, I^2 n.a., low certainty) and sense of competence (SCQ: MD 0.10, 95%CI -3.54 – 3.74, I^2 n.a., very low certainty). One study on 61 participants (Xiao 2016) investigated the effectiveness of a home-based case management intervention led by a care coordinator, and reported an improvement in the treated group compared to controls in caregivers' sense of competence (short-SCQ: MD 9.00, 95%CI 5.09 – 12.91, I^2 n.a., low certainty).

Physical exercise interventions

Three studies investigated the effectiveness of physical exercise as a support for caregivers of people with dementia.
One study on 48 participants (Madruga 2021) investigated a home-based intervention and reported no differences between groups in caregivers' depressive symptoms (GDS: MD -0.80, 95%CI -2.84 – 1.24, I^2 n.a., low certainty) and burden (ZBI: MD -8.30, 95%CI -18.34 – 1.74, I^2 n.a., very low certainty). One study on 31 participants (Hirano 2011) investigated an individualized physical exercise intervention and reported an improvement in the treated group compared to controls in caregivers' depressive symptoms (VAS: MD -4.40, 95%CI -6.97 – -1.83, I^2 n.a., moderate certainty) and burden (ZBI: MD -5.90, 95%CI -6.93 – -4.87, I^2 n.a., moderate certainty). One last study on 137 participants (Connell 2009) investigated a telephone intervention and reported no differences between groups in caregivers' depressive symptoms (CES-D: MD -0.70, 95%CI -2.01 – 0.61, I^2 n.a., low certainty) and burden (RMBPC: MD -0.50, 95%CI -5.79 – 4.79, I^2 n.a., very low certainty).

Multicomponent interventions

Thirty-one studies investigated the effectiveness of multicomponent interventions for supporting caregivers of people with dementia.
Fifteen studies investigated interventions exclusively targeted to caregivers. Of these, only one study on 114 participants (Shata 2017) reported an improvement in the treated group compared to controls in depressive symptoms (HAM-D: MD -10.20, 95%CI -11.28 – -9.12, I^2 n.a., moderate certainty) and anxiety (TMAS: MD -15.05, 95%CI -16.56 – -13.54, I^2 n.a., moderate certainty). Nine studies on 2,491 participants (Berwig 2017, Davis 2011, Gaugler 2015, Gonyea 2006, Hébert 1994, Martindale-Adams 2013, Newcomer 1999, Shata 2017, Yoo 2018) reported no differences between groups in caregiver burden measured with ZBI (MD -4.90, 95%CI -10.80 – 1.00, I^2 96%, very low certainty). One study on46 participants (Chen 2015) also reported no differences between groups in the same outcome measured with CBI (MD -9.40, 95%CI -21.79 – 2.99, I^2 n.a., very low certainty). Six studies on 359 participants (Boots 2018, Davis 2011, Finkel 2007, Gaugler 2015, Martindale-Adams 2013, Mohide 1990) (CES-D: MD -1.15, 95%CI -3.37 – 1.07, I^2 0%, low certainty) and three studies on 2,354 participants (Mittelman 2004, Newcomer 1999, Yoo 2018) (GDS: MD -1.26, 95%CI -2.59 – 0.08, I^2 76%, very low certainty) reported no differences between groups in depressive symptoms. One study on 81 participants (Berwig 2017) (PHQ-4: MD -0.40, 95%CI -1.02 – 0.22, I^2 n.a., low certainty) and one study on 36 participants (Hébert 1994) (BSI-depression: MD 0.86, 95%CI -2.61 – 4.33, I^2 n.a., low certainty) also reported no differences between groups in the same outcome measured with different tools. One study on

36 participants (Hébert 1994) (BSI-anxiety: MD -0.08, 95%CI -3.48 – 3.32, I^2 n.a., low certainty) and one study on 42 participants (Mohide 1990) (STAI: MD -3.02, 95%CI -14.68 – 8.64, I^2 n.a., very low certainty), reported no differences between groups in anxiety. One study on 81 participants (Boots 2018) (HADS: MD 1.46, 95%CI -1.19 – 4.11, I^2 n.a., low certainty) and another study on 81 participants (Berwig 2017) (PHQ-4: MD -0.31, 95%CI -1.18 – 0.56, I^2 n.a., low certainty) also reported no differences between groups in the same outcome measured with different tools. Two studies on 77 participants (Dichter 2020, Mohide 1990) eported no differences between groups in quality of life (SMD 0.22, 95%CI -0.23 – 0.67, I^2 n.a., very low certainty).

Seventeen studies investigated the effectiveness of interventions targeted to both people with dementia and their caregivers. Two studies on 180 participants (Chien 2008, Chien 2011) reported an improvement in the treated group compared to controls in caregiver burden (FCBI: MD -18.99, 95%CI -24.48 – -13.50, I^2 0%, moderate certainty). However, eight studies on 784 participants (Dias 2008, Gaugler 2019, Gitlin 2008, Gitlin 2010, Kwok 2013, Tang 2018, Torkamani 2014, Uyar 2019) and one study on 111 participants (Prick 2015) reported no differences between groups in ZBI (MD -1.58, 95%CI -3.81 – 0.65, I^2 n.a., low certainty) and SPPIC (MD 0.08, 95%CI -1.12 – 1.28, I^2 n.a., low certainty) scores. One study on 61 partcipants (Uyar 2019) reported an improvement in the treated group compared to controls in caregivers' depressive symptoms (BDI: MD -7.35, 95%CI -13.05 – -1.65, I^2 n.a., N=61, very low certainty). Five studies on 1,541 participants (Gaugler 2015, Gitlin 2003, Gitlin 2008, Graff 2007, Prick 2015) reported no differences between groups in caregivers' depressive symptoms measured with CES-D (CES-D: MD -1.41, 95%CI -5.03 – 2.21, I^2 80%, N=1,541, very low certainty). Three studies on 607 participants (Bruvik 2013, Martin-Cook 2005, Waldorff 2012) (GDS: MD 0.44, 95%CI -0.46 – 1.33, I^2 0%, low certainty) and one study on 13 participants (Bottino 2005) (MADRS: MD -1.54, 95%CI -8.10 – 5.02, I^2 n.a., very low certainty) also reported no differences between groups in the same outcome measured with different tools. One study (Uyar 2019) reported an improvement in the treated group compared to controls in anxiety (BAI: MD -7.12, 95%CI -12.89 – -1.35, I^2 n.a., very low certainty), while one study on 13 participants (Bottino 2005) reported no differences between groups in the same outcome measured with HAM-A: MD -4.69, 95%CI -9.72 – 0.34, I^2 n.a., very low certainty). Two studies on 180 participants (Chien 2008, Chien 2011) reported an improvement in the treated group compared to controls in quality of life (WHO-QoL: MD 19.63, 95%CI 13.69 – 25.57, I^2 0%, moderate certainty). However, two studies on 334 participants (Torkamani 2014, Waldorff 2012) (EQ5D-VAS: MD -0.31, 95%CI -4.24 – 3.61, I^2 0%, low certainty) and one study on 40 participants (Torkamani 2014) (QoLS: MD 4.95, 95%CI -4.56 – 14.46, I^2 n.a., very low certainty) reported no differences between groups on the same outcome measured with different tools.

Meditation/mindfulness interventions

Nine studies investigated the effectiveness of meditation/mindfulness interventions for caregivers of people with dementia.

Five studies investigated the effectiveness of meditation. One study on 46 participants (Danucalov 2013) reported an improvement in the treated group compared to controls in depressive symptoms (BDI: MD -9.20, 95%CI -15.74 – -2.66, I^2 n.a., low certainty). However, one study on 39 participants (Lavretsky 2013) reported no differences between groups in the same outcome measured with HAM-D (MD -2.10, 95%CI -4.77 – 0.57, I^2 n.a., N=39, low certainty). One study on 31 participants (Waelde 2017) (CES-D: MD -5.92, 95%CI -14.32 – 2.48, I^2 n.a., N=31, very low certainty), and on study on 17 participants (Leach 2015) (WebNeuro: MD 0.24, 95%CI -1.95 – 2.43, I^2 n.a., N=17, very low certainty) also reported no differences between groups in the same outcome measured with different tools. One study on 46 participants (Danucalov 2013) reported an improvement in the treated group compared to controls in anxiety (BAI: MD -10.90, 95%CI -18.07 – -3.73, I^2 n.a., low certainty). However, one study on 17 participants (Leach 2015) report no differences in the same outcome measured with WebNeuro (MD -0.48, 95%CI -3.07 – 2.11, I^2 n.a., low certainty). Two studies on 192 participants (Pandya 2019, Leach 2015) reported no differences between groups in caregiver burden (ZBI:

MD -29.41, 95%CI -31.78 – -27.04, I^2 n.a., moderate certainty) and stress (WebNeuro: MD 0.37, 95%CI -1.60 – 2.34, N=17, very low certainty).

Four studies investigated the effectiveness of mindfulness interventions. Overall, the four studies (Kor 2019, Kor 2021, Oken 2010, Whitebird 2013), on 247 participants, reported an improvement in caregivers' depressive symptoms (CES-D: MD -5.48, 95%CI -10.02 – -0.93, I^2 20%, low certainty) and stress (PSS: MD -3.70, 95%CI -6.26 – -1.15, I^2 0%, moderate certainty). However, two studies on 149 participants (Kor 2019, Kor 2021) reported no differences between groups in caregiver burden (ZBI: MD -6.83, 95%CI -14.20 – 0.55, I^2 8%, very low certainty) and anxiety (HADS: MD -2.21, 95%CI -4.59 – 0.17, I^2 0%, low certainty). One study on 78 participants (Whitebird 2013) reported no differences between groups in anxiety measured with STAI (MD 0.90, 95%CI -7.03 – 8.83, I^2 n.a., very low certainty).

Analysis of evidence

Caregivers are essential resources for both people requiring care and healthcare professionals, who have a close relationship with them. The amount of time they dedicate to caregiving allows them to acquire an intimate knowledge of the people they care for, and to be able to provide useful information to facilitate treatment or choosing aids. This relationship could also, in cases where the disease prevents communication, allow them to find the most appropriate way to translate visual clues, gestures or other signals, which could also help healthcare professionals.
The relevant burden of caring for and supporting people needing assistance can lead caregivers to be exposed to different conditions that could, in turn, trigger the onset of some pathological conditions. Therefore, preventing negative physical, psychological and social outcomes in caregivers is extremely relevant.
Caregivers' burden and quality of life are extremely relevant factors, that should be monitored in time to allow for timely interventions to reduce burden and ensure maintaining the best quality of life, thus facilitating preventing actions.
Psychoeducational interventions are defined as structured programs aimed at providing information on how to effectively manage dementia-related issues, such as memory and behavioural disorders. Skill training, instead, refers to interventions aimed at providing training on specific practical aspects of care. Evidence suggested that skill training is closely connected to psychoeducational intervention, therefore the WG agreed to stratify evidence from both types of approaches in individual, group, or technology-based interventions. However, interventions reported in the literature were heterogeneous and included different approaches and interactions. Moreover, the choice of the type of intervention might be due to each caregiver's individual or personal preferences, and specific approaches might be more specific to different cultural needs. The WG agreed that, despite the lack of evidence on the effectiveness of psychosocial interventions alone and the limited evidence on skill training alone, the combination of these approaches showed a significant benefit for both people with dementia and their caregivers in several domains.
Therefore, the WG agreed to recommend offering psychoeducational and skill-training interventions including the characteristics that were supported by gathered evidence.
Included studies suggested that group cognitive-behavioural therapy (CBT) could be useful, especially in improving depressive symptoms. On this basis, the WG agreed to include a research recommendation encouraging further studies investigating the effectiveness of these interventions in a more specific group of people at risk of depressive disorders. No effect of CBT was observed on caregivers' anxiety and stress.

Evidence on technology-based CBT interventions reported no benefit on any of the considered caregivers' outcome measures. The WG discussed the applicability of these technology-based interventions, especially the need to select carefully participants, as people who are familiar with web-based technologies could benefit from this type of intervention differently than people who are less familiar with them. However,

anecdotal evidence suggested that CBT in videoconference could be as effective as in presence, especially for people who is familiar with web-based technology.
Evidence on case management was limited and highly heterogeneous. Therefore, the WG agreed that the effectiveness of case management was better assessed as part of other questions such as those on care coordination (Review Question 7), as more evidence was available on that topic.
Multicomponent interventions were defined as including at least two elements of the intervention, and were classified as interventions targeting caregivers or interventions targeting both people with dementia and their caregivers.
Some limitations might have affected the results from these studies, such as the high number of components included in the considered intervention, the short length of interventions, and the heterogeneity of the enrolled population. As an example, some programs appear to have been designed without accounting for the specific needs of the caregivers. This could prevent caregivers from translating the effects of the intervention to their daily life, where their burden could be caused by purely practical issues. Moreover, the short length of some studies might have prevented participating caregivers from perceiving an actual benefit.
Evidence confirmed the relevance of caregivers sharing their experiences, despite the wide heterogeneity of reported experiences mainly due to the different age and severity of disease of the enrolled participants, which might have affected the effect of the intervention.
Analysed evidence suggested a potential effect of mindfulness interventions in improving caregivers' depressive symptoms and stress, despite its apparent inability to improve perceived burden.
Heterogeneity in the results from these studies might be due to several factors, including predisposition and propensity to this type of interventions, along with time. Considering the complexity of these activities, a longer exposure, along with an appropriate guidance, could presumably be associated to a larger effect. Moreover, studies investigating traditional meditation could be further limited by the absence of a direct connection between caregiving and the actual activities offered during a meditation session.
Mindfulness follows a different approach from traditional meditation, though some studies included meditation aspects in mindfulness programs. This, along with some studies including specific training sessions on the role of caregivers and on the use of some supportive tools, could be a potentially effective combination.
The WG considered available evidence as insufficient to recommend this type of interventions over psychoeducational and skill-training interventions.

Recommendations

73	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;	STRONG IN FAVOR

	• information about relevant services (including support services and psychological therapies for carers) and how to access them; • advice on planning for the future.	
74	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.	STRONG IN FAVOR
75	Advise carers about their right to the following and how to get them: • a formal assessment of their own needs, including their physical and mental health; • an assessment of their need for short breaks and other respite care.	STRONG IN FAVOR
76	Be aware that carers of people living with dementia are at an increased risk of depression. For guidance on identifying and managing depression, see Table 6.	WEAK IN FAVOR

Research Recommendations

16R	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?

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PHARMACOLOGICAL INTERVENTIONS FOR COGNITIVE SYMPTOMS

Introduction

The history of clinical trials aimed at identifying disease-modifying treatments for Alzheimer's disease (AD) has been ongoing for more than 30 years. The principle that drove the research is the so-called amyloid cascade hypothesis, which is still considered an integral part of the etiopathogenetic hypothesis underlying degeneration in AD.
Based on this hypothesis, a close time releationship exists in the manifestation of the two aggregations of proteins, amyloid-β (Aβ) plaques and neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau (p-Tau), which characterize the histopathological brain changes pathognomonic of AD. The deposition of Aβ42 peptide in insoluble fibrillar aggregates, due to an imbalance between its production and lower degradation, would be the central event in the progression of the neuropathological alteration characteristic of the disease. Over the years, this hypothesis has been strongly supported not only by neuropathological data but also by genetic evidence resulting from the rare hereditary forms of the disease, due to mutations in the presenilin 1 and 2 genes (PSEN1, PSEN2) and in the Amyloid Precursor Protein (APP), the causes of Autosomal Dominantly Inherited AD (DIAD) (Selkoe 2016).
Pathological changes in the cerebral cortex seem to occur even several decades before the onset of cognitive symptoms characteristic of the disease (Jansen 2015).
According to the original hypothesis, Aβ pathology would drive Tau pathology, with progressive degeneration initially involving the cerebral temporo-basal and fronto-mesial regions and then spreading to the remaining neocortex, sensorimotor cortex, and finally to the corpus striatum (Braak 1991, Braak 1995).
However, recent evidence describes a spatial and temporal disconnection between the cardinal pathological aspects of AD related to the two proteins. The accumulation of Aβ plaques and NFTs follows a distinct regional pattern in the brain as the disease progresses (Hyman 2012). Tau pathology seems to arise before the appearance of Aβ plaques, involving the mesial temporal regions, hippocampus, amygdala, and entorhinal cortex, later extending to the entire cerebral cortex, from the limbic regions to the neocortex (Braak 1991). However, at early stages, Tau-related alterations would be present when no cognitive symptoms are manifested (Crary 2014).
Evidence currently supports the hypothesis that NFTs-related degeneration (Braak stages I-VI) correlates best with the progression of cognitive disorders (Pontecorvo 2017).
However, the sequential order in which these proteinopathies develop, and their potentially synergistic relationship with neurodegeneration, have yet to be clearly understood.
The only currently available pharmacological class available and approved by regulatory agencies for the treatment of AD are the acetylcholinesterase inhibitors (AChEIs) donepezil, galantamine, rivastigmine, and the NMDA receptor antagonist memantine.
The rationale underlying treatment with AChEI is based on one of the first theories hypothesizing that a dysfunction brain cholinergic activity, linked to the neurotransmitter acetylcholine (Ach), may be involved in the development of cognitive decline in AD. Acetylcholine is one of the most important neurotransmitters of the central nervous system (CNS) and peripheral nervous system (PNS). Its action in the CNS is essential since it is involved in memory and learning. For this reason, the main hypothesis is that a drug capable to inhibit the acetylcholinesterase enzyme (AchE) that degrades Ach, allowing the neurotransmitter to be maintained longer within the synaptic cleft, could improve cognitive functions in people with dementia.
Moreover, evidence that a dysfunction in glutamatergic neurotransmission, especially the one mediated by NMDA receptors, affects cognitive decline and neurodegeneration, supported the experimentation and consequent marketing approval of memantine in people with AD.
Memantine, through its action as an NMDA receptor antagonist, can modulate the glutamatergic neurotransmission in the brain that leads to neuronal overstimulation and neurotoxicity
None of these medications showed a neuroprotective action, thus to able to slow the progression of neurodegeneration and cognitive decline. AChEIs and memantine are exclusively a symptomatic treatment causing a modest improvement in cognitive symptoms and helping to maintain functional abilities in daily life in the medium term (as measured by ADAS-Cog, ADL, CDR). However, their safety and efficacy vary among people with AD.

Donepezil, galantamine, and rivastigmine are subject to strict prescription regulations. They are recommended as monotherapy for the treatment of mild to moderate AD only after appropriate assessment by a neurologist, geriatrician, or psychiatrist with specific expertise (Note 85 AIFA, Agenzia Italiana del Farmaco). Prescriptions eligible for refund by the National Health System (NHS) must be provided by neurologists, geriatricians, and psychiatrists within the Centers for Cognitive Disorders and Dementia (CCDDs).

Memantine can be used as monotherapy in people with moderate AD when AChEIs are not tolerated or are contraindicated, and in people with severe AD. Memantine can also be considered in combination with AChEIs in people with moderate to severe AD based on judgement by expert physician.

The tolerability and dose of these medications should be regularly reviewed. Specialists in CCDDs regularly people treated with these drugs in collaboration with their General Practitioners (GP). Special attention should be paid to potential cardiac complications, such as bradycardia and QTc prolongation, which should be monitored with ECG, and gastrointestinal symptoms due to the cholinergic action (nausea and diarrhea).

Treatment with AChEIs and memantine has also been investigated in other dementia subtypes, including frontotemporal dementia (FTD), vascular dementia (VaD), and dementia with Lewy bodies (DLB). However, only rivastigmine capsules is currently indicated for the treatment of mild to moderate Parkinson's disease dementia (PDD).

Currently, the lack of medications that can slow the progression of dementia has also brought attention to existing therapies used to treat other conditions. These drugs, based on a principle of biological plausibility, were tested specifically to assess their ability to slow the progression of the disease or to delay the conversion from Mild Cognitive Impairment (MCI) to dementia by targeting the main known risk factors for dementia, such as cardiovascular and metabolic risk factors (e.g., diabetes, hypertension, dyslipidemia).

No drugs are currently available capable to slow or prevent the progression of the disease. Significant economic efforts over the past two decades allowed to develop extremely innovative therapies aimed at modifying the natural history of the disease (disease-modifying therapies, DMTs). In the United States, the Food and Drug Administration (FDA) approved two monoclonal antibodies (mAbs) targeted against the different forms of Aβ, aducanumab and lecanemab. In Europe, the EMA is evaluating the marketing approval of lecanemab, a mAb reporte to be able to target and remove fibrillar forms of Aβ. Randomized controlled trials reported that lecanemab was able to effectively remove amyloid plaques in the brains of participants with MCI due to AD and mild AD, as defined by the presence of amyloid plaques as measured with amyloid-PET imaging. Another monoclonal antibody, donanemab, which is also currently under evaluation by both the EMA and the FDA, was reported to have an excellent ability to clear insoluble forms of Aβ. However, the improvement in cognitive performance as measured by the CDR-SB scale and functional capacity reported for both drugs was minimal, thus highlighting the discrepancy between cerebral Aβ pathology and clinical symptoms. Aducanumab, lecanemab, and donanemab, as other mAbs in previous studies, were associated with a significantly higher frequency of Amyloid-Related Imaging Abnormalities (ARIA), specifically of ARIA-E (edema) and ARIA-H (microhaemorrhages). ARIA events, as reported by several randomised controlled trials (RCTs), are often asymptomatic. However, they can cause clinical symptoms such as headache, confusion and falls. Some studies also reported fatal ARIA events. ARIA events can also be severe from a radiological point of view, even if clinically asymptomatic. These aspects raise major concerns from a both clinical perspective and in terms of management and monitoring, mainly because the long-term effects of ARIA are currently unknown (Cogswell 2022, Sperling 2011).

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Acetylcholinesterase inhibitors, memantine and new biological treatments for Alzheimer's dementia and Mild Cognitive Impairment

Review question 15a	How useful (in terms of efficacy and safety) are acetylcholinesterase inhibitors and memantine for the treatment of cognitive symptoms in people with Alzheimer's dementia, and how should they be reviewed?
Review question 15b	How useful (in terms of efficacy and safety) are acetylcholinesterase inhibitors and memantine for the treatment of cognitive symptoms in people with Mild Cognitive Impairment, and how should they be reviewed?
Review question 15c	How useful (in terms of efficacy and safety) are biological drugs (active and passive immunization) for the treatment of cognitive symptoms in people with Alzheimer's dementia or Mild Cognitive Impairment, and how should they be reviewed?

Literature review

	15a	15b	15c
Records identified from databases	3,703	1,345	3,015
Studies assessed for eligibility	87	45	96
Included studies	55	6	45
Studies included in the NICE GL	55	6	45
Total number of included studies	3,703	1,345	3,015

Eligibility criteria

Review question 15a

Population	People aged ≥40 years with Alzheimer's dementia.
Interventions	• Acetylcholinesterase inhibitors: donepezil, galantamine, rivastigmine • NMDA receptor antagonist: memantine
Comparator	Placebo.
Outcomes	• Cognitive outcomes including: MMSE, ADAS-Cog • Functional outcomes including: ADCS-ADL • Global functioning including: CIBIC+ • Non-cognitive outcomes including: NPI, withdrawal due to adverse events

Review question 15b

Population	People aged 40 years and over with a diagnosis of MCI.
Interventions	• Acetylcholinesterase inhibitors: donepezil, galantamine, rivastigmine. • NMDA receptor antagonist memantine.
Comparator	Placebo.
Outcomes	• Cognitive, functional, and global measures; • Safety and tolerability; • Mortality; • Conversion to dementia.

Review question 15c

Population	People with a diagnosis of Alzheimer's dementia or MCI.
Interventions	Active or passive immunotherapy: • Active immunotherapy; • Monoclonal antibodies targeting Aβ or Tau.
Comparator	Placebo.
Outcomes	• Clinical outcomes. • Safety and tolerability: – Adverse events; – Serious adverse events; – ARIA-E, ARIA-H; – Mortality. • Clearance of target proteins: – Amyloid clearance as measured with amyloid-PET; – Tau clearance as measured with Tau-PET.

Aim

Review question 15a

The objective of the systematic literature review was to identify all randomized controlled trials (RCT) investigating the safety and efficacy of donepezil, galantamine, rivastigmine and memantine for the treatment of cognitive symptoms, functional abilities and global functions of Alzheimer's dementia (AD). This review question focused on the efficacy and safety of donepezil, galantamine, rivastigmine and memantine as monotherapy. The efficacy and safety of co-prescription of acetylcholinesterase inhibitors or of acetylcholinesterase inhibitors and memantine is analysed in RQ17a.

RQ15a was adapted to the context of the Italian National Health System (NHS). In Italy, in fact, acetylcholinesterase inhibitors and memantine can only be prescribed within the NHS by a neurologist,

psychiatrist or geriatrician with specific competences and experience and within a Centre for Cognitive Disturbances and Dementia (CCDDs). For further information see Nota 85 (AIFA nota 85).

The systematic review was initially targeted at identifying updated systematic reviews on the use of acetylcholinesterase inhibitors and memantine for the treatment of cognitive symptoms in people with AD. Systematic reviews were analysed to identify primary studies. Additional structured literature searches were also performed to identify further relevant studies. Only RCTs reporting data on the efficacy (cognitive, functional and global measures) and safety of acetylcholinesterase inhibitors and memantine were included. Efficacy and safety results are reported both overall and stratified by disease severity.

Review question 15b

The objective of the systematic review of the literature was to summarise available evidence from RCTs investigating the safety and efficacy of acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine) and memantine for the treatment of cognitive symptoms, functional abilities, and global functions in people with a diagnosis of MCI.

Review question 15c

The objective of the systematic review of the literature was to summarise available evidence from RCTs investigating the safety and efficacy of biological drugs (active and passive immunotherapy) targeted against the different forms of Amyloid-β (Aβ) and Tau in people with AD or MCI due to AD.

Summary of evidence

Review question 15a

In line with the strategy defined by the NICE Guideline, the Health Technology Assessment (HTA) TA217 developed by NICE[36] was adopted as the basis for systematic literature review and was therefore updated (Bond 2012).

Donepezil

Overall, 25 RCTs (Black 2007, Burns 1999, Courtney 2004, Feldman 2001, Frölich 2011, Gault 2015, Gault 2016, Gauthier 2002, Haig 2014, Holmes 2004, Homma 2000, Homma 2008, Jia 2017, Johannsen 2006, Krishnan 2003, Maher-Edwards 2011, Mazza 2006, Mohs 2001, Moraes 2006, Rogers 1998, Seltzer 2004, Tariot 2001, Tune 2003, Winblad 2001, Winblad 2006) investigated the safety and efficacy of donepezil in people with AD. Twelve studies (Burns 1999, Frölich 2011, Gault 2015, Gault 2016, Haig 2014, Homma 2000, Johanssen 2006, Maher-Edwards 2011, Moraes 2006, Rogers 1998, Seltzer 2004, Tune 2003) reported an improvement in the intervention group compared to the control group in cognitive functions measured with ADAS-Cog (SMD -0.38, 95%CI -0.49 – -0.26, I^2 42%, N=2,766, moderate certainty). Nineteen studies (Courtney 2004, Black 2007, Feldman 2001, Frölich 2011, Gault 2015, Gault 2016, Gauthier 2002, Haig 2014, Holmes 2004, Jia 2017, Johanssen 2006, Maher-Edwards 2011, Mazza 2006, Mohs 2001, Rogers 1998, Seltzer 2004, Tariot 2001, Winblad 2001, Winblad 2006) reported an improvement in cognitive functions measured with MMSE (MD 0.99, 95%CI 0.79 – 1.19, I^2 0%, N=4,335, high certainty). Six studies (Black 2007, Gault 2015, Gault 2016, Haig 2014, Homma 2008, Winblad 2006) an improvement in the intervention group compared to the control group in functional abilities measured with ADCS-ADL (MD 1.40, 95%CI 0.69 – 2.11, I^2 8%, N=1.220, high certainty). Three studies (Burns 1999, Gauthier 2002, Rogers 1998) reported an improvement in the intervention group in global functions measured with CIBIC+ (MD -0.38, 95%CI -0.49 – -0.28, I^2 0%, N=1.371,

[36] NICE. Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease Technology appraisal guidance [TA217]. Last update: June 2018. Available at: https://www.nice.org.uk/guidance/ta217 (Last access: 30/08/2023).

high certainty). Nine studies (Black 2007, Feldman 2001, Gault 2015, Gault 2016, Haig 2014, Johanssen 2006, Tariot 2001, Tune 2003, Winblad 2006) reported an improvement in neuropsychiatric symptoms measured with NPI on the donepezil group compared with placebo (MD -2.08, 95%CI -3.01 – -1.14, I^2 59%, N=1.671, moderate certainty). In terms of safety, 18 studies (Black 2007, Burns 1999, Feldman 2001, Gault 2015, Gault 2016, Haig 2014, Homma 2000, Homma 2008, Jia 2017, Krishnan 2003, Maher-Edwards 2011, Mazza 2006, Mohs 2001, Rogers 1998, Seltzer 2004, Tariot 2001, Winblad 2001, Winblad 2006) reported a higher risk of withdrawal due to adverse events in the donepezil group compared with placebo (RR 1.42, 95%CI 1.18 – 1.72, I^2 0%, N=4.818, high certainty).

Overall, 19 studies investigated the safety and efficacy of donepezil in people with mild to moderate AD (Burns 1999, Courtney 2004, Frölich 2011, Gault 2015, Gault 2016, Haig 2014, Holmes 2004, Homma 2000, Johanssen 2006, Krishnan 2003, Maher-Edwards 2011, Mazza 2006, Mohs 2001, Moraes 2006, Rogers 1998, Seltzer 2004, Tariot 2001, Tune 2003, Winblad 2001). Twelve studies (Burns 1999, Frölich 2011, Gault 2015, Gault 2016, Haig 2014, Homma 2000, Johanssen 2006, Maher-Edwards 2011, Moraes 2006, Rogers 1998, Seltzer 2004, Tune 2003) reported an improvement in the intervention group compared to the control group in cognitive symptoms measured with ADAS-Cog (SMD -0.37, 95%CI -0.49 – -0.25, I^2 45%, N=2,326, moderate certainty). Eight studies (Frölich 20011, Gault 2015, Gault 2016, Haig 2014, Mazza 2006, Mohs 2001, Rogers 1998, Tariot 2001) reported an improvement in the intervention group in cognitive symptoms measured with MMSE (MD 0.88, 95%CI 0.53 – 1.23, I^2 0%, N=1,253, high certainty). Three studies (Gault 2015, Gault 2016, Haig 2014) reported an improvement in the intervention group in functional abilities (ADCS-ADL: MD 2.43, 95%CI 0.83 – 4.03, I^2 28%, N= 391, high certainty). Two studies (Burns 1999, Rogers 1998) reported an improvement in the intervention group in global functions (CIBIC+: MD -0.36, 95%CI -0.48 – -0.25, I^2 0%, N= 1,268, high certainty). Six studies (Gault 2015, Gault 2016, Haig 2014, Johanssen 2006, Tariot 2001, Tune 2003) reported an improvement in the intervention group in neuropsychiatric symptoms (NPI: MD -1.50, 95%CI -2.79 – -0.21, I^2 27%, N=1.398, high certainty). In terms of safety, 13 studies (Burns 1999, Gault 2015, Gault 2016, Haig 2014, Homma 2000, Krishnan 2003, Maher-Edwards 2011, Mazza 2006, Mohs 2001, Rogers 1998, Seltzer 2004, Tariot 2001, Winblad 2001) reported a higher risk of withdrawal due to adverse events in the donepezil group compared with placebo (RR 1.36, 95%CI 1.07 – 1.72, I^2 0%, N=3,322, high certainty).

Overall, six studies investigated the safety and efficacy of donepezil in people with moderate to severe AD (Black 2007, Feldman 2001, Gauthier 2002, Homma 2008, Jia 2017, Winblad 2006). Five studies (Black 2007, Feldman 2001, Gauthier 2002, Jia 2017, Winblad 2006) reported an improvement in the intervention group compared to the control group in cognitive symptoms measured with MMSE (MD 1.15, 95%CI 0.64 – 1.66, I^2 41%, N=1,293, moderate certainty). Three studies (Black 2007, Homma 2008, Winblad 2006) reported an improvement in the intervention group in functional abilities (ADCS-ADL: MD 1.04, 95%CI 0.26 – 1.81, I^2 0%, N= 829, high certainty). One study (Gauthier 2002) reported an improvement in the donepezil group in global functions (CIBIC+: MD -0.55, 95%CI -0.86 – -0.04, I^2 n.a., N=203, moderate certainty). Three studies (Black 2007, Feldman 2001, Winblad 2006) did not report significant differences on neuropsychiatric symptoms measured with NPI (MD -2.09, 95%CI -5.97 – 1.79, I^2 76%, N= 835, very low certainty). In terms of safety, five studies (Black 2007, Feldman 2001, Homma 2008, Jia 2017, Winblad 2006) reported a higher risk of withdrawal due to adverse events in the donepezil group compared with placebo (RR 1.54, 95%CI 1.13 – 2.10, I^2 0%, N= 1,496, high certainty).

Galantamine

Overall, 10 studies (Brodaty 2005, Bullock 2004, Burns 2009, Liu 2003, Raskind 2000, Rockwood 2001, Rockwood 2006, Tariot 2000, Wilcock 2000, Wilkinson 2001) investigated the safety and efficacy of galantamine in people with AD. Eight studies (Brodaty 2005, Bullock 2004, Raskind 2000, Rockwood 2001, Rockwood 2006, Tariot 2000, Wilcock 2000, Wilkinson 2001) reported an improvement in the intervention group compared to the control group in cognitive outcome measured with ADAS-Cog (SMD -0.47, 95%CI -

0.54 – -0.41, I^2 0%, N= 4,013, high certainty). One study (Liu 2003) reported an improvement in the intervention group in MMSE (MD 1.90, 95%CI 0.79 – 3.01, I^2 n.a., N=102, moderate certainty). Four studies (Brodaty 2005, Burns 2009, Liu 2003, Tariot 2000) reported no differences between groups in functional abilities (ADCS-ADL: MD 1.20, 95%CI -0.31 – 2.71, I^2 79%, N= 1,779, low certainty). Five studies (Brodaty 2005, Raskind 2000, Rockwood 2001, Rockwood 2006, Wilcock 2000) reported an improvement in the intervention group in global functions (CIBIC+: MD -0.26, 95%CI -0.34 – -0.17, I^2 6%, N= 2,588, high certainty). Three studies (Brodaty 2005, Rockwood 2001, Tariot 2000) reported an improvement in the intervention group in neuropsychiatric symptoms (NPI: MD -1.49, 95%CI -2.53 – -0.46, I^2 0%, N=1,656, high certainty). One study (Bullock 2004) on participants with AD, vascular dementia and mixed dementia, reported an improvement in the intervention group compared to the control group in cognitive outcome measured with ADAS-Cog (SMD -0.54, 95%CI -0.81 – -0.27, I^2 n.a., N=230, moderate certainty). In terms of safety, eight studies (Brodaty 2005, Burns 2009, Liu 2003, Raskind 2000, Rockwood 2001, Tariot 2000, Wilcock 2000, Wilkinson 2001) reported a higher risk of withdrawal due to adverse events in the galantamine group compared with placebo (RR 2.12, 95%CI 1.34 – 3.36, I^2 76%, N= 3,953, moderate certainty).

Overall, eight studies (Brodaty 2005, Liu 2003, Raskind 2000, Rockwood 2001, Rockwood 2006, Tariot 2000, Wilcock 2000, Wilkinson 2001) investigated the safety and efficacy of galantamine in people with mild to moderate AD. Seven studies (Brodaty 2005, Raskind 2000, Rockwood 2001, Rockwood 2006, Tariot 2000, Wilcock 2000, Wilkinson 2001) reported an improvement in the intervention group compared to the control group in cognitive outcome measured with ADAS-Cog (SMD -0.47, 95%CI -0.54 – -0.40, I^2 0%, N=3,783, high certainty). One study (Liu 2003) reported an improvement in the intervention group in MMSE (MD 1.90, 95%CI 0.79 – 3.01, I^2 n.a., N=102, moderate certainty). Three studies (Brodaty 2005, Liu 2003, Tariot 2000), reported an improvement in the intervention group compared to the control group in functional abilities (ADCS-ADL: MD 1.86, 95%CI 0.67 – 3.06, I^2 39%, N=1,372, high certainty). Five studies (Brodaty 2005, Raskind 2000, Rockwood 2001, Rockwood 2006, Wilcock 2000) reported an improvement in the intervention group in global functions (CIBIC+: MD -0.26, 95%CI -0.34 – -0.17, I^2 6%, N=2,588, high certainty). Three studies (Brodaty 2005, Rockwood 2001, Tariot 2000) reported an improvement in the intervention group in neuropsychiatric symptoms (NPI: MD -1.41, 95%CI -2.51 – -0.31, I^2 0%, N=1,402, high certainty). In terms of safety, seven studies (Brodaty 2005, Liu 2003, Raskind 2000, Rockwood 2001, Tariot 2000, Wilcock 2000, Wilkinson 2001) reported a higher risk of withdrawal due to adverse events in the galantamine group compared with placebo (RR 2.43, 95%CI 1.57 – 3.75, I^2 66%, N= 3,546, moderate certainty).

Only one study (Burns 2009) investigated the safety and efficacy of galantamine in people with moderate to severe AD. The study reported no differences between groups in functional abilities (ADCS-ADL: MD -0.44, 95%CI -1.34 – 0.46, I^2 n.a., N=407, low certainty) and in the risk of withdrawal due to adverse events (RR 0.94, 95%CI 0.59 – 1.49, I^2 n.a., N=407, very low certainty).

Rivastigmine

Overall, seven studies (Agid 1998, Corey-Bloom 1998, Feldman 2007a, Mowla 2007, Nakamura 2011, Rösler 1999, Winblad 2007) investigated the safety and efficacy of rivastigmine in people with AD. Five studies (Agid 1998, Corey-Bloom 1998, Feldman 2007a, Mowla 2007, Rösler 1999) investigated the efficacy of rivastigmine capsules, one study investigated the efficacy of rivastigmine transdermal patch (Nakamura 2011), and one study investigated the efficacy of transdermal patches (10cm^2 and 20cm^2) compared with either capsules or placebo (Winblad 2007). Four studies (Corey-Bloom 1998, Feldman 2007a, Rösler 1999, Winblad 2007) reported an improvement in the rivastigmine capsules group compared to placebo in cognitive symptoms measured with ADAS-Cog (SMD -0.28, 95%CI -0.43 – -0.14, I^2 69%, N=2,629, moderate certainty). Six studies (Agid 1998, Corey-Bloom 1998, Feldman 2007a, Mowla 2007, Rösler 1999, Winblad 2007) reported an improvement in the rivastigmine capsules group in cognitive symptoms measured with MMSE (MD 0.95, 95%CI 0.55 – 1.36, I^2 66%, N=2,555, moderate certainty). One study (Winblad 2007) reported an

improvement in the rivastigmine capsules group compared to placebo in functional abilities (ADCS-ADL: MD 1.80, 95%CI 0.20 – 3.40, I^2 n.a., N=535, moderate certainty) but not in neuropsychiatric symptoms (NPI: MD -0.50, 95%CI -2.68 – 1.68, I^2 n.a., N=534, low certainty). Three studies (Corey-Bloom 1998, Feldman 2007a, Rösler 1999) reported an improvement in the rivastigmine capsules group compared to placebo in global functions (CIBIC+: MD -0.35, 95%CI -0.50 – -0.21, I^2 28%, N=2,040, high certainty). In terms of safety, three studies (Feldman 2007a, Rösler 1999, Winblad 2007) reported a higher risk of withdrawal due to adverse events in the rivastigmine capsule group compared with placebo (RR 1.98, 95%CI 1.16 – 3.36, I^2 67%, N=1.755, moderate certainty).

Two studies (Nakamura 2011, Winblad 200) reported an improvement in the rivastigmine transdermal patch (10cm^2, 9.5mg day and 20cm^2, 17,4 mg day) group compared to placebo in ADAS-Cog (SMD -0.37, 95%CI -0.48 – -0.26, I^2 1%, N=1,324, high certainty) and MMSE (MD 0.71, 95%CI 0.20 – 1.22, I^2 49%, N=1,290, moderate certainty). One study (Winblad 2007) reported an improvement in the rivastigmine patch group in functional abilities (MD 2.25, 95%CI 0.83 – 3.66, I^2 n.a., N=791, moderate certainty), but not in neuropsychiatric symptoms (MD -0.29, 95%CI -2.23 – 1.65, N=792, low certainty). In terms of safety, two studies (Nakamura 2011, Winblad 2007) reported a higher risk of treatment withdrawal due to adverse events in the rivastigmine patch group compared with placebo (RR 1.69, 95%CI 1.18 – 2.43, I^2 0%, N=1,471, high certainty).

Overall, seven studies (Agid 1998, Corey-Bloom 1998, Feldman 2007a, Mowla 2007, Nakamura 2011, Rösler 1999, Winblad 2007) investigated the efficacy of rivastigmine in people with mild to moderate AD. Five studies (Agid 1998, Corey-Bloom 1998, Feldman 2007a, Mowla 2007, Rösler 1999) investigated the efficacy of rivastigmine in capsules, one study (Nakamura 2011) investigated the efficacy of rivastigmine transdermal patch (5cm^2 and 10cm^2), and one study investigated the efficacy of transdermal patch (10cm2 and 20cm2) compared with either rivastigmine capsules or placebo (Winblad 2007). Four studies (Corey-Bloom 1998, Feldman 2007a, Rösler 1999, Winblad 2007) reported an improvement in the rivastigmine capsules group compared to placebo in cognitive functions measured with ADAS-Cog (SMD -0.32, 95%CI -0.42 – -0.21, I^2 35%, N=2,387, high certainty). Five studies (Agid 1998, Feldman 2007a, Mowla 2007, Rösler 1999, Winblad 2007) reported an improvement in the rivastigmine capsules group in cognitive functions measured with MMSE (MD 0.91, 95%CI 0.42 – 1.40, I^2 72%, N=2,096, moderate certainty). One study (Winblad 2007) reported an improvement in the rivastigmine capsules group compared to placebo in functional abilities (ADCS-ADL: MD 1.80, 95%CI 0.20 – 3.40, I^2 n.a., N=535, moderate certainty). Three studies (Corey-Bloom 1998, Feldman 2007a, Rösler 1999) reported an improvement in the rivastigmine capsules group in global functions (CIBIC+: MD -0.35, 95%CI -0.50 - -0.21, I^2 28%, N=2,040, high certainty). However, one study (Winblad 2007) reported no differences between groups in neuropsychiatric symptoms (NPI: MD -0.50, 95%CI -2.68 – 1.68, I^2 n.a., N=534, low certainty). In terms of safety, four studies (Feldman 2007a, Nakamura 2011, Rösler 1999, Winblad 2007) reported a higher risk of withdrawal due to adverse events in the rivastigmine group compared with placebo (RR 1.88, 95%CI 1.28 – 2.77, I^2 54%, N=2,330, moderate certainty).

When considering rivastigmine transdermal patch (10 cm^2 and 20 cm^2), two studies (Nakamura 2011, Winblad 2007) reported an improvement in the rivastigmine patch group compared to placebo in cognitive functions measured with ADAS-Cog (SMD -0.28, 95%CI -0.40 – -0.17, I^2 0%, N=1,324, high certainty) and MMSE (MD 0.71, 95%CI 0.20 – 1.22, I^2 49%, N=1,290, moderate certainty). One study (Winblad 2007) reported an improvement in the rivastigmine patch group in functional abilities (MD 2.25, 95%CI 0.83 – 3.66, I^2 0%, N=791, high certainty), but not in neuropsychiatric symptoms (MD -0.29, 95%CI -2.23 – 1.65, I2 0%, N=792, low certainty). In terms of safety, two studies (Nakamura 2011, Winblad 2007) reported a higher risk of withdrawal due to adverse events in the rivastigmine group compared with placebo (RR 1.69, 95%CI 1.18 – 2.43, I^2 0%, N=1.471, high certainty).

No studies were identified investigating the efficacy of rivastigmine in people with moderate to severe AD.

Memantine

Overall, 14 studies (Bakchine 2008, Dysken 2014, Fox 2012, Grossberg 2013, Herrmann 2013, Homma 2007, Peskind 2006, Peters 2015, Porsteinsson 2008, Reisberg 2003, Tariot 2004, van Dyck 2007, Wang 2013, Wilkinson 2012) investigated the safety and efficacy of memantine in people with AD. Four studies (Bakchine 2008, Dysken 2014, Peskind 2006, Porsteinsson 2008) reported an improvement in the memantine group compared to placebo in cognitive functions measured with ADAS-Cog (SMD -0.12, 95%CI -0.23 – -0.02, I^2 0%, N=1,417, high certainty). Five studies reported no differences between groups in the same outcome measured with MMSE (MD 2.00, 95%CI -0.36 – 4.35, I^2 69%, N=1,104, low certainty). Nine studies (Bakchine 2008, Grossberg 2013, Homma 2007, Peskind 2006, Peters 2015, Porsteinsson 2008, Reisberg 2003, Tariot 2004, van Dyck 2007) reported an improvement in the memantine group compared to placebo in functional abilities (ADCS-ADL: MD 0.65, 95%CI 0.11 – 1.18, I^2 42%, N=3,256, moderate certainty). Six studies (Grossberg 2013, Peskind 2006, Porsteinsson 2008, Reisberg 2003, Tariot 2004, van Dyck 2007) reported an improvement in the memantine group in global functions (CIBIC+: MD -0.24, 95%CI -0.34 – -0.15, I^2 16%, N=2,445, high certainty). Ten studies (Bakchine 2008, Dysken 2014, Fox 2012, Grossberg 2013, Herrmann 2013, Peskind 2006, Porsteinsson 2008, Reisberg 2003, Tariot 2004, van Dyck 2007) reported an improvement in the memantine group in neuropsychiatric symptoms (NPI: MD -1.19, 95%CI -2.16 – -0.22, I^2 61%, N=3,430, moderate certainty). In terms of safety, eight studies (Bakchine 2008, Grossberg 2013, Herrmann 2013, Peskind 2006, Porsteinsson 2008, Reisberg 2003, Tariot 2004, van Dyck 2007) reported no differences between groups in the risk of withdrawal due to adverse events in the memantine group compared to placebo (RR 1.24, 95%CI 0.90 – 1.72, I^2 49%, N=3,358, low certainty).

Seven studies (Bakchine 2008, Dysken 2014, Herrmann 2013, Peskind 2006, Peters 2015, Porsteinsson 2008, Wilkinson 2012) investigated the safety and efficacy of memantine in people with mild to moderate AD. Four (Bakchine 2008, Dysken 2014, Peskind 2006, Porsteinsson 2008) reported no differences between groups in cognitive functions measured with ADAS-Cog (SMD -0.03, 95%CI -0.19 – 0.13, I2 0%, N=619, moderate certainty). Two studies (Porsteinsson 2008, Wilkinson 2012) reported no differences between groups in the same outcomes measured with MMSE (MD 0.36, 95%CI -0.54 – 1.26, I^2 0%, N=385, moderate certainty). Four studies (Bakchine 2008, Peskind 2006, Peters 2015, Porsteinsson 2008) reported no differences between groups in functional abilities (ADCS-ADL: MD -0.03, 95%CI -1.05 – 0.99, I^2 0%, N=1,412, moderate certainty). Two (Peskind 2006, Porsteinsson 2008) reported no differences between groups in global functions (CIBIC+: MD -0.18, 95%CI -0.45 – 0.10, I^2 75%, n = 820, low certainty). Five studies (Bakchine 2008, Dysken 2014, Herrmann 2013, Peskind 2006, Porsteinsson 2008) reported no differences between groups in neuropsychiatric symptoms (NPI: MD -0.04, 95%CI -1.72 – 1.64, I^2 23%, N=1,517, moderate certainty). In terms of safety, four studies (Bakchine 2008, Herrmann 2013, Peskind 2006, Porsteinsson 2008) reported no differences between groups in the risk of withdrawal due to adverse events in the memantine group compared to placebo (RR 1.45, 95%CI 0.89 – 2.35, I^2 38%, N=1,675, moderate certainty).

Seven studies (Fox 2012, Grossberg 2013, Homma 2007, Reisberg 2003, Tariot 2004, van Dyck 2007, Wang 2013) investigated the safety and efficacy of memantine in people with moderate to severe AD. Three studies (Fox 2012, Reisberg 2003, Wang 2013) reported an improvement in the memantine group compared to placebo in cognitive functions measured with MMSE (MD 0.78, 95%CI 0.15 – 1.39, I^2 0%, N=419, high certainty). Five (Grossberg 2013, Homma 2007, Reisberg 2003, Tariot 2004, van Dyck 2007) reported an improvement in the memantine group compared to placebo in functional abilities (ADCS-ADL: MD 0.91, 95%CI 0.27 – 1.55, I^2 3%, n = 1,844, high certainty). Four (Grossberg 2013, Reisberg 2003, Tariot 2004, van Dyck 2007) reported an improvement in the memantine group in global functions (CIBIC+: MD -0.29, 95%CI -0.39 – -0.18, I^2 0%, N=1,625, high certainty). Five studies (Fox 2012, Grossberg 2013, Reisberg 2003, Tariot 2004, van Dyck 2007) reported an improvement in the memantine group in neuropsychiatric symptoms (NPI: MD -3.00, 95%CI -4.85 – -1.14, I^2 32%, N=835, high certainty). In terms of safety, four studies (Grossberg

2013, Reisberg 2003, Tariot 2004, van Dyck 2007) reported no differences between groups in the risk of withdrawal due to adverse events in the memantine group compared to placebo (RR 1.10, 95%CI 0.69 – 1.77, I^2 62%, N=1,683, low certainty).

Review question 15b

Overall, the systematic review of the literature identified six studies that met the predefined eligibility criteria. Four studies investigated the safety and efficacy of donepezil (Doody 2009, Ozenli 2007, Petersen 2005, Salloway 2004), one study investigated the safety and efficacy of galantamine (Winblad 2008), and one study investigated the safety and efficacy of rivastigmine (Feldman 2007b). No studies were identified investigating the safety and efficacy of memantine in people with MCI.

Donepezil

Overall, four studies (Doody 2009, Ozenli 2007, Petersen 2005, Salloway 2004) investigated the safety and efficacy of donepezil in people with MCI. Participants with MCI were randomized to the treatment with either placebo or donepezil for 24 weeks (Ozenli 2007, Salloway 2004), 48 weeks (Doody 2009), and 24 months with an open label extension up to 36 months (Petersen 2005). Active treatment usually started at an initial dose of 5 mg daily increased up to 10 mg after six weeks. Participants were usually aged 45 to 90 years and had an MMSE score ranging from 24 to 30. A CDR overall score of 0.5 was also required, along with and a Memory Box score of either 0.5 or 1, and no scores > 1. Two studies (Petersen 2005, Salloway 2004) considered among their exclusion criteria the presence of depressive symptoms (HAM-D ≥ 12). All included studies compared the efficacy of donepezil with placebo. One study (Petersen 2005) randomised participants to donepezil, vitamin E, or placebo. In terms of efficacy, three studies (Doody 2009, Petersen 2005, Salloway 2004) reported an improvement in the donepezil group compared to placebo in cognitive functions measured with ADAS-Cog (MD -0.16, 95%CI -0.28 – -0.03, I^2 30%, N=1,531, high certainty). Three studies (Doody 2009, Ozenli 2007, Petersen 2005) reported no differences between groups in the same outcome measured with MMSE (MD 0.14, 95%CI -0.22 – 0.50, I^2 0%, N=1,320, moderate certainty). Two studies (Doody 2009, Petersen 2005) and one study (Petersen 2005) reported no differences between groups in CDR-SB scores (MD -0.08, 95%CI -0.31 – 0.15, I2 0%, N=1,269, moderate certainty) and ADCS-ADL (MD 0.13, 95%CI -1.40 – 1.66, I^2 n.a., N=512, low certainty), respectively. Only one study (Petersen 2005) investigated the efficacy of donepezil on the risk of conversion from MCI to AD. The study reported a lower risk of conversion in the donepezil group at 12 months (HR 0.42, 95%CI 0.24 – 0.76, p=0.004, moderate certainty), 24 months (HR 0.64, 95%CI 0.44 – 0.95, moderate certainty), but not at 36 months (HR 0.80, 95%CI 0.57 – 1.13, moderate certainty). In a subgroup analysis of ApoE ε4 carrier participants, the study reported a lower risk of conversion to AD in the donepezil group at 12, 24 and 36 months (HR 0.66, 95%CI 0.44 – 0.98, low certainty). However, the study concluded not recommending donepezil in ApoE ε4 carriers with MCI as results were based on post-hoc analyses and observed differences, despite statistically significant, could be due to chance.

In terms of safety, two studies (Doody 2009, Salloway 2004) reported a higher risk of adverse events (RR 1.18, 95%CI 1.11 – 1.27, I^2 0%, N=1,048, high certainty) and withdrawal due to adverse events (RR 2.43, 95%CI 1.73 – 3.42, I^2 0%, N=1,090, high certainty) in the donepezil group compared to placebo. Two (Doody 2009, Salloway 2004) reported no differences between groups in the frequency of serious adverse events (RR 1.12, 95%CI 0.77 – 1.63, I^2 0%, N=1,048, moderate certainty), and three studies (Doody 2009, Petersen 2005, Salloway 2004) reported no differences between groups in mortality rate (RR 1.43, 95%CI 0.55 – 3.77, I^2 0%, N=1,552, moderate certainty).

Galantamine

Two RCTs, reported in a single publication (Winblad 2008), investigated the safety and efficacy of galantamine (16-24mg daily). The two 24-month studies enrolled participants aged ≥50 years with MCI presenting with a gradual symptom onset, slowly progressing cognitive decline, a CDR score of 0.5, and an

impairment of daily life activities insufficient to meet the diagnostic criteria for dementia. In terms of efficacy, the two studies reported no differences between groups in cognitive functions measured with ADAS-Cog (MD -0.03, 95%CI -0.12 – 0.06, I^2 43%, N=1,901, low certainty) and in functional abilities measured with ADCS-ADL-MCI (MD 0.30, 95%CI -0.26 – 0.86, I^2 0%, N=1,896, moderate certainty). The two studies d reported no differences between groups in the risk of conversion to dementia at 24 months (study 1: 22.9% galantamine versus 22.6% placebo; study 2: 25.5% galantamine versus 31.2% placebo). In terms of safety, the two studies reported a slightly higher risk of adverse events (RR 1.04, 95%CI 1.00 – 1.07, N=2,048, moderate certainty) and a higher risk of treatment withdrawal due to adverse events (RR 2.20, 95%CI 1.78 – 2.72, I^2 0%, N=2,048, high certainty) in the galantamine group compared to placebo. However, the two studies reported no differences between groups in the risk of serious adverse events (RR 0.99, 95%CI 0.82 – 1.18, N=2,048, moderate certainty) and in mortality rate (RR 1.21, 95%CI 0.83 – 1.77, N=2,048, moderate certainty).

Rivastigmine

Only one study (Feldman 2007b) investigated the safety and efficacy of rivastigmine in people with MCI. Participants were randomized to receive either rivastigmine capsules (3-12mg day) or placebo for 48 months. Based on the original study protocol, the length of the double-blind phase was 36-months. However, since the observed rate of progression to AD was lower than the expected, the protocol was amended to allow for a 12-month extension of the double-blind phase. Participants remained in the double-blind phase until either the end of the study or until receiving a diagnosis of AD. Participants who received a diagnosis of AD could opt for participating in the open-label phase of the study. To be included in the study participants had to be diagnosed with MCI according to the following criteria: cognitive disorders with a CDR score of 0.5 and a New York University delayed paragraph recall test score < 9. No details were included on the onset or progression of the cognitive symptoms of MCI. Participants were excluded if they met the diagnostic criteria for AD or or for depressive disorder (HAM-D < 13). The study reported a mean time to AD diagnosis of 1,318 days (SE, standard error 15.08) in the rivastigmine group (N=508) and 1,289 days (SE 16,28) in the placebo group (N=510). During the study, 88 (17.3%) participants in the rivastigmine group and 109 (21.3%) in the placebo group received a diagnosis of dementia (HR 0.85, 95%CI 0.64 – 1.12, low certainty). In terms of safety, the study reported a slightly higher risk of adverse events (RR 1.03, 95%CI 1.00 – 1.06, I^2 n.a., N=1,014, moderate certainty) and a higher risk of withdrawal due to adverse events (RR 1.84, 95%CI 1.23 – 2.74, I^2 n.a., N=1,014, high certainty) in the rivastigmine group compared to placebo. However, the study d reported no differences between groups in the risk of serious adverse events (RR 0.92, 95%CI 0.76 – 1.11, I^2 n.a., N=1,014, moderate certainty) and in mortality rate (RR 0.71, 95%CI 0.39 – 1.31, I^2 n.a., N=1,014, moderate certainty).

Review question 15c

Overall, the systematic review of the literature identified 45 studies that met the predefined eligibility criteria. Five RCTs assessed the tolerability, safety and efficacy of active immunisation with AN1792 and CAD106, two drugs targeting Aβ.

Overall, 41 studies, reported in 36 publications, assessed the tolerability, safety and efficacy of passive immunisation with different monoclonal antibodies targeting Aβ. The following molecules were investigated in the studies included in the systematic review: AAB-003 (one study), aducanumab (four studies), bapineuzumab (ten studies), crenezumab (five studies), donanemab (four studies), gantenerumab (four studies), GSK933776 (one study), lecanemab (three studies), ponezumab (three studies), solanezumab (six studies).

Four studies investigated the tolerability, safety and efficacy of gosuranemab, semorinemab and tilavonemab, three monoclonal antibodies targeting Tau.

ACTIVE IMMUNOTHERAPY

AN1792

Only one phase-1 RCT (Bayer 2005) and one phase-2a RCT (Gilman 2005) investigated the tolerability, safety and efficacy of AN1792. The phase-1 study (Bayer 2005) enrolled 80 participants (age ≤ 85) with mild to moderate AD (MMSE 14-26) randomized to either AN1792 (four groups treated with ascending doses) (+QS21) or active control (QS21). The study reported a lower level of worsening in the AN1792 group compared to placebo in DAD scores (-14.15 vs -36.42, p=0,002). However, it reported no differences between groups in all the remaining explorative clinical outcomes. The phase 2a study (Gilman 2005) enrolled 352 participants with mild to moderate AD (MMSE 15-26) randomized to either AN1792 225 µg + 50 µg QS-21 or placebo. The study reported 18 cases of meningoencephalitis in the AN1792(+QS-21) group, mainly in the group of treatment responders (72.2%). The study was terminated due to the excessive frequency of meningoencephalitis in the intervention group.

CAD106

Only one phase-1 RCT (Winblad 2012) and two phase-2 RCTs (Farlow 2015, Vandenberghe 2017) investigated the safety and efficacy of CAD106. The phase-1 study (Winblad 2012) investigated the tolerability, safety and efficacy and the Aβ-specific response of CAD106 in 48 participants with mild to moderate AD (MMSE 16-26) randomized either to three subcutaneous injections of CAD106 50µg (cohort 1) or CAD106 150 µg (cohort 2) or to placebo. In terms of safety, two studies (Farlow 2015, Vandenberghe 2017) reported no differences between groups in the frequency of adverse events (RR 0.88, 95%CI 0.41 – 1.90, I^2 54%, N=116), and three studies (Farlow 2015, Vandenberghe 2017, Winblad 2012) reported no differences in the frequency of serious adverse events (RR 1.31, 95%CI 0.32 – 5.43, I^2 58%, N=237).

PASSIVE IMMUNOTHERAPY

AAB-003

Only one phase-1 study (Delnomdedieu 2016) investigated the tolerability, safety and efficacy of ascending doses of AAB-003. The study, including a 1-weeks double-blind phase, followed by a 1-year open-label extension, enrolled 88 participants with mild to moderate AD (MMSE 16-26). The study reported two asymptomatic ARIA-E (Amyloid-Related Imaging Abnormalities-oedema) events in two participants in the AAB-003 (8mg/kg) group (RR 1.43 95%CI 0.07 – 28.56, I^2 n.a., N=88, low certainty), three microhaemorrhages in the AAB-003 group, and one microhaemorrhage in the placebo group (RR 2.57, 95%CI 0.14 – 45.77, I^2 n.a., N=88, low certainty). The study reported no differences between groups in the risk of adverse events (RR 0.83, 95%CI 0.55 – 1.25, I^2 n.a., N=88, low certainty) and serious adverse events (RR 4.86, 95%CI 0.29 – 80.56, I^2 n.a., N=88, low certainty). The study also reported no differences between groups in any of the explorative clinical endpoints.

Aducanumab

Two phase-1 studies (Ferrero 2016, Sevigny 2016) and two phase-3 studies reported in a single publication (Budd Haeberlein 2022) investigated the tolerability, safety and efficacy on both clinical outcomes and amyloid clearance, of aducanumab. The two phase-1 RCTs investigated the effects of ascending doses (up to 60mg/kg) of aducanumab, while the two phase-3 studies investigated the effects of the two fixed doses of 6mg/kg (3mg/kg in ApoE ε4 carriers) and 10mg/kg (6mg/kg in ApoE ε4 carriers). Only participants meeting the diagnostic criteria for mild AD or MCI (MMSE 24-30) with evidence of amyloid pathology were included. In terms of efficacy, studies reported no differences between groups in the CDR-SB scores (MD -0.21, 95%CI -0.46 – 0.05, I^2 0%, N=3,449, low certainty). The CDR-SB scale was considered as an explorative outcome in one phase-1 RCT (Sevigny 2016), and as the primary outcome at 78 weeks in the two phase-3 RCTs (Budd

Haeberlein 2022). One phase-1 study (Sevigny 2016) reported a dose-dependent slowing of the progression of cognitive symptoms measured with CDR-SB ($p<0.05$), especially in the 10mg/kg group ($p<0.05$ vs placebo). One of the two phase-3 RCTs (Bud Haeberlein 2022) reported a significant difference in CDR-SB scores between the 10mg/kg group and placebo (MD -0,39, 95%CI -0.78 – 0.00, I^2 n.a., N=1,638, low certainty). However, the second RCT reported no differences between groups in the same outcome (MD 0.03, 95%CI -0.34 – 0.40, I^2 n.a., N=1,647, very low certainty). In terms of amyloid clearance measured with amyloid PET, four RCTs (Budd Haeberlein 2022, Ferrero 2016, Sevigny 2016) reported higher levels of Aβ clearance in the treated group, irrespective of the dose, compared to placebo (SMD -1.73, 95%CI -2.16 – -1.30, I^2 77%, N=865, very low certainty). In terms of safety, four studies (Budd Haeberlein 2022, Ferrero 2016, Sevigny 2016) reported no differences between groups in the frequency of adverse events (RR 1.10, 95%CI 0.92 – 1.32, I^2 92%, N=3,503, very low certainty) and serious adverse events (RR 0.86, 95%CI 0.62 – 1.19, I^2 58%, N=3,503, very low certainty). However, they reported a higher risk of ARIA-E (RR 9.36, 95%CI 6.20 – 14.14, I^2 10%, N=3,503, low certainty) and ARIA-H (RR 2.73, 95%CI 2.15 – 3.46, I^2 0%, N=3,503, moderate certainty) in the treated group compared to placebo. In the two phase-3 RCTs (Budd Haeberlein 2022), the analyses stratified for ApoE ε4 carriers reported a higher risk in the 10mg/kg group vs placebo of ARIA-E in homozygotes (RR 20.89, 95%CI 9.43 – 46.27, N=377, low certainty) and heterozygotes (RR 19.29, 95%CI 10.34 – 36.01, N=1,108, low certainty) compared to ApoE ε4 non carriers (RR 5.19, 95%CI 2.93 – 9.20, N=701, low certainty).

Bapineuzumab

Overall, 10 RCTs (Arai 2016, Black 2010, Brody 2016, Lu 2018, Rinne 2010, Salloway 2009, Salloway 2014, Vandenberghe 2016), of which four phase-3 RCTs reported in two publications (Salloway 2014, Vandenberghe 2016), investigated the tolerability, safety and efficacy on both clinical outcomes and amyloid clearance, of bapineuzumab. Only participants with a diagnosis of mild to moderate AD (MMSE 16-26) were included. None of the studies required confirmation of amyloid pathology except for one phase-2 study (Brody 2016). Two phase-3 RCTs (Vandenberghe 2016) investigated the safety and efficacy of bapineuzumab separately in ApoE ε4 carriers and non-carriers. Included studies investigated the safety and efficacy of intravenous (IV) and subcutaneous (SC) bapineuzumab. In terms of clinical efficacy, four RCTs (Salloway 2014, Vandenberghe 2016) reported no differences between groups in any of the considered outcomes, including CDR-SB scores (MD 0.00, 95% CI -0.23 – 0.23, I^2 0%, n = 4,121, moderate certainty). Four RCTs (Salloway 2014, Vandenberghe 2016) investigated the efficacy of bapineuzumab-IV on amyloid clearance measured with amyloid PET. The four studies reported a higher level of amyloid clearance in the bapineuzumab group compared to placebo (SMD -0.36, 95%CI -0.62 – -0.10, I^2 1%, N=253, low certainty). One RCT (Brody 2016) on bapineuzumab-SC reported no differences between groups in amyloid clearance (SMD -0.18, 95%CI -0.58 – 0.21, I^2 0%, N=138, low certainty). In terms of safety, eight studies (Arai 2016, Black 2010, Rinne 2010, Salloway 2009, Salloway 2014, Vandenberghe 2016) reported no differences in the risk of adverse events between bapineuzumab-IV and placebo (RR 0.98, 95%CI 0.91 – 1.06, I^2 65%, N=4,733, very low certainty). Two RCTs (Brody 2016, Lu 2018) reported no differences in the risk of adverse events between bapineuzumab-SC and placebo (RR 1.39, 95%CI 0.73 – 2.62, I^2 65%, N=186, very low certainty). Nine studies (Arai 2016, Black 2010, Lu 2018, Rinne 2010, Salloway 2009, Salloway 2014, Vandenberghe 2016) reported a higher risk of serious adverse events (RR 1.16, 95%CI 1.03 – 1.30, I^2 0%, N=4,955, moderate certainty) in the bapineuzumab-IV group compared to placebo. Five studies (Salloway 2009, Salloway 2014, Vandenberghe 2016) reported a higher risk of ARIA-E (RR 20.39, 95%CI 4.93 – 84.34, I^2 67%, N=4,664, very low certainty) in bapineuzumab-IV group compared to placebo.

Crenezumab

Five RCTs, of which one phase-1 (Guthrie 2020), two phase-2 (Cummings 2018, Salloway 2018), and two phase-3 (Ostrowitzki 2022), investigated the tolerability, safety and efficacy on both clinical outcomes and amyloid clearance, of crenezumab. Three studies enrolled participants with a diagnosis of mild to moderate

AD (MMSE 18-28) (Cummings 2018, Guthrie 2020, Salloway 2018) while two studies, reported in a single publication (Ostrowitzki 2022), enrolled participants with a diagnosis of MCI due to AD or mild AD. All studies except for one (Cummings 2018) only included participants with a diagnosis of AD supported by evidence of amyloid pathology based on amyloid PET or CSF. Included studies investigated the safety and efficacy of both intravenous (IV) and subcutaneous (SC) crenezumab. When considering crenezumab-IV, three studies (Cummings 2018, Ostrowitzki 2022) reported no differences between groups in all considered outcomes, including CDR-SB (MD -0.26, 95%CI -1.01 – 0.48, I^2 50%, N=450). Only one phase-2 RCT (Cummings 2018) investigated the efficacy of crenezumab-SC and reported no differences between groups in CDR-SB scores (MD -0.69, 95%CI -1.56 – 0.18, I^2 n.a., N=184, low certainty). When considering amyloid clearance, four RCTs (Cummings 2018, Ostrowitzki 2022, Salloway 2018) reported no differences between groups in amyloid clearance measured with PET for both crenezumab SC (MD -0.01, 95%CI -0.15 – 0.13, I^2 n.a., N=34, very low certainty) and IV (SMD -0.07, 95%CI -0.28 – 0.13, I2 0%, N=381, very low certainty). In terms of safety, four studies (Cummings 2018, Ostrowitzki 2022, Salloway 2018) reported no differences between groups in the frequency of adverse events for both crenezumab IV (RR 1.01, 95%CI 0.97 – 1.06, I^2 0%, N=1,985, moderate certainty) and crenezumab SC (RR 1.01, 95%CI 0.94 – 1.08, I^2 0%, N=223, moderate certainty). Five studies (Cummings 2018, Guthrie 2020, Ostrowitzki 2022, Salloway 2018) reported no differences between groups in the frequency of serious adverse events (RR 1.11, 95%CI 0.89 – 1.38, I^2 0%, N=2,210, moderate certainty). Five studies also reported no differences between groups in the frequency of ARIA-E (RR 1.20, 95%CI 0.15 – 9.70, N=1,860, very low certainty) and ARIA-H (IV: RR 0.82, 95%CI 0.42 – 1.61, I^2 0%, N=376, low certainty; SC: RR 1.14, 95%CI 0.29 – 4.54, I^2 30%, N=223, very low certainty).

Donanemab

Overall, four studies, of which two phase-1 (Lowe 2021a, Lowe 2021b), one phase-2 (Mintun 2021), and one phase-3 (Sims 2023), investigated the tolerability, safety and efficacy on both clinical outcomes and amyloid clearance, of donanemab. Included studies only enrolled participants with a diagnosis of mild to moderate AD or MCI and evidence of amyloid pathology measured with amyloid PET. The phase-2 and phase-3 studies (Mintun 2021, Sims 2023) only enrolled participants with a positive Tau PET with quantitative levels below a predefined threshold. These criteria were based on the hypothesis that treatments targeting amyloid may have limited efficacy in case of extensive tau pathology.

Two RCTs (Mintun 2021, Sims 2023) reported an improvement in the intervention group compared to placebo in the primary endpoint, the iADRS composite score (MD 3.06, 95%CI 1.70 – 4.42, I^2 0%, N=1,855, moderate certainty). These two studies reported also reported an improvement in the treated group in other secondary clinical endpoints (CDR-SB: MD -0.60, 95%CI -0.90 – -0.29, I^2 30%, N=1,527, moderate certainty; MMSE: MD 0.49, 95%CI 0.10 – 0.88, I^2 0%, N=1,993, low certainty; ADCS-iADL: MD 1.66, 95%CI 0.81 – 2.51, I^2 0%, N=1,862, low certainty). When considering amyloid clearance, two studies (Mintun 2021, Sims 2023) reported higher levels of amyloid clearance in the intervention group compared to placebo (MD -87.29, 95%CI -90.67 – -83.92, I^2 0%, N=1,810, moderate certainty). In terms of safety, three studies (Lowe 2021a, Mintun 2021, Sims 2023) reported a higher frequency of adverse events (RR 1.04, 95%CI 0.96 – 1.13, I^2 55%, N=1,983, very low certainty), but not of serious adverse events (RR 1.08, 95%CI 0.89 – 1.32, I^2 0%, N=2,032, low certainty) in the intervention group compared to placebo. Two studies (Mintun 2021, Sims 2023) reported a higher frequency of ARIA-E (RR 13.63, 95%CI 8.51 – 21.84, I^2 2%, N=1,984, low certainty) and ARIA-H (RR 2.85, 95%CI 2.11 – 3.86, I^2 7%, N=2,040, moderate certainty) in the intervention group compared to placebo. When stratifying for ApoE ε4 genotype, the risk of ARIA-E remained higher in the treated group compared to placebo in both non-carriers (RR 16.51, 95%CI 4.65 – 58.56, I^2 0%, N=573, very low certainty) and carriers (heterozygotes: RR 12.81, 95%CI 6.68 – 24.54, I^2 0%, N=1,060, low certainty; homozygotes: RR 11.92, 95%CI 5.32 – 26.71, I^2 0%, N=342, very low certainty) (Mintun 2021, Sims 2023). The risk of ARIA-H also remained higher in the treated group compared to placebo in both non-carriers (RR 1.68, 95%CI 1.09 –

2.68, I^2 n.a., N=505, low certainty) and carriers (heterozygotes: RR 2.69, 95%CI 2.03 – 3.55, I^2 n.a., N=926, low certainty; homozygotes: RR 2.45, 95%CI 1.71 – 3.51, I^2 n.a., N=289, very low certainty) (Sims 2023).

Gantenerumab

Three studies, of which one phase 1 (Ostrowitzki 2012) and three phase 3, reported in two publications (Bateman 2023, Ostrowitzki 2017), investigated the tolerability, safety and efficacy on both clinical outcomes and amyloid clearance, of gantenerumab. The phase-3 studies investigated the efficacy on clinical outcomes of two doses (105mg or 225mg) of subcutaneous (SC) gantenerumab administered every four weeks for 104 weeks (Ostrowitzki 2017), or of a target dose of 510mg of gantenerumab SC administered every two weeks for 116 weeks (Bateman 2023). The studies reported no differences between groups in the primary clinical outcome, CDR-SB (MD -0.12, 95%CI -0.35 – 0.12, I^2 0%, N=2,748, moderate certainty). When considering amyloid clearance, the two studies reported no differences between groups in amyloid clearance for both gantenerumab IV (60mg and 200mg IV: SMD -0.93, 95%CI -2.15 – 0.29, I^2 0%, N=16, very low certainty) (Ostrowitzki 2012) and gantenedumab SC (SC: SMD -1.68, 95%CI -3.39 – 0.03, I^2 97%, N=271, very low certainty) (Bateman 2023, Ostrowitzki 2017). In terms of safety, the two phase-3 studies (Bateman 2023, Ostrowitzki 2017) reported no differences between groups in the frequency of adverse events (RR 1.00, 95%CI 0.93 – 1.07, I^2 87%, N=2,756, low certainty). The two studies reported a lower frequency of serious adverse events in the treatment group compared to placebo (RR 0.84, 95%CI 0.70 – 0.99, I^2 0%, N=2,756, moderate certainty). However, they reported a higher risk of ARIA-E (RR 9.31, 95%CI 6.37 – 13.60, I^2 0%, N=2,649, moderate certainty) and ARIA-H (RR 1.75, 95%CI 1.43 – 2.13, I^2 14%, N=2,736, moderate certainty) in the treatment group compared to placebo. When stratifying for ApoE ε4 genotype, the risk of ARIA-E remained higher in the treated group compared to placebo in both non-carriers (RR 4.20, 95%CI 2.23 – 7.90, I^2 0%, N=881, low certainty) and carriers (heterozygotes: RR 12.45, 95%CI 6.72 – 23.09, I^2 0%, N=1,369, low certainty; homozygotes: RR 10.34, 95%CI 5.06 – 21.14, I^2 0%, N=330, low certainty) (Bateman 2023, Ostrowitzki 2017).

GSK933776

Only one phase-1 study (Andreasen 2015) investigated the tolerability, pharmacokinetic and pharmacodynamic of GSK933776 in 50 participants with mild AD or MCI (MMSE 18-26). The study consisted of two phases, a first phase where a single dose of GSK933776 was administered to participants with MCI, and a second phase where repeated doses of GSK933776 IV (6 mg/kg) were administered only in participants with mild AD. No ARIA-E and ARIA-H events were observed in either of the two phases. The study reported no data on cognitive symptoms, functional abilities and global functions.

Lecanemab

Three RCTs (Logovinsky 2016, Swanson 2021, van Dyck 2022), of which one phase-2b (Swanson 2021) and one phase-3 (van Dyck 2022) investigated the tolerability, safety and efficacy, on both clinical outcomes and amyloid clearance, of lecanemab. One RCT (Logovinsky 2016) enrolled participants with a diagnosis of mild to moderate AD (MMSE 16-28) without evidence of amyloid pathology, while the remaining two RCTs (Swanson 2021, van Dyck 2022) enrolled participants with a diagnosis of mild AD or MCI due to AD. The phase-2b study (Swanson 2021) reported no differences between groups in CDR-SB scores in a pooled analysis of all investigated doses (2.5mg/kg – 10mg/kg biweekly) (MD -0.17, 95%CI -0.56 – 0.22, I^2 0%, N=776, moderate certainty). The phase-3 study (van Dyck 2022) reported a better performance of the lecanemab 10mg/kg group compared to placebo in the same outcome, CDR-SB scores (aMD -0.45, 95%CI -0.63 – -0.22, I^2 n.a., N=1,734, high certainty). It also reported a better performance in secondary outcomes, ADAS-Cog14 (aMD -1.44, 95%CI -2.27 – -0.61, I^2 n.a., N=1,734, moderate certainty), ADCOMS (aMD -0.050, 95%CI -0.074 – -0.027, I^2 n.a., N=1,734, moderate certainty) and ADCS-MCI-ADL (aMD 2.00, 95%CI 1.20 – 2.80, I^2 n.a., N=1,734, moderate certainty). When considering clearance, two studies (Swanson 2021, van Dyck 2022)

reported a higher clearance in the intervention group compared to placebo of amyloid burden measured with amyloid PET (Standardized Uptake Value ratio, SUVr: SMD -1.59, 95%CI -2.15 – -1.04, I^2 74%, N=315, very low certainty; Centiloids: MD -59,12, 95%CI -62.64 – -55.60, N=698, high certainty). In terms of safety, three studies (Logovinsky 2016, Swanson 2021, van Dyck 2022) reported a higher frequency of adverse events in the lecanemab group compared to placebo (RR 1.05, 95%CI 1.00 – 1.11, I2 49%, N=2,649, very low certainty). Two studies reported no differences between groups in the frequency of serious adverse events (RR 1.02, 95%CI 0.66 – 1.56, I^2 77%, N=2,649, very low certainty). Two studies (Swanson 2021, van Dyck 2022) reported a higher frequency in the intervention group compared to placebo of ARIA-E (RR 7.66, 95%CI 4.66 – 12.59, I^2 0%, N=2,649, low certainty) and ARIA-H (RR 1.89, 95%CI 1.50 – 2.37, I2 0%, N=2,733, moderate certainty). When stratifying for ApoE ε4 genotype, the risk of ARIA-E remained higher in the treated group compared to placebo in both non-carriers (ARIA-E: RR 13.13, 95%CI 2.55 – 67.72, I^2 n.a., N=800, very low certainty; ARIA-H: RR 2.83, 95%CI 1.49 – 5.36, I2 n.a., N=534, moderate certainty) and carriers (ARIA-E: RR 6.92, 95%CI 4.15 – 11.54, I^2 n.a., N=1,820, low certainty; ARIA-H: RR 1.74, 95%CI 1.33 – 2.29, I^2 n.a., N=1,231, moderate certainty).

Ponezumab

Three RCTs (Landen 2013, Landen 2017a, Landen 2017b) investigated the tolerability, safety and efficacy, on both clinical outcomes and amyloid removal, of ponezumab in people with mild to moderate AD (MMSE 16-26). One study (Landen 2017b) including three treatment arms (cohort Q, cohort M, placebo) reported no differences between groups in cognitive functions. All included studies reported no differences between groups in all considered clinical outcomes. In terms of safety, the three studies (Landen 2013, Landen 2017a, Landen 2017b) reported a lower frequency of adverse events in the intervention group compared to placebo (RR 0.92, 95%CI 0.87 – 0.97, I^2 0%, N=267, moderate certainty). However, they reported a higher frequency of serious adverse events in the intervention group compared to placebo (RR 2.58, 95%CI 1.25 – 5.33, I^2 0%, N=267, moderate certainty). One study (Landen 2017b) reported no differences between groups in the frequency of ARIA-E (RR 0.99, 95%CI 0.04 – 23.46, I^2 n.a., N=99, very low certainty), and two studies (Landen 2017a, Landen 2017b) reported no differences between groups in the frequency of ARIA-H (RR 0.58, 95%CI 0.27 – 1.25, I^2 0%, N=230, low certainty).

Solanezumab

Five studies (Doody 2014, Honig 2018, Siemers 2010, Uenaka 2012), of which three phase-3 studies reported in two publications (Doody 2014, Honig 2018), investigated the tolerability, safety and efficacy, on both clinical outcomes and amyloid clearance, of solanezumab. All studies enrolled participants with a diagnosis of mild to moderate AD (MMSE 15-26), except for one phase-3 RCT (Honig 2018) enrolling only participants with a diagnosis of mild AD and evidence of amyloid pathology measured with amyloid PET or CSF. The three phase-3 RCTs (Doody 2014, Honig 2018) reported better CDR-SB scores in the intervention group compared to controls (MD -0.29, 95%CI -0.54 – -0.04, I^2 8%, N=4,181, low certainty). However, the significance of this results was due to only one study (Honig 2018) considering CDR_SB as a descriptive secondary outcome (CDR-SB: MD -0.34, 95%CI -0.63 – -0.05, I^2 n.a., N=2,129, low certainty). None of the phase-3 studies reported differences between groups in the considered clinical outcomes in both the mild AD and moderate AD subgroups. One phase-3 RCT (Honig 2018) reported no differences between groups in amyloid clearance measured with amyloid PET (SMD -0.07, 95%CI -0.17 – 0.03, I^2 n.a., N=1,596, low certainty). In terms of safety, one study reported no differences between groups in the frequency of adverse events (RR 1.01, 95%CI 0.98 – 1.05, I^2 0%, N=2,121, moderate certainty) (Honig 2018). Four studies (Doody 2014, Honig 2018, Siemers 2010, Uenaka 2012) reported no differences in the frequency of serious adverse events (RR 0.94, 95%CI 0.84 – 1.05, I^2 0%, N=4,208, moderate certainty). Two studies reported no differences in the frequency of ARIA-E (RR 1.56, 95%CI 0.45 – 5.47, I^2 16%, N=4,181, low certainty) and ARIA-H (RR 1.01, 95%CI 0.72 – 1.43, I^2 26%, N=4,181, low certainty).

PASSIVE IMMUNOTHERAPY TARGETED AGAINST DIFFERENT FORMS OF TAU

Gosuranemab

One phase-2 study (Shulman 2023) investigated the safety and efficacy of three doses (low dose, 125mg every four weeks or 375mg every 12 weeks; intermediate dose, 600mg every four weeks; high dose, 2.000mg every four weeks) of gosuranemab in 650 participants with AD or MCI due to AD (MMSE 22-30). The study reported no differences between groups in its secondary cognitive outcome, CDR-SB (low dose, MD 0.35, 95%CI -0.25 – 0.95, I^2 n.a., N=187, low certainty; intermediate dose, MD 0.39, 95%CI -0.22 – 1.00, I^2 n.a., N=177, low certainty; high dose, MD 0.00, 95%CI -0.73 – 0.73, I^2 n.a., n=286, low certainty). In terms of safety, the study reported no differences between groups in the frequency of adverse events (RR 1.03, 95%CI 0.97 – 1.11, I^2 n.a., N=650, low certainty) and serious adverse events (RR 0.94, 95%CI 0.61 – 1.47, I^2 n.a., N=650, very low certainty).

Semorinemab

One phase-2 RCT (Teng 2022) investigated the safety and efficacy of three doses (1,500mg; 4,500mg; 8,100mg) of semorinemab in 422 participants with AD or MCI due to AD (MMSE 20-30). The study reported no significant differences between any dose of semorineman and placebo in CDR-SB scores (MD 0.19, 95%CI -0.19 – 0.57, I^2 0%, N=422, moderate certainty). The study reported no differences between any dose of semorineman and placebo in Tau clearance (1.500mg: MD 0.00, 95%CI -0.10 – 0.10, I^2 n.a., N=117, low certainty; 4.500mg: MD 0.00, 95%CI -0.09 – 0.09, I^2 n.a., N=143, low certainty; 8.100mg: MD 0.02, 95%CI -0.10 – 0.14, I^2 n.a., N=115, moderate certainty). In terms of safety, the study reported no differences between groups in the frequency of adverse events (RR 0.99, 95%CI 0.85 – 1.16, I^2 n.a., N=441, low certainty) and serious adverse events (RR 1.42, 95%CI 0.81 – 2.50, I2 n.a., N=441, very low certainty).

One phase-2 study (Monteiro 2023) investigated the safety and efficacy of 4,500mg of semorinemab administered every four weeks for either 48 or 61 weeks in 272 participants with mild to moderate AD (MMSE 16-21). The study two primary outcomes: ADAS-Cog11 and ADCS-ADL. The study reported a significant difference between groups in ADAS-Cog11 scores at both 48 weeks (MD -2.89, 95% CI -4.56 – -1.21, I^2 n.a., n = 198, low certainty), and 61 weeks (MD -2.75, 95% CI -5.31 – -0.20, I^2 n.a., n = 68, low certainty). The study reported no differences between groups in ADCS-ADL scored at both 48 weeks (MD -0.83, 95%CI -3.39 – 1.72, I^2 n.a., N=208, low certainty) and 61 weeks (MD -1.72, 95%CI -5.50 – 2.07, I^2 n.a., N=73, low certainty). It also reported no differences between groups at both 48 and 61 weeks in CDR-SB scores (MD 0.26, 95%CI -0.29 – 0.82, I^2 n.a., N=210, low certainty; MD 0.17, 95%CI -0.87 – 1.22, I^2 n.a., N=73, low certainty) and MMSE (MD 0.27, 95%CI -0.58 – 1.11, I^2 n.a., N=202, low certainty; MD 1.08, 95%CI -0.15 – 2.30, I^2 n.a., N=68, low certainty). The study reported no differences between groups in Tau clearance measured with Tau PET (MD 0.00, 95%CI -0.02 – 0.02, I^2 n.a., N=188, low certainty). In terms of safety, the study reported no differences between groups in the frequency of adverse events (RR 1.02, 95%CI 0.91 – 1.14, I^2 n.a., N=267, low certainty) and serious adverse events (RR 0.98, 95%CI 0.58 – 1.65, I^2 n.a., N=267, very low certainty).

Tilavonemab

One phase-2 RCT (Florian 2023) investigated the safety and efficacy of three doses (300mg; 1,000mg; 2,000mg) of tilavonemab in 453 participants with mild AD or MCI due to AD (MMSE 22-30). The study reported no differences between any dose of tilavonemab and placebo in CDR-SB scores (300 mg: MD -0.07, 95%CI -0.83 – 0.69, I^2 n.a., N=85, low certainty; 1,000 mg: MD -0.06, 95%CI -0.81 – 0.68, I^2 n.a., N=91, low certainty; 2,000 mg: MD 0.16, 95%CI -0.60 – 0.93, I^2 n.a., N=81, low certainty). In terms of safety, the study no differences between groups in the frequency of adverse events (RR 0.98, 95%CI 0.92 – 1.04, I^2 n.a., N=453, moderate certainty), serious adverse events (RR 0.77, 95%CI 0.51 – 1.16, I^2 n.a., N=453, moderate certainty) and withdrawal due to adverse events (RR 1.38, 95%CI 0.47 – 4.03, I^2 n.a., N=453, very low certainty).

Analysis of evidence

Review question 15a

The acetylcholinesterase inhibitors (AChEIs) donepezil, galantamine and rivastigmine, and memantine, an NMDA receptor antagonist, are currently the only approved pharmacological treatment for cognitive symptoms of Alzheimer's dementia (AD). Drugs for the treatment of cognitive symptoms of AD are an extremely useful resource for specialists in the management on cognitive symptoms of dementia. The prescription of a pharmacological treatment for AD should be part of a structured care plan that should start with a timely diagnosis and appropriate definition of the dementia subtype, considering that AChEIs are more effective in the mild stage of the disease.

The systematic review identified many studies investigating the safety and efficacy of AChEIs and memantine compared to placebo.

Despite the known efficacy of AChEIs and memantine in the treatment of cognitive symptoms of AD, evidence was stratified according to disease severity.

The outcomes considered as relevant for the review included cognitive (ADAS-Cog, MMSE), functional (ADCS-ADL) and global (CIBIC+) measures, neuropsychiatric symptoms (NPI), and safety (treatment withdrawal due to adverse events). Most of the included studies investigated the efficacy of AChEIs and memantine using MMSE as their primary outcome. However, considering that MMSE is a tool that was originally designed for the initial assessment of global cognitive functions, thus less sensitive to changes in the more specific cognitive domains, the assessment should always be contextualised in a wider specialistic evaluation allowing for a more specific definition of the stage of the disease. The decision to continue the treatment with AChEIs or memantine even in the later stages of the disease needs to be reassessed based on clinical judgement, accounting for all possible benefits and risks. Moreover, the MMSE alone might not be sensible enough to identify the severity of dementia in people with AD and learning disabilities, sensory deficits, or language or communication difficulties, even due to low educational level or lack of an adequate understanding of the language of the test. On this basis, the WG confirmed the recommendation from the NICE guideline (GL) to start or continue treatment with AChEIs or memantine based on a clinical judgement including a global evaluation of the health status of people with AD.

Overall, 55 studies were included investigating the efficacy and safety of AChEIs and memantine. Evidence reported that donepezil, galantamine, and rivastigmine are effective on cognitive, functional, and global outcomes in people with AD, while evidence on memantine was less certain. Most uncertainties were due to the lack of long-term data, as included studies mainly had a 6-month follow up and only a few of them reached 1 year of follow-up. The lack of studies with longer follow up did not allow adequately assessing long-term outcomes such as the effect of treatment on quality of life, time to institutionalisation, mortality rate.

Currently available evidence showed that donepezil, mainly at a dose of 10 mg per day, improves cognitive symptoms, functional abilities, and global functioning, and has a positive effect on behavioural symptoms. However, most studies had a 6-month follow up, with few of them reaching one year of follow up. The AD 2000 study (Courtney 2004), with three years of follow up, should be considered separately as it is the longest study performed on people with AD treated with AChEIs. Moreover, this study is also one of the few published studies that considered the risk of institutionalisation as its primary outcome. The study also assessed the effect of donepezil on disability, dependence, behavioural disorders, and caregivers' wellbeing. Participants were maintained in the double-blind phase until considered appropriate by clinicians. No long-term differences were reported between groups in progression of disability and time to institutionalisation. Authors underlined that people treated with donepezil, despite showing a significant improvement in clinical scores such as MMSE and ADL during the first 12 weeks of treatment, showed a similar disease progression

in time as people on placebo. Therefore, evidence support the short-term efficacy of donepezil on cognitive symptoms and functional abilities, but do not indicate a long-term efficacy of this treatment. The AD 2000 study concluded that participants who received donepezil showed statistically significant improvements that were however not clinically relevant, questioning the cost-effectiveness profile of the drug.

Available evidence, when stratified according to disease severity, supported the efficacy of donepezil in improving cognitive, functional, global and behavioural outcomes in people with mild to moderate AD, and in improving cognitive, functional, and global outcomes in people with moderate to severe AD. In terms of safety, donepezil has mainly been associated with side effects related to its increased cholinergic activity, potentially causing nausea and diarrhoea. Included studies only considered the risk of discontinuation due to adverse events, which was higher in the intervention group compared to placebo and remained significantly higher even when stratifying for disease severity.

Pooled estimates from studies on the efficacy of 16 to 36 mg day of galantamine in people with AD reported a significant improvement in the intervention group of cognitive functions, global outcomes, and behavioural symptoms, but not on functional abilities. None of the included studies had a follow up longer than six months, thus limiting any consideration on the long-term efficacy of the treatment. No long-term studies similar to AD2000 were identified aiming at analysing the cost-effectiveness of galantamine on long-term outcomes such as institutionalisation. Most of the available studies on galantamine enrolled people with mild to moderate AD. Galantamine in this population was reported as improving cognitive symptoms, functional abilities, global functions, and behavioural symptoms. One single study enrolled people with severe AD (MMSE 5-12) reporting that the treatment was safe and potentially effective. However, evidence was of limited certainty mainly due to the lack of further studies supporting these results. Treatment with galantamine, as for donepezil, was associated to a higher risk of cholinergic events. The frequency of withdrawal due to adverse events was higher in the intervention group compared to placebo.

Included studies reported data on treatment with both rivastigmine capsules and transdermal patch. Rivastigmine is the only symptomatic treatment for AD for which a transdermal patch is available. Rivastigmine capsules were reported as effective in improving cognitive symptoms, functional abilities, and global functions, but not in improving behavioural disorders. Results on the efficacy and safety of rivastigmine capsules were similar when stratifying for disease severity. No evidence was identified supporting the use of rivastigmine capsules in people with moderate to severe AD. Rivastigmine patch (10 m^2 and 20 m^2) was tested with the aim of improving compliance and reducing the burden on caregivers, who are usually responsible for the appropriate and regular administration of pharmacological treatments in the care process. Results from included studies on rivastigmine patch reported an improvement in the intervention group compared to control in cognitive symptoms, functional abilities, and global functions, but not in behavioural disorders, in line with rivastigmine capsules. Transdermal patches are an essential tool for specialists, as they can improve compliance, mainly in the advanced phases of the disease, when dysphagia or behavioural disorders can hinder the administration of capsules, thus increasing the burden of caregivers. The improvement of both caregivers' burden and patients' compliance should be counterbalanced by an efficacy on clinical outcomes at least comparable to rivastigmine capsules. One study (Winblad 2007) investigated the comparative efficacy and safety of rivastigmine capsules and transdermal patches (10 m^2 and 20 m^2) reporting a non-inferiority of transdermal patches compared to capsules, with a statistically significant improvement of at least four points in the ADAS-Cog scale compared to placebo after 24 weeks of treatment. The adverse events of rivastigmine are similar to those reported for the other AChEIs, and can be easily managed by specialists, mainly by gradually decreasing the dose. Rivastigmine patch 10 m^2 was not associated with a higher risk of adverse events compared to placebo, and resulted as more tolerable compared to capsules, with a similar efficacy and a higher flexibility compared to capsules (12 mg day). Rivastigmine patch 20 m^2, instead, was associated to a higher risk of adverse events compared to both placebo and rivastigmine capsules.

Studies investigating the safety and efficacy of memantine reported an improvement in the intervention group compared to placebo in ADAS-Cog scores, functional abilities, global functions, and behavioural disorders, but not in MMSE scores, in people with AD at any stage of the disease. The high heterogeneity in results was mainly due to differences in disease severity among enrolled participants. Memantine, in fact, was reported as having little to no effect in people with mild to moderate AD, while it had significant effects on all considered outcomes in people with moderate to severe AD. Overall, in people at any disease stage, memantine was well tolerated and treatment was not associated with an increased risk of adverse events.

In Italy, the prescription of AChEIs and memantine is regulated by Note 85 issued by the Italian Italian Medicine Agency (Agenzia Italiana del Farmaco, AIFA), that allows treatment with AChEIs (donepezil, galantine, rivastigmine) in people with mild to moderate AD, and treatment with memantine in people with moderate to severe AD. However, no assessment tools are available predicting who will respond to treatment, thus AIFA in its Note 85 requires, as a prescription strategy, the assessment of treatment response after 3 months. In case people treated with AChEI or memantine are judged by clinicians as tolerating treatment and responding to it with significant improvements in clinical outcomes, they will be eligible to continue therapy.

As reported in the analysis of evidence and in several real-world studies, AChEIs and memantine have a favourable risk-benefit profile. Memantine is associated to some common adverse effects such as somnolence, dizziness, hypertension, dyspnoea, and headache, and to some less common adverse events such as hallucinations, especially in people with severe AD, and other vascular and gastrointestinal disorders. However, analyses of the risk-benefit profile of memantine did not report a higher risk of withdrawal due to adverse events in people treated to memantine compared to placebo. When considering AChEIs, their cholinergic action can cause adverse effects related to an increased parasympathetic outflow affecting heart rate, with bradycardia and QT prolongation, thus requiring regular ECG monitoring. When prescribing an AChEI, clinician should always assess the full clinical history, especially heart diseases and potential electrolyte unbalances, and carefully evaluate concomitant medications.

Evidence from studies on AChEIs and memantine showed that these drugs have a key role in the symptomatic management of people with AD. However, the effect of these drugs on cognitive symptoms, functional abilities, global functioning, and behavioural disorders should be considered as mild, sometimes not clinically relevant, and short-term. Most of the included studies followed up participants only up to six months. This is extremely relevant, as long-term outcomes, such as institutionalisation, dependence, progression of disability, and mortality were not explored. Only one study investigated the long-term effect of donepezil and reported no differences between treatment and placebo. One further issue was the use of clinical tools (e.g., MMSE and ADAS-Cog) that were not considered sensitive enough to detect changes in the clinical picture.

Review question 15b

The WG analysed available evidence on the efficacy and safety of AChEI for the treatment of Mild Cognitive Impairment (MCI). Results from available studies reported no effect of AChEIs on any of the considered cognitive and functional outcomes, and no reduction in the rate of progression from MCI to AD. The WG underlined that this class of drug, on top of not showing any clinical benefit, especially in terms of slowing disease progression, is also associated with a higher incidence of several adverse events, including gastrointestinal symptoms and heart complications, which should not be underestimated. Included studies investigated the efficacy and safety of all currently available AChEIs, donepezil, galantamine, and rivastigmine. Therefore, the WG agreed to include a recommendation not to offer any AChEI for the treatment of MCI. Moreover, the WG agreed, despite the lack of evidence, to extend to memantine the recommendation not to offer these treatments to people with MCI.

The WG also underlined that analysed studies did not account for the different subtypes of MCI. Therefore, currently available evidence on the efficacy of AChEIs and memantine is insufficient to support their use in the treatment of MCI. The WG emphasised that MCI is a clinical condition characterised by an initial cognitive decline that only in a percentage of cases progresses to dementia, and, despite the large number of studies, no evidence is available identifying specific factors associated to its progression or on specific subtypes of MCI at a higher risk of conversion to dementia. The availability in recent years of more advanced structural and functional neuroimaging techniques as well as plasmatic and CSF tests has allowed the definition of biomarkers that could support both the differential diagnosis of dementia subtypes and the identification of people at a higher risk of developing dementia. However, this approach is currently only indicated for research purposes and within clinical trials. The availability of biomarkers able to define of a prognostic trajectory could allow for a timely management of people with MCI.

Based on these considerations, the WG agreed to include a research recommendation for further studies on the potential efficacy of AChEIs and memantine in specific subtypes of MCI.

Review question 15c

In Italy and in Europe, the use of biological drugs for the treatment of AD is currently limited to research purposes, as no drug in this class has currently received marketing authorisation. Despite the use of these drugs does not currently affect clinical practice, it is a priority issue in public health, which requires to be further explored through a systematic review. Monoclonal antibodies targeting the different forms of Aβ currently appear to be the closest to receive a European regulatory evaluation, while two drugs already received marketing authorisation in the US. The WG discussed the opportunity to also review the evidence for two other classes of drugs: monoclonal antibodies targeted against Tau, and active immunotherapies (vaccines) targeted against Aβ. The WG agreed to include these two categories of drugs in the systematic review of the literature to provide healthcare professionals and people with dementia and their caregivers a comprehensive overview on drugs under research. Moreover, in absence of treatments able to stop or at least delay the progression of the disease, summarising data on drugs that are currently considered as potentially disease-modifying is essential. The WG also discussed the opportunity to include active immunotherapies, even though they are historically the farthest along the spectrum of clinical pharmacology for AD, and the absence of ongoing trials suggesting their availability in clinical practice in the short-medium term. The WG agreed to include evidence on monoclonal antibodies targeted against Tau, even though they are still under investigation, as they are considered the future target of clinical research on anti-AD medications despite less promising results on their efficacy.

Analysed evidence showed that some of the investigated drugs had good target engagement, were able to reduce the burden of abnormal protein aggregates in the brain, mainly the amyloid burden, and caused significant changes in the main biomarkers considered to be typical of AD. However, the WG agreed that the focus had to be their clinical efficacy and safety profile, as these are the most relevant aspect to be considered by health professionals in clinical practice. On this basis, to answer the needs of healthcare professionals, people with dementia and their caregivers, results from available studies were analysed not only considering their statistical significance, but also considering their clinical relevance, including the effectiveness perceived by people treated with these drugs and by their caregivers. The biological efficacy of these drugs was limited to their ability to remove aggregates of the target protein from the brain of people with AD. When discussing evidence, the WG underlined that included studies, especially the most recently published, enrolled participants with progressively earlier stages of disease, from mild to moderate AD to prodromic phases defined as MCI due to AD. This is the consequence of evidence from a growing number of studies suggesting that treatment in AD should be started in the early phases, with some authors even suggesting starting intervention in an asymptomatic phase. However, despite some evidence is currently available from studies on biological drugs, mainly monoclonal antibodies, in people in a clinically asymptomatic phase, where in

absence of clinical symptoms the diagnosis of AD is only based on biological criteria (positivity to some biomarkers), the WG agreed not to consider this evidence.

Recent studies enrolled clinically heterogeneous populations, including people with a clinical diagnosis of AD and people with a diagnosis of MCI along with positive biomarkers for Tau or amyloid pathology. This is due to the changes that were made to the diagnostic criteria for AD during the last 15 years.

The 1984 NINCDS-ADRDA consensus criteria supporting the diagnosis of AD (McKhann 1984), have been, in fact, updated on the basis of new findings about the physiopathology and the relation between molecular pathology and course of the disease leading to the onset of symptoms (National Institute on Aging and Alzheimer's Association-NIA-AA criteria; Sperling 2011, Albert 2011, McKhann 2011). These documents and their subsequent updates report on two series of consensus criteria developed by NIA-AA distinguishing between the Core Clinical Criteria, which can be used in all specialized clinical and care settings without the need to perform advanced tests and/or procedures, and the Clinical Research Criteria, which are to be adopted in and academic and research settings, including clinical trials, and require the use of biomarkers such as neuroimaging and CSF tests.

It is therefore essentially inappropriate to considerthe populations enrolled in the first trials based on exclusively clinical criteria as comparable to those enrolled in the most recent trials. Evidence on drugs that are still under investigation were thus analysed separately from that on drugs that are currently under regulatory assessment. In particular, evidence on two monoclonal antibodies, lecanemab and donanemab, both under regulatory assessment, were discussed separately to analyse data on efficacy and safety that could be potentially specific to a single treatment.

MONOCLONAL ANTIBODIES TARGETED AGAINST THE DIFFERENT FORMS OF Aβ

CONCLUDED/TERMINATED TRIALS

Several included studies reported data on trials that were terminated due to futility (e.g., AAB-003, bapineuzumab, crenezumab, gantenerumab, GSK933776, ponezumab, solanezumab). Some of the investigated drugs showed no clear ability to target both central amyloid depositions and peripheral markers (plasma and CSF). However, some monoclonal antibodies (mAbs) were reported to be able to remove amyloid plaques in different ways and at different levels, without this causing, however, any significant clinical effect. No statistically significant or clinically relevant effects of mAbs on cognitive, functional, and global outcomes were reported. When considering safety, as observed with the first investigated mAb (bapineuzumab) and then with all other mAbs, these drugs can cause Amyloid-Related Imaging Abnormalities (ARIA) that can occur as vasogenic oedemas (ARIA-E) or as microhaemorrhages (ARIA-H).

Only studies on aducanumab reported significant differences between groups in some clinical outcomes, along with a significant reduction of Aβ burden and measured with amyloid PET. Only one of the two phase-3 RCTs (EMERGE) (Budd Haberlein 2022) reported a statistically significant but not clinically relevant effect of the drug on the primary outcome (CDR-SB) and other secondary cognitive and functional outcomes. Evidence was not considered sufficient to consider aducanumab as effective in improving clinical outcomes, considering also its safety profile. In particular, its risk/benefit profile cannot be considered as favourable due to the increased risk of ARIA. ARIA-E and ARIA-H are concerning both for their clinical implications, and when considering the management and monitoring process outside of a controlled setting such as that of an RCT.

ONGOING TRIALS/ONGOING REGULATORY PROCESS

Lecanemab

Lecanemab was investigated in a phase-3 trial (van Dyck 2022) enrolling people with MCI due to AD (62% of enrolled participants), and mild AD (38% of enrolled participants). Inclusion criteria required participants to have evidence of amyloid pathology measured with amyloid PET. Almost half of the enrolled participants were taking concomitant AChEIs or memantine, and 68% was ApoE ε4 carrier (53% in heterozygosis e 15% in homozygosis). Participants in the intervention group received 10 mg/kg of intravenous lecanemab every two weeks. At 18 months, a significantly slower cognitive decline (around 27%) was observed in the intervention group compared to placebo, as measured by CDR-SB, the primary outcome. However, the observed result, althoughstatistically significant, translates to a difference of 0,45 points in the CDR-SB scale, which has a score ranging from 0 to 18 points, and a difference of 1-2,5 points considered as clinically relevant (Andrews 2019, Landsdall 2023). From a clinical point of view, it is essential to consider results as absolute values, rather than relative to placebo. Results also showed a significant difference between groups on other cognitive and functional outcomes, including ADAS-Cog. However, this result was also considered as not clinically relevant, as it was below the 2-5 points difference considered as clinically relevant (Landsdall 2023). Statistically significant differences between groups were also reported for other secondary outcomes, ADCS-ADL-MCI and ADCOMS. However, currently available evidence is insufficient to identify the clinically relevant differences for these scales.

Included studies reported a significant reduction in the intervention group compared to placebo of the amyloid burden measured with amyloid PET. Moreover, some changes in both plasmatic and CSF biomarkers were also consistent with a reduction of the amyloid burden in the treatment group. Participants on lecanemab also reported some changes in the levels of Tau. Participant in the intervention group also showed a significant reduction in brain volume and an increase in ventricular volume. These relevant brain changes should be further investigated to understand the impact of the reduction of brain volume on the health outcomes of people treated with lecanemab. More than 50% of participants in the phase-3 study had two or more comorbidities, and around 4.5% of them was in treatment with anticoagulants. Adjunctive analyses showed that none of the comorbidity subgroup, including obesity, hypercholesterolemia, hypertension, diabetes, and use of anticoagulants, had less benefit from lecanemab compared to placebo. However, further subgroup analyses showed that ApoE ε4 carriers, especially homozygotes, women, and people aged <65 years had less benefit from treatment with lecanemab. These were all post-hoc analyses that were not adjusted for multiple comparisons, thus significance could be due to chance.

Treatment with lecanemab should be closely monitored especially due to its association with a higher frequency of ARIA-E e ARIA-H events, which can occur in almost one out of five people under treatment. Despite these events being often asymptomatic, a notable proportion of them causes clinical symptoms characterised by headache, dizziness, and confusion. Evidence also showed that symptoms of ARIA are not linked to ARIA severity. In fact, clinically asymptomatic ARIA events can be radiologically severe, thus leading to treatment discontinuation. These considerations highlight the complexity of managing ARIA in a clinical practice setting and the subsequent challenges for the National Health System. Moreover, ApoE ε4 carriers show a higher risk of ARIA events. This is especially relevant in a public health perspective as the need to carry out a genetic test before administering lecanemab would require high economic resources from the National Health System. Three deaths were reported during the open label extension of the phase-3 study. One of the deceased participants had received anticoagulant treatment with apixaban, while the other was treated with a plasminogen activator. However, currently available data does not allow limiting the use of anticoagulant in people treated with lecanemab. Some considerations were also raised on the generalizability of results, as studies on lecanemab mainly enrolled participants aged >75 years from the US, with a higher probability of having some comorbidities. Moreover, some ethnicities were underrepresented thus limiting external validity.

Donanemab

The two phase-2 and phase-3 RCTs (Mintun 2021, Sims 2023) investigating the efficacy and safety of donanemab showed some differences in terms of eligibility criteria for enrolling participants. The phase-2 study only enrolled participants with mild AD or MCI due to AD along with a low to medium tau pathology, while the phase-3 study extends the inclusion criteria also to people with a higher level of tau pathology. The phase-3 study also introduced flexible criteria for treatment discontinuation in case of ARIA. Compared to lecanemab, intravenous donanemab was administered every four weeks instead of every two weeks. This is extremely relevant, as longer intervals between the infusions could improve the compliance of participants and caregivers, who would need to visit the infusion centre less frequently.

Participants in the phase-3 RCT, once reaching the threshold levels of amyloid burden established in the protocol, discontinued treatment with donanemab and started placebo while maintaining blindness. After 52 weeks of treatment, almost 50% of participants randomised to donanemab had switched to placebo. Treatment discontinuation based on amyloid clearance could lead to a reduction in costs related to treatment and monitoring, thus a lower burden for people under treatment and their caregivers. However, whether people who discontinued treatment should receive further infusions, and under which conditions, remains unclear. As observed with lecanemab, donanemab has a unique action on amyloid clearance. Despite being reported to have a significant effect on removing amyloid plaques and a moderate effect on clinical, functional, and global outcomes, donanemab has not been proven able to stop disease progression. Clinical trials, in fact, reported a progression of the disease in both treatment arms, with a slightly lower worsening, measured with CDR-SB, in the intervention group compared to placebo. The differences observed in the CDR-SB were similar to those reported in the phase-3 study on lecanemab. However, it is inappropriate to compare the efficacy of these two treatments, as the study on lecanemab did not require among its eligibility criteria the presence of tauopathy as reported by Tau-PET. This difference could lead to some differences in the type of participants included in the studies. Moreover, donanemab seems to delay the progression of the disease of around 4 months, but only in the subgroup with low to medium Tau levels (measured with Tau-PET). The assessment with CDR-SB showed that 47% of participants on donanemab compared to 29% of participants in on placebo remained stable at one year. This finding is important, as it could be considered as clinically and personally relevant by people receiving treatment and their caregivers. However, despite its statistically significant clinical results, treatment with donanemab is associated to relevant safety concerns. Therefore, further considerations in terms of its risk/benefit profile are essential. Subgroup analyses on the entire sample (combined tau population) showed that treatment with donanemab was more effective in the subgroup of participants with low to medium levels of Tau, and less effective in the subgroup of participants ApoE ε4 carriers and in younger participants (<65 years).

Around one out of four participants treated with donanemab reported at least one ARIA event, with a sensibly higher incidence rate compared to lecanemab. This highlights some relevant limitations of these studies, including selection bias. ARIA events are expected to occur in a higher percentage of participants in the intervention arm, as in a real-world context eligible population could be frailer due to a higher number of comorbidities or clinical conditions that would be considered as exclusion criteria in a clinical trial. This implies, as mentioned for lecanemab, a substantial challenge in terms of organisation and resources for the National Health System that should ensure people an adequate and timely diagnosis and management of ARIA. Evidence on donanemab also reported a higher risk in ApoE ε4 carriers of ARIA events, especially ARIA-H.

No differences were observed in terms of efficacy and safety in people receiving antithrombotic treatments. Currently available data do not support limiting the use of donanemab to people who are eligible and not treated with other medications. In conclusion, results from studies on donanemab can have limitations in terms of generalizability. Studies mainly enrolled people in the US and Canada. As some ethnicities were

underrepresented in the study populations, the actual efficacy and safety of the treatment in these subgroups is still unclear.

Further considerations

Some concerns were raised on some methodological aspects of the trials on mAbs targeting amyloid, as study results could have been biased by a possible lack of blindness. In fact, the occurrence of ARIA events could have affected the blindness of both participants and investigators during the evaluation with cognitive tools. ARIA events are adverse events typically occurring during treatment with anti-amyloid mAbs. Therefore, participants and investigators could have guessed the treatment arm based on the occurrence of these easily identifiable episodes, characterised by confusion, headache, and dizziness. This could have caused a functional unblinding that could have biased results. Therefore, designing studies with an adequate methodology to maintain blindness is essential. The best approach to unblinding would be to ensure an equal management and monitoring to both participants in the intervention group and in the placebo group.

Another essential aspect in the management of these drugs from a public health perspective, would be to ensure that different professionals, including neurologists, geriatricians, radiologists and emergency care professionals, develop specific expertise to improve the specific training on adverse events associated to mAbs, in order to prevent severe neurological consequences and minimising the need for further care.

MONOCLONAL ANTIBODIES TARGETED AGAINST THE DIFFERENT FORMS OF TAU

Four RCTs (Florian 2023, Teng 2022, Shulman 2023, Monteiro 2023) investigated the efficacy and safety of the monoclonal antibodies gosuranemab, tilavonemab and semorinemab targeted against the different forms of Tau. The three investigated molecules are humanised mAbs targeted against the Tau N-terminal domain, binding also the different isoforms of Tau protein (including insoluble aggregate and phosphorylated specie). The four RCTs included participants with a diagnosis of MCI due to AD, mild AD, or mild to moderate AD based on standardised criteria, and a positive PET with radiotracer for Tau. None of the included studies reported an effect of these drugs on cognitive, functional and global outcomes. None of the investigated mAbs was reported as having a target engagement effect against Tau at a central level, as measured by Tau-PET. However, they were reported to have a target engagement effect at the peripheral level, as measured by a reduction of free Tau levels. Based on currently available evidence, no protein Tau targets are currently identified which can be considered responsible for disease progression. Moreover, these drugs could have a limited ability to cross the blood–brain barrier, thus having no effect at a brain level. When considering safety, these drugs were reported as being well tolerated, with no specific adverse events. Research on new drugs targeting other Tau isoforms is crucial. Currently available evidence on monoclonal antibodies against Tau are limited to small phase-2 studies and reported no effect of these drugs on clinical outcomes. Based on this evidence, the WG agreed not to include a clinical practice recommendation as these molecules are still in a preliminary research phase.

ACTIVE IMMUNOTHERAPIES

Available evidence on two drugs for the active immunisation against Aβ were analysed. These drugs, AN1792 e CAD106, are both currently no more under investigation. Included studies reported no effect of these drugs on cognitive outcomes. A higher frequency of severe adverse events, including meningoencephalitis, some of which leading to death, was reported in people treated with AN1792, thus leading to trial termination. No evidence is currently available supporting the use of active immunisation in people with AD.

Recommendations

Acetylcholinesterase inhibitors, memantine and new biological treatments for Alzheimer's dementia and Mild Cognitive Impairment

77	The three acetylcholinesterase (AChE) inhibitors donepezil, galantamine and rivastigmine as monotherapies are recommended as options for managing mild to moderate Alzheimer's dementia under all of the conditions specified in recommendations 82 and 83.	STRONG IN FAVOUR
78	Offer donepezil as monotherapy for managing moderate to severe Alzheimer's dementia based on the conditions specified in recommendations 82 and 83.	WEAK IN FAVOUR
79	Memantine monotherapy is recommended as an option for managing Alzheimer's dementia for people with: • moderate Alzheimer's dementia who are intolerant of or have a contraindication to AChE inhibitors or • severe Alzheimer's dementia. Treatment should be under the conditions specified in recommendation 82.	WEAK IN FAVOUR
80	For people who are not taking an AChE inhibitor or memantine, prescribers should only start treatment with these on the advice of a specialist (neurologist, geriatrician, psychiatrist) who has the necessary knowledge and skills. Only specialists in Centres for Cognitive Disorders and Dementias (CCDDs) can provide refundable prescriptions for these drugs within the National Health System.	WEAK IN FAVOUR
81	If prescribing an AChE inhibitor, 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.	WEAK IN FAVOUR
82	When using assessment scales to determine the severity of Alzheimer's dementia, 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.	WEAK IN FAVOUR
83	When assessing the severity of Alzheimer's dementia 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 person's dementia because of the person'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 person is sufficiently fluent for it to be appropriate for assessing the severity of dementia or	WEAK AGAINST

	• 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.	

Acetylcholinesterase inhibitors and memantine in people with mild cognitive impairment

84	Do not offer AChE inhibitors (donepezil, galantamine, and rivastigmine) and memantine for the treatment of Mild Cognitive Impairment.	STRONG AGAINST

Biological drugs in people with Alzheimer's dementia and mild cognitive impairment

85	Do not offer monoclonal antibodies against the different forms of amyloid β as a treatment for Alzheimer's dementia or Mild Cognitive Impairment.*	STRONG AGAINST

* Three panel members abstained from voting recommendation 85: Annalisa Chiari, Fabrizio Piazza e Patrizia Spadin

Research Recommendations

Acetylcholinesterase inhibitors and memantine in people with mild cognitive impairment

17R	What is the efficacy of AChE inhibitors and memantine for the treatment of the different subtypes of Mild Cognitive Impairment?

Biological drugs in people with Alzheimer's dementia and mild cognitive impairment

18R	What is the safety and efficacy of monoclonal antibodies targeted to the different forms of amyloid β for the treatment of Alzheimer's dementia or Mild Cognitive Impairment in terms of: • long-term safety and efficacy (e.g., ARIA events), • generalizability of results (e.g., interactions with other treatments for comorbidities), • choice of outcomes proving the clinical relevance of treatment effects?

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Repurposing of pharmacological interventions

Review question 16a	**What effect does modifying risk factors (repositioning drugs acting on possible etiological causes of dementia) have on slowing the progression of dementia?**
Review question 16b	**What effect does modifying risk factors (repositioning drugs acting on possible etiological causes of dementia) have on slowing the progression of MCI?**

Literature review

	16a	16b
Records identified from databases	7,530	3,024
Studies assessed for eligibility	8	12
Included studies	1	4
Studies included in the NICE GL	21	–
Total number of included studies	22	4

Eligibility criteria

Population	People (aged 40 years and over) with dementia or MCI.
Interventions	Interventions to modify risk factors for dementia progression. Potentially modifiable risk factors may include: • Alcohol consumption; • Smoking; • Obesity; • Diabetes; • Hypertension; • Hypercholesterolemia; • Diet; • Non-steroidal anti-inflammatory drugs; • Antipsychotics.
Comparator	No intervention.
Outcomes	• Rates of dementia/MCI progression or conversion from MCI to dementia. • Clinical outcomes including cognitive, functional and behavioural ability. • Patient and carer experience and satisfaction. • Patient and carer health-related quality of life. • Adverse events. • Resource use and costs.

Aim

The objective of the systematic literature review, in line with the strategy defined by the NICE Guideline, was to identify experimental studies investigating the safety and efficacy of interventions targeting underlying risk factors for dementia or Mild Cognitive Impairment (MCI) to slow the progression of dementia and its symptoms or the conversion from MCI to dementia. Considered interventions were based on the twelve known modifiable risk factors for dementia (Livingston 2020). The systematic review was initially targeted at identifying updated systematic reviews on pharmacological interventions used to treat risk factors for dementia. Systematic reviews were analysed to identify primary studies. Additional structured literature searches were also performed to identify further relevant studies. Only RCTs reporting data on the efficacy (cognitive, functional and global measures) and safety of investigated treatments were included. The NICE guideline (GL) for this question only included studies with a follow up of at least 12 months. However, due to the relatively small number of identified studies, the required minimum length of follow up was reduced to six months.

Summary of evidence

Review question 16a

The systematic review performed for the NICE GL identified 20 studies (reported in 21 publications) meeting the predefined eligibility criteria. Two studies investigated the safety and efficacy of antidiabetic drugs, four studies investigated the safety and efficacy of antihypertensive drugs, four studies (included in five publications) investigated the safety and efficacy of statins, and ten studies investigated the safety and efficacy of non-steroidal anti-inflammatory drugs (NSAIDs). Only one study was identified after updating the systematic review, investigating the safety and efficacy of nilvadipine, a calcium channel blocker used for the treatment of hypertension.

In all included studies, participants were allowed to use other drugs, including antipsychotics, antidepressants, and vitamin E supplements during the study period, which may have influenced the results.

Antidiabetic drugs

Two studies (Gold 2010, Risner 2006) investigated the safety and efficacy of rosiglitazone (2mg and 8mg) in slowing cognitive decline in participants with Alzheimer's dementia (AD) without a diagnosis of diabetes. The two studies reported no significant differences between groups in cognitive functions measured with ADAS-Cog when considering any dose (MD -0.42, 95%CI -1.35 – 0.51, I^2 0%, N=764, very low certainty), 2mg (MD -0.29, 95%CI -1.61 – 1.02, N=382, very low certainty), and 8mg (MD -0.55, 95%CI -1.86 – 0.77, N=382, very low certainty). One RCT (Gold 2010) reported no differences between groups in functional abilities measured with CIBIC+ (MD -0.05, 95%CI -0.27 – 0.17, I^2 n.a., N=391, low certainty). In terms of safety, the studies reported differences between groups in the frequency of adverse events when considering any dose (RR 0.97, 95%CI 0.80 – 1.17, I^2 0%, N=882, low certainty), 2mg (RR 0.89, 95%CI 0.68 – 1.16, I^2 n.a., N=438, low certainty), and 8mg (RR 1.04, 95%CI 0.81 – 1.35, I^2 n.a., N=444, low certainty).

Antihypertensive drugs

Overall, five studies investigated the safety and efficacy of antihypertensive drugs, specifically telmisartan, nimodipine, amlodipine, perindopril, captopril, enalapril, imidapril, nifedipine, and nilvadipine in slowing cognitive decline. Four studies (Kume 2012, Lawlor 2018, Morich 2012, Ohrui 2004) enrolled participants with AD, while one study (Pantoni 2005) enrolled participants with subcortical vascular dementia. Three studies investigated the safety and efficacy of calcium channel blockers compared to placebo (Lawlor 2018, Morich 2012, Pantoni 2005). One study investigated the comparative efficacy and safety of the angiotensin-II receptor blocker telmisartan (40 to 80mg) and the calcium channel blocker (CCB) amlodipine (5 to 10 mg)

(Kume 2012). One study investigated the comparative efficacy and safety of CCB and brain-penetrating ACE-inhibitors (captopril 37.5mg or perindopril 2mg) or non-brain-penetrating ACE-inhibitors (enalapril 5mg or imidapril 5mg) (Ohrui 2004).

The study on nimodipine (Morich 2012) reported an improvement in the intervention group compared to the control group in cognitive functions measured with MMSE (90mg: MD 0.29, 95%CI 0.05 – 0.53, I^2 n.a., N=713, moderate certainty; 180mg: MD 0.60, 95%CI 0.1 – 1.1, I^2 n.a., N=729, moderate certainty). However, it reported no differences in the same outcome measured with ADAS-Cog (90mg: MD -0.44, 95%CI -1.36 – 0.48, I^2 n.a., N=713, low certainty; 180mg: MD -0.45, 95%CI -1.35 – 0.45, I^2 n.a., N=729, low certainty). In terms of safety, the study reported no differences between groups on the frequency of adverse events when considering both the 90 mg dose (RR 1.00, 95%CI 0.91 – 1.10, I^2 n.a., N=811, low certainty) and the 180mg dose (RR 1.03, 95%CI 0.94 – 1.10, I^2 n.a., N=825, low certainty).

The study on nilvadipine (Lawlor 2018) reported no differences between groups in cognitive functions measured with ADAS-Cog (MD -0.22, 95%CI -2.06 – 1.62, I^2 n.a., N=498, low certainty). In terms of safety, the study reported no differences between groups in the frequency of adverse events (RR 1.05, 95%CI 0.96 – 1.14, I^2 n.a., N=509, low certainty).

One study (Kume 2012) investigated the comparative safety and efficacy of telmisartan and amlodipine. The study reported no differences between groups in cognitive functions measured with MMSE (MD 1.30, 95%CI -1.80 – 4.40, I^2 n.a., N=20, very low certainty) and ADAS-Cog (MD -4.20, 95%CI -9.42 – 1.02, I^2 n.a., N=20, very low certainty).

One study (Ohrui 2004) investigated the comparative efficacy of ACE-inhibitors and calcium-channel blockers. The study reported an improvement in MMSE scores in the brain-penetrating ACE-inhibitors group compared to CCBs (MD 4.30, 95%CI 4.22 – 4.38, I^2 n.a., N=108, low certainty), and in the non-brain-penetrating ACE-inhibitors compare to CCBs (MD 0.30, 95%CI 0.19 – 0.38, I^2 n.a., N=108, low certainty).

One study (Pantoni 2005) investigated the safety and efficacy of nimodipine in participants with subcortical vascular dementia. The study reported no differences between groups in cognitive functions measured with MMSE (MD 0.60, 95%CI -1.64 – 2.84, I^2 n.a., N=149, very low certainty).

Lipid-lowering agents: statins

Overall, four studies reported in five publications (Feldman 2010, Sano 2011, Simons 2002, Sparks 2005, Sparks 2006) investigated the safety and efficacy of statins, specifically atorvastatin and simvastatin, in slowing cognitive decline in people with AD.

Two studies reported in three publications investigated the safety and efficacy of atorvastatin (Feldman 2010, Sparks 2005, Sparks 2006). The studies reported no differences between groups in cognitive functions measured with MMSE (MD 0.84, 95%CI -0.35 – 2.02, I^2 59%, N=577, low certainty) and ADAS-Cog (MD -0.51, 95%CI -1.72 – 0.70, I^2 63%, N=560, low certainty). They also reported no differences in neuropsychiatric symptoms measured with NPI (MD -2.07, 95%CI -5.73 – 1.59, I^2 77%, N=577, very low certainty). In terms of safety, one study (Feldman 2010) reported a higher risk of adverse events in the treatment group compared to placebo (RR 2.86, 95%CI 2.20 – 3.71, I^2 n.a., N=517, moderate certainty).

Two studies reported data on the efficacy and safety of simvastatin (Sano 2011, Simons 2002). The studies reported no differences between groups in cognitive functions measured with MMSE (MD 0.78, 95%CI -1.44 – 2.99, I^2 78%, N=450, very low certainty) and ADAS-Cog (MD 0.30, 95%CI -1.05 – 1.65, I^2 0%, N=450, very low certainty). One study (Sano 2011) reported no differences between groups in neuropsychiatric symptoms measured with NPI (MD -1.65, 95%CI -3.69 – 0.39, I^2 n.a., N=406, very low certainty). In terms of safety, one study (Sano 2011) reported no differences between groups in the frequency of adverse events (RR 1.03, 95%CI 0.97 – 1.10, I^2 n.a., N=406, low certainty).

Non-steroidal anti-inflammatory (NSAIDs) drugs

Overall, ten studies investigated the safety and efficacy of NSAIDs in slowing cognitive decline in people with AD (Aisen 2003, Bentham 2008, De Jong 2008, Green 2009, Pasqualetti 2009, Reines 2004, Rogers 1993, Scharf 1999, Soininen 2007, Wilcock 2008). Included studies investigated naproxen, acetylsalicylic acid, indomethacin, tarenflurbil (a single R enantiomer of flurbiprofen), ibuprofen, diclofenac, celecoxib, and rofecoxib. Six studies (Bentham 2008, De Jong 2008, Green 2009, Pasqualetti 2009, Reines 2004, Soininen 2007) reported no differences between groups in cognitive functions measured with MMSE (MD -0.22, 95%CI -0.47 – 0.03, I^2 0%, N=2,606, very low certainty). Eight studies (Aisen 2003, Bentham 2008, De Jong 2008, Green 2009, Pasqualetti 2009, Reines 2004, Soininen 2007, Wilcock 2008) reported no differences between groups in cognitive functions measured with ADAS-Cog (MD -0.37, 95%CI -1.94 – 1.19, I^2 81%, N=3,315, very low certainty). Four studies (Aisen 2003, Green 2009, Reines 2004, Wilcock 2008) reported an improvement in the intervention group compared to placebo in functional abilities measured with ADCS-ADL (MD 1.60, 95%CI 0.31 – 2.90, I^2 47%, N=2,671, low certainty). However, four studies (Aisen 2003, De Jong 2008, Green 2009, Pasqualetti 2009) reported no differences between groups in neuropsychiatric symptoms measured with NPI (MD -0.26, 95%CI -1.30 – 0.77, I^2 39%, N=2,073, low certainty). Four studies (De Jong 2008, Pasqualetti 2009, Reines 2004, Soininen 2007) reported no differences between groups in global functions measured with CIBIC+ (MD 0.04, 95%CI -0.08 – 0.16, I^2 0%, N=1,196, low certainty). In terms of safety, four studies (Green 2009, Reines 2004, Soininen 2007, Wilcock 2008) reported a higher risk of adverse events in the intervention group compared to placebo (RR 1.03, 95%CI 1.00 – 1.07, I^2 0%, N=2,934, moderate certainty). Six studies (Aisen 2003, Bentham 2008, De Jong 2008, Green 2009, Reines 2004, Soininen 2007) reported no differences between groups on the frequency of serious adverse events (RR 1.13, 95%CI 0.97 – 1.32, I^2 21%, N=3,475, low certainty).

Question 16b

The systematic review of the literature identified four studies meeting the predefined eligibility criteria. One study investigated the safety and efficacy of the antidiabetic drug metformin (Luchsinger 2016), two studies investigated the safety and efficacy of the NSAIDs rofecoxib (Thal 2005) and triflusal (Gómez-Isla 2008), and one study investigated the safety and efficacy of the antihypertensive drug candesartan (Hajjar 2022).

Antidiabetic drugs

One study (Luchsinger 2016) investigated the safety and efficacy of metformin in participants aged 55 to 90 years with amnesic MCI, no diagnosis of diabetes, and a body mass index (BMI) ≥ 25. The study considered a BMI of 25 as a surrogate marker of hyperinsulinemia, which could benefit from the reduction in insulin levels induced by metformin. The study reported no differences between groups in cognitive functions measured with ADAS-Cog (MD 0.90, 95%CI -0.90 – 2.70, I^2 n.a., N=80, very low certainty).

Antihypertensive drugs

One study (Hajjar 2022) investigated the safety and efficacy of the angiotensin-II receptor blocker candesartan in 77 participants with MCI, evidence of amyloid pathology (Aβ 42, t-Tau, p-Tau), and no diagnosis of hypertension. The study reported no significant differences between groups in cognitive functions measured with TMT-A (MD -3.18, 95%CI -20.73 – 14.37, I^2 n.a., very low certainty) and on functional abilities measured with IADL (MD 0.45, 95%CI -0.35 – 1.25, I^2 n.a., low certainty). In terms of safety, the study reported a higher risk of hypotensive episodes (blood pressure ≤ 100/40 mmHg) in the treatment group (RR 4.11, 95%CI 1.51 – 11.16, I^2 n.a., very low certainty) while it reported no differences between groups in the frequency of adverse events (RR 1.18, 95%CI 0.48 – 2.94, I^2 n.a., very low certainty).

Non-steroidal anti-inflammatory (NSAIDs) drugs

One study (Thal 2005) investigated the safety and efficacy of rofecoxib in participants with MCI aged > 65 years. Participants were allowed, when needed, any cardio protective treatment including acetylsalicylic acid (100mg) and clopidogrel. The study reported a higher risk of conversion from MCI to AD in the rofecoxib group compared to placebo (adjusted HR 1.46, 95%CI 1.09 – 1.94, I^2 n.a., N=1,457, moderate certainty). It reported no differences between groups in cognitive functions measured with ADAS-Cog (MD 0.30, 95%CI -0.40 – 1.10, I^2 n.a., N=1,457, low certainty) and MMSE (MD 0.20, 95%CI -0.70 – 0.30, I^2 n.a., N=1,457, low certainty). In terms of safety, the study reported no differences between groups in the frequency of withdrawal due to adverse events (RR 1.07, 95%CI 0.87 – 1.31, I^2 n.a., N=1,451, low certainty).

One study (Gómez-Isla 2008) terminated due to recruitments difficulties investigated the safety and efficacy of Triflusal (900mg) in participants with amnesic MCI who were not in treatment with any cardio protective drugs (e.g., antiplatelet medication) or acetylcholinesterase inhibitor. The study reported no differences between groups in cognitive functions measured with ADAS-Cog (MD -0.90, 95%CI -2.30 – 0.50, I^2 n.a., N=257, very low certainty) and MMSE (MD 0.19, 95%CI -0.47 – 0.85, I^2 n.a., N=257, very low certainty). In terms of safety, the study reported a higher risk of withdrawal due to adverse events in the intervention group compared to placebo (RR 2.76, 95%CI 1.34 – 5.67, I^2 n.a., N=257, moderate certainty).

Analysis of evidence

Review question 16a

The working group (WG) discussed available evidence considering that the update of the literature review performed by the NICE GL only identified one study (Lawlor 2018) meeting the predefined inclusion criteria.

Antidiabetic drugs

No new studies were identified when updating the literature review performed by the NICE GL. Therefore, the WG, despite evidence only referring to rosiglitazone, agreed to recommend not to offer any antidiabetic drug to people with AD specifically to slow the progression of the disease.

Antihypertensive drugs

One study was identified for this class of drugs after updating the literature review performed by the NICE GL, investigating the efficacy of the calcium channel blocker (CCB), nilvadipine (Lowlor 2018). As observed in previous studies, study reported no differences between participants on nilvadipine and participants on placebo in any of the considered outcomes. One study comparing ACE inhibitors and CCBs reported an improvement in participants on ACE inhibitors. However, the study had substantial methodological limitations including both investigators and participants not being blinded to treatment allocation. Therfore, the WG agreed to confirm the recommendation from the NICE GL not to offer antihypertensive drugs specifically to slow the progression of AD.

Lipid-lowering agents: statins

No new studies were identified when updating the literature review performed by the NICE GL. Low-quality evidence on the two statins atorvastatin and simvastatin reported no difference between people treated with these medications and placebo in any of the considered outcomes. The WG agreed to confirm the recommendation from the NICE GL not to offer statins specifically to slow the progression of AD.

Non-steroidal anti-inflammatory (NSAIDs) drugs

No new studies were identified when updating the literature review performed by the NICE GL. Low-quality evidence only reported a statistically significant improvement, which was considered as not clinically relevant, in functional abilities measured with ADCS-ADL. A higher frequency of adverse events was observed

in people treated with NSAIDs, which is generally considered as common in studies on NSAIDs due some adverse events being specifically associated to this class of drugs. The WG, despite the lack of evidence, agreed to confirm the recommendation from the NICE GL not to offer NSAIDs, including acetylsalicylic acid, specifically to slow the progression of AD.

Further considerations

The WG underlined that the recommendation exclusively refers to specific cases when these medications are offered to the sole purpose of slowing the progression of dementia, and not for the treatment of diabetes, hypertension or hypercholesterolemia. The WG also underlines the importance of appropriately prescribe these classes of drugs for the management of the specific conditions for which they are indicated in clinical practice, especially in people with dementia, who are often exposed to polypharmacy, due to comorbidities. Therefore, the WG agreed to refer to valid guidelines for the diagnosis and management of conditions such as hypertension, diabetes, hypercholesterolemia, and obesity (see Table 6).

Question 16b

The lack of evidence on treatments specifically targeted at delaying the conversion from mild cognitive impairment (MCI) to dementia led to the need to identify specific treatments for the prevention and management of the main known risk factors for dementia. Some observational studies reported that conditions such as type 2 diabetes (T2D), insulin resistance, overweight and obesity, and several other cardiovascular diseases are associated with a higher risk of dementia, especially Alzheimer's dementia. The growing attention to cardiovascular factors has probably led to a higher number of studies aiming at reducing the vascular burden in people at risk for dementia. Only three studies were identified investigating the efficacy of pharmacological treatments specifically aimed at delaying the progression from MCI to dementia. Specifically, the three trials investigated the use of the antidiabetic drug metformin, rofecoxib, and the NSAID triflusal.

Antidiabetic drugs

One RCT investigated the efficacy of metformin, an inexpensive and safe antidiabetic drug used to reduce the risk of insulin resistance and T2D, two conditions that can increase the risk of cerebrovascular diseases and AD. The study enrolled only participants with amnesic MCI and a body mass index (BMI) ≥ 25, which thus were considered at a higher risk of T2D. The choice of using a BMI cut-off value was due to the lack of standard criteria for the diagnosis of hyperinsulinemia in both research and clinical practice. Therefore, the study only enrolled participants with MCI who were either overweight or obese. These were considered as potentially benefit from the insulin lowering action of metformin, as a BMI ≥ 25 was defined as a surrogate marker of hyperinsulinemia. This was considered as a limitation for the generalizability of results. However, data from the study reported no differences between groups in cognitive functions measured with ADAS-Cog. Despite evidence was limited to one single study, the WG agreed to include a recommendation not to offer any antidiabetic drug to people with MCI specifically to slow or stop the conversion from MCI to AD.

Non-steroidal anti-inflammatory (NSAIDs) drugs

One study reported no difference between people treated with the selective COX-2 inhibitor rofecoxib and placebo on any of the considered outcomes. The study also reported a higher rate of progression from MCI to AD in the group on rofecoxib compared to placebo, even though the higher risk was not confirmed by data on remaining secondary clinical outcomes. However, starting from 2004 all medications containing rofecoxib have been withdrawn in Italy and worldwide from the drug company due to the higher frequency of severe cardiovascular events observed in a clinical trial.

One study investigated triflusal in people with MCI based on its possible neuroprotective effect due to its ability to decrease, at a central level, the activity of some inflammatory mediators that are considered

responsible for mechanisms such as excitotoxicity, microglial activation, cerebral ischemia, and Alzheimer's disease due to β-amyloid deposits. However, the study reported no differences between the triflusal group and placebo in cognitive functions measured with MMSE and ADAS-Cog, and a significantly higher frequency in withdrawals due to adverse events in the triflusal group.

The WG, despite the lack of evidence on other NSAIDs in people with MCI, agreed to extend the recommendation not to offer any NSAID to people with MCI specifically to slow or stop the conversion from MCI to AD.

Antihypertensive drugs

Only one study was identified investigating the efficacy and safety of an antihypertensive drug, candesartan, in people with MCI. The study reported no differences between the candesartan group and placebo in any of the considered clinical outcomes, with a higher frequency of hypotensive episodes in the candesartan group. Therefore, the WG agreed to include the recommendation not to offer any antihypertensive drug to people with MCI specifically to slow or stop the conversion from MCI to AD.

Further considerations

The WG underlined that the recommendation exclusively refers to specific cases when these medications are offered to the sole purpose of slowing or stopping the conversion from MCI to dementia, and not for the treatment of vascular diseases, inflammatory conditions, or diabetes. The WG also underlines the importance of appropriately prescribe these classes of drugs for the management of the specific conditions for which they are effective and indicated. Therefore, people who need these treatments for the conditions they are meant to treat should continue receiving them. The WG agreed to refer to valid guidelines for the diagnosis and management of conditions such as hypertension, diabetes, hypercholesterolemia, and obesity (see Table 6).

Recommendations

86	Do not offer the following treatments specifically to slow the progression of Alzheimer's disease or to slow or stop the conversion from Mild Cognitive Impairment to dementia: • antidiabetic drugs; • antihypertensive drugs; • statins; • non-steroidal anti-inflammatory drugs (NSAIDs), including acetylsalicylic acid.	STRONG AGAINST

Research Recommendations

No research recommendations were made.

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Acetylcholinesterase inhibitors and memantine for Alzheimer's dementia: co-prescription and withdrawal

Review question 17a	**How effective is the co-prescription of acetylcholinesterase inhibitors and memantine for the treatment of Alzheimer's dementia?**
Review question 17b	**When should treatment with donepezil, galantamine, rivastigmine, and memantine be withdrawn for people with Alzheimer's dementia?**

Literature review

	17a	17b
Records identified from databases	1,453	711
Studies assessed for eligibility	38	5
Included studies	2	1
Studies included in the NICE GL	8	3
Total number of included studies	10	4

Eligibility criteria

Review question 17a

Population	People aged ≥ 40 years with a diagnosis of Alzheimer's dementia.
Interventions	Memantine plus an acetylcholinesterase inhibitor.
Comparator	• Memantine; • Acetylcholinesterase inhibitors; • Placebo; • Dose escalation as a possible alternative to co-prescription.
Outcomes	• Clinical outcomes including cognitive, functional and behavioural abilities. • Adverse events. • Patient and carer experience and satisfaction. • Patient and carer health-related quality of life. • Resource use and costs.

Review question 17b

Population	People aged ≥ 40 years with a diagnosis of Alzheimer's disease and currently being treated with donepezil, galantamine, rivastigmine and/or memantine.
Interventions	Withdrawal of pharmacological treatment.

Comparator	• Continuation of previous treatment. • Change of treatment drug (to another of the specified four drugs). • Change of treatment dose. • Alternative stopping rules.
Outcomes	• Clinical outcomes including cognitive, functional and behavioural ability. • Adverse events. • Patient and carer experience and satisfaction. • Patient and carer health-related quality of life. • Resource use and costs.

Aim

Review question 17a

The objective of the systematic review, according to the strategy defined in the NICE guideline, was to identify all randomized controlled trials (RCTs) investigating the safety, efficacy and cost-efficacy of the memantine in combination with an acetylcholinesterase inhibitor (AChEI) for the treatment of cognitive symptoms in people with Alzheimer's dementia (AD). The systematic review was initially targeted at identifying updated systematic reviews on the co-prescription of memantine and AChEIs in people with AD. Systematic reviews were analysed to identify primary studies. Additional structured literature searches were also performed to identify further relevant studies. Only RCTs reporting data on the efficacy (cognitive, functional and global measures) and safety of investigated treatments were included.

Review question 17b

The objective of the systematic review, according to the strategy defined in the NICE guideline, was to identify all randomized controlled trials (RCTs) investigating the safety, efficacy and cost-efficacy in people with AD of continuing treatment with acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine) and/or memantine compared to discontinuing it and determining the clinically appropriate points to withdraw treatment. The systematic review was initially targeted at identifying updated systematic reviews. Systematic reviews were analysed to identify primary studies. Additional structured literature searches were also performed to identify further relevant studies. Only RCTs reporting data on the efficacy (cognitive, functional and global measures) and safety of investigated treatments were included.

Summary of evidence

Co-prescription of acetylcholinesterase inhibitors and memantine

Review question 17a

Overall, five studies (Dysken 2014, Grossberg 2013, Howard 2012, Porsteinsson 2008, Tariot 2004) investigated the safety and efficacy of the co-prescription of acetylcholinesterase inhibitors (AChEIs) and memantine compared with the co-prescription of AChEIs and placebo. Three studies (Araki 2014, Choi 2011, Kim 2023) investigated the combination of AChEIs and memantine compared with AChEIs as monotherapy. One study (Shao 2015) investigated the safety and efficacy of the combination of different AChEIs and memantine compared with memantine and placebo in people with mild to moderate AD. One study (Young 2021), identified after updating the systematic review, investigated the combination of one AChEI and memantine compared with one AChEI as monotherapy for the treatment of neuropsychiatric symptoms in people with moderate AD. One study (Howard 2012) investigated the safety and efficacy of switching treatment with AChEI to treatment with memantine, in people with moderate to severe AD.

Acetylcholinesterase inhibitor plus memantine versus acetylcholinesterase inhibitor plus placebo

Mild AD

Two studies (Dysken 2014, Porsteinsson 2008) reported data from post-hoc analyses in a subgroup of participants with mild AD. Results showed no differences between groups in global functions (SMD -0.09, 95%CI -0.45 – 0.26, I^2 n.a., N=121, very low certainty) (Porsteinsson 2008), cognitive symptoms (SMD -0.05, 95% -0.27 – 0.17, I^2 0%, N=315, very low certainty), and ADL (SMD -0.04, 95%CI -0.26 – 0.19, I^2 0%, N=315, very low certainty) (Dysken 2014, Porsteinsson 2008).

Mild to moderate AD

Three studies (Dysken 2014, Howard 2012, Porsteinsson 2008) reported no differences between groups in cognitive functions measured with MMSE (MD -0.08, 95%CI -0.80 – 0.65, I^2 0%, N=709, moderate certainty) (Dysken 2014, Howard 2012) and ADAS-Cog (MD -1.17, 95%CI -2.81 – 0.47, I^2 0%, N=709, moderate certainty). Two studies reported no differences in ADL (SMD 0.06, 95%CI -0.09 – 0.20, I^2 2%, N=709, moderate certainty) (Dysken 2014, Porsteinsson 2008). One study (Porsteinsson 2008) reported no differences in global functions measured with CIBIC+ (MD -0.04, 95%CI -0.23 – 0.15, I^2 n.a., N=427, low certainty), and two studies reported no differences in neuropsychiatric symptoms measured with NPI (MD 0.57, 95%CI -2.76 – 3.91, I^2 0%, N=579, moderate certainty) (Dysken 2014, Porsteinsson 2008). In terms of safety, two studies (Dysken 2014, Porsteinsson 2008) reported no differences between groups in the frequency of adverse events (RR 0.91, 95%CI 0.62 – 1.33, I^2 0%, N=740, moderate certainty). One study (Porsteinsson 2008) reported no differences in the frequency of withdrawal due to adverse events (RR 0.76, 95%CI 0.38 – 1.53, I^2 n.a., N=433, low certainty).

Moderate AD

Four RCTs (Dysken 2014, Howard 2012, Porsteinsson 2008, Tariot 2004) reported data from post-hoc analyses in a subgroup of participants with mild AD. Two studies reported no differences between groups in global functions (SMD -0.17, 95%CI -0.35 – 0.00, I^2 59%, N=121, very low certainty) (Porsteinsson 2008, Tariot 2004). The four studies (Dysken 2014, Howard 2012, Porsteinsson 2008, Tariot 2004) reported no differences in the activities of daily living (SMD -0.11, 95%CI -0.26 – 0.04, I^2 12%, very low certainty). One study (Howard 2012) reported no differences in neuropsychiatric symptoms measured with NPI (MD 0.47, 95%CI -10.43 – 11.37, N=57, very low certainty) and quality of life measured with DEMQOL (MD -4.45, 95%CI -11.34 – 2.44, I^2 n.a., N=57, very low certainty). However, the four studies (Dysken 2014, Howard 2012, Porsteinsson 2008, Tariot 2004) reported an improvement in the co-prescription group compared to the control group in cognitive functions (SMD -0.23, 95%CI -0.39 – -0.08, I^2 0%, N=657, low certainty).

One study (Youn 2021) reported no differences between groups in neuropsychiatric symptoms measured with NPI (MD -1.13, 95%CI -5.06 – 2.80, I^2 n.a., N=148, low certainty) and in cognitive functions measured with MMSE (MD 0.12, 95%CI -0.79 – 1.03, I^2 n.a., N=148, low certainty).

Moderate to severe AD

Four studies (Grossberg 2013, Howard 2012, Porsteinsson 2008, Tariot 2004) enrolling participants with moderate to severe AD reported an improvement in the intervention group compared to the control group in activities of daily living (SMD 0.13, 95%CI 0.01 – 0.24, I^2 0%, N=1,166, high certainty). They also reported an improvement in the intervention group in global functions measured with CIBIC+ (MD -0.28, 95%CI -0.41 – -0.14, I^2 0%, N=1,056, high certainty) and neuropsychiatric symptoms measured with NPI (MD -3.19, 95%CI -4.83 – -1.56, I^2 0%, N=1,133, high certainty). One study (Howard 2012) reported no differences between groups in cognitive function measured with MMSE (MD 0.27, 95%CI -1.13 – 1.67, I^2 n.a., N=112, low certainty) and quality of life measured with DEMQOL (MD -2.00, 95%CI -6.44 – 2.44, I^2 n.a., N=113, low certainty). Two studies reported no differences between groups in cognitive function measured with SIB (MD 1.22, 95%CI -

1.15 – 3.59, I^2 71%, N=1,063, low certainty). In terms of safety, two studies (Grossberg 2013, Howard 2012) reported no differences between groups in the frequency of adverse events (RR 0.99, 95%CI 0.63 – 1.57, I^2 58%, N=825, low certainty). Two studies (Grossberg 2013, Tariot 2004) reported no differences between groups in the risk of withdrawal due to adverse events (RR 0.99, 95%CI 0.38 – 2.58, I^2 83%, N=1,079, very low certainty).

Severe AD

Two studies (Howard 2012, Tariot 2004) reported data from post-hoc analyses in a subgroup of participants with severe AD. The two studies (Howard 2012, Tariot 2004) reported an improvement in the intervention group compared to the control group in cognitive functions (SMD -0.54, 95%CI -0.84 – -0.30, I^2 55%, low certainty) and activities of daily living (SMD -0.33, 95%CI -0.60 – -0.06, I^2 0%, low certainty). One study (Howard 2012) reported an improvement in the intervention group in neuropsychiatric symptoms measured with NPI (MD -10.24, 95%CI -20.30 – -0.18, I^2 n.a., N=57, low certainty). However, the two studies (Tariot 2004) reported no differences between groups in global functions (SMD -0.22, 95%CI -0.53 – 0.09, I^2 n.a., N=161, very low certainty). One study (Howard 2012) also reported no differences between groups in quality of life measured with DEMQOL (MD 0.49, 95%CI -6.02 – 7.00, I^2 n.a., N=57, very low certainty).

Acetylcholinesterase inhibitor plus memantine versus acetylcholinesterase inhibitor monotherapy

Two studies (Araki 2014, Choi 2011) enrolling participants with mild to moderate and moderate to severe AD reported no differences between groups in cognitive functions measured with MMSE (MD 0.88, 95%CI -1.98 – 3.75, I^2 82%, N=183, very low certainty). When stratifying for disease severity, one study (Choi 2011) reported no differences between groups in MMSE in the subgroup of mild to moderate AD (MD -0.40, 95%CI -1.29 – 0.49, I^2 n.a., N=158, low certainty). The other study (Araki 2014) reported an improvement in the intervention group compared to the control group in MMSE in the subgroup of moderate to severe AD (MD 2.55, 95%CI 0.28 – 4.82, I^2 n.a., N=25, very low certainty).

One study (Kim 2023) investigated the efficacy of an adjunctive treatment with memantine oral pump (solution) in people already receiving donepezil compared to donepezil monotherapy in 188 participants with moderate to severe AD. The study reported no differences between groups in cognitive functions measured with MMSE (MD 0.20, 95%CI -1.48 – 1.88, I^2 n.a., low certainty) and CDR-SB (MD -0.24, 95%CI -1.05 – 1.53, I^2 n.a., low certainty), and in neuropsychiatric symptoms measured with NPI (NPI: MD 0.19, 95%CI -2.23 – 2.68, I^2 n.a., low certainty).

Acetylcholinesterase inhibitor plus memantine versus memantine plus placebo

One RCT (Shao 2015) enrolling participants with mild to moderate AD reported no differences between groups in cognitive functions measured with MMSE for donepezil (MD 0.37, 95%CI -1.04 – 1.78, I^2 n.a., N=44, very low certainty), rivastigmine (MD 0.41, 95%CI -1.17 – 1.99, I^2 n.a., N=44, very low certainty), galantamine (MD 0.82, 95%CI -0.58 – 2.22, I^2 n.a., N=44, very low certainty). The study also reported no differences between groups in functional abilities measured with ADCS-ADL for donepezil (MD -0.64, 95%CI -1.88 – 0.60, I^2 n.a., N=44, very low certainty), rivastigmine (MD -0.18, 95%CI -1.43 – 1.07, I^2 n.a., N=44, very low certainty), galantamine (MD -1.14, 95%CI -2.47 – 0.19, I^2 n.a., N=44, very low certainty). In terms of safety, the study reported no differences between groups in the frequency of adverse events for donepezil (RR 1.40, 95%CI 0.52 – 3.74, I^2 n.a., N=44, very low certainty), rivastigmine (RR 1.60, 95%CI 0.62 – 4.13, I^2 n.a., N=44, very low certainty) and galantamine (RR 1.20, 95%CI 0.43 – 3.36, I^2 n.a., N=44, very low certainty).

Acetylcholinesterase inhibitors switch to memantine

One RCT (Howard 2012) enrolling participants with moderate to severe AD reported no differences between groups in cognitive functions measured with MMSE (MD -0.47, 95%CI -1.77 – 0.83, I^2 n.a., N=105, low certainty) and in activities of daily living (BADLS, Bristol Activities of Daily Living Scale: MD 0.21, 95%CI -2.91

– 3.34, I^2 n.a., N=105, low certainty). It also reported no differences in neuropsychiatric symptoms measured with NPI (MD -9.28, 95%CI -20.49 – 1.93, I^2 n.a., N=105, very low certainty), quality of life measured with DEMQOL (MD 2.62, 95%CI -3.43 – 8.66, I^2 n.a., N=105, very low certainty), and risk of institutionalization (HR 1.40, 95%CI 0.90 – 2.20, N=149, low certainty).

Acetylcholinesterase inhibitors or memantine withdrawal

Review question 17b

The systematic review preformed for the NICE guideline identified two studies meeting the predefined eligibility criteria. Updating the SR allowed to identify one additional study.

Two studies (Howard 2012 [additional analyses in Howard 2015], Herrmann 2016) investigated the comparative efficacy of either continuing or withdrawing treatment with acetylcholinesterase inhibitors or memantine. The two studies enrolled participants with a diagnosis of AD. One study (Howard 2012) investigated the effects of withdrawing treatment with donepezil, with adjunctive analyses included in a secondary publication published in 2015 (Howard 2015). The study enrolled participants with moderate to severe AD and included the following treatment arms: 1) continuing treatment with donepezil and initiating treatment with placebo plus memantine; 2) discontinuing treatment with donepezil and initiating treatment with placebo plus memantine; 3) discontinuing treatment with donepezil and initiating treatment with memantine; 4) continuing treatment with donepezil and initiating treatment with memantine. The second RCT (Herrmann 2016) investigated continuing treatment with an acetylcholinesterase inhibitor versus discontinuing treatment and switching to placebo in institutionalised participants with moderate to severe AD. One study (Hong 2018) investigated continuing treatment with an acetylcholinesterase inhibitor or memantine versus discontinuing it in participants with severe AD (MMSE ≤ 5).

The three studies (Herrmann 2016, Hong 2018, Howard 2012) reported a significant worsening in participants discontinuing treatment compared to participants continuing it in cognitive functions measured with MMSE (MD -1.32, 95%CI -2.53 – -0.11, I^2 62%, N=205, low certainty). When stratifying for disease severity one study reported a significant worsening of cognitive functions measured with MMSE only in the moderate AD subgroup (MD -3.72, 95%CI -5.92 – -1.52, I^2 n.a., N=54, moderate certainty) (Howard 2012). The remaining two studies reported no differences between groups in the moderate to severe AD subgroup (MD -1.70, 95%CI -3.93 – 0.53, I^2 n.a., N=40, very low certainty) (Herrmann 2016) and in the severe AD subgroup (MD -1.70, 95%CI -3.93 – 0.53, I^2 n.a., N=40, very low certainty) (Hong 2018).

Analysis of evidence

Co-prescription of acetylcholinesterase inhibitors and memantine

Review question 17a

Co-prescription of acetylcholinesterase inhibitor plus memantine

Treatment with acetylcholinesterase inhibitors (AChEI) and memantine in people with Alzheimer's dementia usually consists in one of the three AChEIs donepezil, galantamine or rivastigmine in the mild to moderate phase, and memantine in the moderate to severe phase. However, when discussing on the co-prescription of AChEIs and memantine, evidence on people with mild AD should be considered separately from that on people with moderate to severe AD. Evidence on memantine monotherapy, in fact, reported no effect of this treatment on any of the considered clinical outcomes in people with mild to moderate AD. The four studies investigating co-prescription of AChEIs and memantine versus AChEIs monotherapy also reported no improvement with co-prescription compared to monotherapy. This evidence is in line with what observed for memantine monotherapy in mild to moderate AD. However, initiating treatment with memantine in people already taking an AChEI was reported as more effective than AChEI monotherapy in people with

moderate to severe AD. Studies reported an improvement in the intervention arm compared to the control arm mainly in functional abilities, global functions, and behavioural symptoms. Moreover, initiating treatment with memantine did not increase the incidence of withdrawal due to adverse events compared to monotherapy.

Post-hoc analyses from some of the included studies reported no effect of co-prescription of AChEIs plus memantine in people with mild AD. However, post-hoc analyses on people with moderate AD showed a slight improvement in cognitive outcomes, and post-hoc analyses in people with severe AD showed an improvement in cognitive outcomes, activities of daily living and behavioural symptoms. Based on the differences observed between people with moderate AD and people with severe AD, the WG agreed to confirm the recommendation from the NICE guideline to consider memantine in addition to AChEIs in people with moderate AD, and to offer memantine in addition to AChEIs in people with severe AD.

Acetylcholinesterase inhibitors switch to memantine

Only one study investigated switching from monotherapy with AChEIs to monotherapy with memantine. However, evidence did not report any benefit from switching from AChEIs to memantine on any of the considered outcomes. Moreover, it is important in clinical practice to consider the potential harms to people when switching treatments, especially if the previous treatments is effective and well tolerated. Therefore, people switching from a well-tolerated treatment to a new treatment could experience severe harms. Discontinuing a well-tolerated treatment and initiating a treatment that could not be well tolerated could expose people to potentially severe harms thus causing severe burden to their caregivers. Therefore, based on currently available evidence, the WG agreed to recommend adding memantine to the AChEIs rather that switching from AChEIs monotherapy to memantine monotherapy in people with severe AD.

Acetylcholinesterase inhibitors or memantine withdrawal

Review question 17b

Only one new study was retrieved after updating the systematic review (SR) performed for the NICE GL. However, the WG underlined that evidence, despite being from small studies, reported a significant worsening in cognitive functions measured with MMSE in people discontinuing treatment compared to those continuing it. The WG observed that included studies used the MMSE alone to define whether to discontinue or continue treatment. However, the WG also agreed that the decision was not based only on the severity of cognitive symptoms as measured by MMSE but was also based on several other aspects including global functions, quality of life, safety, and tolerability. Based on included studies, the WG 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. However, the WG observed that the included evidence referred to AChEIs, while only the study identified when updating the SR investigated memantine in people with severe AD. This study reported no significant improvement in continuing treatment and was likely underpowered to detect any significant difference. Therefore, the WG agreed to confirm the recommendation from the NICE GL not to stop AChEIs inhibitors because of disease severity alone, but to consider with the progression of the disease whether the risks (adverse events) associated to the treatment outweigh the benefits (cognitive, functional, and global outcomes).

Recommendations

Co-prescription of acetylcholinesterase inhibitors and memantine in Alzheimer's dementia

87	For people with moderate Alzheimer's dementia who are already taking an AChE inhibitor consider memantine in addition to the AChE inhibitor.	WEAK IN FAVOR

88	For people with severe Alzheimer's dementia who are already taking an AChE inhibitor offer memantine in addition to the AChE inhibitor.	STRONG IN FAVOR

Discontinuation of acetylcholinesterase inhibitors and memantine in Alzheimer's dementia

89	Do not stop AChE inhibitors or memantine in people with Alzheimer's dementia because of disease severity alone.	STRONG AGAINST

Research Recommendations

No research recommendations were made.

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Acetylcholinesterase inhibitors and memantine for Parkinson's disease dementia and dementia with Lewy bodies

Review question 18a	**What is the comparative effectiveness of donepezil, galantamine, memantine and rivastigmine for cognitive enhancement in dementia associated with Parkinson's disease?**
Review question 18b	**What is the comparative effectiveness of donepezil, galantamine, memantine and rivastigmine for cognitive enhancement in dementia with Lewy bodies?**

Literature review

	18a	18b
Records identified from databases	1,362*	1,362*
Studies assessed for eligibility	22	22
Included studies	0	0
Studies included in the NICE GL	7	4
Total number of included studies	7	4

* RQ18a and RQ18b shared a common search strategy.

Eligibility criteria

Population	People with a diagnosis of Parkinson's disease dementia or dementia with Lewy bodies.
Interventions	• Donepezil. • Galantamine. • Memantine. • Rivastigmine.[37] • Memantine plus acetylcholinesterase inhibitor.
Comparator	• Placebo. • Each other. • Combination of memantine plus acetylcholinesterase inhibitor.
Outcomes	• Cognitive outcomes, including: – MMSE; – ADAS-Cog; – MoCA. • Global functions, including: – UPDRS; – Global Impression of Change.

[37] Rivastigmine capsules is currently the only AChEI with an indication for the treatment of mild to moderate PDD. Use of donepezil, galantamine and rivastigmine patches is off label.

	• Activities of daily living (ADL), including: – UPDRS-ADL. • Other non-cognitive outcomes, including: – NPI; – Motor symptoms, such as tremor and rigidity. • Adverse events, such as hallucinations. • Study withdrawal. • Health-related quality of life. • Carer-reported outcomes. • Resource use and cost. • Time to institutionalised care.

Aim

Review question 18a

The objective of the systematic review, according to the strategy defined in the NICE guideline, was to identify all randomized controlled trials (RCTs) investigating the efficacy and safety of pharmacological interventions for cognitive enhancing in people with dementia associated with Parkinson's disease (PDD). The systematic review was initially targeted at identifying updated systematic reviews on the use of acetylcholinesterase inhibitors (AChEIs) and memantine for the treatment of Parkinson's disease dementia (PDD). Systematic reviews were analysed to identify primary studies. Additional structured literature searches were also performed to identify further relevant studies. Only RCTs reporting data on the efficacy (cognitive, functional and global measures) and safety of investigated treatments were included.

Review question 18b

The objective of the systematic review, according to the strategy defined in the NICE guideline, was to identify all randomized controlled trials (RCTs) investigating the efficacy and safety of pharmacological interventions for cognitive enhancing in people with dementia with Lewy bodies. While maintaining the same search strategy as question 18a, the guideline Working Group (WG) agreed to separate the question on the effectiveness of AChEIs in people with dementia with Lewy bodies (DLB). The systematic review was initially targeted at identifying updated systematic reviews on the use of acetylcholinesterase inhibitors (AChEIs) and memantine for the treatment of DLB. Systematic reviews were analysed to identify primary studies. Additional structured literature searches were also performed to identify further relevant studies. Only RCTs reporting data on the efficacy (cognitive, functional and global measures) and safety of investigated treatments were included.

Summary of evidence

Acetylcholinesterase inhibitors in PDD

Review question 18a

The systematic review performed for the NICE guideline identified six RCTs and one open-label study that met predefined eligibility criteria. No studies were identified after updating the systematic review.

Four studies, reported in five publications, investigated the efficacy of acetylcholinesterase inhibitors (AChEIs) in people with PDD:

- three RCTs compared donepezil with placebo (Aarsland 2002, Dubois 2012, Ravina 2005);

- one RCT compared rivastigmine with placebo (Emre 2004, Dujardin 2006 [secondary study]).

One open-label study (Emre 2004) investigated the efficacy of rivastigmine capsules compared with rivastigmine patch in people with mild to moderate PDD.

Two RCTs, reported in three publications (Emre 2010, Leroi 2009, Leroi 2014 [secondary study]), investigated the efficacy of memantine in people with PDD.

No studies were identified investigating the efficacy of galantamine and of the co-prescription of AChEis plus memantine in people with PDD.

Acetylcholinesterase inhibitors in PDD

Four RCTs (Aarsland 2002, Dubois 2012, Emre 2004, Ravina 2005) reported an improvement in the intervention group compared to the control group in cognitive functions measured with MMSE (MD 1.36, 95%CI 0.94 – 1.77, I^2 0%, N=1,119, high certainty). Three studies (Aarsland 2002, Dubois 2012, Ravina 2005) reported an improvement in the intervention group in the same outcome measured with ADAS-Cog (MD -2.28, 95%CI -3.40 – -1.15, I^2 0%, N=1,035, high certainty). When stratifying by specific inhibitor, three studies (Aarsland 2002, Dubois 2012, Ravina 2005) reported an improvement in the donepezil group compared to placebo in cognitive functions measured with MMSE (MD 1.57, 95%CI 1.05 – 2.09, I^2 0%, N=618, high certainty). One study an improvement in the rivastigmine group compared to placebo in the same cognitive outcome (MMSE: MD 1.00, 95%CI 0.33 – 1.67, I^2 n.a., N=507, high certainty) (Emre 2004). Three studies (Aarsland 2002, Dubois 2012, Ravina 2005) reported an improvement in the AChEIs group compared to placebo in cognitive functions measured with ADAS-Cog (MD -2.28, 95%CI -3.40 – -1.15, I^2 0%, N=1,035, high certainty). When stratifying by specific inhibitor, only one study (Emre 2004) reported an improvement in the rivastigmine group compared to placebo in ADAS-Cog (MD -2.80, 95%CI -4.26 – -1.34, I^2 n.a., N=490, high certainty). The study (Emre 2004), assessing the comparative efficacy of rivastigmine capsules and rivastigmine patch, also reported an improvement in the rivastigmine patch group in cognitive functions measured with MDRS (Mattis Dementia Rating Scale) (MD -5,30, 95%CI -8.17 – -2.43, I^2 n.a., N=546, high certainty).

Three studies (Aarsland 2002, Dubois 2012, Emre 2004) reported an improvement in the intervention group compared to the control group in global functions measured with CIBIC+ or ADCS-CGIC (RR 1.24, 95%CI 1.05 – 1.47, I^2 15%, N=1,035, high certainty). However, only results for rivastigmine were significant (MD -0.50, 95%CI -0.77 – -0.23, N=494, high certainty). Two RCTs (Aarsland 2002, Dubois 2012) reported no differences between donepezil and placebo in global functions measured with CIBIC+ (MD -0.43, 95%CI -0.93 – 0.08, I^2 56%, N=541, low certainty). Two RCTs (Aarsland 2002, Ravina 2005) reported no differences between donepezil and placebo in signs and symptoms of Parkinson's disease measured with UPDRS (MD -1.50, 95%CI -7.87 – 4.87, I^2 0%, N=65, low certainty). One RCT (Emre 2004) reported an improvement in the rivastigmine group compared to placebo in activities of daily living measured with ADCS-ADL (MD 2.50, 95%CI 0.43 – 4.57, I^2 n.a., N=498, high certainty) and neuropsychiatric symptoms measured with NPI (MD -2.00, 95%CI -3.91 – -0.09, I^2 n.a., N=500, high certainty).

In terms of safety, three RCTs (Aarsland 2002, Dubois 2012, Ravina 2005) reported no differences between donepezil and placebo in the frequency of adverse events (RR 1.07, 95%CI 0.96 – 1.19, I^2 0%, N=617, moderate certainty). Two studies (Aarsland 2002, Dubois 2012) reported no differences between donepezil and placebo in the frequency of withdrawals due to adverse events (RR 1.46, 95%CI 0.91 – 2.35, I^2 0%, N=576, moderate certainty). One study (Emre 2004) reported a higher risk in the rivastigmine group compared to placebo of adverse events (RR 1.18, 95%CI 1.06 – 1.31, I^2 n.a., N=541, high certainty) and withdrawal due to adverse events (RR 2.19, 95%CI 1.26 – 3.80, I^2 n.a., N=576, high certainty).

Memantine in PDD

Two RCTs (Emre 2010, Leroi 2009, Leroi 2014 [secondary study]) investigated the efficacy and safety of memantine in people with PDD. One study (Leroi 2009) reported no differences between groups in cognitive functions measured with MMSE (MD -1.00, 95%CI -6.01 – 4.01, I^2 n.a., N=24, very low certainty). Two studies (Emre 2010, Leroi 2009) reported no differences between groups in global functions measured with ADCS-CGIC (Emre 2010) (MD -0.20, 95%CI -0.69 – 0.29, I^2 n.a., N=116, moderate certainty) and CIBIC+ (Leroi 2009) (RR 1.40, 95%CI 0.64 – 3.08, I^2 n.a., N=24, low certainty). One study (Emre 2010) d reported no differences between groups in activities of daily living measured with ADCS-ADL (MD 0.80, 95%CI -3.22 – 4.82, I^2 n.a., N=116, very low certainty).

Two studies (Emre 2010, Leroi 2009) reported no differences between groups in neuropsychiatric symptoms measured with NPI-12 (MD -1.50, 95%CI -6.35 – 3.35, I^2 n.a., N=116, very low certainty), and NPI-10 (MD -2.00, 95%CI -11.64 – 7.64, I^2 n.a., N=24, very low certainty). They also reported no differences in signs and symptoms of Parkinson's disease measured with UPDRS (MD 0.88, 95%CI -2.35 – 4.10, I^2 0%, N=140, low certainty). In terms of safety, two studies (Emre 2010, Leroi 2009) reported no differences between groups in the frequency of adverse events (RR 0.97, 95%CI 0.69 – 1.37, I^2 0%, N=145, moderate certainty), serious adverse events (RR 1.09, 95%CI 0.45 – 2.67, N=145, low certainty) and withdrawal due to adverse events (RR 1.12, 95%CI 0.36 – 3.48, N=120, low certainty).

Acetylcholinesterase inhibitors in DLB

Review question 18b

The systematic review performed for the NICE guideline identified four RCTs that met predefined eligibility criteria. No studies were identified after updating the systematic review.

Three RCTs investigated the efficacy of acetylcholinesterase inhibitors for the treatment of people with DLB:

- two RCTs compared donepezil with placebo (Ikeda 2015, Mori 2012);
- one RCT compared rivastigmine with placebo (McKeith 2000).

One RCT investigated the efficacy of memantine in people with DLB (Emre 2010). No studies were identified investigating the efficacy of galantamine and of the co-prescription of AChEIs plus memantine in people with DLB.

Acetylcholinesterase inhibitors in DLB

Three RCTs (Ikeda 2015, McKeith 2000, Mori 2012) reported an improvement in the intervention group compared to the control group in cognitive functions measured with MMSE (MD 1.77, 95%CI 1.06 – 2.47, I^2 49%, N=394, moderate certainty).

When stratifying by specific inhibitor, two studies (Ikeda 2015, Mori 2012) reported an improvement in the donepezil group compared to placebo in MMSE (MD 1.95, 95%CI 0.70 – 3.40, I^2 70%, N=272, moderate certainty). One study (McKeith 2000) reported no differences between rivastigmine and placebo in the same outcome (MD 1.24, 95%CI -0.28 – 2.76, I^2 n.a., N=120, low certainty). One RCT (Mori 2012) reported an improvement in the donepezil group compared to placebo in global functions measured with CIBIC+ (MD -1.17, 95%CI -1.66 – -0.68, I^2 n.a., N=121, high certainty).

Two studies (McKeith 2000, Mori 2012) reported an improvement in the intervention group compared to the control group in neuropsychiatric symptoms measured with NPI-10 (MD -2.49, 95%CI -4.64 – -0.33, I^2 0%, N=254, low certainty). When stratifying by specific inhibitor, one study (Mori 2012) reported an improvement in the donepezil group compared to placebo in NPI-10 scores (MD -3.59, 95%CI -6.93 – -0.25, I^2 n.a., N=134, low certainty). One RCT (McKeith 2000) reported no differences between rivastigmine and placebo in the same outcome (MD -1.70, 95%CI -4.52 – 1.12, I^2 n.a., N=100, low certainty).

Two studies (Ikeda 2015, Mori 2012) reported no differences between groups in signs and symptoms of Parkinson's disease measured with UPDRS-III (MD -0.65, 95%CI -2.24 – 0.95, I^2 21%, N=372, moderate certainty). In terms of safety, three RCTs (Ikeda 2015, McKeith 2000, Mori 2012) reported a higher risk in the intervention group compared to placebo of adverse events (RR 1.14, 95%CI 1.02 – 1.28, I^2 0%, N=401, moderate certainty), but not of serious adverse events (RR 0.98, 95%CI 0.53 – 1.82, I^2 0%, N=401, moderate certainty) and withdrawal due to adverse events (RR 0.89, 95%CI 0.49 – 1.62, I^2 0%, N=401, moderate certainty).

Memantine in DLB

One RCT (Emre 2010) investigated the safety and efficacy of memantine in people with DLB. The study reported no differences between groups in global functions measured with ADCS-CGIC (MD -0.60, 95%CI -1.22 – 0.02, I^2 n.a., N=74, low certainty) and functional abilities measured with ADCS-ADL (MD 1.60, 95%CI -4.90 – 8.10, I^2 n.a., N=74, very low certainty).

The study reported no differences between groups in signs and symptoms of Parkinson's disease measured with UPDRS-III (MD -1.40, 95%CI -5.52 – 2.72, I^2 n.a., N=74, low certainty) and in neuropsychiatric symptoms measured with NPI-12 (MD -6.00, 95%CI -12.23 – 0.23, I^2 n.a., N=74, very low certainty). In terms of safety, the study reported no differences between groups in the risk of adverse events (RR 1.28, 95%CI 0.79 – 2.07, I^2 n.a., N=75, low certainty), serious adverse events (RR 2.41, 95%CI 0.65 – 8.93, I^2 n.a., N=75, very low certainty) and withdrawal due to adverse events (RR 0.86, 95%CI 0.30 – 2.47, I^2 n.a., N=75, very low certainty).

Analysis of evidence

Acetylcholinesterase inhibitors in PDD

Review question 18a

The WG, in line with the approach adopted by the NICE guideline (GL), referred to the NICE GL on Parkinson's disease (NG71) for indications on the treatment of Parkinson's disease dementia (PDD). Recommendations were, therefore, based on the recommendations included in NG71 and on evidence from updating the systematic literature review. Evidence reported that treatment with acetylcholinesterase inhibitors (AChEIs) improves cognitive outcomes, including MMSE and ADAS-Cog, in people with PDD. The WG underlined that both donepezil and rivastigmine were reported as effective in improving MMSE scores, with a higher improvement (1.6 points) reported for donepezil by a pooled analysis of results from three studies.
The WG discussed the opportunity of generalising results from studies on donepezil and rivastigmine to the whole class of AChEIs. However, considering the risk-benefit profile of galantamine, the WG agreed, despite the lack of evidence, to confirm the recommendation to offer AChEIs, including galantamine, in people with PDD. The WG underlined that rivastigmine is currently the only AChEI with an indication for the treatment of PDD. However, evidence showed that donepezil has a better safety profile compared to rivastigmine, which showed an association with a higher risk of adverse events and withdrawals due to adverse events. Despite only evidence on AChEIs in people with mild to moderate PDD was available, the WG agreed to confirm the recommendation to consider treatment with AChEIs in people with severe PDD. The WG, in fact, agreed with the considerations reported in the NICE GL on the possible adverse events associated with discontinuing treatment with AChEIs.
A lower number of studies was available on the use of memantine in people with PDD. Two studies investigated the use of memantine in PDD compared to placebo reporting no differences between groups in any of the considered outcomes. However, the WG agreed to confirm the recommendation from the NICE GL to consider the use of memantine in people with PDD only if cholinesterase inhibitors are not tolerated or are contraindicated.
No evidence was identified on the co-prescription of AChEIs and memantine.

Acetylcholinesterase inhibitors in DLB

Review question 18b

Analysed evidence reported that people treated with AChEIs showed an improvement of around 1.8 point of the MMSE scale compared to placebo. However, only two studies reported a significant improvement in people treated with donepezil compared to placebo, while one study reported no difference between rivastigmine and placebo for the same outcome.

Both the systematic review preformed for the NICE GL and its update only identified studies on donepezil and rivastigmine. No studies were found on the use of galantamine in people with PDD. The WG discussed the opportunity of generalising results from studies on donepezil and rivastigmine to all the class of AChEIs. However, considering the risk-benefit profile of galantamine, the WG agreed, despite the lack of evidence, to confirm the recommendation to offer galantamine in people with DLB if donepezil and rivastigmine are not tolerated.

Available evidence supported the use of donepezil to improve global functions.

Evidence reported no effect of AChEIs in managing neuropsychiatric symptoms in people with DLB. Results suggested that rivastigmine might be more effective than donepezil in managing behavioural symptoms. However, only one study analysed this outcome, and results might be affected by the small sample size. Donepezil was generally better tolerated than rivastigmine. However, rivastigmine patch could improve compliance. Analysed studies, none of which were included after updating the systematic review, enrolled people with mild to moderate DLB. Given the lack of evidence on the safety of donepezil and rivastigmine in people with severe DLB, the WG agreed on a weak recommendation to consider donepezil and rivastigmine in people with severe DLB. Therefore, in people who started treatment with AChEIs in the mild to moderate phase of the disease, the decision to continue treatment should be individualised, considering the need for continuous monitoring and review of treatment in case of relevant adverse events.

A significantly lower number of studies was available on the use of memantine in people with DLB. Only one study investigated the use of memantine in DLB compared to placebo reporting no differences between groups in any of the considered outcomes. However, the WG agreed to confirm the recommendation from the NICE GL to consider the use of memantine in people with DLB only if cholinesterase inhibitors are not tolerated or are contraindicated.

No evidence was identified on the co-prescription of AChEIs and memantine.

The WG agreed to confirm the research recommendation from the NICE guideline for further studies to investigate the efficacy and safety of combination treatment with an AChEI and memantine for people with DLB.

Recommendations

Acetylcholinesterase inhibitors in PDD

90	Offer AChE inhibitors[38] for people with mild or moderate Parkinson's disease dementia.	STRONG IN FAVOR
91	Consider AChE inhibitors[39] for people with severe Parkinson's disease dementia.	WEAK IN FAVOR
92	Consider memantine[40] for people with Parkinson's disease dementia, only if AChE inhibitors are not tolerated or are contraindicated.	WEAK IN FAVOR

[38] Rivastigmine capsules is currently the only AChEI with an indication for the treatment of mild to moderate PDD. Use of donepezil, galantamine and rivastigmine patches is off label.

[39] Use of AChEI, including rivastigmine capsules, for the treatment of severe PDD is off label.

[40] Use of memantine for the treatment of PDD is off label.

Acetylcholinesterase inhibitors in DLB

93	Offer donepezil or rivastigmine to people with mild to moderate dementia with Lewy bodies.	STRONG IN FAVOR
94	Only consider galantamine for people with mild to moderate dementia with Lewy bodies if donepezil and rivastigmine are not tolerated.	WEAK IN FAVOR
95	Consider donepezil or rivastigmine for people with severe dementia with Lewy bodies.	WEAK IN FAVOR
96	Consider memantine for people with dementia with Lewy bodies if cholinesterase inhibitors are not tolerated or are contraindicated.	WEAK IN FAVOR

Research Recommendations

Acetylcholinesterase inhibitors for the treatment of DLB

19R	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?

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Acetylcholinesterase inhibitors and memantine for types of dementia other than Alzheimer's disease

Review question 19	**How effective are acetylcholinesterase inhibitors and memantine for types of dementia other than Alzheimer's disease?**

Literature review

	19
Records identified from databases	828
Studies assessed for eligibility	19
Included studies	0
Studies included in the NICE GL	16
Total number of included studies	16

Eligibility criteria

Population	People with a diagnosis of dementia other than Alzheimer's disease.
Interventions	• Donepezil. • Galantamine. • Memantine. • Rivastigmine. • Memantine plus acetylcholinesterase inhibitor.
Comparator	• Placebo • Each other • Combination of memantine plus acetylcholinesterase inhibitor
Outcomes	• Cognitive outcomes, including: – MMSE; – ADAS-Cog; – MoCA. • Global functions, including: – Global impression of change • Activities of daily living • Non-cognitive outcomes, including: – NPI; – Adverse events; – Study withdrawal; – Health-related quality of life; – Carer-reported outcomes; – Resource use and cost; – Entry to long stay care.

Aim

The objective of the systematic review, according to the strategy defined in the NICE guideline, was to identify all randomized controlled trials (RCTs) investigating the comparative efficacy of donepezil, galantamine, rivastigmine, and memantine for cognitive enhancement in dementia types other than Alzheimer's disease (AD). The use of cholinesterase inhibitors and memantine for Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB) is covered in questions 18a and 18b. The systematic review was initially targeted at identifying updated systematic reviews on the use of acetylcholinesterase inhibitors (AChEIs) and memantine in people with dementia types other than AD. Systematic reviews were analysed to identify primary studies. Additional structured literature searches were also performed to identify further relevant studies. Only RCTs reporting data on the efficacy (cognitive, functional and global measures) and safety of investigated treatments were included.

Summary of evidence

The systematic review performed for the NICE guideline identified 16 RCTs and one open-label study that met the predefined eligibility criteria. No studies were identified after updating the systematic review. All included studies compared the treatment with placebo.

Nine studies investigated the efficacy of acetylcholinesterase inhibitors (AChEIs) and memantine in people with vascular dementia:

- three studies compared donepezil with placebo (Black 2003, Román 2010, Wilkinson 2003);
- two studies compared galantamine with placebo (Auchus 2007, Small 2003);
- two studies compared rivastigmine with placebo (Ballard 2008, Mok 2007);
- two studies compared memantine with placebo (Orgogozo 2002, Wilcock 2002).

Three studies investigated the efficacy of AChEIs and memantine in people with frontotemporal dementia:

- one study compared galantamine with placebo (Kertesz 2008);
- two studies compared memantine with placebo (Boxer 2013, Vercelletto 2011).

Three studies investigated the efficacy of AChEIs and memantine in people with cognitive impairment in people witrh multiple sclerosis:

- one study compared donepezil with placebo (Krupp 2011)
- one study compared rivastigmine with placebo (Mäurer 2012);
- one study compared memantine with placebo (Peyro Saint-Paul 2016).

One study investigated the efficacy of rivastigmine in people with Huntington disease (Sešok 2014).

Acetylcholinesterase inhibitors in vascular dementia

Four studies (Ballard 2008, Black 2003, Mok 2007, Román 2010) reported an improvement in the intervention group compared to placebo in cognitive functions measured with MMSE (MD 0.58, 95%CI 0.30 – 0.86, I^2 0%, N=2,301, high certainty). Four studies (Ballard 2008, Black 2003, Román 2010, Wilkinson 2003) reported an improvement in the intervention group compared to placebo in the same outcome measured with ADAS-Cog (MD -1.36, 95%CI -2.03 – -0.70, I^2 52%, N=2,734, moderate certainty). Two studies (Auchus 2007, Small 2003) reported an improvement in the galantamine group compared to placebo in cognitive functions measured with ADAS-Cog (MD -1.59, 95%CI -2.39 – -0.78, I^2 0%, n = 926, high certainty). One study (Román 2010) reported an improvement in the donepezil group compared to placebo in cognitive functions measured with the VaDAS-cognitive subscale (MD -1.15, 95%CI -1.99 – -0.31, I^2 n.a., N=818, high certainty). Two studies (Auchus 2007, Román 2010) reported no differences between groups in the EXIT-25 scale (Executive interview 25 items) scores (MD -0.57, 95%CI -1.40 – 0.25, I^2 66%, N=1,683, low certainty). Four studies (Black

2003, Mok 2007, Román 2010, Wilkinson 2003) reported no differences between donepezil and placebo in global functions measured with CDR-SB (MD -0.17, 95%CI -0.33 – -0.00, I^2 58%, N=2,036, moderate certainty). One study (Ballard 2008) reported no differences between rivastigmine and placebo in global functions measured with VaD Assessment Scale (MD -1.03, 95%CI -2.62 – 0.02, I^2 n.a., N=682, low certainty). Two studies (Auchus 2007, Mok 2007) reported a worsening in the AChEIs group compared to placebo in neuropsychiatric symptoms measured with NPI (MD 1.76, 95%CI 0.28 – 3.24, I^2 0%, N=757, high certainty). One study (Ballard 2008) reported no differences between rivastigmine and placebo in neuropsychiatric symptoms measured with NPI-12 (MD 0.40, 95%CI -1.36 – 2.16, I^2 n.a., N=706, moderate certainty). Two studies (Auchus 2007, Ballard 2008) reported no differences between groups in functional abilities measured with ADCS-ADL (MD -0.13, 95%CI -1.16 – 0.90, I^2 20%, N=1,444, moderate certainty). Three studies (Black 2003, Mok 2007, Wilkinson 2003) reported no differences between groups in functional abilities measured with IADL (MD -0.38, 95%CI -1.04 – 0.27, I^2 68%, N=1,126, very low certainty). In terms of safety, five studies (Auchus 2007, Black 2003, Mok 2007, Román 2010, Wilkinson 2003) reported a higher risk of adverse events (RR 1.05, 95%CI 1.01 – 1.09, I^2 0%, N=2,949, high certainty) in the AChEIs group compared to placebo. Five studies (Auchus 2007, Ballard 2008, Black 2003, Román 2010, Wilkinson 2003) reported a higher risk of withdrawal due to adverse events (RR 2.40, 95%CI 1.61 – 3.59, I^2 39%, N=1,533, high certainty). Three studies (Auchus 2007, Ballard 2008, Mok 2007) reported no differences between groups in the frequency of serious adverse events (RR 1.11, 95%CI 0.95 – 1.30, I^2 0%, N=3,471, moderate certainty), and six studies (Auchus 2007, Ballard 2008, Black 2003, Mok 2007, Román 2010, Wilkinson 2003) reported no differences in mortality (RR 0.99, 95%CI 0.43 – 2.30, I^2 43%, N=3,726, low certainty).

Memantine in vascular dementia

One study (Orgogozo 2002) reported an improvement in the memantine group compared to placebo in cognitive functions measured with MMSE (MD 1.23, 95%CI 0.23 – 2.23, I^2 n.a., N=213, moderate certainty). Two studies (Orgogozo 2002, Wilcock 2002) reported an improvement in the memantine group in the same outcome measured with ADAS-Cog (MD -2.19, 95%CI -3.16 – -1.21, I^2 11%, N=752, high certainty). In terms of safety, one study (Wilcock 2002) reported no differences between groups in the frequency of adverse events (RR 1.03, 95%CI 0.94 – 1.13, I^2 n.a., N=579, moderate certainty), and one study (Orgogozo 2002) did reported differences between groups in the frequency of serious adverse events (RR 0.97, 95%CI 0.69 – 1.36, I^2 n.a., N=188, low certainty).

Acetylcholinesterase inhibitors in frontotemporal dementia

One study (Kerstesz 2008) investigated the efficacy and safety of galantamine for the treatment of the behavioural variant of frontotemporal dementia and primary progressive aphasia. The study enrolled 36 participants that were followed up for 26 weeks. The study reported no differences between the galantamine group and placebo in any of the considered cognitive, functional and behavioural outcomes (MMSE: MD 4.40, 95%CI -1.02 – 9.82, I^2 n.a., N=34, very low certainty; ADCS-ADL: MD 7.00, 95%CI -7.55 – 21.55, I^2 n.a., N=34, very low certainty; NPI: MD 5.80, 95%CI -7.25 – 18.85, I^2 n.a., N=34, very low certainty). In terms of safety, the study reported no differences between groups in the frequency of adverse events (RR 0.80, 95%CI 0.26 – 2.50, I^2 n.a., N=34, very low certainty) and withdrawals due to adverse events (RR 1.00, 95%CI 0.07 – 14.79, I^2 n.a., N=34, very low certainty).

Memantine in frontotemporal dementia

Two studies (Boxer 2013, Vercelletto 2011) investigated the efficacy and safety of memantine in people with the behavioural variant of frontotemporal dementia. The two studies (Boxer 2013, Vercelletto 2011) reported no differences between groups in cognitive functions (MMSE: MD 0.26, 95%CI -1.43 – 1.95, I^2 14%, N=105, very low certainty), and neuropsychiatric symptoms (NPI: MD -3.61, 95%CI -8.79 – 1.57, I^2 0%, N=103, very low certainty). One study (Boxer 2013) also reported no differences in global (CGIC: MD -0.50, 95%CI -

1.35 – 0.35, I^2 n.a., N=64, very low certainty; CDR-SB: MD -0.10, 95%CI -2.22 – 2.02, I^2 n.a., N=64, very low certainty) and motor functions (UPDRS: MD -0.30, 95%CI -3.46 – 2.86, I^2 n.a., N=64, very low certainty). In terms of safety, two studies reported no differences between groups in the frequency of serious adverse events (RR 0.65, 95%CI 0.29 – 1.48, I^2 1%, N=113, very low certainty) (Boxer 2013, Vercelletto 2011). One study (Vercelletto 2011) reported no differences between groups in the frequency of adverse events (RR 0.90, 95%CI 0.43 – 1.90, I^2 n.a., N=49, very low certainty), and withdrawals due to adverse events (RR 1.13, 95%CI 0.25 – 5.06, I^2 n.a., N=49, very low certainty), and in mortality rate (RR 5.63, 95%CI 0.28 – 111.43, I^2 n.a., N=49, very low certainty).

One study (n=17) (Boxer 2013) investigated the efficacy and safety of memantine in people with the semantic variant of frontotemporal dementia. The study reported no differences between groups in cognitive functions measured with MMSE (MD -0.40, 95%CI -3.09 – 2.29, I^2 n.a., N=17, very low certainty), and neuropsychiatric symptoms measured with NPI (MD 0.00, 95%CI -5.36 – 5.36, I^2 n.a., N=17, very low certainty). It also reported no differences in global (CGIC: MD 0.00, 95%CI -0.36 – 0.36, I^2 n.a., N=17, very low certainty; CDR-R-SB: MD 0.90, 95%CI -0.28 – 2.08, I^2 n.a., N=17, very low certainty) and motor functions (UPDRS: MD 3.30, 95%CI -3.14 – 9.74, I^2 n.a., N=17, very low certainty).

Acetylcholinesterase inhibitors in multiple sclerosis and cognitive impairment

One study (Mäurer 2012) reported no differences between groups in cognitive functions measured with MuSIC (Multiple Sclerosis Inventarium Cognition Score) (MD -0.86, 95%CI -3.17 – 1.45, I^2 n.a., N=81, low certainty). One study (Krupp 2011) reported no differences between groups in depressive symptoms measured with MADRS (MD -1.58, 95%CI -3.66 – 0.50, I^2 n.a., N=81, low certainty). In terms of safety, one study (Mäurer 2012) reported no differences between groups in the frequency of adverse events (RR 1.18, 95%CI 0.90 – 1.55, I^2 n.a., N=86, low certainty). Two studies (Krupp 2011, Mäurer 2012) reported no differences between groups in the frequency of serious adverse events (RR 0.46, 95%CI 0.12 – 1.70, N=206, very low certainty). One study (Mäurer 2012) reported no differences between groups in the frequency of multiple sclerosis relapses (RR 0.61, 95%CI 0.18 – 2.00, I^2 n.a., N=86, very low certainty).

Memantine in multiple sclerosis and cognitive impairment

One study (Peyro Saint-Paul 2016) investigated the efficacy and safety of memantine in people with cognitive decline and multiple sclerosis. The study reported no differences between groups in disease progression (MD -0.47, 95%CI -1.08 – 0.12, I^2 n.a., N=68, low certainty). In terms of safety, the study reported a higher risk of adverse events (RR 3.56, 95%CI 1.88 – 6.74, I^2 n.a., N=86, low certainty) in the memantine group compared to placebo. However, it reported no differences between groups in the frequency of withdrawals due to adverse events (RR 3.44, 95%CI 0.77 – 15.34, I^2 n.a., N=83, very low certainty).

Rivastigmine in Huntington's disease

One study on 18 participants (Sešok 2014) investigated the efficacy of rivastigmine from 1.5mg twice daily, increased to 3mg twice daily after three months of treatment in people with cognitive decline and Huntington's disease. The study reported no differences between groups in the Rey Complex Figure Test scores (RCFT delayed recall: MD -2.86, 95%CI -10.90 – 5.18, I^2 n.a., low certainty; RCFT immediate recall: MD -3.77, 95%CI -11.92 – 4.38, I^2 n.a., low certainty).

Analysis of evidence

Vascular dementia

Evidence from some studies reported an improvement in cognitive functions measured with MMSE in people with vascular dementia treated with acetylcholinesterase inhibitors (AChEIs) or memantine. However, this improvement appeared below the threshold considered as clinically relevant (MMSE >1.4 points). Evidence also reported an improvement of around 1.4 points of the ADAS-Cog scale. However, the heterogeneity among studies did not allow to consider results as consistently positive. Treatment with AChEIs, as reported in two studies, was also associated to a worsening of behavioural symptoms measured with the NPI scale. Moreover, studies reported an improvement in people treated with AChEIs compared to placebo in global functions and functional abilities, especially activities of daily living and independence in instrumental activities. Most of the included studies used the criteria for possible or probable vascular dementia and underlined that included participants with vascular dementia could have an underlying Alzheimer's dementia (AD). This is relevant as observed benefits could be due to the presence of a concomitant AD. As reported in some studies, in fact, no differences between AChEIs and placebo were observed in younger participants, where the presence of underlying AD is less likely, while a higher risk of cerebrovascular events and a higher mortality rate was observed. Therefore, the WG, in absence of new evidence, agreed to confirm the recommendation from the NICE guideline (GL) to consider AChE inhibitors or memantine for people with vascular dementia if they have suspected comorbid Alzheimer's disease, Parkinson's disease dementia or dementia with Lewy bodies. The lack of evidence on the comparative efficacy of AChEIs and memantine did not allow to indicate a treatment as more effective that the other, as all studies compared each treatment to placebo.

Frontotemporal dementia

Included studies had small samples and investigated the treatment of AChEIs and memantine in people with the behavioural variant of frontotemporal dementia (FTD) or with primary progressive aphasia. Studies did not have enough power to detect the expected differences. Moreover, there is currently no biological hypothesis to support the treatment with AChEIs as frontotemporal dementia does not cause deficits in cholinergic neurotransmission. As for memantine, its potential effectiveness was supported by its efficacy in treating behavioural symptoms in people with AD, and by the fact that people with vascular dementia also experience this type of symptoms. However, included studies reported no differences between memantine and placebo in behavioural symptoms, functional abilities, and global functions. Therefore, the WG, in absence of new evidence, agreed to confirm the recommendation from the NICE guideline not to offer AChE inhibitors or memantine to people with FTD.

Multiple sclerosis

The three studies investigating the efficacy of AChEIs in people with cognitive decline due to multiple sclerosis reported no differences between these drugs and placebo in any of the clinical outcomes and reported a higher risk of adverse events in people treated with memantine. This higher risk was one of the reasons, in line with the NICE GL, that led to the inclusion of cognitive decline due to multiple sclerosis in the systematic review. The aetiology of this type of cognitive decline, in fact, is still unclear, and no evidence is available indicating an impaired cholinergic neurotransmission or an increased glutamatergic activity in people with this type of cognitive decline. Therefore, to avoid inappropriate prescriptions of AChEIs or memantine in people with this type of cognitive decline, the WG, in absence of new evidence, agreed to confirm the recommendation from the NICE GL not to offer AChE inhibitors or memantine to people with cognitive impairment caused by multiple sclerosis.

Huntington's disease

Only one pilot study was available investigating the efficacy of rivastigmine compared to placebo in people with Huntington's disease, which reported no differences between groups in any of the clinical outcomes.

However, the study was small and the WG, in line with the approach adopted by the NICE GL, agreed that it would not be appropriate to make any recommendations for this population.

Recommendations

Acetylcholinesterase inhibitors in types of dementia other than Alzheimer's disease

97	Only consider cholinesterase inhibitors or memantine for people with vascular dementia if they have suspected comorbid Alzheimer's disease, Parkinson's disease dementia or dementia with Lewy bodies.	WEAK IN FAVOR
98	Do not offer cholinesterase inhibitors or memantine to people with frontotemporal dementia.	STRONG AGAINST
99	Do not offer cholinesterase inhibitors or memantine to people with cognitive impairment caused by multiple sclerosis.	STRONG AGAINST

Research Recommendations

No research recommendations were made.

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NON-PHARMACOLOGICAL INTERVENTIONS FOR COGNITIVE SYMPTOMS

Introduction

Based on the approach adopted by the NICE guideline (GL), the definition "non-pharmacological interventions" was used to refer to the entire spectrum of interventions that do not include the use of drugs (e.g., rehabilitative, psychosocial interventions, and/or the use of dietary supplements).
A non-pharmacological approach may improve and/or preserve cognitive functions in people with dementia, allowing them to continue performing their occupations and addressing behavioural symptoms.
Several different factors can have a role in the onset of symptoms related to cognitive impairment. Therefore, different types of interventions or treatments may be necessary based on specific individual needs. Differences in treatment needs can also be due diffences in the stage of the disease. Treatments in the early stages aim to preserve cognitive functions and facilitate the use of compensatory strategies. As the disease progresses, personalised interventions can help maintaining independence and managing activities of daily living. Offering group activities can provide opportunities for socialisation and peer support and can facilitate engagement. Moreover, creative and leisure activities can promote wellbeing in people with dementia at any stage of the disease.
This chapter summarises evidence from studies enrolling larger groups of people with dementia, at different stages of the disease, and have the primary objective of improving cognitive functions, functional abilities, and/or overall wellbeing. Analysed evidence does not include studies on interventions specifically aimed at treating non-cognitive symptoms, which are the topic of Question 21.
The non-pharmacological interventions investigated in the considered studies include acupuncture, aromatherapy, art therapy, physical activity, light therapy, games and video games, multimodal interventions, nutritional interventions, psychosocial interventions, specific interventions on cognitive functions, music therapy, psychotherapy, therapeutic robots, transcranial stimulation, animal-assisted therapy, reminiscence therapy, and occupational therapy.

When considering specific interventions on cognitive functions, literature reported significantly inconsistent definitions of cognitive stimulation, cognitive training, and cognitive rehabilitation in people with dementia. In particular, cognitive training and cognitive rehabilitation are often used interchangeably despite coming from different disciplines and having different objectives. For the purposes of this guideline, the following definitions were adopted:

- cognitive rehabilitation: aiming at identifying functional objectives that are relevant to the person living with dementia and working with them and their family members/caregivers towards their achievement. The focus is on improving or maintaining functioning in daily life based on the person's strengths, finding ways to compensate for impairment, and supporting independence. Cognitive rehabilitation does not aim at improving cognitive functions but at addressing the disability resulting from the impact of cognitive impairment on everyday functioning and activity;
- cognitive stimulation: including a range of activities and discussions (usually in a group) that are aimed at general improvement of cognitive and social functioning;
- cognitive training: training, with adaptable intensity and difficulty, based on a set of standard excercises and tasks that are designed to address specific cognitive functions (e.g. memory, language, attention).

Specific interventions for memory (memory training) and multimodal cognitive interventions were also included in this category.

Non-pharmacological interventions for people with dementia

Review question 20a	**What are the most effective non-pharmacological interventions for supporting cognitive functioning in people living with dementia?**
Review question 20b	**What are the most effective non-pharmacological interventions for supporting functional ability in people living with dementia?**
Review question 20c	**What are the most effective non-pharmacological interventions to support wellbeing in people living with dementia?**
Review question 20d	**What are the most effective methods of supporting people living with dementia to reduce harm and stay independent?**
Review question 20e	**What are the most effective non-pharmacological interventions for supporting cognitive functioning, functional ability and wellbeing in people with Mild Cognitive Impairment?**

Literature review

	20a, 20b, 20c, 20d	20e
Records identified from databases	20,824	6,864
Studies assessed for eligibility	317	139
Included studies	58	62
Studies included in the NICE GL	110	-
Total number of included studies	168	62

Eligibility criteria

Population	People aged ≥40 years living with dementia.
Interventions	Non-pharmacological interventions which may have a positive impact on cognitive functioning.
Comparator	Standard care.
Outcomes	• Clinical outcomes including cognitive, functional and behavioural ability. • Admissions to hospitals/care homes. • Access to health and social care support. • Experience and satisfaction of people with dementia and their carers. • Health-related quality of life of people with dementia and their carers. • Adverse events. • Resource use and costs.

Aim

The objective of the systematic literature review, in line with the strategy defined by the NICE Guideline, was to identify randomised controlled trials (RCT) investigating the effectiveness of any type of non-pharmacological intervention in the treatment of cognitive and functional symptoms and in maintaining the independence and well-being of people with dementia or Mild Cognitive Impairment (MCI).

The search strategy was initially aimed at identifying systematic reviews on the different considered interventions. Systematic reviews were then analysed to identify primary studies. Further structured and targeted literature searches were then carried out to identify further potentially relevant primary studies.

Studies were classified by type of intervention and, where possible within each category of interventions, they were classified by severity of dementia (e.g. mild, moderate, severe dementia). Only studies considering as their primary objective the treatment of cognitive symptoms and functional abilities in people with dementia, and reporting as secondary and/or safety outcomes non-cognitive measures such as schizophrenia or other psychotic disorders, and depressive or other behavioural symptoms, were included.

Summary of evidence

Non-pharmacological interventions in people with dementia

Review questions 20a, 20b, 20c and 20d

ACUPUNCTURE

Overall, four studies investigated acupuncture for the treatment of cognitive symptoms in people with dementia. Of these, two studies on 223 participants (Liu 2016, Wang 2014) reported no differences between groups in cognitive symptoms in people with mild to moderate dementia (MMSE: MD 1.88, 95% CI -3.31 – 7.07, I^2 88%, very low certainty). One study on 50 participants (Peng 2017) reported no differences between groups in cognitive symptoms in people with moderate to severe dementia (MD 3.53, 95% CI -0.74 – 7.80, I^2 NA, very low certainty). One study on 87 participants with mild to moderate dementia (Jia 2017), reported an improvement in in the intervention group compared to the control group in cognitive symptoms measured with ADAS-Cog (MD -4.20, 95% CI -6.26 – -2.14, I^2 NA, moderate certainty), but reported no differences between groups in ADL (MD 0.57, 95% CI -1.58 – 2.72, I^2 NA, low certainty).

ART THERAPY

Overall, two studies investigated art therapy for the treatment of cognitive symptoms in people with dementia. One study, on 40 participants with mild to severe dementia (Li 2017) reported no differences between groups in cognitive symptoms measured with MMSE (MD 3.85, 95% CI -0.19 – 7.89, I^2 NA, very low certainty). The second study, on 69 participants with moderate dementia (Johnson 2020), reported no differences between groups in cognitive functions measured with MoCA (MD 0.20, 95% CI -4.18 – 4.58, I^2 NA, very low certainty).

PHYSICAL EXERCISE

Dance

Two studies investigated the effectiveness of dance in people with dementia. The two studies (Hwang 2010, Van de Winckel 2004) reported no differences between groups in cognitive symptoms measured with MMSE (MD 2.86, 95% CI -0.44 – 6.17, n = 42, I^2 0%, very low certainty) in people with moderate dementia.

Aerobic exercise

Overall, seven studies investigated the effectiveness of aerobic exercise interventions. Two studies on 70 participants with mild dementia (Arcoverde 2014, Yang 2015) reported an improvement in cognitive symptoms measured with MMSE in the intervention group compared to the control group (MD 2.20, 95% CI 1.04 – 3.36, I^2 0%, moderate certainty). However, three studies on 292 participants (Cancela 2016, Miu 2008, Venturelli 2011) reported no differences between groups in cognitive symptoms in people with moderate dementia (MMSE: MD 1.98, 95% CI -1.57 – 5.53, I^2 91%, very low certainty). One study on 36 participants (Pedroso 2017) reported no differences between groups in cognitive symptoms in people with moderate to severe dementia (MMSE: MD 0.40, CI 95% -4.57 – 5.37, n = 36, I^2 NA, very low certainty). Three studies on 280 participants with moderate dementia (Bossers 2016, Cancela 2016, Venturelli 2011) reported no differences in functional abilities measured with different instruments (SMD 0.70, 95% CI -0.03 – 1.43, I^2 82%, very low certainty). One study on 50 participants (Yang 2015) reported no differences between groups in quality of life (MD 2.16, CI 95% -0.44 – 4.76, I^2 NA, low certainty).

Non-aerobic exercise

Overall, five studies investigated the effectiveness of non-aerobic physical exercise. When considering cognitive symptoms, one study on 114 participants (Papatsimpas 2023) reported an improvement in the intervention group compared to the control group in cognitive functions in people with mild dementia (ACE-R: MD 11.44, 95% CI 7.50 – 15.38, I^2 NA, low certainty). One study on 45 participants (Todri 2019) reported an improvement in the intervention group in the same outcome in people with mild to moderate dementia (MMSE: MD 2.26, 95% CI 0.42 – 4.10, I^2 NA, very low certainty). Two studies on 190 participants (Christofoletti 2008, Telenius 2015) reported no differenced between groups in the same outcome in people with moderate dementia (MMSE: MD 1.34, 95% CI 0.12 – 2.80, I^2 47%, very low certainty). One study on 114 participants (Papatsimpas 2023) reported an improvement in the intervention group compared to the control group in IADL in people with mild dementia (MD 1.67, 95% CI 0.77 – 2.57, I^2 NA, very low certainty). Two studies on 258 participants (Littbrand 2009, Telenius 2015) reported an improvement in the intervention group in functional abilities measured with different instruments in people with moderate dementia (SMD 0.29, 95% CI 0.04 – 0.54, I^2 0%, moderate certainty). When considering quality of life, one study on 90 participants with mild to moderate dementia (Todri 2019) reported an improvement in the intervention group compared to the control group (MD 3.72, 95% CI 0.44 – 7.00, I^2 NA, low certainty). However, another study on 163 participants with moderate dementia (Telenius 2015) reported no differences between groups (MD -0.90, 95% CI -2.99 – 1.19, I^2 NA, very low certainty).

Aerobic/non-aerobic combined exercise

Overall, 13 studies investigated aerobic/non-aerobic combined exercise. When considering cognitive outcomes, three studies on 302 participants (Hoffman 2015, Lok 2023, Vreugdenhil 2012) reported no differences between groups in cognitive functions in people with mild dementia (MMSE MD 1.62, 95% CI -0.14 – 3.39, I^2 85%, very low certainty). Two studies on 194 participants (Pitkälä 2013, Shaw 2021) showed no differences between groups in cognitive functions in people with moderate dementia (MMSE: MD 0.55, 95% CI -0.74 – 1.85, I^2 0%, low certainty). One study on 32 participants (Parvin 2020) and one study on 114 participants (Papatsimpas 2023) reported an improvement in cognitive status measured respectively with MoCA (MD 6.40, 95% CI 4.07 – 8.73, I^2 NA, moderate certainty) and ACE-R (MD 11.49, 95% CI 8.01 – 14.91, I^2 NA, low certainty) in people with mild dementia. Three studies on 344 participants (Hoffman 2015, Papatsimpas 2023, Vreugdenhil 2012) reported no differences in functional abilities measured with different instruments respectively in people with mild dementia (SMD 0.34, 95% CI -0.18 – 0.85, I2 79%, very low certainty). One study on 35 participants (Cezar 2021) and one study on 110 participants (Rolland 2007) reported no differences in functional abilities measured with different instruments respectively in people

with mild-to-moderate dementia (MD -8.70, 95% CI -25.18 – 7.78, I^2 NA, low certainty) and severe dementia (SMD 0.40, 95% CI -0.16 – 0.96, I^2 NA, moderate certainty). Four studies on 455 participants (Bossers 2016, Pitkälä 2013, Shaw 2021, Toots 2016) reported an improvement in functional abilities in the intervention group compared to the control group in people with moderate dementia (SMD 0.30, 95% CI 0.11 – 0.49, n = 455, I^2 0%, moderate certainty). When considering quality of life, two studies on219 participants (Hoffman 2015, Suttanon 2013) and two studies on 61 participants (Shaw 2021, Steinberg 2009) reported no differences between groups respectively in people with mild dementia (SMD 0.02, 95% CI -0.24 – 0.29, I^2 0%, low certainty) and moderate dementia (SMD -0.14, 95% CI -0.75 – 0.47, I^2 30%, low certainty).

Tai chi

Two studies investigated participation in Tai Chi sessions. One study, on 74 participants with mild to moderate dementia (Huang 2019) reported no differences between groups in cognitive functions measured with MoCA (MD 2.93, 95% CI -0.26 – 6.12, I^2 NA, very low certainty) and MMSE (MD 1.77, 95% CI -1.82 – 5,36, I^2 NA, very low certainty). One study on 74 participants (Cheng 2014) reported an improvement in the intervention group compared to the control group in cognitive functions in people with moderate dementia (MMSE: MD 3.70, 95% CI 1.40 – 6.00, I^2 NA, very low certainty).

LIGHT THERAPY

Two studies on people with moderate to severe dementia (Burns 2009, Graf 2001) investigated light therapy interventions with high intensity bright light. The two studies reported no differences between groups in cognitive symptoms measured with MMSE (MD 0.68, 95% CI -2.46 – 3.81, n = 64, I^2 0%, very low certainty).

MULTIMODAL INTERVENTIONS

Overall, six studies investigated multimodal interventions in people with dementia. One study (Christofoletti 2008) investigated the effects of a multidisciplinary program that included physiotherapy, occupational therapy and physical education reporting an improvement in cognitive functions measured with MMSE in the intervention group compared to the control group in people with moderate dementia (MD 1.3, 95% CI 0.19 – 2.41, n = 27, I^2 NA, moderate certainty). One study on 43 participants (Burgener 2008) reported no differences between groups in people with mild dementia after a multimodal intervention that included Tai Chi, Cognitive Behavioral Therapy (CBT) and participation in a support group (MMSE: MD 0.90, 95% CI -2.27 – 4.07, I^2 NA, very low certainty). One study (Luttenberger 2012) investigated an intervention including motor stimulation, training of activities of daily living and cognitive stimulation in people with moderate dementia and it report no differences between groups in ADL (MD 0.8, 95% CI -5.35 – 6.95, n = 119, I^2 NA, certainty very low).

One study (Young 2020) investigated a cognitive stimulation intervention in combination with Tai Chi and reported an improvement in the intervention group compared in cognitive functions (MMSE: MD 3.16, 95% CI 2.35 – 3.97, n = 80, I^2 NA, low certainty) in people with mild to moderate dementia. However, it reported no differences between groups in quality of life (MD -0.15, 95% CI -0.59 – 0.28, n = 80, I^2 NA, low certainty).

One study on 22 participants (Koltai 2001) with mild dementia investigated cognitive training and coping strategies administered both in groups and individually and reported no differences between groups in cognitive functions (MMSE: MD -0.96, 95% CI -3.21 – 1.29, I^2 NA, low certainty).

One study on 50 participants with mild to moderate dementia (Gebhard 2022) investigated physical exercise in combination with music listening and personalized support based on the preferences and habits of individual participants, provided by specifically trained multidisciplinary staff. The study reported no differences between groups in activities of daily living (B-ADL: MD -1.18, 95% CI -2.98 – 0.62, I^2 NA, very low certainty) and quality of life (QUALIDEM: MD -4.19, 95% CI -15.11 – 6.73, I^2 NA, low certainty).

NUTRITIONAL INTERVENTIONS

Folic acid

Overall, three studies investigated folic acid supplementation in people with dementia. One study on 26 participants (Shinto 2014) and two studies on 162 participants (Chen 2016, Connelly 2008) reported no differences between groups respectively in cognitive symptoms (MMSE: MD -0.40, 95% CI -1.06 – 0.26, n = 26, I^2 NA, low certainty) and in ADL (SMD 0.28, 95% CI -0.38 – 0.95, n = 162, I^2 70%, very low certainty).

Ketogenic diet

Only one study (Phillips 2021) investigated the effectiveness of a ketogenic diet reporting improved cognitive outcomes measured with MMSE (MD 3.13, 95% CI 1.14 – 5.12, n = 52, I^2 NA, low certainty) and quality of life (MD 3.37, 95% CI 0.43 – 6.31, n = 52, I^2 NA, very low certainty) in the intervention group compared to the control group.

Ginkgo biloba

Overall, six studies (Herrschaft 2012, Ihl 2012, Kanowski 2003, Napryenko 2007, Nikolova 2013, van Dongen 2000) investigated the effectiveness of ginkgo biloba extract in people with dementia. The six studies, on 1,922 participants, and two of them (Herrschaft 2012, Ihl 2012), on 806 participants, reported an improvement respectively in ADL (SMD 0.41, 95% CI 0.11 – 0.71, I^2 90%, very low certainty) and in quality of life (SMD 0.24, 95% CI 0.11 – 0.38, I^2 0%, moderate certainty) in the intervention group compared to the control group.

Ginseng

Three studies (Heo 2008, Heo 2012, Lee 2008) on 226 participants investigated the effectiveness of different doses of ginseng extract in people with dementia and reported no differences between groups in cognitive symptoms for all considered doses (1.5 g, 3 g, 4.5 g, 9 g) (MMSE: MD 0.31, 95% CI -0.52 – 1.15, I^2 90%, very low certainty).

Omega-3

Three studies investigated the effectiveness of omega-3 antioxidants in people with dementia. The three studies on 604 participants (Freund-Levi 2006, Quinn 2010, Shinto 2014) and two studies on 426 participants (Quinn 2010, Shinto 2014) reported no differences between groups respectively in cognitive functions (MMSE: MD 0.17, 95% CI -0.38 – 0.72, I^2 0%, low certainty) and ADL (SMD -0.05, 95% CI -0.48 – 0.39, I^2 38%, low certainty).

Selenium

Only one study (Tamtaji 2019) on 52 participants investigated the effectiveness of selenium and reported an improvement in the intervention group compared to the control group in cognitive outcomes (MMSE: MD 0.70, 95% CI 0.07 – 1.33, I^2 NA, low certainty).

Sodium oligomannate

Overall, three studies investigated the effectiveness of different doses of sodium oligomannate in people with dementia. The three studies (Wang 2020, Xiao 2021, Zhang 2022) on 1,108 participants reported an improvement in the intervention group compared to the control group in cognitive functions (ADAS-Cog: MD -2.77, 95% CI -6.80 – 1.26, I^2 97%, very low certainty) and ADL (SMD 0.13, 95% CI -0.04 – 0.30, I^2 12%, very low certainty).

Huperzine A

Overall, seven studies investigated the effectiveness of huperzine A in people with dementia. The seven studies, on 648 participants (Dong 2002, Liu 1995, Rafii 2011, Xu 1997, Yang 2003, Zhang 2002, Zhou 2004), reported an improvement in the intervention group compared to the control group in cognitive functions (MMSE: MD 2.80, 95% CI 1.61 – 3.99, I^2 76%, very low certainty) and ADL (SMD 0.54, 95% CI 0.23 – 0.85, I^2 65%, low certainty).

Other supplements

Three studies (Scheltens 2010, Scheltens 2012, Shah 2013) investigated the effectiveness of a supplement based on EPA, DHA, phospholipids, choline, uridine monophosphate, vitamin E, vitamin C, selenium, vitamin B12, vitamin B6, folic acid. One study (Scheltens 2010) on 210 participants reported no differences in cognitive functions measured with MMSE (MD -0.30, 95% CI -1.46 – 0.86, I^2 NA, low certainty). One study on 515 participants (Shah 2013) and one study on 206 participants (Scheltens 2012) reported no differences in the same outcome measured with ADAS-Cog (MD 0.52, 95% CI -2.01 – 3.05, I^2 NA, very low certainty) and the composite scores of the Neuropsychological Test Battery (NTB) (MD z-score 0.09, 95% CI -0.03 – 0.21, I^2 NA, very low certainty). Two studies on 739 participants (Scheltens 2010, Shah 2013) reported no differences between groups in ADCS-ADL (MD -0.25, 95% CI -2.91 – 2.42, I^2 0%, very low certainty).

PSYCHOSOCIAL INTERVENTIONS

One study (Mountain 2022) investigated a psychosocial intervention (Journeying through dementia) aimed at promoting the autonomy and independence of people in the early stages of the disease. The study reported no differences between the intervention group and the control group in IADL (MD 0.10, 95% CI -0.30 – 0.40, n = 371, I^2 NA, moderate certainty) and in the ability to manage the disease independently measured with the Self-Management Ability Scale (SMAS) (MD 1.50, 95% CI -2.30 – 5.30, n = 347, I^2 NA, moderate certainty).

COGNITIVE INTERVENTIONS

Cognitive rehabilitation (individual)

Overall, six studies investigated the effectiveness of individual cognitive rehabilitation in people with mild dementia. When considering cognitive outcomes, one study on 16 participants (Brueggen 2017) reported no differences between groups in cognitive functions (MMSE: MD 0.87, 95% CI -0.96 – 2.70, I^2 NA, low certainty). When considering functional outcomes, four studies on 728 participants (Amieva 2016, Clare 2010, Clare 2019, Kim 2015) reported an improvement in the intervention group compared to the control group in ADL (SMD 0.52, 95% CI 0.04 – 1.00, I^2 86%, low certainty). However, two studies on 484 participants (Brueggen 2017, Clarkson 2021) reported no differences in ADL (SMD -0.15, 95% CI -0.89 – 0.59, I^2 59%, very low certainty). Five studies on 789 participants (Amieva 2016, Brueggen 2017, Clare 2010, Clare 2019, Kim 2015) reported no differences between groups in quality of life (SMD 0.22, CI 95% -0.08 – 0.53, I^2 62%, very low certainty).

Cognitive stimulation (group)

Overall, 23 studies investigated the effectiveness of group cognitive stimulation in people with dementia. Ten studies on 408 participants (Baldelli 1993, Baldelli 2002, Bottino 2005, Breuil 1994, Buschert 2011, Chapman 2004, Cove 2014, Juárez-Cedillo 2020, Requena 2004, Requena 2006) reported an improvement in the intervention group compared to the control group in cognitive functions in people with mild dementia (MMSE: MD 2.61, CI 95% 1.45 – 3.77, I^2 42%, moderate certainty). Two studies on 121 participants (López 2020, Young 2018) reported an improvement in the intervention group in cognitive functions in people with mild to moderate dementia (MMSE: MD 2.24, 95% CI 0.01 – 4.46, n = 121, I^2 40%, very low certainty). Nine studies on 639 participants (Alves 2014, Capotosto 2017, Coen 2011, Kim 2016, Mapelli 2013, Orrell 2014,

Spector 2001, Spector 2003, Yamanaka 2013) reported an improvement in cognitive functions in people with moderate dementia (MMSE: MD 1.31, 95% CI 0.59 – 2.04, I^2 21%, moderate certainty). Two studies on 125 participants (Alvares-Pereira 2020, López 2020) reported an improvement in the intervention group in cognitive functions measured with ADAS-Cog in people with mild to moderate dementia (MD -2.76, 95% CI -4.7 – -0.83, I^2 0%, moderate certainty). However, one study on 50 participants (Juárez-Cedillo 2020) reported no differences between groups in the same outcome in people with mild dementia (MD -4.21, 95% CI -10.26 – 1.84, I^2 NA, low certainty). One study on 57 participants (Bhowmik 2023) reported no differences between groups in cognitive functions measured with ADAS-Cog (MD -5.89, 95% CI -11.01 – 0.77, I^2 NA, very low certainty) and MoCA (MD 3.59, 95% CI 0.72 – 6.46, I^2 NA, very low certainty) in people with dementia of unspecified severity.

When considering functional abilities, four studies on 142 participants (Baldelli 1993, Baldelli 2002, Bottino 2005, Ferrario 1991) reported no differences between groups in ADL in people with mild dementia (SMD 0.19, 95% CI -0.2 – 0.57, I^2 0%, low certainty). Two studies on 275 participants (Capotosto 2017, Orrell 2014) reported no differences between groups in the same outcome in people with moderate dementia (SMD 0.07, 95% CI -0.17 – 0.31, n = 275, I^2 0%, low certainty).

Seven studies on 595 participants (Alves 2014, Capotosto 2017, Coen 2011, Kim 2016, Orrell 2014, Spector 2003, Yamanaka 2013) reported an improvement in the intervention group compared with the control group in quality of life in people with moderate dementia (SMD 0.25, 95% CI 0.09 – 0.41, I^2 0%, moderate certainty). However, three studies on 111 participants (Buschert 2011, Chapman 2004, Cove 2014) and one study on 105 participants (Alvares-Pereira 2020) reported no differences between groups in the same outcome respectively in people with mild dementia (SMD 0.09, CI 95% -0.29 – 0.46, I^2 0%, low certainty) and mild to moderate dementia (MD 0.47, 95% CI -1.11 – 2.05, I^2 NA, low certainty).

Cognitive stimulation (individual)

Overall, six studies investigated the effectiveness of individual cognitive stimulation. When considering cognitive outcomes, two studies on 63 participants with mild to moderate dementia (Justo-Henriques 2023, Oliveira 2021) reported an improvement in the intervention group compared to the control group in cognitive function measured respectively with MMSE (MD 4.96, 95% CI 2.61 – 7.3, n = 63, I^2 0%, moderate certainty). One study on 46 participants with mild to moderate dementia (Justo-Henriques 2023) reported an improvement in the same outcome measured with MoCA (MD 7.01, 95% CI 3.91 – 10.11, n = 46, I^2 NA, moderate certainty). However, four studies on 457 participants (Camargo 2015, Onder 2005, Orgeta 2015, Tsantali 2017) reported no differences between groups in cognitive functions measured with MMSE in people with mild dementia (MD 0.38, 95% CI -0.66 – 1.41, I^2 66%, very low certainty). Two studies on 406 participants (Onder 2005, Orgeta 2015) reported no differences between groups in functional abilities in people with mild dementia (SMD 0.15, 95% CI -0.04 – 0.35, I^2 0%, moderate certainty).
Two studies on 272 participants (Orgeta 2015) and one study on 46 participants (Justo-Henriques 2023) reported no differences in quality of life respectively in people with mild dementia (MD -0.02, 95% CI -1.04 – 1.00, I^2 NA, moderate certainty) and mild to moderate dementia (MD 4.14, 95% CI -0.07 – 8.35, I^2 NA, low certainty).

Cognitive training (group)

Overall, five studies investigated the effectiveness of group cognitive training. Two studies on 172 participants (Bergamaschi 2013, Trebbastoni 2018) reported an improvement in the intervention group compared to the control group in cognitive functions in people with mild dementia (MMSE: MD 5.18, 95% CI 3.04 – 7.31, I^2 69%, very low certainty). However, one study on 25 participants (Tanaka 2021) reported no differences between groups in the same outcome in people with moderate dementia (MMSE: MD 0.00, 95% CI -5.41 – 5.41, I^2 NA, very low certainty). The same study (Tanaka 2021) reported no differences between

groups in quality of life (MD 3.4, 95% CI -1.32 – 8.12, I^2 NA, very low certainty). Three studies on 299 participants (Amieva 2016, Bergamaschi 2013, Cahn-Weiner 2003) with mild dementia reported no differences between groups in ADL (SMD 0.13, 95% CI -0.34 – 0.60, I^2 57%, very low certainty).

Cognitive training (individual)

Overall, 13 studies investigated the effectiveness of individual cognitive training in people with dementia. When considering cognitive outcomes, nine studies on 311 participants (Cavallo 2019, Davis 2001, de Luca 2016, Galante 2007, Heiss 1994, Kang 2019, Shyu 2022, Tsantali 2017, Yang 2017) reported an improvement in the intervention group in cognitive functions measured with MMSE in people with mild dementia (MD 2.43, 95% CI 0.86 – 4.00, I^2 75%, very low certainty). However, two studies on 31 participants with moderate dementia (de Vreese 1999, Lee 2013a) reported no differences between groups in cognitive functions measured with MMSE (MD -0.80, 95% CI -3.75 – 2.16, I^2 0%, very low certainty). One study on 147 participants with mild to moderate dementia (Kallio 2018) also reported no differences in cognitive functions measured with ADAS-Cog (MD -0.90, 95% CI -2.36 – 0.56, I^2 NA, low certainty). When considering functional abilities, two studies on 277 participants (Galante 2007, Loewenstein 2004) and two studies on 31 participants (de Vreese 1999, Lee 2013a) reported no differences between groups in ADL respectively in people with mild (SMD 0.02, 95% CI -0.22 – 0.25, I^2 0%, very low certainty) and moderate dementia (SMD 0.42, 95% CI -0.29 – 1.14, I^2 0%, low certainty). One study on 147 participants (Kallio 2018) reported no differences between groups in health-related quality of life in people with mild to moderate dementia (MD 0.00, 95% CI -0.03 – 0.03, I^2 NA, low certainty).

MUSIC THERAPY

Overall, nine studies investigated the effectiveness of active or receptive music therapy in people with dementia. Eight studies investigated active music therapy, including the use of musical instruments and singing, in people with dementia. When considering cognitive outcomes, two studies on 173 participants (Chu 2014, Zhang 2020b) reported an improvement in cognitive symptoms measured with MMSE in the intervention group compared to the control group in people with moderate to severe dementia (MD 2.19, 95% CI 0.48 – 3.89, I^2 0%, low certainty). However, two studies on 94 participants (Särkämö 2016, Wang 2018) reported no differences between groups in cognitive functions in people with mild-to-moderate dementia (MMSE: MD 0.45, 95% CI -0.5 – 1.39, I^2 0%, very low certainty). Three studies on 272 participants (Ceccato 2012, Hong 2011, Lyu 2018) also reported no differences between groups in cognitive functions in people with moderate dementia (MMSE: MD 1.29, 95% CI -1.62 – 4.21, I^2 88%, very low certainty). One study on 60 participants (Wang 2018) reported no differences in the same outcome measured with MoCA in people with mild dementia (MD 0.7, 95% CI -0.67 – 2.07, I^2 NA, low certainty). Two studies, the first on 46 participants (Särkämö 2016) and the second on 80 participants (Raglio 2015) reported no differences between groups in quality of life respectively in people with mild to moderate dementia (MD 0.80, 95% CI -1.83 – 3.43, I^2 NA, low certainty) and moderate to severe dementia (MD 2.20, 95% CI -1.32 – 5.72, I^2 NA, low certainty).

Three studies investigated receptive music therapy, including listening to personalized music, in people with dementia. When considering cognitive outcomes, two studies on 70 participants (Guétin 2009, Särkämö 2016) reported no differences between groups in people with mild to moderate dementia (MMSE: MD 1.66, CI 95% -0.42 – 3.74, I^2 0%, very low certainty). When considering quality of life, one study on 51 participants (Särkämö 2016) reported an improvement in QoL in people with mild to moderate dementia (MD 3.60, 95% CI 1.18 – 6.02, I^2 NA, low certainty). However, on study on 80 participants (Raglio 2015) reported no differences between groups in people with moderate to severe dementia (MD 2.30, 95% CI -1.64 – 6.24, I^2 NA, low certainty).

PSYCHOTHERAPY

Two studies (Burns 2005, Marshall 2015) investigated the effectiveness of psychotherapy in 92 participants with mild to moderate dementia and reported no differences between groups in cognitive symptoms (MMSE: MD -0.82, 95% CI -2.47 – 0.84, I^2 0%, moderate certainty).

ROBOT THERAPY

Only one study on 103 participants with moderate dementia (Chen 2020) investigated the effectiveness of an intervention with an interactive electronic doll capable of responding to different stimuli. The study reported no differences between groups in cognitive functions (MoCA: MD 1.00, 95% CI -1.39 – 3.39, I^2 NA, low certainty), functional abilities (ADL: MD -1.90, CI 95% -17.02 – 13.22, I^2 NA, very low certainty) and in quality of life (QoL: MD 1.3, 95% CI -1.94 – 4.54, I^2 NA, low certainty).

TRANSCRANICAL STIMULATION

Repetitive Transcranial Magnetic Stimulation

Overall, nine studies investigated the effectiveness of transcranial stimulation interventions via rTMS (repetitive Transcranial Magnetic Stimulation). When considering cognitive outcomes, nine studies on 295 participants (Ahmed 2012, Cotelli 2011, Jia 2021, Khedr 2020, Koch 2022, Lee 2016, Rabey 2013, Yao 2022, Zhao 2017) reported no differences between groups in cognitive functions measured with MMSE in people with mild to moderate dementia (MD 1.57, 95% CI -0.14 – 3.29, I^2 59%, very low certainty). However, one study on 9 participants with severe dementia (Ahmed 2012) reported no differences between groups in cognitive outcomes measured with MMSE (MD 0.80, 95% CI -1.13 – 2.73, I^2 NA, low certainty). Three studies on 107 participants with mild to moderate dementia (Koch 2022, Yao 2022, Zhao 2017) reported no differences in cognitive functions measured with ADAS-Cog (MD -2.41, 95% CI -5.73 – 0.91, I^2 0%, very low certainty). Three studies on 90 participants with mild to moderate dementia (Khedr 2020, Yao 2022, Zhao 2017) also reported no differences in cognitive functions measured with MoCA (MD 1.59, CI 95% -1.04 – 4.22, I^2 0%, low certainty). When considering functional abilities, three studies on 107 participants with mild to moderate dementia (Cotelli 2011, Khedr 2020, Koch 2022) reported no differences between groups in ADL (SMD 0.19, 95% CI -0.19 – 0.57, I^2 0%, low certainty). One study on 47 participants with mild to moderate dementia (Wu 2022) investigated the effectiveness of a different form of rTMS, intermittent theta burst protocol (intermittent Theta Burst Stimulation, iTBS). The study reported no differences between groups in cognitive functions measured with MMSE (MD 2.41, 95% CI -1.59 – 6.41, I^2 NA, very low certainty) and MoCA (MD 2.88, 95% CI -1.7 – 7.46, I^2 NA, very low certainty) and in functional abilities (ADL: MD -1.02, 95% CI -6.93 – 4.89, I^2 NA, very low certainty).

Transcranial Direct-Current Stimulation

Two studies investigated the effectiveness of tDCS (transcranial Direct-Current Stimulation) in people with mild to moderate dementia. The two studies, on 28 participants (Cotelli 2014, Im 2019), reported no differences between groups in cognitive outcomes (MMSE: MD 1.72, 95% CI -2.32 – 5.76, n = 28, I^2 0%, very low certainty). One study on nine participants (Cotelli 2014) also reported no differences between groups in IADL (MD 0.00, 95% CI -2.8 – 2.8, I^2 NA, very low certainty).

PET THERAPY

Two studies investigated the effectiveness of pet therapy with service dogs specifically trained to interact with people with dementia. The two studies, on 374 participants with moderate to severe dementia (Quintavalla 2021, Vegue Parra 2021), reported no differences between groups in cognitive symptoms (MMSE: MD 2.07, 95% CI -2.22 – 6.37, I^2 51%, very low certainty).

DOLL THERAPY

One study on 29 participants with mild to moderate dementia (Yilmaz 2021) investigated the effectiveness of an intervention based on the use of dolls and reported no differences between groups in cognitive symptoms measured with MMSE (MD -0.40, 95% CI -1.87 – 2.67, I^2 NA, low certainty).

REMINESCENCE THERAPY

Overall, 11 studies investigated the effectiveness of group reminiscence therapy in people with dementia. When considering cognitive outcomes, five studies on 278 participants (Ito 2007, Lök 2019, Tadaka 2007, Tanaka 2017, Wang 2007) reported an improvement in cognitive symptoms in people with moderate dementia (MMSE: MD 2.33, 95% CI 1.69 – 2.97, I^2 0%, moderate certainty). One study on 103 participants (Wu 2016) and one study on 18 participants (Deponte 2007) reported no differences between groups in cognitive functions respectively in people with mild dementia (MMSE: MD 0.5, 95% CI -0.1 – 1.10, I^2 NA, low certainty) and moderate to severe dementia (MMSE: MD 3.3, 95% CI -1.03 – 7.63, I^2 NA, low certainty). Two studies, reported in three publications, on 684 participants (Charlesworth 2016, Woods 2012, Woods 2016) reported no differences between groups in functional abilities measured with different tools in people with mild to moderate dementia (SMD -0.04, 95% CI -0.28 – 0.20, I^2 56%, low certainty). One study on 18 participants (Deponte 2007) also reported no differences between groups inin the same outcome in people with moderate to severe dementia (MD -2.40, 95% CI -6.93 – 2.13, I^2 NA, very low certainty). When considering quality of life, one study on 227 participants (Amieva 2016) and two studies on 639 participants (Charlesworth 2016, Woods 2012, Woods 2016) reported no differences between groups respectively in people with mild dementia (MD 0.11, 95% CI -1.13 – 1.35, I^2 NA, moderate certainty) and mild to moderate dementia (SMD 0.07, 95% CI -0.09 – 0.23, I^2 0%, moderate certainty).

Overall, four studies investigated the effectiveness of individual reminiscence therapy. When considering cognitive outcomes, two studies on 96 participants (Tanaka 2017, Van Bogaert 2013) reported an improvement in the intervention group compared to the control group in cognitive functions in people with moderate dementia (MMSE: MD 1.68, 95% CI 0.43 – 2.94, I^2 18%, low certainty). However, two studies on 81 participants (Lopes 2016, Van Bogaert 2013) reported no differences between groups in people with mild dementia (MMSE: MD 1.18, 95% CI -1.99 – 4.36, I^2 72%, very low certainty). One study on 23 participants (Subramaniam 2014) reported an improvement in the intervention group compared to the control group in quality of life in people with mild to moderate dementia (MD 7, 95% CI 2.13 – 11.87, n = 23, I^2 NA, moderate certainty).

OCCUPATIONAL THERAPY

Overall, seven studies investigated the effectiveness of occupational therapy in people with mild to moderate dementia (Gitlin 2008, Gitlin 2010, Gitlin 2018, Graff 2007, Kim 2020, Voigt-Radloff 2011, Wenborn 2021). Of these, two studies on 503 participants (Kim 2020, Wenborn 2021) reported no differences between groups on cognitive functions (MMSE: MD 0.68, 95% CI -0.37 – 1.73, I^2 4%, low certainty). Three studies on 781 participants (Gitlin 2010, Voigt-Radloff 2011, Wenborn 2021) reported no differences between groups in functional outcomes (SMD 0.09, 95% CI -0.14 – 0.31, I^2 53%, low certainty). Six studies on 994 participants (Gitlin 2008, Gitlin 2010, Graff 2007, Kim 2020, Voigt-Radloff 2011, Wenborn 2021) reported no differences between groups in quality of life (SMD 0.39, 95% CI 0.04 – 0.73, I^2 83%, low certainty). One study on 160 participants (Gitlin 2018) investigated the effectiveness of the Tailored Activity Program (TAP), a program of personalised activities provided by an occupational therapist. The study reported a lower mean number of ADLs and IADLs which assistance was required in the intervention group compared to the control group (MD -0.80, 95% CI -1.41 – -0.20, I^2 NA, low certainty). It also reported a lower number specifically of ADLs (MD -0.61, 95% CI -1, 08 – -0.14, I^2 NA, low certainty) and IADL for which assistance was required (MD -0.25, 95% CI -0.54 – -0.04, I^2 NA, low certainty). The study also reported an improvement in the overall level of dependence both in ADL and IADL (MD 4.09, 95% CI, 1.06 – 7.13, I^2 NA, very low certainty), and specifically

in ADLs (MD 2.37, 95% CI 0.32 – 4.42, I^2 NA, very low certainty) and in IADLs (MD 1.57, 95% CI 0.05 – 3.08, I^2 NA, very low certainty).

Non-pharmacological interventions in people with mild cognitive impairment

Review question 20e

ACUPUNCTURE

Overall, three studies investigated acupuncture in people with Mild Cognitive Impairment (MCI). The three studies (Choi 2021, Sun 2021, Tan 2017), on 147 participants, reported an improvement in cognitive symptoms measured with MoCA (MD 2.73, 95% CI 0.60 – 4.87, I^2 85%, very low certainty). Two studies on 108 participants (Sun 2021, Tan 2017), reported an improvement in cognitive symptoms (MMSE: MD 2.72, 95% CI 2.06 – 3.39, n = 108, I^2 0%, low certainty). Two of the three studies (Choi 2021, Tan 2017) reported an improvement in cognitive symptoms measured with ADAS-Cog (MD -1.57, 95% CI -2.42 – -0.72, n = 71, I^2 0%, low certainty).

AROMATHERAPY

Only one study (Kohanpour 2017) investigated aromatherapy and reported an improvement in cognitive symptoms (MMSE: MD 1.6, 95% CI 0.35 – 2.85, n = 20, I^2 NA, very low certainty) in the intervention group compared to controls.

ART THERAPY

Two studies investigated art therapy in people with MCI. One study on 90 participants (Lin 2022) reported an improvement in the intervention group compared to the control group in cognitive symptoms measured with MMSE (MD 1.72, 95% CI 0.58 – 2.87, I^2 NA, low certainty), MoCA (MD 1.88, 95% CI 0.42 – 3.34, I^2 NA, low certainty). It also reported an improvement in the specific RAVL (Rey Auditory Verbal Learning) scores for recognition (MD 2.94, 95% CI 1.41 – 4.48, I^2 NA, moderate certainty), immediate recall (MD 4.23, 95% CI 1.67 – 6.80, I^2 NA, moderate certainty) and delayed recall (MD 1.58, 95% CI 0.24 – 2.92, I^2 NA, moderate certainty). The second study (Mahendran 2018), on 44 participants, reported an improvement in the intervention group compared to the control group in the memory domains of the RAVL test (MD z-score 0.31, 95% CI 0.03 – 0.59, n = 44, I^2 NA, moderate certainty). However, it reported no differences between groups in the recognition (MD z-score 0.32, 95% CI -0.25 – 0.89, n = 44, I^2 NA, low certainty) and delayed recall (MD z-score 0.14, 95% CI -0.12 – 0.40, I^2 NA, low certainty) scores of the same scale. The two studies (Lin 2022, Mahendran 2018), on 134 participants, reported no differences between groups in depressive symptoms (GDS: MD -1.70, 95% CI -4.11 – 0.72, I^2 64%, low certainty) and anxiety (SMD -0.37, 95% CI -0.96 – 0.21, I^2 62%, low certainty).

PHYSICAL EXERCISE

Dance

Overall, six studies investigated the effectiveness of ballroom dancing or other dance routines in people with MCI. Four studies (Chang 2021, Dominguez 2018, Qi 2019, Zhu 2018) on 371 participants reported an improvement in the intervention group compared to the control group in cognitive functions measured with MoCA (MD 0.99, 95% CI 0.27 – 1.71, n = 371, I^2 26%, moderate certainty). One study (Dominguez 2018) on 171 participants also reported an improvement in cognitive functions measured with ADAS-Cog (MD -2.30, 95% CI -4.56 – -0.04, n = 171, I^2 NA, low certainty). However, three studies on 295 participants (Doi 2017, Lazarou 2017, Qi 2019) reported no differences between groups in the same outcome measured with MMSE (MD 0.48, 95% CI -1.09 – 2.05, I^2 86%, very low certainty). Two studies (Qi 2019, Zhu 2018) on 92 participants reported an improvement in WMS-RLM scores (Wechsler Memory Scale-Revised Logical Memory) (MD 3.84,

95% CI 1.42 – 6.25, I^2 31%, low certainty). However, three studies (Doi 2017, Qi 2019, Zhu 2018) on 225 participants reported no differences between groups in TMT-A (Trail Making Test A) (MD -5.83, 95% CI -15.34 – 3.68, I^2 51%, very low certainty) and TMT-B (MD -8.29, 95% CI -23.75 – 7.17, I^2 35%, low certainty) scores. Three studies (Chang 2021, Dominguez 2018, Zhu 2018) on 340 participants reported an improvement in depressive symptoms in the intervention group compared to controls (GDS: MD -0.81, 95% CI -1.32 – -0.29, I^2 0%, moderate certainty), while one study (Dominguez 2018) on 171 participants reported no significant differences in IADL (MD -0.5, 95% CI -1.62 – 0.62, I^2 NA, low certainty).

Aerobic exercise

Overall, six studies investigated the effectiveness of aerobic physical exercise in people with MCI. Three studies (Avenali 2021, Bademli 2019, Kohanpour 2017) on 114 participants reported an improvement in cognitive functions measured with MMSE (MD 2.36, 95% CI 0.03 – 4.69, I^2 86%, very low certainty). However, two studies (Avenali 2021, Tao 2019) on 71 participants reported no differences between groups in the same outcome measured with MoCA (MD 0.10, 95% CI -1.04 – 1.24, I^2 11%, low certainty). One study on 32 participants (Combourieu Donnezan 2018) reported no differences between groups in Digit Span Forward (MD 0.41, 95% CI -0.49 – 1.31, I^2 NA, low certainty) and Digit Span Backward (MD 0.57, 95% CI -0.35 – 1.49, I^2 NA, low certainty) scores. When considering functional outcomes, one study (Law 2022) on 73 participants reported no differences between groups in IADL (MD 0.83, CI 95% -1.90 – 3.56, n = 73, I^2 NA, low certainty).

Non-aerobic exercise

Overall, four studies investigated the effectiveness of non-aerobic physical exercise in people with MCI. One study on 60 participants (Wei 2014) and one study on 45 participants (Lü 2016) reported an improvement in cognitive functions measured respectively with MMSE (MD 1.53, 95% CI 0.61 – 2.45, I^2 NA, moderate certainty) and ADAS-Cog (MD -4.32, 95% CI -6.95 – -1.69, I^2 NA, moderate certainty). However, two studies on 62 participants (Hong 2018, Tao 2019) reported no differences between groups in the same outcome measured with MoCA (MD 0.97, 95% CI -0.17 – 2.11, I^2 0%, low certainty). Two studies on 67 participants (Hong 2018, Lü 2016) reported no differences between groups in Digit Span Forward (MD -0.02, 95% CI -0.61 – 0.58, I^2 0%, low certainty) and Digit Span Backward (MD 0.64, 95% CI -0.52 – 1.81, I^2 65%, very low certainty) scores. When considering functional outcomes one study on 73 participants (Wei 2014) reported an improvement in ADL performance in the intervention group compared to controls (MD -1.27, 95% CI -2.25 – -0.29, I^2 NA, moderate certainty).

Aerobic/non-aerobic combined exercise

Three studies investigated the effectiveness of the combination of aerobic and non-aerobic physical exercise in people with MCI. Two studies on 111 participants (de Oliveira Silva 2019, Suzuki 2013) and one study on 92participants (Suzuki 2013) reported no differences between groups in cognitive outcomes measured respectively with MMSE (MD 0.41, 95% CI -0.58 – 1.4, n = 111, I^2 0%, low certainty) and ADAS-Cog (MD -0.60, 95% CI -1.43 – 0.23, n = 92, I^2 NA, low certainty). When considering functional outcomes, one study on 57 participants (Fonte 2019) reported an improvement in IADL in the intervention group compared to the control group (MD 21.6, 95% CI 3.07 – 40.13, I^2 NA, low certainty), but reported no differences between groups in executive functions (MD 0.00, 95% CI -2.19 – 2.19, I^2 NA, low certainty).

Tai chi

Only two studies assessed the effectiveness of Tai Chi in people with MCI. Of these, one study (Liu 2022) on 34 participants reported no differences between groups in cognitive outcomes measured with MoCA (MD 1.00, 95% CI -1.78 – 3.78, I^2 NA, low certainty). The second study (Sungkarat 2018), on 66 participants, reported an improvement in the intervention group compared to the control group in TMT B-A (Trail Making

Test B-A) scores (MD -0.4, 95% CI -0.57 – -0.23, I^2 NA, low certainty). However, it reported no differences between groups in Digit Span scores (MD 0.04, 95% CI -0.04 – 0.12, I^2 NA, low certainty).

GAMES AND VIDEOGAMES

Overall, six studies investigated the effectiveness of interventions based on the use of games or video games in people with MCI.

Two studies (Xue 2021, Zhang 2020a) investigated the effectiveness of interventions based on group games or board games. One study on 72 participants (Xue 2021) reported an improvement in depressive symptoms (GDS: MD -1.36, CI 95% -1.91 – -0.81, I^2 NA, moderate certainty), while the two studies, on 141 participants, reported no differences between groups in cognitive outcomes (MoCA: MD 0.97, 95% CI -0.73 – 2.67, I^2 73%, low certainty).

Four studies investigated the effectiveness of video-game based interventions. Three studies on 88 participants (Liu 2022, Park 2020, Schwenk 2016) and one study on 68 participants (Thapa 2020) reported no differences between groups in cognitive outcomes measured respectively with MoCA (MD 1.10, 95% CI -1.37 – 3.58, I^2 64%, very low certainty) and MMSE (MD 0.80, 95% CI -0.83 – 2.43, I^2 NA, low certainty). However, two studies on 55 participants (Park 2020, Schwenk 2016) reported an improvement in the intervention group compared to the control group in TMT-A (Trail Making Test A) (MD -7.05, 95% CI -10.35 – -3.76, I^2 0%, moderate certainty), but not in TMT-B (MD -6.06, 95% CI -14.57 – 2.46, I^2 0%, low certainty) scores. One study on 35 participants (Park 2020) reported an improvement in the intervention group in Digit Span Backward (MD 1.1, 95% CI 0.39 – 1.81, I^2 NA, moderate certainty), but not in Digit Span Forward (MD 0.2, 95% CI -0.35 – 0.75, I^2 NA, low certainty), scores.

COGNITIVE INTERVENTIONS

Multimodal cognitive interventions

Overall, three studies investigated the effectiveness of multimodal cognitive interventions delivered either as individual sessions at home or as group sessions in local facilities.

When considering home-based interventions, one study on 153 participants (Jeong 2016) reported an improvement in the intervention group compared to the control group in cognitive functions measured with modified-ADAS-Cog (MD -1.70, 95% CI -3.17 – -0.23, I^2 NA, moderate certainty) and CDR-SB (MD -0.24, 95% CI -0.43 – -0.05, I^2 NA, moderate certainty). However, it reported no differences between groups in the same outcome measured with MMSE (MD 0.40, 95% CI -0.20 – 1.00, I^2 NA, low certainty), and in ADL (B-ADL: MD 0.10, 95% CI -0.19 – 0.39, I^2 NA, low certainty) and depressive symptoms (MD -0.40, 95% CI -1.22 – 0.42, I^2 NA, low certainty).

When considering group interventions, two studies on 193 participants (Jeong 2016, Rojas 2013) and one study on 147 participants (Jeong 2016) reported no differences between groups in cognitive functions measured respectively with MMSE (MD 0.69, 95% CI -1.00 – 2.38, I^2 72%, very low certainty) and modified-ADAS-Cog (MD -1.50, 95% CI -3.02 – 0.02, I^2 NA, low certainty). This last study (Jeong 2016) reported no differences between groups in the same outcome measured with CDR-SB (MD -0.09, 95% CI -0.29 – 0.11, I^2 NA, low certainty). One study on 46 participants (Rojas 2013) and one study on 30 participants (Kurz 2009) also reported no differences between groups in the same outcome measured respectively CDR (MD -0.06, 95% CI -0.16 – 0.04, I^2 NA, low certainty) and CVLT (California Verbal Learning Test) (MD 1.40, 95% CI -2.73 – 5.53, I^2 NA, low certainty). Two studies on 177 participants (Jeong 2016, Kurz 2009) reported no differences between groups in ADL (B-ADL: MD -0.03, 95% CI -0.35 – 0.29, I^2 0%, low certainty) and in depressive symptoms (SMD -0.38, 95% CI -1.12 – 0.37, I^2 80%, very low certainty).

Memory training

Overall, three studies investigated the effectiveness of memory training in people with MCI. Specifically, two studies investigated visual imagery interventions (Konsztowicz 2013, Lajeunesse 2022), one study investigated an intervention based on memory aids and supports (Greenaway 2013), and one study investigated a compensatory intervention (Konsztowicz 2013).

When considering visual imagery interventions, one study on 24 participants (Lajeunesse 2022) reported no differences between groups in depressive symptoms (GDS: MD -0.85, 95% CI -6.26 – 4.56, I^2 NA, low certainty). It also reported no differences in memory assessed using the CAPM scale (Comprehensive Assessment of Perspective Memory) (MD frequency -2.90, 95% CI -18.64 – 12.84, I^2 NA, low certainty; MD impact -10.85, 95% CI -33.66 – 11.96, I^2 NA, low certainty). One study on 12 participants (Konsztowicz 2013) reported no differences between groups in immediate WL (Word List) scores (MD -0.42, 95% CI -2.33 – 1.49, I^2 NA, certainty low), delayed WL scores (MD -0.25, 95% CI -2.79 – 2.29, I^2 NA, low certainty), and MMQ scores (Multifactorial Memory Questionnaire) (MD 4.10, 95% CI -9.43 – 17.63, I^2 NA, low certainty).

When considering memory supports, one study on 40 participants (Greenaway 2013) reported no differences between groups in cognitive functions (MMSE: MD -0.40, 95% CI -2.17 – 1.37, I^2 NA, low certainty) and in depressive symptoms (CES-D: MD 0.30, 95% CI -6.45 – 7.05, I^2 NA, low certainty).

When considering compensatory interventions, one study on 11 participants (Konsztowicz 2013) reported an improvement in the intervention group compared to the control group in immediate WL test scores (MD -0.94, 95% CI -1.85 – -0.03, I^2 NA, moderate certainty). However, it reported no differences between groups delayed WL scores (MD 1.67, 95% CI -0.56 – 3.90, I^2 NA, low certainty) and MMQ scores (MD -1.00, 95% CI -16.9 – 14.9, I^2 NA, low certainty).

Cognitive rehabilitation

Two studies investigated the effectiveness of cognitive rehabilitation using pen and paper or computer support. One study (Bernini 2021) enrolled 48 participants randomised to three treatment arms (18 randomised to computer-based – CB – cognitive rehabilitation, 12 treated with cognitive rehabilitation using pen and paper – PP – and 18 controls). The study reported no differences between groups in cognitive functions (MMSE: CB MD -0.18, 95%CI -2.31 – 1.95, I^2 NA, very low certainty; PP MD -0.29, 95% CI -2.35 – 1.77, I^2 NA, very low certainty; MoCA: CB MD 2.42, 95% CI -0.23 – 5.07, I^2 NA, very low certainty; MD PP 0.63, 95%CI -2.56 – 3.82, I^2 NA, very low certainty). It also reported no differences in executive functions (CB MD 0.25, 95% CI -0.49 – 0.99, I^2 NA, low certainty; PP MD 0.40, 95% CI -0.31 – 1.11, I^2 NA, low certainty). One study on 60 participants (Fonte 2019) reported an improvement in the PP group compared to the control group in cognitive and behavioural functions (FAB, Frontal Assessment Battery: MD 2.90, 95% CI 0.90 – 4.90, I^2 NA, moderate certainty). It also reported an improvement in memory functions (RBMT, Rivermead Behavioral Memory Test: MD 25.4, 95% CI 6.09 – 44.71, I^2 NA, moderate certainty) and in IADL (MD 30.00, 95% CI 12.55 – 47.45, I^2 NA, moderate certainty).

Cognitive training

Seven studies investigated the effectiveness of cognitive training in people with MCI. One study on 141 participants (Li 2019) reported an improvement in the intervention group compared to the control group in cognitive functions measured with standardized MMSE (MD 0.73, CI 95% 0.42 – 1.04, n = 141, I^2 NA, moderate certainty). However, three studies on 258 participants (Giuli 2016, Han 2017, Sun 2021), reported no differences between groups in the same outcome measured respectively with MMSE (MD 1.31, 95% CI -0.13 – 2.76, I^2 77%, very low certainty). Two studies on 136 participants (Sukontapol 2018, Sun 2021) and one study on 29 participants (Law 2019) reported no differences between groups in the same outcome measured respectively with MoCA (MD 3.36, 95% CI -0.11 – 6.83, I^2 93%, very low certainty) and NCSE (Neurobehavioral Cognitive Status Examination) (MD 0.10, 95% CI -8.65 – 8.85, I^2 NA, low certainty). One study on 141

participants (Li 2019) and one study on 97 participants (Giuli 2016) reported an improvement in the intervention group in RAVL scores (Rey Auditory Verbal Learning) (MD standardized scores 0.4, 95% CI 0.06 – 0.74, I^2 NA, moderate certainty) and WLMT scores (Wechsler Logical Memory Test) (MD 17.48, 95% CI 16.22 – 18.74, I^2 NA, moderate certainty). One study on 85 participants (Han 2017) and one study on 30 participants (Comborieu Donnezan 2018) reported an improvement in the intervention group compared to the control group in Verbal Span Backward scores (MD 0.63, 95% CI 0.17 – 1.09, I^2 NA, moderate certainty) and reasoning matrix (MD 5.73, 95% CI 0.45 – 11.01, I^2 NA, moderate certainty) scores.

One study on 29 participants (Law 2019) reported no differences between groups in CVVLT scores (MD -1.56, 95% CI -6.07 – 2.95, I^2 NA, low certainty). One study on 97 participants (Giuli 2016) and one study on 30 participants (Comborieu Donnezan 2018) also reported no differences in Verbal Span Forward (MD 0.35, 95% CI -0.10 – 0.80, I^2 NA, low certainty), and Digit Span Forward (MD 0.85, CI 95% -0.07 – 1.77, I^2 NA, low certainty) and Backward (MD 0.64, 95% CI -0.21 – 1.49, I^2 NA, low certainty). Three studies on 242 participants (Giuli 2016, Han 2017, Sukontapol 2018) and two studies on 126 participants (Giuli 2016, Law 2019) reported no differences between groups respectively in depressive symptoms (GDS: MD -0.59, 95% CI -1.30 – 0.12, I^2 0%, low certainty) and in IADL (MD 0.33, 95% CI -0.21 – 0.87, I^2 0%, low certainty). One study on 160participants (Li 2019) reported no differences between groups in the rate of conversion from MCI to AD (RR 0.57, 95% CI 0.30 – 1.08, I^2 NA, low certainty).

MULTIMODAL INTERVENTIONS

Overall, six studies investigated the effectiveness of multimodal interventions in people with MCI. These included the combination of dietary interventions, physical and cognitive training, monitoring of metabolic and vascular risk indicators (Yang 2022); aerobic exercise, promotion of physical activity, cognitive, behavioural and multi-task exercises (Jeong 2021, Park 2019a); aerobic, strength, balance and coordination training, and sensory stimulation (Li 2021a); aerobic and muscle strength training, postural balance, and dual-task exercises (Shimada 2018, Suzuki 2012).

Five studies on 517 participants (Jeong 2021, Li 2021a, Park 2019a, Shimada 2018, Suzuki 2012), and two studies on 63 participants (Jeong 2021, Park 2019a), reported no differences between groups in cognitive functions measured with MMSE (MD 1.00, 95% CI -0.01 – 2.01, I^2 66%, very low certainty) and ADAS-Cog (MD -2.04, 95% CI -4.14 – 0.06, I^2 0%, very low certainty). Two studies on 196 participants (Li 2021a, Yang 2022) reported an improvement in the intervention group compared to the control group in cognitive outcomes measured with MoCA (MD 3.96, 95% CI 1.29 – 6.62, I^2 95%, very low certainty). Two studies on 358 participants (Shimada 2018, Suzuki 2012) reported no differences between groups in the logic memory WMS-RLM (Wechsler Memory Scale-Revised Logical Memory) scores (MD 0.52, 95% CI -1.00 – 2.04, I^2 66%, low certainty). Two studies on 161 participants (Park 2019a, Yang 2022) reported no differences between groups in depressive symptoms (GDS: MD -1.24, 95% CI -3.06 – 0.58, I^2 91%, very low certainty).

NUTRITIONAL INTERVENTIONS

Polyunsaturated fatty acids

Overall, four studies investigated the effectiveness of dietary supplements based on polyunsaturated fatty acids in people with MCI. Overall, the four studies (Bai 2021[41], Lee 2013b, Li 2021b, Mengelberg 2022), on 270 participants, reported an improvement in the intervention group compared to the control group, in the Digit Span test scores (MD 0.98, 95% CI 0.30 – 1.66, I^2 34%, moderate certainty). Two studies on 175 participants (Bai 2021[1], Li 2021b) reported no differences between groups in WAIS scores (Wechsler Adult Intelligence Scale) (MD 0.81, 95% CI -0.70 – 2.32, I^2 0%, low certainty). One study on 35 participants (Lee

[41] Study retracted due to issues with ethical approval and clinical trial registry.

2013b) reported no differences in cognitive functions measured with MMSE (MD 0.10, 95% CI -1.83 – 2.03, I^2 NA, low certainty) and in the RAVL test scores (Rey Auditory Verbal Learning) (immediate MD 3.00, 95% CI -3.26 – 9.26, I^2 NA, low certainty; delayed MD 2.50, 95% CI -0.23 – 5.23, I^2 NA, low certainty). Two studies on 95 participants (Lee 2013b, Mengelberg 2022) and one study on 60 participants (Mengelberg 2022) reported no differences between groups respectively in depressive symptoms (SMD 0.00, 95% CI -0.40 – 0.41, I^2 0%, low certainty) and RBANS scale (Repeatable Battery for Assessment of Neuropsychological Status) scores (MD 1.30, 95% CI -2.06 – 4.66, I^2 NA, low certainty).

Ginkgo biloba

One study (DeKosky 2008) on 452 participants investigated the effectiveness of ginkgo biloba extract and reported no differences between groups in the risk of conversion from MCI to AD (RR 1.14, 95% CI, 0.92 – 1.41, I^2 NA, low certainty).

Ginseng

One study on 83 participants (Park 2019b) investigated the effectiveness of ginseng extract in people with MCI. The study reported an improvement in the intervention group compared to the control group in Rey Complex Figure Test and Recognition Trial (RCFT) scores (immediate MD 2.56, 95% CI 0.23 – 4.89, I^2 NA, low certainty; delayed MD 2.42, 95% CI 0.21 to 4.63, I^2 NA, low certainty). It reported no differences between groups in Seoul Verbal Learning Test (SVLT) scores (immediate MD 0.14, 95% CI -2.08 to 2.36, I^2 NA, low certainty; delayed MD -0.04, 95%CI -2.19 – 2.11, I^2 NA, low certainty), cognitive functions (MMSE: MD 0.06, 95% CI -0.6 – 0.72, I^2 NA, low certainty), and IADL (MD -0.16, 95% CI -0.69 – 0.37, I^2 NA, low certainty).

Resveratrol

One study on 40 participants (Köbe 2017) investigated the effectiveness of resveratrol in people with MCI. The study reported no differences between groups in RAVL (Rey Auditory Verbal Learning) learning (MD 0.40, 95% CI -8.16 – 8.96, I^2 NA, low certainty), memory (deferred recall MD -1.30, 95% CI -4.28 – 1.68, I2 NA, low certainty), retention (MD -0.90, 95%CI -2.78 – 0.98, I^2 NA, low certainty), and recognition (MD 0.20, 95% CI -4.47 – 4.87, I^2 NA, low certainty) scores.

Vitamin B

Overall, four studies investigated the effectiveness of vitamin B supplements in people with MCI. Three studies on 355 participants (Bai 2021, Li 2021b, Ma 2017) reported no differences between groups in WAIS (Wechsler Adult Intelligence Scale) (MD 2.52, 95% CI -2.45 – 7.50, I^2 93%, very low certainty) and Digit Span test (MD 1.92, 95% CI -1.04 – 4.89, I^2 98%, very low certainty) scores. One study on 241 participants (Kwok 2020) reported no differences between groups in cognitive functions (CDR-SB: MD 0.14, 95% CI -0.13 – 0.41, I^2 NA, low certainty) and depressive symptoms (HDRS, Hamilton Depression Rating Scale: MD -0.32, 95% CI -1.08 – 0.44, I^2 NA, low certainty).

Vitamin E

One study on 516 participants (Petersen 2005) investigated the effectiveness of vitamin E in people with MCI. The study reported no differences between groups in cognitive functions measured with MMSE (MD 0.55, 95% CI -0.11 – 1.21, I^2 NA, certainty low), ADAS-Cog (MD 0.85, 95% CI -0.32 – 2.02, I^2 NA, low certainty) and CDR (MD 0.03, 95% CI -0.38 – 0.44, I^2 NA, low certainty). It also reported no differences in ADL (ADCS-ADL-MCI: MD 0.76, 95% CI -0.77 – 2.29, I^2 NA, low certainty).

Other supplements

Four studies investigated the effectiveness of different types of supplements containing different combinations of ingredients. One study on 36 participants investigated the effectiveness of a supplement containing omega 3 and omega 6 fatty acids (Stavrinou 2020). The study reported no differences between groups in cognitive functions measured with MMSE (MD 2.5, 95% CI -0.61 – 5.61, I^2 NA, very low certainty) and ACE-R (Addenbrooke's cognitive examination) (MD 8.20, 95% CI -2.33 – 18.73, I^2 NA, very low certainty). One study on 14 participants investigated the effectiveness of a supplement containing astaxanthin and sesamin (Ito 2019). The study reported no differences between groups in cognitive outcomes (ADAS-Cog: MD -0.99, 95% CI -4.01 – 2.00, I^2 NA, very low certainty), memory (MD -8.80, 95% CI -27.95 – 10.35, I^2 NA, very low certainty) and executive functions (MD -7.10, 95% CI -19.74 – 5.54, I^2 NA, very low certainty). One study on 275 participants (Soininen 2017) investigated the effectiveness of a supplement containing EPA, DHA, phospholipids, choline, uridine monophosphate, vitamin E, vitamin C, selenium, vitamin B12, vitamin B6, folic acid. The study reported an improvement in the intervention group compared to the control group in cognitive functions measured with CDR-SB (MD -0.56, 95% CI -0.95 – -0.17, I^2 NA, low certainty). However, it reported no differences between groups in the same outcome measured with the NTB (Neuropsychological Test Battery) (composite z-score MD 0.08, 95% CI -0.04 – 0.20, I^2 NA, low certainty; MD total z-score 0.01, 95% CI -0.08 – 0.10, I^2 NA, low certainty). One study on 39 participants (Fortier 2019) investigated the effectiveness of a food supplement containing medium chain ketogenic triglycerides (ketogenic Medium Chain Triglycerides, kMCT). The study reported no differences between groups in episodic memory (z-score) (MD 0.28, 95% CI -0.47 – 1.03, I^2 NA, low certainty), executive functions (MD 0.01, 95% CI -0.74 – 0.76, I^2 NA, low certainty), attention (MD 0.2, 95% CI -0.42 – 0.82, I^2 NA, low certainty), and language (MD 0.04, 95% CI -1.08 – 1.16, I^2 NA, low certainty).

PSYCHOSOCIAL INTERVENTIONS

One study (Young 2017) investigated the effectiveness of a holistic group intervention on 38 participants with MCI. The study reported an improvement in the intervention group compared to the control group in cognitive functions (MoCA: MD 2.56, 95% CI 1.07 – 4.05, n = 38, I^2 NA, low certainty).

MUSIC THERAPY

Two studies investigated music therapy in people with MCI. One study on 134 participants (Doi 2017) investigated active music therapy involving the use of percussion instruments and reported an improvement in the intervention group compared to the control group in cognitive functions (MMSE: MD 0.82, 95% CI 0.07 – 1.57, I^2 NA, low certainty), but reported no differences between groups in performance on the TMT-A (Trail Making Test A) (MD -1.38, 95% CI -3.13 – 0.37, I^2 NA, low certainty) and in the TMT-B (MD -1.00, 95% CI -4.96 – 2.96, I^2 NA, low certainty).

The second study, enrolling 46 participants (Mahendran 2018), investigated receptive music therapy aimed at recalling memories and experiences relating to the songs listened to and reported an improvement in the intervention group compared to controls in depressive symptoms (GDS: MD -0.68, 95% CI -1.03 – -0.33, I^2 NA, moderate certainty) and anxiety (MD -0.7, 95% CI -1.1 – -0.3, I^2 NA, moderate certainty), but reported no differences between groups in scores related to the memory domains of the RAVL test (Rey Auditory Verbal Learning) (MD z-score 0.12, 95% CI -0.16 – 0.4, I^2 NA, low certainty).

TRANSCRANICAL STIMULATION

Repetitive Transcranial Magnetic Stimulation

Two studies investigated the effectiveness of repetitive Transcranial Magnetic Stimulation (rTMS) in people with MCI. One study on 24 participants (Roque Roque 2021) reported an improvement in the intervention group compared to the control group in cognitive symptoms measured with MMSE (MD 1.4, 95% CI 0.2 – 2.6, I^2 NA, low certainty). However, it reported no differences in the same outcome measured with MoCA (MD

1.1, 95% CI -0.56 – 2.76, I^2 NA, low certainty). It also reported no differences in depressive symptoms (GDS: MD 0.3, 95% CI -2.11 – 2.71, I^2 NA, low certainty). Another study (Drumond Marra 2015), on 34 participants, reported no differences between groups in memory measured with the RBMT scale (Rivermead Behavioral Memory Test: MD 1.47, 95% CI -0.01 – 2.95, n = 34, I^2 NA, low certainty).

One study investigated the effectiveness of a form of repetitive transcranial magnetic stimulation (rTMS), intermittent theta burst stimulation (iTBS) in people with MCI and Parkinson's disease. The study, on 40 participants (He 2021), reported an improvement in the control group compared to the intervention group in cognitive functions measured with the RBANS scale (Repeatable Battery for Assessment of Neuropsychological Status) (MD 12, 95% CI 1.37 – 22.63, I^2 NA, low certainty). However, it reported no differences between groups in the same outcome measured with MoCA (MD 2.7, 95% CI -0.12 – 5.52, I^2 NA, low certainty).

Transcranial Direct-Current Stimulation

Three studies investigated transcranial Direct-Current Simulation (tDCS) in people with MCI. Two of the studies (Gomes 2019, Lawrence 2018), on 72 participants, and one study (Gu 2022) on 40 participants reported no differences between groups in cognitive outcomes measured respectively with MMSE (MD 0.07, 95% CI -1.27 – 1.4, I^2 0%, very low certainty) and MoCA (MD -0.05, 95% CI -2.25 – 2.15, I^2 NA, low certainty). One study on 58 participants (Gomes 2019) reported no differences in depressive symptoms (HDRS: MD 0.74, 95% CI -0.04 – 1.52, I^2 NA, low certainty).

Analysis of evidence

Non-pharmacological interventions in people with dementia

Review questions 20a, 20b, 20c, 20d

Evidence was gathered on the following four main outcomes: cognitive functions, functional abilities, independence, and wellbeing (often measured through quality of life).
Given the heterogeneity of both the included studies and the clinical practice reported by the WG, some differences are likely to exist between what is reported in the literature and the actual clinical practice across territorial services. Moreover, the effectiveness of interventions was assessed using tools that might have some limitations in terms of sensitivity and accuracy.
Evidence reported an improvement in cognitive functions after treatment with cognitive stimulation compared to usual care in people with mild to moderate dementia, with apparently better results in group interventions compared to individual interventions. No differences between groups were reported for the remaining outcomes.
Evidence on reminiscence therapy reported similar results, with an improvement in cognitive functions in the intervention group compared to usual care, but the number of studies was lower, and they only included people with moderate dementia. However, it should be noted that within considered studies the two interventions were somewhat overlapping, with cognitive stimulation often including elements of reminiscence.
The WG agreed to confirm both recommendations for cognitive stimulation and reminiscence therapy.
There were several studies available on cognitive training. As most studies were on people with mild to moderate Alzheimer's dementia (AD), and evidence only reported an improvement in people with mild AD, the WG agreed to restrict the recommendation to this population. The WG also agreed that there are other types of dementia (e.g. semantic dementia) where cognitive training may be beneficial, and where it has not

yet been tested. Therefore, a research recommendation was also included to investigate the effectiveness of this intervention in people with moderate AD or other types of dementia.
Evidence highlighted the need to further investigate those interventions for which marginally significant results were available.
Results from the studies, when compared to the assessment tools they adopted, suggested a way to interpret data that might be useful for future research.
The link between outcomes and assessment tools is essential, as each tool is known to measure a specific function, ability, or situation, and it tries to identify and/or provide a picture of the clinical situation at a specific point in time. On this basis, a connection can be identified between exclusively cognitive interventions and interventions also involving the motor component in specific activities closely linked to the social environment of each person.
Almost all studies on cognitive interventions, with the exception of one study on occupational therapy, reported no significant results for all scales considered for measuring activities. However, they reported significant results for scales measuring cognitive functions.
Most of the included studies appeared to focus on improving cognitive functions through activities that are very different from daily living and social activities, as if implying that eating, getting dressed, going shopping, or having a conversation do not involve a cognitive component, and that the only way to train or stabilize it was through board games, bricolage or reading. It might be useful trying to design studies using large samples and different tools to investigate the effectiveness of interventions based on daily life activities on cognitive functions and quality of life. As an alternative, it might be useful to build activities that include the typical features of cognitive training and cognitive stimulations, trying to connect them as much as possible both to each other and to the interests of people with dementia.
In fact, when improvements were reported by using daily life activities, these were personalised.
Studies on cognitive rehabilitation reported improvements in ADL, but not in cognitive functions and quality of life in people with mild to moderate dementia. Based on evidence, the WG agreed to recommend considering this intervention to improve functional abilities. In some of the included studies interventions were led by occupational therapists using specific tools. This could mean that the authors designed goal-oriented interventions, which are characteristic of occupational therapy, including cognitive rehabilitation, thus supporting its definition as containing multifactorial and interdisciplinary intervention. However, this could also disorient readers, when appropriate definitions are not adopted.
Considering the use of interventions based on daily life activities that are significant for people with dementia and their caregivers could be a successful strategy.
A person -centred approach appears to be the most effective element in involving people with dementia, supporting their motivation in a way that could lead to overcome the limitations caused by the disease. The natural drive to engage what people like or are interested in could also help caregivers in managing mood, thus avoiding potential episodes of aggression.
This could also help preventing, most likely during the earlier phases of the disease, people with dementia from losing their self-esteem, helping them to still feel independent in some aspects of their life. On this basis, the WG agreed to recommend offering activities that are tailored to individual preferences.
The WG agreed that evidence on the effectiveness use of supplements and other nutritional interventions, including omega-3 fatty acids, ginseng, combinations of supplements containing fatty acids, omega 3, phospholipids, choline, uridine monophosphate, vitamin E, vitamin C, selenium, vitamin B12, vitamin B6, folic acid, and several other vitamin and herbal supplements was insufficient. Therefore, the WG agreed to recommend not to offer supplements for the treatment of dementia. Some studies reported promising results for huperzine A, but evidence was of low quality and often lacked information on concomitant treatments and diagnostic criteria for dementia. The WG agreed that this evidence was insufficient to support an either a negative or positive recommendation.

Included studies reported no meaningful benefit from psychotherapy, acupuncture, light therapy, and therapeutic robots, therefore the WG agreed recommend not to offer these treatments.
Evidence on art therapy, dance, and pet therapy was insufficient to support a recommendation. Therefore, the WG agreed to include specific research recommendations for each of these interventions.

Non-pharmacological interventions in people with mild cognitive impairment

Review question 20e

Evidence on non-pharmacological treatments in people with mild cognitive impairment (MCI), as observed for people with dementia, was limited and included heterogeneous interventions. The effectiveness of these interventions was investigated for the treatment of the following outcomes: cognitive functions, independence, and depressive symptoms and anxiety as secondary outcomes.
When considering cognitive functions, the interventions for which evidence reported an improvement were: cognitive rehabilitation, cognitive training, physical exercise, dance, board games, and music therapy.
Studies on physical exercise and cognitive rehabilitation also reported an improvement in independence, while art therapy, music therapy, dance, and board games appeared to be effective in managing anxiety and/or depressive symptoms.
When considering videogames (such as serious games and virtual reality), evidence was insufficient to support a recommendation. However, as research in this area is still active and growing, the WG agreed to include a research recommendation. Evidence on transcranial stimulation and psychosocial interventions was also insufficient to support a recommendation, thus specific research recommendations were included for these interventions in people with MCI.
Most of the evidence included interventions aimed at improving or maintaining cognitive functions through similar techniques. These have simple objectives and focus mainly on repetition, gradual increase of task difficulty, and recognition and/or association of images and names.
These techniques might also be used within activities that are significant for people with MCI, even when there are no difficulties or need for intervention. This could lead to a positive reinforcement considering those activities that, within the studies on people with dementia, were reported as having promising results.
Based on the included research recommendations, an opportunity for research could be to investigate the effectiveness of specific interventions designed by merging the specificity of the person-centred approach, of the significant and tailored activities, and of cognitive rehabilitation and training, using different assessment tools.
Despite studies on acupuncture reported promising results for this intervention, most studies did not report information on concomitant use of medications and/or other treatments such as physical exercise.
Overall, studies on nutritional interventions reported no significant benefit for people with MCI.

Recommendations

Non-pharmacological interventions for cognitive symptoms in dementia

100	Do not offer acupuncture to treat cognitive symptoms in dementia.	STRONG AGAINST
101	Consider aerobic physical exercise to treat cognitive symptoms in people with mild Alzheimer's dementia.	WEAK IN FAVOR
102	Consider non-aerobic physical exercise to treat cognitive symptoms in people with mild to moderate dementia.	WEAK IN FAVOR

103	Consider the combination of aerobic and non-aerobic physical exercise to treat cognitive symptoms in people with moderate dementia.	WEAK IN FAVOR
104	Do not offer specific formulas, including the combinations of supplements containing omega 3 fatty acids, phospholipids, choline, uridine monophosphate, vitamin E, vitamin C, vitamin B6, vitamin B12, folic acid, and selenium to treat cognitive symptoms in people with dementia in absence of documented deficiencies.	STRONG AGAINST
105	Do not offer vitamin E and folic acid supplements to treat cognitive symptoms in people with dementia in absence of documented deficiencies.	STRONG AGAINST
106	Do not offer ginseng, ginkgo biloba, huperzine A, and other herbal supplements, antioxidants such as omega-3, selenium and sodium oligomannate to treat cognitive symptoms in people with dementia.	STRONG AGAINST
107	Do not offer ketogenic dietary interventions to treat cognitive symptoms in people with dementia.	STRONG AGAINST
108	Do not offer light therapy to treat cognitive symptoms in people with moderate to severe dementia.	STRONG AGAINST
109	Consider music therapy to treat cognitive symptoms in people with mild to severe dementia.	WEAK IN FAVOR
110	Do not offer psychotherapy to treat cognitive symptoms in people with mild to moderate dementia.	STRONG AGAINST
111	Consider reminiscence therapy to treat cognitive symptoms in people with moderate dementia.	WEAK IN FAVOR
112	Do not offer therapeutic robots to treat cognitive symptoms in people with dementia.	STRONG AGAINST
113	Consider occupational therapy to support functional abilities in people with mild to moderate dementia.	WEAK IN FAVOR
114	Consider cognitive rehabilitation to support functional abilities in people with mild to moderate dementia.	WEAK IN FAVOR
115	Offer cognitive stimulation to treat cognitive symptoms in people with mild to moderate dementia.	STRONG IN FAVOR
116	Consider cognitive training to treat cognitive symptoms in people with mild Alzheimer's dementia.	WEAK IN FAVOR
117	Offer a range of activities to promote wellbeing and autonomy that are tailored to the person’s individual preferences.	STRONG IN FAVOR

Non-pharmacological interventions for cognitive symptoms in Mild Cognitive Impairment

118	Do not consider acupuncture to treat cognitive symptoms in people with Mild Cognitive Impairment.	WEAK AGAINST
119	Do not offer aromatherapy to treat cognitive symptoms in people with Mild Cognitive Impairment.	STRONG AGAINST
120	Consider art therapy to treat cognitive symptoms and improve depressive symptoms and anxiety in people with Mild Cognitive Impairment.	WEAK IN FAVOR

121	Consider physical exercise to treat cognitive symptoms and promote independence in people with Mild Cognitive Impairment.	WEAK IN FAVOR
122	Consider dance to treat cognitive symptoms and improve depressive symptoms in people with Mild Cognitive Impairment.	WEAK IN FAVOR
123	Consider games (e.g., cards, board games) to treat cognitive symptoms and improve depressive symptoms in people with Mild Cognitive Impairment.	WEAK IN FAVOR
124	Consider cognitive rehabilitation to treat cognitive symptoms and promote independence in people with Mild Cognitive Impairment.	WEAK IN FAVOR
125	Offer cognitive training to treat cognitive symptoms in people with Mild Cognitive Impairment.	STRONG IN FAVOR
126	Do not offer specific formulas, including combinations of supplements containing omega 3 fatty acids, phospholipids, choline, uridine monophosphate, vitamin E, vitamin C, vitamin B6, vitamin B12, folic acid and selenium, supplements based on combinations of fatty acids polyunsaturated, such as omega-3 and omega-6, and monounsaturated and multivitamins and/or antioxidants supplements to treat cognitive symptoms in people with Mild Cognitive Impairment in absence of documented deficiencies.	STRONG AGAINST
127	Do not offer ginkgo biloba, ginseng, omega 3, resveratrol or other antioxidants to treat cognitive symptoms in people with Mild Cognitive Impairment.	STRONG AGAINST
128	Do not offer vitamin B and vitamin E supplements to treat cognitive symptoms in people with Mild Cognitive Impairment in absence of documented deficiencies.	STRONG AGAINST
129	Do not offer ketogenic dietary interventions to treat cognitive symptoms in people with Mild Cognitive Impairment.	STRONG AGAINST
130	Do not consider transcranial stimulation interventions to treat people with Mild Cognitive Impairment.	WEAK AGAINST
131	Consider music therapy to treat cognitive symptoms and improve depressive symptoms and anxiety in people with Mild Cognitive Impairment.	WEAK IN FAVOR

Research Recommendations

Non-pharmacological interventions for cognitive symptoms in dementia

20R	What is the effectiveness of art therapy for improving cognition in people with dementia?
21R	What is the effectiveness of dance for improving cognition in people with dementia?
22R	What is the effectiveness of pet therapy for improving cognition in people with dementia?
23R	What is the effectiveness of cognitive training for improving cognition in people with moderate Alzheimer's dementia or other types of dementia?
24R	What is the effectiveness of interventions targeted at promoting cognitive, communication, and linguistic abilities in people with dementia?

Non-pharmacological interventions for cognitive symptoms in Mild Cognitive Impairment

25R	What is the effectiveness of specific memory interventions for the treatment of people with Mild Cognitive Impairment?
26R	What is the effectiveness of transcranial stimulation for the treatment of people with Mild Cognitive Impairment?
27R	What is the effectiveness of psychosocial interventions for the treatment of people with Mild Cognitive Impairment?
28R	What is the effectiveness of rehabilitative interventions based on serious games or virtual reality for improving cognition in people with Mild Cognitive Impairment?
29R	What is the effectiveness of interventions targeted at promoting cognitive, communication, and linguistic abilities in people with Mild Cognitive Impairment?

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NON-COGNITIVE SYMPTOMS, INTERCURRENT ILLNESSES AND PALLIATIVE CARE

Introduction

Non-cognitive symptoms of dementia (NCSD) include behavioural and psychological symptoms of dementia (BPSD), with focus on several psychological, affective, and behavioural disorders. These clinical conditions are very frequent and affect most people with dementia during the course of the disease. Therefore, these are considered as core manifestations of dementia, along with cognitive disorders and deficits in functional autonomy. Neuropsychiatric symptoms are often associated with negative outcomes, including faster cognitive decline, higher level of dependency, and a higher risk of institutionalization and death. They deeply affect the overall wellbeing and quality of life of people with dementia and their caregivers, along with direct and indirect costs. Their management is challenging for healthcare professionals and requires specific training and expertise.

The clinical assessment of neuropsychiatric symptoms of dementia should be aimed at identifying potential medical, psychological, and environmental causes/triggers. Most of the scientific community currently agrees that the first line approach to manage these symptoms should be through non-pharmacological interventions. However, in a high percentage of cases, these symptoms are managed with psychotropic agents, despite their use is not approved by regulatory agencies and is associated with a still unclear risk-benefit profile.

Most people with dementia lives with other comorbid chronic conditions. Comorbidities, multimorbidity and frailty are frequently reported in clinical practice, and are associated to a higher risk of disability and death, and a lower quality of life. As discussed for question 11 on the management of coexisting conditions, comorbidities increase the complexity of care, and requires a higher level of coordination in managing the different conditions. The diagnosis of dementia can significantly change the objectives of managing the other chronic conditions.

The process of caring for people with dementia should be planned considering that the clinical picture can change significantly, sometimes erratically, due to acute events requiring hospitalisation and a timely adjustment of the already complex care plan. As discussed for the transition between care settings (question 13), and especially in cases of people with dementia experiencing clinical emergencies requiring hospitalization, a more accurate medicine optimization is required, including transferring information on existing prescriptions for pre-existing conditions, and the need for new treatments. This would optimise the risk/benefit profile accounting for the unique condition of frailty of people with dementia. Therefore, caring for people with dementia should include a careful assessment of the main manifestation of the index conditions, but also a careful consideration of those coexisting conditions that contribute to the clinical complexity and the individual care needs.

People with advanced dementia live and die at their home or in residential facilities, often with serious symptoms and complications such as pain, feeding disorders, dyspnoea, neuropsychiatric symptoms, and complications including respiratory or urinary tract infections. Therefore, offering them flexible palliative and end-of-life care targeted to their physical, emotional, and environmental needs is essential, in line with their cultural, spiritual, or religious attitudes.

Palliative care should start early in the course of the disease.

Interventions for treating non-cognitive symptoms in people with dementia

Review question 21a	**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?**
Review question 21b	**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?**

Literature review

	21a	21b
Records identified from databases	10,557	10,557
Studies assessed for eligibility	49	67
Included studies	16	34
Studies included in the NICE GL	56	37
Total number of included studies	72	71

Eligibility criteria

Population	People aged ≥40 years living with dementia.
Interventions	• Pharmacological interventions for treating non-cognitive symptoms, which may include: – Antipsychotics; – Cholinesterase inhibitors; – Memantine; – Carbamazepine; – Valproate (mood stabilisers); – Antidepressants; – Anxiolytics; – Propranolol; – Hypnotics. • Non-pharmacological interventions for treating non-cognitive symptoms.
Comparator	Standard care.
Outcomes	• Change in/resolution of non-cognitive symptoms. • Clinical outcomes including cognitive, functional and behavioural ability. • Adverse events. • Access to health and social care support. • Patient and carer experience and satisfaction. • Patient and carer health-related quality of life.

	• Resource use and costs.

Aim

The objective of the systematic literature review, in line with the strategy defined by the NICE Guideline, was to identify all Randomized Controlled Trials (RCT) that investigate the efficacy and safety of any type of pharmacological and non-pharmacological intervention for the treatment of non-cognitive symptoms in people with dementia. Only studies having as their primary objective the treatment of non-cognitive symptoms of dementia, such as psychotic disorders, depressive disorders, and other behavioural symptoms and considering cognitive and functional measures and safety data as secondary outcomes were included.

Summary of evidence

Pharmacological interventions

Review question 21a

ANTIDEPRESSANTS

Overall, 14 studies investigated the efficacy and safety of antidepressant drugs in people with dementia and depressive symptoms. Two studies on 160 participants (An 2017, Jeong 2022) reported an improvement in depressive symptoms in the intervention group compared to controls (GDS-15:MD -0.60, 95% CI -1.00 – -0.19, I^2 0%, moderate certainty). Five studies on 561 participants (An 2017, Banerjee 2011, Jeong 2022, Lyketsos 2003, Weintraub 2010), five studies on 675 participants (Auchus 1997, Banerjee 2021, Finkel 2004, Porsteinsson 2014, Teri 2000) and two studies on 274 participants (Banerjee 2011, Banerjee 2021) reported no differences between groups in the same outcome (CSDD: MD -1.17, 95% CI -2.37 – 0.03, I^2 52%, low certainty), and in agitation (CMAI: MD -0.63, 95% CI -2.55 – 1.28, I^2 0%, very low certainty) and quality of life (DEM-QoL: MD -0.58, 95% CI -3.55 – 2.40, I^2 0%, very low certainty). Seven studies on 1,041 participants (Banerjee 2011, Banerjee 2021, Finkel 2004, Lyketsos 2003, Maier 2020, Porsteinsson 2014, Zhou 2019) and two studies on 250 participants (Auchus 1997, Finkel 2004) reported no differences between groups in psychological and behavioural symptoms measured with both NPI (MD 0.04, 95% CI -2.88 – 2.96, I^2 51%, very low certainty) and BEHAVEAD (MD -0.59, 95% CI -1.80 – 0.62, I^2 0%, low certainty). Five studies on 538 participants (An 2017, Banerjee 2011, Jeong 2022, Lyketsos 2003, Maier 2020) reported no differences in performing ADL (SMD -0.08, 95% CI -0.29 – 0.13, I^2 29%, low certainty). In terms of safety, nine studies on f 1,092 participants (An 2017, Banerjee 2011, Banerjee 2021, Finkel 2004, Jeong 2022, Lyketsos 2003, Maier 2020, Porsteinsson 2014, Zhou 2019) and three studies on 408 participants (An 2017, Finkel 2004, Maier 2020) reported no differences between groups in cognitive functions (MMSE: MD 0.21, 95% CI -0.25 – 0.67, I^2 45%, low certainty; ADAS-Cog: MD -0.24, CI 95% -1.50 – 1.01, I^2 0%, low certainty). Six studies on 1,000 participants (An 2017, Banerjee 2011, Banerjee 2021, Lyketsos 2003, Maier 2020, Weintraub 2010) reported an higher risk of adverse events (AEs) in the intervention group compared to controls (RR 1.32, 95% CI 1.11 – 1.58, I^2 44%, low certainty). Five studies on 961 participants (An 2017, Banerjee 2011, Banerjee 2021, Maier 2020, Weintraub 2010) and five studies on 499 participants (Auchus 1997, Finkel 2004, Nyth 1990, Olafsson 1992, Jeong 2022) reported no differences between groups in the risk of serious adverse events (SAEs) (RR 1.03, 95% CI 0.62 – 1.73, I^2 49%, very low certainty) and discontinuation due to AEs (RR 1.08, 95% CI 0.72 – 1.62, I^2 0%, low certainty).

Bupropion

One study investigated the efficacy and safety of flexible doses of bupropion up to a maximum dose of 300 mg/day in 108 participants with dementia (Maier 2020). The study reported a worsening in the intervention

group compared to controls in depressive symptoms (MADRaS: MD 2.10, 95% CI 0.40 – 3.80, I^2 NA, moderate certainty) and psychological and behavioural symptoms (NPI: MD 5.51, 95% CI 1.69 – 9.33, I^2 NA, moderate certainty). However, it reported no differences between groups in cognitive symptoms (MMSE: MD -0.45, CI 95% -2.00 – 1.10, I^2 NA, very low certainty; ADAS-Cog: MD -0.27, 95% CI -3.55 – 3.01, I^2 NA, very low certainty), ADLs (ADCS-ADL: MD -2.92, 95% CI -6.10 – 0.26, I^2 NA, low certainty). No differences between groups were also observed in the frequency of AEs (RR 1.18, 95% CI 0.90 – 1.55, I^2 NA, low certainty) and SAEs (RR 2.50, 95% CI 0.51 – 12.33, I^2 NA, very low certainty).

Citalopram

Four studies investigated the efficacy and safety of flexible doses of citalopram up to a maximum dose of 30 mg/day. Two studies on 264 participants (Porsteinsson 2014, Zhou 2019) reported an improvement in psychological and behavioral symptoms (NPI: MD -4.67, 95% CI -8.97 – -0.38, I^2 0%, moderate certainty), but reported no differences between groups in cognitive functions (MMSE: MD 0.03, 95% CI -1.37 – 1.44, I^2 55%, low certainty). Two studies on 238 participants (Pollock 2002, Porsteinsson 2014), one study on 186 participants (Porsteinsson 2014), and one study on 98 participants (Nyth 1990) reported no differences between groups in behavioural symptoms (NBRS, Neurobehavioral Rating Scale: MD -0.85, 95% CI -2.06 – 0.37, I^2 52%, very low certainty), agitation (CMAI: MD -1.38, 95% CI -3.93 – 1.17, I^2 NA, low certainty), and frequency of AEs (RR 1.25, 95% CI 0.36 – 4.38, I^2 NA, very low certainty).

Escitalopram

Only one study on 60 participants (An 2017) investigated the efficacy and safety of escalating doses of escitalopram from 5 mg/day up to 15 mg/day. The study reported no differences between groups in depressive symptoms measured with CSDD (MD -1.25, CI 95% -5.50 – 3.00, I^2 NA, very low certainty), GDS (MD -0.90, 95% CI -3.28 – 1.48, I^2 NA, very low certainty) and NPI (MD -0.01, 95% CI -2.58 – 2.56, I^2 NA, very low certainty). No differences between groups were also reported in sleep quality (PSQI, Pittsburgh Sleep Quality Index: MD 0.38, 95% CI -2.54 – 3.30, I^2 NA, very low certainty), ADL (MD 0.55, 95% CI -6.87 – 7.97, I^2 NA, very low certainty), cognitive functions (MMSE: MD 0.97, 95% CI -2.20 – 4.14, I^2 NA, very low certainty; ADAS-Cog: MD 0.99, 95% CI -5.28 – 7.26, I^2 NA, very low certainty), and frequency of AEs (RR 1.42, 95% CI 0.90 – 2.24, I^2 NA, low certainty) and SAEs (RR 1.05, 95% CI 0.22 – 4.90, I^2 NA, very low certainty).

Fluoxetine

One study investigated the efficacy and safety of graduated doses of fluoxetine up to a maximum of 150 mg/day on 10 participants with dementia (Auchus 1997). The study reported no differences between groups in behavioral symptoms (BEHAVE-AD: MD 0.80, CI 95% -3.73 – 5.33, I^2 NA, very low certainty), agitation (CMAI: MD 2.8, 95% CI -5.83 – 11.43, I^2 NA, very low certainty), and frequency of discontinuation due to AEs (RR 0.33, 95% CI 0.02 – 6.65, I^2 NA, very low certainty).

Fluvoxamine

Only one study investigated the efficacy and safety of 20 mg/day of fluvoxamine on 46 participants with dementia (Olafsson 1992). The study reported no differences between groups in the frequency of discontinuation due to AEs (RR 0.55, 95% CI 0.19 – 1.56, I^2 NA, low certainty).

Mirtazapine

Two studies investigated the efficacy and safety of escalating doses of mirtazapine up to a maximum of 45 mg/day. One study on 158 participants (Banerjee 2011) reported no differences between groups in depressive symptoms (CSDD: MD -0.66, CI 95% -2.12 – 0.80, I^2 NA, low certainty) and in performing ADL (BADLS: MD 1.19, 95% CI -1.37 – 3.75, I^2 NA, low certainty). The second study (Banerjee 2021), on 166

participants, reported no differences between groups in agitation (CMAI: MD -0.70, 95% CI -9.05 – 7.65, I^2 NA, very low certainty). The two studies (Banerjee 2011, Banerjee 2021), on 423 participants, reported no differences between groups in psychological and behavioural symptoms (NPI: MD -1.00, 95% CI -5.05 – 3.06, I^2 0%, very low certainty), cognitive functions (MMSE: MD 1.19, 95% CI -5.41 – 7.79, I^2 83%, very low certainty). No differences were also observed in quality of life (DEM-QoL: MD 0.11, 95% CI -3.16 – 3.38, I^2 0%, n=423, low certainty), and frequency of AEs (RR 1.23, 95% CI 0.81 – 1.88, I^2 74%, n=423, very low certainty) and SAEs (RR 0.67, 95% CI 0.32 – 1.42, I^2 53%, n=423, very low certainty).

Sertraline

Four studies investigated the efficacy and safety of sertraline at a mean dose of 100 mg/day. Three studies on 325 participants (Banerjee 2011, Lyketsos 2003, Weintraub 2010) and one study on 240 participants (Finkel 2004) reported no differences between groups in depressive symptoms measured with CSDD (MD -1.70, 95% CI -5.02 – 1.62, I^2 76%, very low certainty) and HDRS (MD 0.00, 95% CI -1.11 – 1.11, I^2 NA, low certainty). One study on 240 participants (Finkel 2004), one study on 150 participants (Banerjee 2011), and two studies on 194 participants (Banerjee 2011, Lyketsos 2003) reported no differences between groups respectively in agitation (CMAI: MD -0.90, 95% CI -4.51 – 2.71, I^2 NA, very low certainty), quality of life (DEM-QoL: MD -1.76, 95% CI -5.75 – 2.23, I^2 NA, very low certainty) and ADL (MD 0.30, 95% CI -3.81 – 4.41, I^2 41%, very low certainty). Three studies on 434 participants (Banerjee 2011, Finkel 2004, Lyketsos 2003) and one study on 240 participants (Finkel 2004) reported no differences between groups in behavioural and psychological symptoms of dementia (BPSD) (NPI: MD 1.51, 95% CI -1.43 – 4.45, I^2 0%, very low certainty; BEHAVE-AD: MD -0.70, 95% CI -1.95 – 0.55, I^2 NA, low certainty).

In terms of safety, three studies on 434 participants (Banerjee 2011, Finkel 2004, Lyketsos 2003) and one study on 240 participants (Finkel 2004) reported no differences between groups in cognitive functions (MMSE: MD 0.13, 95% CI -0.80 – 1.07, I^2 23%, low certainty; ADASCog: MD -0.30, 95% CI -1.69 – 1.09, I^2 NA, low certainty). Three studies on 385 participants (Banerjee 2011, Lyketsos 2003, Weintraub 2010) reported a higher frequency of AEs in the intervention group compared to controls (RR 1.59, 95% CI 1.23 – 2.04, I^2 0%, moderate certainty). Two studies on 347 participants (Banerjee 2011, Weintraub 2010) and one study on 245 participants (Finkel 2004) reported no differences between groups respectively in the frequency of SAEs (RR 1.34, 95% CI 0.51 – 3.54, I^2 71%, very low certainty) and discontinuation due to adverse events (RR 1.83, 95% CI 0.81 – 4.16, I^2 NA, very low certainty).

Trazodone

Only one study investigated the efficacy and safety of escalating doses of trazodone up to a maximum of 300 mg/day. The study (Teri 2000), enrolling 73 participants, reported no differences between groups in agitation (CMAI: MD 5.18, 95% CI -2.86 – 13.22, I^2 NA, low certainty).

Vortioxetine

One study investigated the efficacy and safety of vortioxetine up to a maximum of 20 mg/day on 100 participants with dementia (Jeong 2022). The study reported an improvement in the intervention group compared to the control group in depressive symptoms (CSDD: MD -1.62, 95% CI -2.27 – -0.97, I^2 NA, moderate certainty; GDS: MD -0.59, 95% CI -1.00 – -0.18, I^2 NA, moderate certainty) and cognitive functions (MMSE: MD 0.59, 95% CI 0.18 – 1.00, I^2 NA, moderate certainty). However, it reported no differences between groups in ADL (MD -0.17, 95% CI -0.39 – 0.05, I^2 NA, low certainty) and in the frequency of discontinuations due toAEs (RR 1.04, 95% CI 0.59 – 1.84, I^2 NA, low certainty).

ANTIPSYCHOTICS

Overall, 22 studies investigated the efficacy and safety of antipsychotic drugs in people with dementia and psychological and behavioural symptoms. Thirteen studies on one total of 3,479 participants (Ballard 2018, Deberdt 2005, De Deyn 2004, De Deyn 2005, Kurlan 2007, Lee 2023, Mintzer 2007, Paleacu 2008, Schneider 2006, Street 2000, Streim 2008, Tariot 2006, Zhong 2007), seven studies on 1,957 participants (Deberdt 2005, De Deyn 2004, De Deyn 2005, Schneider 2006, Street 2000, Streim 2008, Tariot 2006) and 12 studies on a 3,432 participants (Auchus 1997, Ballard 2005, Ballard 2018, Brodaty 2003, Deberdt 2005, De Deyn 1999, Grossberg 2020, Katz 1999, Lee 2023, Streim 2008, Teri 2000, Zhong 2007) reported an improvement respectively in psychological and behavioral symptoms (NPI: MD -3.44, CI 95% -4.82 – -2.06, I^2 0%, moderate certainty), behavioural symptoms (BPRS: MD -1.70, 95% CI -2.73 – -0.67, I^2 0%, moderate certainty) and agitation (CMAI: MD -1.87, 95% CI -2.83 – -0.92, I^2 41%, moderate certainty). In terms of safety, three studies on 1,224 participants (Ballard 2018, Grossberg 2020, Lee 2023) reported no differences between groups in the frequency of AEs (RR 1.10, 95% CI 0.95 – 1.28, I^2 64%, low certainty). Fourteen studies on 5,505 participants (Brodaty 2003, Deberdt 2005, De Deyn 1999, De Deyn 2005, Grossberg 2020, Katz 1999, Lee 2023, Mintzer 2006, Mintzer 2007, Paleacu 2008, Schneider 2006, Streim 2008, Tariot 2006, Zhong 2007), 13 studies on 4,543 participants (Brodaty 2003, Deberdt 2005, De Deyn 1999, De Deyn 2005, Grossberg 2020, Katz 1999, Lee 2023, Mintzer 2006, Mintzer 2007, Street 2000, Streim 2008, Tariot 2006, Zhong 2007) and nine studies on 3,568 participants (Brodaty 2003, Deberdt 2005, De Deyn 2005, Mintzer 2006, Mintzer 2007, Schneider 2006, Streim 2008, Tariot 2006, Zhong 2007) reported respectively a higher risk of extrapyramidal AEs (RR 1.47, 95% CI 1.17 – 1.85, I^2 24%, moderate certainty), drowsiness (RR 2.58, 95% CI 1.96 – 3.38, I^2 31%, low certainty) and cerebrovascular AEs (RR 2.65, 95% CI 1.34 – 5.25, I2 0%, low certainty). Two studies on 523 participants (Ballard 2018, Lee 2023) reported no differences between groups in the frequency of SAEs (RR 1.43, 95% CI 0.69 – 2.99, I2 0%, low certainty). Seventeen studies (Ballard 2005, Ballard 2018, Brodaty 2003, Deberdt 2005, De Deyn 1999, De Deyn 2004, De Deyn 2005, Grossberg 2020, Katz 1999, Lee 2023, Mintzer 2006, Mintzer 2007, Schneider 2006, Street 2000, Streim 2008, Tariot 2006, Zhong 2007) reported a higher mortality rate in the intervention group (RR 1.47, CI 95% 1.03 – 2.11, I^2 0%, n=6,252 moderate certainty).

Haloperidol

Two studies investigated the efficacy and safety of escalating doses of haloperidol up to a maximum of 3 mg/day on 80 participants (Auchus 1997, Teri 2000). The two studies and one of the two studies (Auchus 1997), on 10 participants, reported no differences between groups respectively in agitation (CMAI: MD -1.15, 95% CI -7.85 – 5.54, I^2 0%, very low certainty) and in behavioural symptoms (BEHAVE-AD: MD -3.60, 95% CI -9.73 – 2.53, I^2 n.d., very low certainty).

Aripiprazole

Three studies investigated the efficacy and safety of escalating doses of aripiprazole up to a maximum of 15 mg/day. Three studies on 926 participants (De Deyn 2005, Mintzer 2007, Streim 2008), two studies on 435 participants (De Deyn 2005, Streim 2008) and one study of 247 participants (Streim 2008) reported an improvement respectively in BPSDs (NPI: MD -3.82, 95% CI -6.36 – -1.27, I^2 0%, moderate certainty), behavioural symptoms (BPRS, Brief Psychiatric Rating Scale: MD -2.41, 95% CI -4.24 – -0.58, I^2 0%, moderate certainty) and agitation (CMAI: MD -4.09, 95% CI -7.52 – -0.66, I^2 NA, moderate certainty). One study (Mintzer 2007) reported an improvement in NPI scores in the 10 mg/day arm compared to controls (MD -4.60, CI 95% -8.79 – -0.41, I^2 NA, low certainty). However, it reported no differences between groups in the 2 mg/day (MD -1.10, 95% CI -5.70 – 3.50, I^2 NA, low certainty) and 5 mg/day arms (MD -2.90, 95% CI -7.31 – 1.51, I^2 NA, low certainty). As for safety, the three studies reported a higher risk of drowsiness in the intervention group compared to controls (RR 2.95, 95% CI 1.46 – 5.96, I^2 0%, moderate certainty). However, they reported no differences between groups in the risk of extrapyramidal events (RR 1.28, 95% CI 0.71 – 2.29, I^2 0%, low

certainty), cerebrovascular events (RR 1.25, 95% CI 0.23 – 6.76, I^2 0%, very low certainty) and in mortality rate (RR 1.62, 95% CI 0.65 – 4.06, I^2 0%, very low certainty).

Brexpiprazole

One study investigated the efficacy and safety of either a fixed dose (1 or 2 mg/day) or flexible doses (0.5 to 2 mg/day) of brexpiprazole 669 participants with dementia (Grossberg 2020). The study reported an improvement in agitation measured with the specific item of the NPI in the intervention group compared to controls (NPI-ag: MD -0.53, 95% CI -0.98 – -0.09, I^2 21%, moderate certainty). However, it reported no differences between groups in the same outcome measured with CMAI (MD -2.03, 95% CI -4.23 – 0.18, I^2 18%, low certainty). No differences between groups were also reported in the frequency of AEs (RR 1.09, 95% CI 0.87 – 1.38, I^2 60%, very low certainty), extrapyramidal events (RR 2.64, 95% CI 0.29 – 23.80, I^2 0%, very low certainty) and mortality rate (RR 2.70, 95% CI 0.42 – 17.46, I^2 0%, very low certainty). When considering fixed doses, the study reported an improvement of agitation in the 2 mg/day arm compared to controls (CMAI: MD -3.80, 95% CI -6.92 – -0.68, I^2 NA, moderate certainty) and a higher risk of AEs in the intervention groups compared to controls (RR 1.23, 95% CI 1.00 – 1.52, I^2 NA, moderate certainty). The study reported no differences between groups in agitation in the 1 mg/day arm (CMAI: MD 0.20, 95% CI -2.92 – 3.32, I^2 NA, low certainty), and in both arms (NPI-ag: 1 mg/day MD -0.10, 95% CI -0.72 – 0.52, I^2 NA, low certainty; 2 mg/day MD -0.55, 95% CI -1.16 – 0.06, I^2 NA, low certainty). It also reported no differences between groups for both doses in the frequency of extrapyramidal events (RR 2.28, 95% CI 0.11 – 47.21, I^2 NA, very low certainty), and mortality rate (RR 5.13, 95% CI 0.28 – 93.50, I^2 NA, very low certainty). When considering flexible doses, the study reported an improvement in the intervention group compared to controls in agitation (NPI-ag: MD -0.88, 95% CI -1.52 – -0.24, I^2 NA, moderate certainty), while it reported no differences between groups in agitation (CMAI: MD -2.40, 95% CI -5.59 – 0.79, I^2 NA, low certainty). It also reported no differences between groups in frequency of AEs (RR 0.97, 95% CI 0.79 – 1.19, I^2 NA, low certainty), extrapyramidal events (RR 3.11, 95% CI 0.13 – 75.74, I^2 NA, very low certainty), drowsiness (RR 1.66, CI 95% 0.56 – 4.95, I^2 NA, very low certainty), and mortality rate (RR 1.03, CI 95% 0.06 – 16.64, I^2 NA, very low certainty).
One study investigated the efficacy and safety of 2 or 3 mg/day of brexpiprazole in 342 participants with AD. The study (Lee 2023) reported an improvement in the intervention group compared to the control group in agitation (CMAI: MD -5.30, 95% CI -8.79 – -1.81, I^2 NA, low certainty) and psychological and behavioural symptoms (NPI: MD -4.60, 95% CI -7.54 – -1.66, I^2 NA, moderate certainty). In terms of safety, the study reported no differences between groups in frequency of AEs (RR 1.31, 95% CI 0.96 – 1.79, I^2 NA, low certainty), SAEs (RR 1.03, 95% CI 0.25 – 4.18, I^2 NA, very low certainty), extrapyramidal events (RR 2.58, 95% CI 0.12 – 53.24, I^2 NA, very low certainty), drowsiness (RR 4.11, 95% CI 0.52 – 32.44, I^2 NA, very low certainty) and mortality rate (RR 1.55, CI 95% 0.06 – 37.66, I^2 NA, very low certainty).

Olanzapine

Four studies investigated the efficacy and safety of escalating doses of olanzapine up to a maximum of 15 mg/day on 1,212 participants with dementia (Deberdt 2005, De Deyn 2004, Schneider 2006, Street 2000). Overall, the four studies reported no differences between groups in psychological and behavioural symptoms (NPI: MD -2.13, 95% CI -4.90 – 0.64, I^2 0%, low certainty) and behavioral symptoms (BPRS: MD -1.20, 95% CI -2.66 – 0.25, I^2 0%, n = 1,098, low certainty). One study on 283 participants (Deberdt 2005) reported no differences between groups in agitation (CMAI: MD -0.40, 95% CI -1.33 – 0.53, I^2 NA, low certainty). In terms of safety, two studies on 504 participants (Deberdt 2005, Street 2000) reported a higher risk of drowsiness in the intervention group compared to conrtols (RR 3.14, 95% CI 1.72 – 5.71, I^2 0%, low certainty). Two studies on 537 participants (Deberdt 2005, Schneider 2006) reported no differences in the risk of extrapyramidal (RR 5.06, 95% CI 0.13 – 191.77, I^2 65%, very low certainty) and cerebrovascular events (RR 5.90, 95% CI 0.73 – 47.60, I2 0%, very low certainty). Overall, the four studies reported no differences between groups in

mortality rate (RR 2.45, 95% CI 0.82 – 7.27, I^2 0%, very low certainty). When considering the different doses, one study (De Deyn 2004) reported no differences between groups in psychological and behavioural symptoms in the 1 mg/day (NPI: MD -1.10, 95% CI -5.59 – 3.39, I^2 NA, low certainty; BPRS: MD 0.60, 95% CI -2.09 – 3.29, I2 NA, low certainty), 2.5 mg/day (NPI: MD -2.00, 95% CI -6.32 – 2.32, I^2 NA, low certainty; BPRS: MD -1.80, 95% CI -4.40 – 0.80, I^2 NA, low certainty) and 7.5 mg/day arms (NPI: MD -4.00, 95% CI -8.43 – 0.43, I^2 NA, low certainty; BPRS: MD -2.60 95% CI -5.32 – 0.12, I^2 NA, low certainty). Two studies on 352 participants (De Deyn 2004, Street 2000) reported no differences between groups in same outcomes in the 5 mg/day arm (NPI: MD -3.63, 95% CI -7.81 – 0.54, I^2 6%, low certainty; BPRS: MD -1.02, 95% CI -3.36 – 1.33, I2 78%, very low certainty). One study (Street 2000) reported no differences between groups in the same outcomes in the 10 mg/day (NPI: MD -3.60, 95% CI -13.67 – 6.47, I^2 NA, very low certainty; BPRS: MD -4.20, 95% CI -9.17 – 0.77, I^2 NA, very low certainty) and 15 mg/day arms (NPI: MD 0.70, 95% CI -10.06 – 11.46, I^2 NA, very low certainty; BPRS: MD -2.60, 95% CI -7.70 – 2.50, I^2 NA, very low certainty).

Perphenazine

Only one study investigated the efficacy and safety of escalating doses of perphenazine up to a maximum of 0.1 mg/day. The study (Pollock 2002), on 54 participants, reported no differences between groups in behavioural symptoms measured with the NBRS (Neurobehavioral Rating Scale) (MD -4.90, 95% CI -15.05 – 5.25, I^2 NA, very low certainty).

Pimavanserin

One study investigated the effectiveness of 34 mg/day of pimavanserin in 181 participants with dementia (Ballard 2018). The study reported an improvement in psychotic symptoms (NPI-Ps: MD -1.83, 95% CI -3.60 – -0.06, I^2 NA, moderate certainty) in the intervention group compared to controls. The study reported no differences between groups in psychological and behavioural symptoms (NPI: MD -5.12, CI 95% -10.73 – 0.29, I^2 NA, very low certainty), agitation (CMAI: MD 0.30, 95% CI -2.04 – 2.64, I^2 NA, low certainty), and ADL (ADCSADL: MD -0.22, 95% CI -2.23 – 1.79, I^2 NA, low certainty). The study also reported no differences in the frequency of AEs (RR 1.05, 95% CI 0.98 – 1.11, I^2 NA, low certainty) and SAEs (RR 1.52, 95% CI 0.72 – 3.20, I^2 NA, very low certainty), and mortality rate (RR 1.01, 95% CI 0.26 – 3.92, I^2 NA, very low certainty).

Quetiapine

Six studies investigated the efficacy and safety of escalating or flexible doses of quetiapine up to a maximum of 200 mg/day. Five studies on 659 participants (Kurlan 2007, Paleacu 2008, Schneider 2006, Tariot 2006, Zhong 2007) reported an improvement in the intervention group compared to controls respectively in psychological and behavioral symptoms (NPI: MD -3.45, 95% CI -6.78, – -0.11, I^2 0%, moderate certainty). Two studies on 257 participants (Schneider 2006, Tariot 2006) reported an improvement in the intervention group compared to controls in behavioural symptoms (BPRS: MD -2.70, 95% CI -5.24 – -0.16, I^2 0%, moderate certainty). Two studies on 382 participants (Ballard 2005, Zhong 2007) reported no differences between groups in agitation (CMAI: MD -0.33, 95% CI -4.86 – 4.21, I^2 0%, very low certainty). In terms of safety, two studies on 423 participants (Tariot 2006, Zhong 2007) reported a higher frequency of drowsiness in the intervention group compared to controls (RR 5.38, 95% CI 2.34 – 12.37, I^2 0%, low certainty). Four studies on 796 participants (Paleacu 2008, Schneider 2006, Tariot 2006, Zhong 2007) and three studies on 664 participants (Schneider 2006, Tariot 2006, Zhong 2007) reported no differences between groups respectively in the frequency of extrapyramidal (RR 0.87, 95% CI 0.40 – 1.87, I^2 26%, low certainty) and cerebrovascular events (RR 0.64, 95% CI 0.15 – 2.76, I^2 0%, very low certainty). Four studies on 877 participants (Ballard 2005, Schneider 2006, Tariot 2006, Zhong 2007) eported no differences between groups in mortality rate (RR 1.80, 95% CI 0.80 – 4.06, I^2 0%, very low certainty).

When considering specific doses, a three-arm study (Zhong 2007) reported no differences between groups in agitation and psychological and behavioural symptoms in the 100 mg/day (CMAI: MD -0.40, 95% CI -6.37, 5.57 – I^2 NA, very low certainty; NPI: MD -0.70, 95% CI -6.9 – 5.55, I^2 NA, very low certainty) and 200 mg/day arms (CMAI: MD -2.20, 95% CI -8.30 – 3.90, I^2 NA, very low certainty; NPI: MD -1.50, 95% CI -7.88 – 4.88, I^2 NA, very low certainty).

Risperidone

Six studies investigated the efficacy and safety of escalating doses of risperidone up to a maximum of 1.5 mg/day. Four studies on 1,339 participants (Brodaty 2003, Deberdt 2005, De Deyn 1999, Katz 1999) reported an improvement in agitation (CMAI: MD -2.37, 95% CI -4.18 – -0.57, I^2 72%, low certainty). Two studies (Deberdt 2005, Scheider 2006) reported no differences between groups in psychological and behavioural symptoms (NPI: MD -1.97, 95% CI -11.73 – 7.80, I^2 77%, n = 359, very low certainty) and psychiatric symptoms (BPRS: MD -1.51, CI 95% -6.51 – 3.50, I^2 66%, n = 347, very low certainty). The six studies (Brodaty 2003, Deberdt 2005, De Deyn 1999, Katz 1999, Mintzer 2006, Scheider 2006), on 2,178 participants, reported a higher risk of extrapyramidal events in the intervention group (RR 1.71, 95% CI 1.29 – 2.26, I2 26%, moderate certainty), but no differences in mortality rate (RR 1.45, 95% CI 0.83 – 2.54, I^2 0%, low certainty). Five studies (Brodaty 2003, Deberdt 2005, De Deyn 1999, Katz 1999, Mintzer 2006) and four studies (Brodaty 2003, Deberdt 2005, Mintzer 2006, Scheider 2006) reported a higher risk of drowsiness (RR 2.17, 95% CI 1.50 – 3.15, I^2 48%, n=1,954, low certainty) and cerebrovascular events (RR 4.03, 95% CI 1.55 – 10.46, I^2 0%, n=1,185, low certainty).

Antipsychotic suspension versus continuation

Nine studies investigated the discontinuation versus continuation of antipsychotic treatment. Seven studies on 366 participants (Ballard 2004, Bridges-Parlet 1997, Devanand 2011, Devanand 2012, Ruths 2004, Ruths 2008, van Reekum 2002) reported a higher risk of worsening of BPSDs (RR 1.78, 95% CI 1.31 – 2.41, I^2 0%, moderate certainty). Three studies on f 214 participants (Ballard 2004, Ballard 2008, Ruths 2008) reported no differences between groups in BPSD severity (SMD 0.19, 95% CI -0.20 – 0.58, I^2 51%, low certainty). Five studies on 407 participants (Ballard 2004, Ballard 2008, Bridges-Parlet 1997, Devanand 2012, van Reekum 2002) reported no differences between groups in mortality rate (RR 0.83, 95% CI 0.49 – 1.39, I^2 0%, low certainty). One study on 194 participants (Tariot 2021) specifically investigated the discontinuation of treatment with pimavanserin. The study reported a higher risk of relapse of psychotic episodes (RR 2.24, 95% CI 1.21 – 4.14, I^2 NA, low certainty), while reported no differences between groups in the SAPS (Scale for the Assessment of Positive Symptoms) scores relating to hallucinations and delusions (MD -0.10, CI 95% -2.78 – 2.58, I^2 NA, low certainty). It also reported no differences in the frequency of AEs (RR 0.89, CI 95% 0.64 – 1.25, I^2 NA, low certainty), migraine (RR 0.47, 95% CI 0.17 – 1.33, I^2 NA, low certainty), and prolongation QT interval (RR 0.13, 95% CI 0.01 – 2.56, I^2 NA, low certainty).

Change in antipsychotic versus continuation

One study on 164 participants with dementia (Ballard 2015) investigated the efficacy and safety of switching from antipsychotic to memantine compared to continuing treatment with antipsychotics. The study reported no differences between groups in BPSDs (NPI: MD 3.39, 95% CI -3.23 – 10.01, I^2 NA, very low certainty), agitation (CMAI: MD 3.24, 95% CI -3.81 – 10.29, I^2 NA, very low certainty), and cognitive functions (MMSE: MD 2.38, 95% CI -0.92 – 5.68, I^2 NA, very low certainty). It also reported no differences in the frequency of SAEs (RR 0.74, 95% CI 0.44 – 1.24, I^2 NA, low certainty).

CANNABINOIDS

Two studies investigated the efficacy and safety of cannabinoids for the treatment of non-cognitive symptoms. One study investigated the efficacy and safety of 1.5 mg of delta-9-tetrahydrocannabinol (THC) three times a day in 57 participants with dementia (Hermush 2022). The study reported no differences between groups in agitation (CMAI: MD -10.90, CI 95% -26.59 – 4.79, I^2 NA, very low certainty), BPSDs (NPI: MD -8.50, 95% CI -23.29 – 6.29, I^2 NA, very low certainty), and cognitive functions (MMSE: MD -0.30, 95% CI -5.35 – 4.75, I^2 NA, very low certainty). The study also reported no differences in the risk of memory impairment (RR 3.24, 95% CI 0.80 – 13.08, I^2 NA, very low certainty), AEs (RR 1.02, 95% CI 0.86 – 1.22, I^2 NA, low certainty), and hallucinations (RR 4.32, 95% CI 0.58 – 32.16, I^2 NA, very low certainty). The second study investigated the efficacy and safety of a maximum of 21 drops of a cannabis oil extract (1 drop: 11.8 mg cannabidiol [CBD] + 0.5 mg THC) in 47 participants with dementia (van den Elsen 2015). The study reported no differences between groups in agitation (CMAI: MD 5.60, 95% CI -7.95 – 19.15, I^2 NA, very low certainty) and BPSDs (NPI: MD 2.10, 95% CI -8.79 – 12.99, I^2 NA, very low certainty).

CHOLINE ALPHOSCERATE

One study investigated the efficacy and safety of choline alphoscerate in combination with donepezil compared to donepezil alone specifically for the treatment of non-cognitive symptoms in 113 participants with dementia (Rea 2015). The study reported an improvement in the intervention group compared to controls in BPSDs (NPI: MD -12.10, 95% CI -20.49 – -3.71, I^2 NA, low certainty), apathy (NPI-ap: MD -3.90, 95% CI -6.40 – -1.40, I^2 NA, moderate certainty), and cognitive functions (MMSE: MD 2.90, CI 95% 0.73 – 5.07, I^2 NA, low certainty; ADAS-Cog: MD -5.80, 95% CI -11.58 – -0.02, I^2 NA, low certainty). It reported no differences between groups in executive functions (FAB, Frontal Assessment Battery: MD 1.20, 95% CI -0.39 – 2.79, I^2 NA, low certainty).

DEXTROMETHORPHAN/QUINIDINE

One study investigated the efficacy and safety of a combination of 20 mg/day escalated to 60 mg/day of dextromethorphan and 10 mg/day escalated to 20 mg/day of quinidine on 279 participants with dementia (Cummings 2015). The study reported an improvement in psychological and behavioural symptoms (NPI: MD -5.90, 95% CI -11.58 – -0.22, I^2 NA, moderate certainty), agitation (NPI-ag: MD -1.70, 95% CI -2.82 – -0.58, I^2 NA, moderate certainty) and depressive symptoms (CSDD: MD -1.60, 95% CI -2.86 – -0.34, I^2 NA, moderate certainty). It reported no differences between groups in cognitive functions (MMSE: MD 0.70, 95% CI -0.36 – 1.76, I^2 NA, low certainty). It also reported a higher risk of AEs (RR 1.41, 95% CI 1.12 – 1.79, I^2 NA, moderate certainty) in the intervention group compared to the control group.

DRUGS FOR SLEEP DISORDERS

Orexin antagonists

One study investigated the efficacy and safety of flexible doses of Lemborexant on 62 participants with dementia (Moline 2021). The study reported no differences between groups in the mean total night-time sleep time (MD -12.07, 95% CI -50.65 – 26.52, I^2 0%, very low certainty) and daytime sleep time (MD 25.07, 95% CI -37.07 – 87.21, I^2 0%, very low certainty).
One study investigated the efficacy and safety of escalating doses of suvorexant, up to a maximum of 20 mg/day in 285 participants (Herring 2020). The study reported an increase in the average total night-time sleep time in the intervention group compared to controls (MD 28.2, 95% CI 11.37 – 45.03, I^2 NA, moderate certainty).

Hypnotics analogous to benzodiazepines

A three-arm study investigated the efficacy and safety of zopiclone 7.5 mg/day and 10 mg/day zolpidem in 49 participants with dementia (Louzada 2022). The study reported no differences between the group

allocated to zolpidem and the control group in the average of total night-time sleep time (MD 17.00, 95% CI -58.29 – 92.29, I^2 NA, very low certainty) and daytime sleep time (MD 39.30, 95% CI -76.39 – 154.99, I^2 NA, very low certainty). It reported no differences between the group allocated to zopiclone and the control in the same outcomes (night-time sleep time MD 79.10, 95% CI -10.59 – 168.79, I^2 NA, very low certainty; daytime sleep time MD -35.50, 95% CI -152.93 – 81.93, I^2 NA, very low certainty).

Melatonin

Five studies investigated the efficacy and safety of different doses of melatonin immediate-release or extended-release. Two studies investigated the effectiveness of 5 mg/day or 10 mg/day of immediate-release melatonin. The studies (Dowling 2008, Singer 2003), on 106 participants, reported no differences between groups in mean total night-time sleep time (MD -1.34, 95% CI -37.13 – 34.45, I^2 0%, low certainty) and in the ratio between daytime and night-time sleep time (MD -0.12, 95% CI -0.28 – 0.05, I^2 NA, low certainty). One study investigated the efficacy and safety of 2.5 mg/day of medium/fast-release melatonin. The study (Riemersma-van der Lek 2008), on 91 participants, showed no differences between groups in mean total night-time sleep time (MD 48.00, 95% CI -14.46 – 110.46, I^2 NA, very low certainty). Two studies investigated the efficacy and safety of 2 mg/day or 2.5 mg/day of sustained-release melatonin. The two studies (Singer 2003, Wade 2014), on 89 participants, reported no differences between groups in the mean total night time sleep time (MD 26.18, 95% CI -9.17 – 61.52, I^2 0%, very low certainty). One of the two studies (Singer 2003), on 78 participants, reported no differences between groups in the ratio between daytime and night time sleep time (MD -0.25, 95% CI -0.78 – 0.28, I^2 NA, low certainty). One study investigated the efficacy and safety of 5 mg/day of melatonin without specifying the type of release. The study (Morales-Delgado 2018), on 31 participants, reported no differences between groups in sleep quality assessed with PSQI (Pittsburgh Sleep Quality Index) (MD 0.17, 95% CI -1.45 – 1.79, I^2 NA, low certainty).

Memantine

One study investigated the efficacy and safety of memantine specifically for the treatment of sleep disorders in people with DLB and PDD in 60 participants with dementia (Larsson 2010). The study reported an improvement in the memantine group compared to placebo in sleep disorders measured with SSQ (Stavanger Sleep Questionnaire) (MD 0.48, 95% CI 0.06 - 0.90, I^2 NA, n = 55, moderate certainty). However, it reported no differences between groups in sleep disorders assessed using the ESS (Epworth Sleepiness Scale) (MD 0.40, 95% CI -3.52 – 4.32, I^2 NA, very low certainty).

Paracetamol/buprenorphine

Two studies investigated the efficacy and safety of 3 g/day of paracetamol in people who never received analgesics or were currently receiving 1 g/day of paracetamol, and of 5-10 mg/hour of transdermal buprenorphine in people with swallowing difficulties who never received analgesics or in people currently receiving non-opioid analgesics or > 1 g/day of paracetamol and/or other NSAIDs. One of the two studies (Blytt 2018), on 106 participants, reported a decrease in the mean total daytime sleep time in the intervention groups compared to the control group (MD -48.30, 95% CI -93.39 – -3.21, I^2 NA, low certainty). However, it reported no differences between groups in the average total night time sleep time (MD 40.20, 95% CI -15.08 – 95.48, I^2 NA, very low certainty). The second study (Erdal 2018), on 162 participants, reported an improvement in depressive symptoms (CSDD: MD 2.64, 95% CI 0.55 – 4.73, I^2 NA, moderate certainty) in the intervention groups compared to the control group.

Trazodone

One study investigated the efficacy and safety of 50 mg/day of trazodone for the treatment of sleep disorders. The study (Camargos 2014), on 30 participants, reported no differences between groups in the

mean total night-time sleep time (MD 42.50, 95% CI -31.62 – 116.62, I^2 NA, very low certainty) and daytime sleep time (MD 5.10, 95% CI -53.19 – 63.39, I^2 NA, very low certainty).

GINKGO BILOBA

Four studies investigated the efficacy and safety of 240 mg/day of ginkgo biloba. The four studies (Herrschaft 2012, Ihl 2011, Napryeyenko 2007, Nikolova 2013), on 1,598 participants, reported an improvement in the intervention group compared to the control group in psychological and behavioural symptoms (NPI: MD -3.86, 95% CI -7.62 – -0.10, I^2 97%, very low certainty) and ADL (SMD -0.54, 95% CI -0.91 – -0.18, I^2 93%, very low certainty). Two studies (Herrschaft 2012, Ihl 2011), on 806 participants, reported an improvement in quality of life in the intervention group compared to controls (MD 2.00, 95% CI 0.88 – 3.12, I^2 0%, moderate certainty).

ACETYLCHOLINESTERASE INHIBITORS

Overall, four studies investigated the efficacy and safety of acetylcholinesterase inhibitors specifically for the treatment of non-cognitive symptoms in people with dementia.
One study investigated the efficacy and safety of donepezil in 221 participants with dementia (Howard 2007). The study reported an improvement in cognitive symptoms in the intervention group compared to placebo (standardized MMSE: MD 1.50, 95% CI 0.15 – 2.85, I^2 NA, low certainty). However, it showed no differences between groups in psychological and behavioural symptoms (NPI: MD -0.22, 95% CI -4.69 – 5.13, I^2 NA, very low certainty) and agitation (CMAI: MD 1.35, 95% CI -3.84 – 6.54, I^2 NA, very low certainty). One study investigated, in 96 participants with dementia, the efficacy and safety of discontinuing versus continuing treatment with donepezil (Holmes 2004). The study reported an improvement in the group continuing treatment compared to the group discontinuing it in cognitive functions (MMSE: MD 1.70, 95% CI 0.17 – 3.23, I^2 NA, moderate certainty), psychological and behavioral symptoms (NPI: MD -6.20, 95% CI -11.37 – -1.03, I^2 NA, moderate certainty) and depressive symptoms (NPI-dep: MD -2.80, 95% CI -5.36 – -0.24, I^2 NA, moderate certainty).
Two studies investigated the efficacy and safety of rivastigmine. One study on 20 participants (Mahlberg 2007) reported no differences between groups in BPSD (NPI: MD -11.90, 95% CI -26.87 – 3.07, I^2 NA, very low certainty) and agitation (NPI-ag: MD -2.70, 95% CI -6.62 – 1.22, I^2 NA, very low certainty). The second study (Ballard 2005), on 54 participants, showed no differences between groups in agitation (CMAI: MD -1.80, 95% CI -11.71 – 8.11, I^2 NA, very low certainty).

MEMANTINE

Four studies investigated the efficacy and safety of memantine for the treatment of non-cognitive symptoms in people with dementia. The four studies (Bakchine 2008, Fox 2012, Peskind 2006, Porsteinsson 2008), on a 565 participants, reported no differences between groups in psychological and behavioural symptoms (NPI: MD -1.75, 95% CI -5.49 – 1.99, I^2 53%, very low certainty). Three studies on 427 participants (Bakchine 2008, Peskind 2006, Porsteinsson 2008) reported no differences between groups in cognitive functions (ADAS-Cog: MD -0.17, 95% CI -1.60 – 1.26, I^2 0%, low certainty) and ADL (ADCS-ADL: MD 0.70, 95% CI -1.54 – 2.93, I^2 10%, low certainty). One study on 149 participants (Fox 2012) reported no differences between groups in cognitive functions (standardized MMSE: MD 1.40, 95% CI -1.41 – 4.21, I^2 NA, very low certainty) and agitation (CMAI: MD -3.80, 95% CI -12.09 – 4.49, I^2 NA, very low certainty).

METHYLPHENIDATE

Four studies investigated the efficacy and safety of escalating doses of methylphenidate up to a maximum of 20 mg/day. Three studies on 144 participants (Herrmann 2008, Padala 2018, Rosenberg 2013) reported an improvement in apathy measured with AES (Apathy Evaluation Scale) in the intervention group compared to

the control group (MD -5.11, 95% CI -9.93 – -0.29, I^2 80%, very low certainty). Three studies on 265 participants (Herrmann 2008, Mintzer 2021, Rosenberg 2013) reported no differences between groups in the same outcome measured with NPI (MD -0.78, 95% CI -2.50 – 0.94, I^2 65%, very low certainty).
One study on 59 participants (Padala 2018) reported an improvement in the intervention group compared to the control group in depressive symptoms (CSDD: MD -2.50, CI 95% -4.13 – -0.87, I^2 NA, moderate certainty), IADLs (MD 2.30, 95% CI 0.88 – 3.72, I^2 NA, moderate certainty), and global functions (ADCS-CGIC: MD -1.20, CI 95% -1.88 – -0.52, I^2 NA, moderate certainty). However, one study on 180 participants (Mintzer 2021) reported no differences between groups in the same outcome (RR 1.25, 95% CI 0.87 – 1.79, I^2 NA, low certainty). In terms of safety, two studies on 84 participants (Herrmann 2008, Padala 2018) reported no differences between groups respectively in cognitive functions (MMSE: MD 1.71, 95% CI -0.32 – 3.74, I2 63, very low certainty). One study on 59 participants (Padala 2018) reported no differences between groups in the frequency of adverse events (RR 1.40, 95% CI 0.71 – 2.75, I2 NA, low certainty). Three studies on 298 participants (Mintzer 2021, Padala 2018, Rosenberg 2013) reported no differences between groups in the frequency of adverse events (RR 1.40, 95% CI 0.71 – 2.75, I^2 NA, low certainty) and in serious adverse events (RR 1.87, 95% CI 0.96 – 3.63, I^2 0%, low certainty).

MODAFINIL

One study investigated the efficacy and safety of modafinil at increasing doses from 100 mg/day to 200 mg/day. The study (Frakey 2012), on 22 participants, reported no differences between groups in apathy measured with the FrSBe scale (Frontal Systems Behavior Scale) (MD 0.27, 95% CI -11.74 – 12.28, I^2 NA, very low certainty).

PRAZOSIN

One study investigated the efficacy and safety of escalating doses of prazosin up to a maximum of 6 mg/day. The study (Wang 2009), on 13 participants, showed an improvement in the intervention group compared to controls in psychiatric symptom (BPRS: MD -12.00, 95% CI -19.15 – -4.85, I^2 NA, low certainty), while it reported no differences between groups in psychological and behavioral symptoms (NPI: MD -18.00, 95% CI -41.93 – 5.93, I^2 NA, very low certainty).

MOOD STABILIZERS

Carbamazepine

Two studies investigated the efficacy and safety of graduated doses of carbamazepine up to a maximum of 300 mg per day on 72 participants with dementia (Olin 2001, Tariot 1998). The two studies reported an improvement in the intervention group compared to controls in psychiatric symptoms (BPRS: MD -5.48, 95% CI -8.49 – -2.47, I^2 68%, low certainty), while they showed no differences between groups in the risk of adverse events (RR 1.19, 95% CI 0.40 – 3.58, I^2 76%, very low certainty). One of the two studies (Olin 2001), on 21 participants, reported no differences between groups in ADL (PSMS: MD 0.10, 95% CI -1.28 – 1.48, I^2 NA, low certainty) and cognitive symptoms (MMSE: MD 0.40, 95% CI -2.01 – 2.81, I^2 NA, very low certainty).

Valproate

Four studies investigated the effectiveness of escalating doses of valproate up to a maximum of 1,500 mg/day. Three studies on 230 participants (Herrmann 2007, Porsteinsson 2001, Tariot 2005) reported no differences between groups in agitation (CMAI: MD 1.81, 95% CI -7.64 – 11.27, I2 72%, very low certainty). Two studies on 47 participants (Herrmann 2007, Profenno 2005) reported no differences between groups in psychological and behavioral symptoms (NPI: MD 4.05, 95% CI -0.19 – 8.29, I2 58%, very low certainty). Two studies on 224 participants (Porsteinsson 2001, Tariot 2005) reported no differences between groups in psychiatric symptoms (BPRS: MD 0.23, 95% CI -2.14 – 2.59, I^2 0%, very low certainty). Two studies on 203

participants (Porsteinsson 2001, Tariot 2005) reported no differences in performing ADL as measured with the Physical Self-Maintenance Scale (PSMS) (MD 0.76, CI 95% -0.03 – 1.55, I^2 0%, low certainty). In terms of safety, four studies on 248 participants (Herrmann 2007, Porsteinsson 2001, Profenno 2005, Tariot 2005) reported a worsening of cognitive symptoms (MMSE: MD -1.02, 95% CI -1.89 – -0.16, I^2 0%, moderate certainty). Three studies on 149 participants (Herrmann 2007, Porsteinsson 2001, Tariot 2005) reported no differences between groups in the risk of adverse events (RR 1.33, 95% CI 0.85 – 2.09, I^2 71%, very low certainty).

Non-pharmacological interventions **Review question 21b**

ACUPUNCTURE

Only one study investigated acupuncture for the treatment of non-cognitive symptoms in people with dementia. The study (Kwan 2017) reported no differences between groups in anxiety (CMAI: MD 2.21, 95% CI -4.96 – 9.38, n = 78, I^2 NA, very low certainty).

AROMATHERAPY

Five studies investigated aromatherapy for the treatment of non-cognitive symptoms. Two studies (Lin 2007, Yang 2015) and one study (Ballard 2002) reported an improvement in the intervention group compared to controls in depressive symptoms using either lavender (CMAI: MD -6.32, 95% CI -9.21 – -3.44, n = 200, I^2 0%, moderate certainty) or lemon balm (CMAI: MD -8.10, 95% CI -14.78 – -1.42, n = 72, I^2 NA, low certainty). Two studies (Fujii 2008, Lin 2007) reported an improvement in psychological and behavioral symptoms in the intervention group compared to controls using lavender (NPI: MD -7.24, 95% CI -12.60 – -1.89, n = 98, I^2 0%, very low certainty). One study (Burns 2011) reported no differences between groups in the same outcome using lemon balm (NPI: MD 2.80, 95% CI -5.84 – 11.44, n = 63, I^2 NA, very low certainty).

RECREATIONAL ACTIVITIES

Four studies investigated interventions based on participation in different types of recreational activities. One study investigated the effectiveness of participating in a program based on recreational and creative activities to relieve pain. The study (Tse 2018) reported a decrease in the level of pain measured with the PAINAD scale (Pain Assessment in Advanced Dementia) (MD -1.70, 95% CI -2.52 – -0.88, n = 53, I^2 NA, moderate certainty), but reported no differences between groups in depressive symptoms (GDS: MD -1.60, 95% CI -4.25 – 1.05, n = 53, I^2 NA, very low certainty).
Three studies investigated the effectiveness of interventions based on personalized activities including recreational and individual/group artistic activities, aimed at treating specific symptoms. One study (Yuen 2019) reported an improvement in the intervention group compared to controls in agitation (CMAI: MD 8.52, 95% CI 0.72 – 16.32, n = 46, I^2 NA, low certainty). Two studies (Cohen-Mansfield 2007, Cohen-Mansfield 2012) reported no differences between groups in the same outcome measured with the ABMI (Agitated Behaviors Mapping Instrument) (MD -3.94, 95% CI -10.24 – 2.35, n = 292, I^2 89%, very low certainty).

COMPUTER

One study investigated the effectiveness of an intervention based on supporting people with dementia in using a computer specifically adapted to be easier to access and use. The study (Sautter 2021), enrolling 62 participants, reported an improvement in the intervention group compared to controls in cognitive symptoms (MoCA: MD 5.57, 95% CI 0.28 – 10.86, I^2 NA, low certainty) and depressive symptoms (GDS: MD -5.00, 95% CI -8.08 – -1.92, I^2 NA, low certainty) in the group with mild dementia. However, it reported no

differences between groups in depressive symptoms in the group with severe dementia (GDS: MD 0.42, 95% CI -6.07 – 6.91, I^2 NA, very low certainty).

PHYSICAL EXERCISE

Three studies investigated the effectiveness of different types of physical exercise in people with dementia. One study investigated an intervention based on increasing levels of physical exercise aimed at improving activities of daily living. The study (Böstrom 2016), enrolling 148 participants, reported no differences between groups in depressive symptoms measured with GDS (MD -0.06, 95% CI -0.87 – 0.75, I^2 NA, low certainty) and MADRaS (MD 0.16, 95% CI -1.54 – 1.86, I^2 NA, low certainty).
One study investigated an intervention based on exercises specifically aimed at strengthening both upper and lower limbs in hospitalized people with dementia. The study (Fleiner 2017), enrolling 70 participants, reported no differences between groups in agitation (CMAI: MD -3.90, 95% CI -11.25 – 3.45, I^2 NA, very low certainty) and psychological and behavioral symptoms (NPI: MD -5.90, 95% CI -13.01 – 1.21, I^2 NA, low certainty).
One study investigated an intervention based on exercises specifically targeted to muscle strengthening, balance, and motor coordination. The study (Maltais 2019) reported no differences between groups in psychological and behavioral symptoms (NPI: MD -4.60, CI 95% -14.02 – 4.82, n = 98, I^2 NA, very low certainty).

LIGHT THERAPY

Five studies investigated the effectiveness of interventions based on the exposure to bright light. One study (Zou 2022) reported an improvement in confusion (CAM: MD -1.68, 95% CI -3.20 – -0.16, n = 61, I^2 NA, moderate certainty). Two studies (Burns 2009, Riemersma-van der Lek 2008) reported no differences between groups in in agitation (CMAI: MD -3.08, 95% CI -10.32 – 4.17, n = 142, I^2 0%, very low certainty). Two studies (Dowling 2005, Zou 2022) reported no differences between groups in psychological and behavioral symptoms (NPI: MD -1.89, 95% CI -7.79 – 4.00, n = 131, I^2 0%, very low certainty). One study (Lyketsos 1999) reported no differences between groups in behavioral symptoms (BEHAVE-AD: MD 0.70, 95% CI -3.25 – 4.65, n = 30, I^2 NA, low certainty). One study on 94 participants (Riemersma-van der Lek 2008) reported no differences between groups in depressive symptoms (CSDD: MD -0.10, 95% CI -3.91 – 3.71, I^2 NA, low certainty) and cognitive symptoms (MMSE: MD 1.50, 95% CI -1.77 – 4.77, I^2 NA, very low certainty). One study on 48 participants (Burns 2009) reported no differences between groups in behavioral (CRBRS: (MD 1.00, 95% CI -3.11 – 5.11, I^2 NA, low certainty) and psychobehavioral symptoms (MOUSEPAD: MD 0.20, 95% CI -6.32 – 6.72, I^2 NA, very low certainty).

THERAPEUTIC GARDEN

One study investigated the effectiveness of a six-month intervention based on allowing people with dementia to interact with a therapeutic garden. The study (Pedrinolla 2019), enrolling 163 participants, reported an improvement in psychological and behavioral symptoms (NPI: MD -32.60, 95% CI -39.64 – -25.56, I^2 NA, moderate certainty) and a reduction in the mean dose (in mg) of quetiapine (MD -160, 95% CI -179.29 – -140.71, I^2 NA, moderate certainty).

SLEEP INTERVENTIONS

Six studies investigated the effectiveness of interventions aimed at treating sleep disorders. One study investigated an intervention based on personalized activities specifically tailored based on disease severity. The study (Richards 2005), enrolling 50 participants, reported a reduction in the intervention group compared to the control group in the mean total daytime sleep time (MD -43.59, 95% CI -82.84 – -4.34, I^2

NA, very low certainty). However, it reported no differences between groups in mean total night-time sleep time (MD 39.76, 95% CI -43.02 – 122.54, I^2 NA, very low certainty).
Two studies investigated the effectiveness of multicomponent interventions including improving sleep hygiene, exposure to light, and physical activity. Both studies (Alessi 2005, McCurry 2011) reported no differences between groups in the mean total night-time sleep time (MD 18.04, 95% CI -14.05 – 50.13, n = 184, I^2 0%, low certainty). One of the two studies (McCurry 2011) reported no differences between groups in the mean total daytime sleep time (MD 14.90, 95% CI -62.17 – 91.97, n = 66, I^2 NA, very low certainty).
Four studies investigated interventions based on exposure to bright light and controlled light. The four studies (Dowling 2005, Hjetland 2021, McCurry 2011, Riemersma-van der Lek 2008) reported no differences between groups in the mean total night-time sleep time (MD 9.58, 95% CI -23.38 – 42.54, n = 300, I2 0%, low certainty). Two studies (Hjetland 2021, McCurry 2011) reported no differences between groups in the mean total daytime sleep time (MD 0.81, 95% CI -43.49 – 45.11, n = 136, I^2 0%, low certainty).
One study investigated the effectiveness of an intervention based on a daily 30-minute walk. The study (McCurry 2011), enrolling 65 participants, reported no differences between groups in mean total night-time sleep time (MD 16.10, 95% CI -57.48 – 89.68, I^2 NA, very low certainty) and mean total daytime sleep time (MD 13.10, CI 95% -64.25 – 90.45, I^2 0%, very low certainty).

PSYCHOLOGICAL INTERVENTIONS

Eleven studies investigated the effectiveness of psychological and supportive interventions, and counselling. Three studies investigated the effectiveness of Cognitive Behavioral Therapy for the treatment of psychological and behavioral disorders. Two studies on 112 participants (Spector 2015, Teri 1997) reported no differences between groups in cognitive function (MMSE: MD -0.02, 95% CI -1.65 – 1.60, I^2 0%, very low certainty). However, they reported an improvement in the intervention group compared to controls in depressive symptoms (CSDD: MD -4.30, 95% CI -6.09 – -2.52, I^2 0%, moderate certainty). Another study (Stanley 2013) reported no differences between groups in the same outcome measured with GDS (MD 1.70, 95% CI -3.49 – 6.89, n = 32, I^2 NA, very low certainty). Two studies on 82 participants (Spector 2015, Stanley 2013) reported an improvement in the intervention group compared to controls in anxiety (RAID: MD -4.64, 95% CI -8.87 – -0.40, I^2 0%, low certainty), but they reported no differences between groups in quality of life (QoL-AD: MD -0.69, 95% CI -3.78 – 2.39, I^2 0%, low certainty). One study on 50 participants (Spector 2015) reported no differences between groups in psychological and behavioral symptoms (NPI: MD -10.06, 95% CI -20.63 – 0.51, I^2 NA, very low certainty) and anxiety measured with HADS (Hospital Anxiety and Depression Scale) (MD -0.05, 95% CI -5.60 – 5.50, I^2 NA, very low certainty).
Two studies investigated the effectiveness of psychodynamic and interpersonal therapy. One study (Tappen 2009) reported an improvement in the intervention group compared to controls in depressive symptoms measured with MADRaS (MD -8.46, CI 95% -16.66 – -0.26, n = 30, I^2 NA, low certainty). The second study (Burns 2005), enrolling 40 participants, reported no differences between groups in the same outcome measured with CSDD (MD -0.90, 95% CI -3.18 – 1.38, I^2 NA, low certainty). It also reported no differences between groups in cognitive functions (MMSE: MD -0.90, 95% CI -4.20 – 2.40, I^2 NA, very low certainty) and in ADL (BADLS: MD 1.80, 95% CI -3.10 – 6.70, I^2 NA, very low certainty).

Two studies investigated the effectiveness of individual/group sessions of counselling and structured support. One study (Young 2014) reported an improvement in the intervention group compared to controls in depressive symptoms (GDS: MD -8.67, 95% CI -10.05 – -7.29, n = 36, I^2 NA, moderate certainty). The second study (Waldorff 2012), enrolling 330 participants, reported an improvement in the intervention group compared to controls in depressive symptoms measured with CSDD (MD -1.58, 95% CI -2.79 – -0.37, I^2 NA, moderate certainty). It reported no differences between groups in cognitive functions (MMSE: MD 0.25, 95% CI -0.74 – 1.24, I^2 NA, low certainty), BPSDs (NPI: MD 0.42, 95% CI -0.55 – 1.39, I^2 NA, low certainty), QoL

(QoL-AD: MD 0.22, 95% CI -1.15 – 1.59, I^2 NA, low certainty) and ADL (ADSC-ADL: MD -1.76, 95% CI -4.86 – 1.34, I^2 NA, low certainty).
Only one study investigated the effectiveness of an intervention of mindfulness on 31 participants with dementia (Churcher Clarke 2017). The study reported no differences between groups in depressive symptoms (CSDD: MD 1.58, 95% CI -2.53 – 5.69, I^2 NA, very low certainty) and anxiety (RAID: MD 0.07, 95% CI -4.82 – 4.96, I^2 NA, very low certainty). It also reported no differences between groups in QoL (QoL-AD: MD 4.14, 95% CI -0.03 – 8.31, I^2 NA, very low certainty) and cognitive functions (MMSE: MD 1.65, 95% CI -2.97 – 6.27, I^2 NA, very low certainty).

Three studies investigated the effectiveness of interventions of reminiscence based on recalling personal memories, history, and traditions. One study on 32 participants (Inel Manav 2019) reported an improvement in the intervention group compared to controls in apathy (AES, Apathy Evaluation Scale: MD 11.82, 95% CI 7.97 – 15.67, I^2 NA, low certainty). One study on 24 participants (Ching-Teng 2020) reported an improvement in the intervention group compared to controls in depressive symptoms measured using the short form of the GDS scale (MD -7.10, 95% CI -12.64 – -1.56, I^2 NA, low certainty). One study on 60 participants (Bademli 2018), reported an improvement in the intervention group compared to controls in the same outcome measured using the CSDD (MD -2.13, 95% CI -4.09 – -0.17, I^2 NA, low certainty) respectively.

PSYCHOSOCIAL INTERVENTIONS

Three studies investigated the effectiveness of psychosocial interventions in treating non-cognitive symptoms in people with dementia. Two studies investigated multicomponent interventions including the participation in group activities and supportive meetings. The two studies, one enrolling 334 participants (Fossey 2006) and one enrolling 226 participants (Bruvik 2013) reported no differences between groups respectively in agitation (CMAI: MD -0.4, 95% CI -1.81 – 1.01, I^2 NA, low certainty) and depressive symptoms (CSDD: MD -0.20, 95% CI -2.27, 1.87, I^2 NA, low certainty).
One study investigated an intervention aimed at identifying determinants of stress on which to develop targeted interventions. The study (Yang 2021), enrolling 215 participants, reported an improvement in the intervention group compared to controls in quality of life (QoL-AD: MD 2.20, 95% CI 1.19 – 3.21, I^2 NA, moderate certainty) and depressive symptoms (GDS: MD -1.66, 95% CI -2.77 – -0.55, I^2 NA, moderate certainty). However, it reported no differences between groups in cognitive symptoms (MMSE: MD 0.06, 95% CI -1.54 – 1.66, I^2 NA, low certainty), anxiety (RAID, Rating Anxiety in Dementia: MD 0.00, 95% CI -0.92 – 0.92, I^2 NA, low certainty) and psychological and behavioral symptoms (NPI: MD -2.02, 95% CI -5.59 – 1.55, I^2 NA, low certainty).

MUSIC THERAPY

Overall, 14 studies investigated the effectiveness of active, receptive, or combined active/receptive music therapy.

Seven studies investigated the effectiveness of interventions of active music therapy, including group sessions based on singing and playing musical instruments. Four studies on 496 participants (Baker 2022, Choi 2009, Giovagnoli 2018, Lyu 2018) reported an improvement in the intervention group compared to the control group in psychological and behavioral symptoms (NPI: MD -3.92, 95% CI -5.35 – -2.48, I^2 0%, moderate certainty). One study on 239 participants (Baker 2022) reported an improvement in the intervention group compared to the control group in depressive symptoms measured using the MADRaS scale (MD -4.65, 95% CI -7.68 – -1.62, I^2 0%, moderate certainty). One study on 50 participants (Liu 2021) reported an improvement in the intervention group compared to the control group in agitation (HAMA: MD -2.88, 95% CI -3.87 – -1.89, I^2 NA, moderate certainty). One study on 20 participants (Choi 2009) reported an improvement in the intervention group compared to the control group in agitation measured with the specific item of the NPI scale (MD -0.80, 95% CI -1.41 – -0.19, I^2 NA, moderate certainty). Three studies on 120 participants (Ceccato

2012, Choi 2009, Liu 2021) reported no differences between groups in depressive symptoms (GDS: MD -0.21, 95% CI -0.62 – 0.20, I^2 60%, low certainty). Two studies on 89 participants (Ceccato 2012, Sung 2012) reported no differences between groups in agitation (CMAI: MD 1.05, 95% CI -3.59 – 5.68, I^2 0%, very low certainty). One study on 55 participants (Sung 2012) reported no differences between groups in anxiety (RAID: MD 0.63, 95% CI -5.12 – 6.38, I^2 NA, very low certainty). Two studies (Ceccato 2012, Giovagnoli 2018) and one study (Baker 2022) reported an improvement in the intervention group compared to controls respectively in ADL (MD -0.57, 95% CI -1.02 – -0.12, n = 79, I^2 0%, low certainty) and quality of life (QoL-AD: MD -3.51, 95% CI -6.05 – -0.98, n = 239, I^2 0%, moderate certainty). One study (Giovagnoli 2018) and three studies (Ceccato 2012, Giovagnoli 2018, Lyu 2018) reported no differences between groups respectively in IADL (MD 0.53, 95% CI -1.56 – 2.62, n = 45, I^2 NA, certainty low) and cognitive functions (MMSE: MD -0.24, 95% CI -1.34 – 0.86, n = 287, I^2 0%, low certainty).

Three studies investigated the effectiveness of interventions of receptive music therapy in people with dementia based on listening to their preferred music. One study (D'Aniello 2021) reported an improvement in the intervention group compared to controls in psychological and behavioral symptoms (NPI: MD -10.00, 95% CI -16.42 – -3.58, n = 60, I^2 NA, low certainty). One study on 52 participants (Sung 2010) and one study on 976 participants (McCreedy 2022) reported no differences between groups respectively in anxiety (RAID: MD -1.83, 95% CI -5.21 – 1.55, I^2 NA, low certainty) and agitation (CMAI: MD 1.33, 95% CI -7.93 – 10.59, I^2 NA, low certainty). The last study (McCreedy 2022) also reported no differences in the mean number of participants receiving antipsychotics (MD -3.40, 95% CI -7.14 – 0.34, I^2 NA, very low certainty), antidepressants (MD 1.30, 95% CI -5.46 – 2.86, I^2 NA, very low certainty) and anxiolytics (MD -3.50, 95% CI -7.94 – 0.94, I^2 NA, very low certainty) at follow-up.
Five studies investigated combined interventions of active and receptive music therapy including listening to songs and group sessions based on singing or playing musical instruments. Two studies (Lin 2011, Ridder 2013) reported an improvement in the intervention group compared to controls in agitation (CMAI: MD -6.23, 95% CI -11.97 – -0.49, n = 142, I^2 0%, moderate certainty). One study on 159 participants (Baker 2022) reported an improvement in depressive symptoms measured with MADRaS (MD -5.30, 95% CI -8.79 – -1.81, I^2 NA, moderate certainty), in psychological and behavioral symptoms (NPI: MD -3.10, 95% CI -5.74 – -0.46, I^2 NA, moderate certainty) and in quality of life (QoL-AD: MD -3.70, 95% CI -6.78 – -0.62, I^2 NA, moderate certainty). Two studies on 181 participants (Chu 2014, Tang 2018) reported no differences between groups in cognitive functions (MMSE: MD 1.37, 95% CI -0.73 – 3.46, I^2 NA, very low certainty). One study on 77 participants (Tang 2018) reported no differences between groups in apathy (AES, Apathy Evaluation Scale: MD -3.85, 95% CI -9.45 – 1.75, I^2 NA, very low certainty). One study on 104 participants (Chu 2014) reported no differences between groups in depressive symptoms (CSDD: MD -1.89, CI 95% -7.07 – 3.29, I^2 NA, very low certainty).

CARE COORDINATION

Two studies investigated the effectiveness of specific interventions based on the coordination and reorganization of the care process. One study investigated the implementation of the Guidelines produced by the American Geriatrics Society and the American Association of Geriatric Psychiatry. The study (Rapp 2013) reported an improvement in the intervention group compared to controls in agitation (CMAI: MD -9.22, 95% CI -15.03, -3.41, n = 304, I^2 NA, low certainty).
The second study investigated the implementation of an interdisciplinary model for the treatment of neuropsychiatric symptoms (TIME, Targeted Interdisciplinary Model for Evaluation and Treatment of Neuropsychiatric Symptoms). The study (Lichtwarck 2018), on 229 participants, reported an improvement in the intervention group compared to controls in agitation measured using the specific item of the NPI scale (MD -1.60, 95% CI -2.93 – -0.27, I^2 NA, moderate certainty). However, it reported no differences between groups in the same outcome measured with CMAI (MD -6.00, 95% CI -13.69 – 1.69, I^2 NA, low certainty), in

depressive symptoms (CSDD: MD -2.00, 95% CI -4.94 – 0.94, I^2 NA, low certainty) and in psychological and behavioral symptoms in general (NPI: MD -5.50, 95% CI -13.72 – 2.72, I^2 NA, low certainty).

ROBOT THERAPY

Overall, six studies investigated interventions based on the interaction with therapeutic robot. Of these, five studies investigated the effectiveness of interacting with an interactive robot with the appearance of a baby seal. Three studies (Liang 2017, Petersen 2017, Pu 2020) reported an improvement in the intervention group compared to control in depressive symptoms (CSDD: MD -1.85, 95% CI -3.08 – -0.62, n = 128, I^2 7%, moderate certainty). Two studies (Petersen 2017, Pu 2020) reported an improvement in the intervention group compared to control in anxiety (RAID: MD -1.92, 95% CI -3.13 – -0.72, n = 104, I^2 0%, low certainty). One study (Koh 2018) reported an improvement in the intervention group compared to controls in agitation measured with the full version of the CMAI (MD -6.07, 95% CI -9.57 – -2.57, n = 33, I^2 NA, moderate certainty). Three studies (Liang 2017, Moyle 2017, Pu 2020) reported no differences between groups in anxiety measured using the short form of the CMAI scale (MD -1.40, 95% CI -4.36 – 1.56, n = 342, I^2 0%, low certainty). One study (Koh 2018) reported no differences between groups in cognitive functions (MMSE: MD 0.74, 95% CI -0.15 – 1.63, n = 33, I^2 NA, low certainty). One study (Liang 2017) reported no differences between groups in neuropsychiatric symptoms (NPI: MD 0.26, 95% CI -5.41 – 5.93, n = 24, I^2 NA, very low certainty).

One study investigated the interaction with a humanoid therapeutic robot dressed in knitted cloth. This study (Chen 2020), enrolling 103 participants, reported no differences between groups in neuropsychiatric symptoms (NPI: MD -0.60, 95% CI -3.04 – 1.84, I^2 NA, low certainty) and depressive symptoms (GDS: MD -0.10, 95% CI -1.31 – 1.11, I^2 NA, low certainty).

TRANSCRANIAL STIMULATION

Two studies investigated the effectiveness of repetitive Transcranial Magnetic Stimulation (rTMS). The two studies (Padala 2020, Zhou 2022) reported no differences between groups in ADL (MD -0.19, 95% CI -1.21 – 0.83, n = 84, I^2 0%, low certainty). One study on 19 participants (Padala 2020) reported an improvement in apathy (AES, Apathy Evaluation Scale: MD -10.20, 95% CI -15.18 – -5.22, I^2 NA, low certainty), but no differences between groups in IADL (MD 3.40, 95% CI -0.42 – 7.22, I^2 NA, very low certainty) and cognitive functions (MMSE: MD 0.90, 95% CI -1.53 – 3.33, I^2 NA, very low certainty). The second study (Zhou 2022) reported an improvement in the intervention group compared to controls in sleep quality (PSQI, Pittsburgh Sleep Quality Index: MD -2.31, 95% CI -3.56 – -1.06, n = 65, I^2 NA, moderate certainty), but no differences between groups in cognitive functions (ADASCog: MD 1.59, 95% CI -0.92 – 4.10, n = 65, I^2 NA, low certainty).

TAILORED ACTIVITY PROGRAM

Four studies investigated an intervention of occupational therapy (Tailored Activity Program, TAP) including a first assessment of the person's abilities, skills, environment and interests, followed by the implementation of specific activities selected by people with dementia and adapted to their disease severity. Two studies (de Oliveira 2019, Oliveira 2021), on 75 participants, reported an improvement in agitation (NPI-ag: MD -6.05, 95% CI -10.46 – -1.64, I^2 0%, moderate certainty), aggressive behaviours (NPIagg: MD -3.48, 95% CI -5.80 – -1.15, I^2 0%, moderate certainty), and anxiety (NPI-an: MD -5.06, 95% CI -9.58 – -0.53, I^2 0%, moderate certainty). One study on 206 participants (Gitlin 2021) and one study on 30 participants (Novelli 2018) reported no differences between groups respectively in anxiety and agitation (NPIan+ ag: MD 2.39, 95% CI -13.41 – 18.19, I^2 NA, very low certainty), and in psychological and behavioral symptoms (NPI: MD -10.07, 95% CI -25.73 – 5.59, I^2 NA, very low certainty).

ANIMAL ASSISTED THERAPY

One study investigated an intervention of animal-assisted therapy involving specifically trained dogs. The study (Olsen 2016) reported no differences between groups in depressive symptoms (CSDD: MD -3.64, 95% CI -7.62 – 0.34, n = 51, I^2 NA, very low certainty) and in agitation (BARS, Brief Agitation Rating Scale: MD 0.62, 95% CI -7.02 – 8.26, n = 51, I^2 NA, very low certainty).

DOLL THERAPY

Three studies investigated the effectiveness of using dolls as a therapeutic intervention. One study on 29 participants (Yilmaz 2021) and one study on 35 participants (Moyle 2019) reported no differences between groups in anxiety measured respectively with CMAI (MD -17.10, 95% CI -39.64 – 5.44, I^2 NA, very low certainty) and its short version CMAI-SF (CMAI short form: MD 0.01, 95% CI -3.18 – 3.30, I^2 NA, very low certainty). Two studies (Molteni 2022, Yilmaz 2021) reported no differences between groups in psychological and behavioural symptoms (NPI: MD -18.95, 95% CI -41.64 – 3.75, n = 158, I^2 75%, very low certainty).

Analysis of evidence

As mentioned, BPSDs (Behavioural and Psychological Symptoms of Dementia) include a wide spectrum of conditions and significant behavioural changes including aggression, anxiety, apathy, agitation, depressive disorders, delusions, hallucinations, and sleep disorders. In some types of dementia, neuropsychiatric symptoms can be present during the earlier stages of the disease and be typical of the clinical picture. However, most people with dementia suffer from NCSDs (Non-Cognitive Symptoms of Dementia) during the course of the disease. In clinical practice, the pharmacological management of these symptoms is based on the use, according to specialist judgement, of psychotropic agents such as antipsychotics, mood stabilizers (especially valproate and carbamazepine), antidepressants, anxiolytics, hypnotics and beta-blockers (propranolol). However, the use of these medications in people with dementia is limited, and sometimes not approved by regulatory agencies due to their controversial risk-benefit profile. For this reason, scientific research has focused on the evaluation of the actual efficacy of these molecules and their risk and safety profile, and on the identification of non-pharmacological treatments that are effective in managing neuropsychiatric symptoms in people with dementia.

Therefore, the analysis of the evidence identified for these questions focuses on pharmacological and non-pharmacological interventions for which data are available from randomized clinical trials (RCTs) aimed at the management of NCSDs in people with dementia.

Pharmacological treatments

Review question 21a

The Working Group (WG) discussed both available evidence and experiences from clinical practice suggesting that psychotropic medications have a worse safety profile in people with dementia, mainly due to their specific profile of frailty and comorbidity.

As a first indication, the WG underlined the crucial need, in case of NCSDs in people with dementia, of a careful and specific assessment of potential causes of distress. The assessment should be aimed at identifying possible environmental or physical causes, in particular pain, delirium, inappropriate medications or care, triggering a condition of distress, agitation, aggression, sleep disorders, and more generally psychological and behavioural disorders overlapping with the underlying cognitive decline. Professionals should always take into due consideration the difficulty that people with dementia have in reporting possible physical and/or environmental causes of distress, or even being aware of their perception of distress.

The analysis of available evidence on the efficacy of any type of pharmacological and non-pharmacological treatment for the management of NCSDs in people with dementia was based on predefined outcomes. These

outcomes included the ability of the intervention of improving specific target symptoms, the wider impact on cognitive functions, functional abilities and quality of life, access to health and social care, satisfaction of people with dementia and their caregivers, and safety profile. The WG underlined the need of a careful and cautious approach to prescribing psychotropic medications in people with dementia, which should always include the assessment of the appropriate indication to prescription (assessment of the prevalence, type, severity, and persistency of symptoms) and the balance between efficacy and incidence of adverse events (see Table 9).

Depressive disorders are one of the most frequent neuropsychiatric conditions in people with dementia, affecting negatively the cognitive performance and sometimes reducing life expectancy. The appropriate diagnosis of depressive disorders in people with cognitive decline, and a careful anamnesis assessing the time of onset of depressive symptoms within the clinical history of people with dementia, including the time before the diagnosis, are crucial elements that can guide clinicians in offering a treatment with antidepressants. Available evidence on the use of antidepressant medications for the management of NCSDs in dementia consider clinical outcomes including depressive symptoms, agitation, and cognitive functions mainly measured with standardized scales. The analysis of evidence reported no substantial benefit from treating mild to moderate depressive disorders with these medications in people with mild to moderate dementia. Only two RCTs enrolling a small number of participants with dementia and depressive symptoms reported a significant effect of antidepressants compared to placebo on depressive symptoms measured with GDS, but other studies using different scales to measure the same outcome did not support this result. No effect of antidepressants was reported on agitation, quality of life, and psychological and behavioural disorders. Treatment with antidepressant agents had also no effect on cognitive performance (MMSE and ADAS-Cog) in several studies enrolling an overall large sample of people with dementia. Several low-quality studies also reported a significantly higher frequency of non-serious adverse events in the intervention group compared to the control group. When considering the efficacy of each molecule included in the antidepressants category, only two molecules showed an effect on NCSDs. Moderate-quality studies reported an improvement of psychological and behavioural disorders assessed with NPI in people with dementia treated with citalopram (20-30 mg/day) compared to placebo but reported no differences between groups in other outcomes. One RCT reported an improvement in cognitive functions (MMSE) and depressive symptoms (CSDD), but not ADL, in people with dementia treated with vortioxetine (20mg/day) compared to placebo.

No evidence of efficacy was reported for the remaining considered molecules. One study investigated the efficacy of escitalopram on sleep quality, cognitive functions, ADL, and BPSDs. Four studies investigated the efficacy of sertraline on depressive symptoms, agitation, and quality of life. Two studies investigated the efficacy of mirtazapine on depressive symptoms, ADLs, agitation, psychological and behavioural symptoms, cognitive functions, and quality of life. One study investigated the efficacy of fluoxetine on behavioural symptoms and agitation. One study investigated the efficacy of trazodone on agitation.

The safety is heterogeneous for the different considered molecules. One study on bupropion enrolling people with apathy reported a worsening of depressive, and psychological and behavioural symptoms in the intervention group, along with a non-significant increase in the frequency of adverse events.

Despite the lack of evidence on the overall efficacy of antidepressant drugs and considering that obtaining prospective evidence on the efficacy of these drugs in the advanced stages of the disease is usually unfeasible, though some people can benefit from a treatment with antidepressants, the WG discussed the need of underlining some specific warnings. In particular, the WG considered inappropriate inferring or generalizing evidence from studies on people with mild to moderate disease to people with severe depressive disorders or severe dementia. Moreover, in case of people reporting to have benefited from the treatment with a specific antidepressant before the onset of dementia, clinicians can consider using the same treatment if considered appropriate.

Based on the analysis of evidence, the WG confirmed the recommendation provided in the NICE guideline not to routinely offer antidepressants to manage mild to moderate depression in people living with mild to moderate dementia, if not indicated for a pre-existing severe mental health condition.

A new specific recommendation was also included not to offer bupropion for the treatment of depressive symptoms in people with dementia, based on its risk-benefit profile. Moreover, the WG, considering available evidence on citalopram and vortioxetine, deemed appropriate including a research recommendation to assess their efficacy and safety for the treatment of depressive symptoms in people with dementia.

The use of antipsychotic agents in people with dementia for the treatment of non-cognitive symptoms is widely debated and discussed in published literature. The analysis of evidence showed that available studies are of overall high quality and enrol large samples of participants. Considered outcomes included the efficacy of each molecule in treated the target symptom, the effect of discontinuing the treatment, and the frequency of adverse events such as somnolence/sedation, extrapyramidal symptoms, cerebrovascular events. Long-term studies on the effect of antipsychotics on mortality rates were also included.

The WG underlined that the analysis of moderate-quality studies reported an overall improvement of the symptom defined as "agitation" and of all BPSDs (assessed with NPI and CMAI), along with a significant increase in the frequency of any type of adverse events and, in some cases, of mortality rate. Most of the included studies investigated the efficacy of this class of drugs for the treatment of agitation and not for the treatment of schizophrenia spectrum and other psychotic disorders.

When considering evidence for each different molecule, two studies reported no improvement in agitation and behavioural symptoms in people with dementia treated with haloperidol compared to placebo. Two individual studies reported an improvement in psychotic symptoms and agitation, along with an increase in the frequency of adverse events, in people with dementia treated with either pimavanserin or brexpiprazole compared to placebo. Three studies reported an improvement in BPSDs, psychiatric symptoms, and agitation, along with an increase in the frequency on somnolence, in people with dementia treated with different doses of aripiprazole compared to placebo. Six moderate-quality studies reported an improvement in BPSDs (assessed with NPI), along with an increase in the frequency of adverse events, in particular somnolence, in people with dementia treated with different doses (up to a maximum of 200 mg/day) of quetiapine compared to placebo. Six studies reported an improvement in agitation but not in other BPSDs, along with an increase in the frequency of extrapyramidal and cerebrovascular adverse events, somnolence, but not mortality, in people with dementia treated with different doses of risperidone, up to a maximum of 1.5 mg/day, compared to placebo.

Evidence on the effect of the discontinuing the treatment with antipsychotics compared to continuing it on a relapse or worsening of BPSDs was conflicting across included studies. Only one study investigated switching to a different antipsychotic drug compared to continuing the treatment on the same medication reporting no differences between groups for all considered outcomes.

The WG discussed on the safety of antipsychotics in people with dementia, and on their uncertain risk-benefit profile. Available evidence of a significant increase of adverse events consequent to the use of antipsychotics in a frail population such as people with dementia requires limiting their use only to urgent needs of preventing harms in severe cases of agitation, hallucinations or delusions causing severe distress. Therefore, treatment with antipsychotics would be aimed at the basic management of psychotic disorders and would be considered appropriate based on standard indications for people without dementia.

Both potential benefits of the treatment and mainly its related risks should be equally discussed with people receiving the medication and their caregivers. The higher risk of adverse events requires starting with the lowest effective dose for the shortest possible time, reassessing treatment after a short period, considering its discontinuation, according to appropriate procedures, in case of an evident improvement of the clinical picture and after discussion with both patients and their caregivers. To this purpose, the WG underlines the

importance of programming a regular assessment of people treated with antipsychotics and providing contact information in case of need for further assessment in addition to the regular appointments. The period indicated as appropriate for reassessment was defined according to the document issued in 2016 by the American Psychiatric Association (Reus 2016). Clinicians at each appointment should discuss with patients and their caregivers the efficacy and safety of the treatment and the possibility of discontinuing it.

The WG also agreed that people who are offered antipsychotics should not be prevented from continuing or starting, when appropriate, other non-pharmacological treatments.

A specific discussion was dedicated to the treatment of NCSDs in people with Parkinson's disease dementia (PDD) or dementia with Lewy's bodies (DLB). Hallucinations in people with DLB are a core symptom of the disease, associated to a spectrum of psychological and behavioural symptoms.

The use of dopaminergic drugs such as antipsychotics, and in particular some of these molecules, can worsen motor symptoms in PDD and negatively affect cognitive functions. In people with DLB, the use of antipsychotics causes severe neuroleptic sensitivity, which is included among the core disease criteria. Therefore, the treatment of NCSDs in people with this condition is even more complex.1

Six studies were analysed on the use of mood stabilizers. Four of these studies reported no improvement in BPSDs, especially agitation, aggression, and apathy, nor in ADLs, in people with dementia treated with valproate, up to a maximum dose of 1.500 mg/day, compared to placebo, and some studies also reported a worsening of cognitive functions. Two studies reported an improvement in psychiatric symptoms in people with dementia treated with carbamazepine compared to placebo, and no differences between groups in ADLs, cognitive functions, and in the frequency of adverse events.

The WG agreed, in line with the consideration from the NICE guideline, that available evidence does not support the use of valproate in people with dementia, despite the positive effect of mood stabilizers in people without dementia. Therefore, the WG agreed to confirm the recommendation included in the NICE guideline to limit the use of valproate only in people with dementia who have pre-existing persistent mood disorders and, in particular, in people who already responded to treatment with valproate.

Available evidence on cannabinoids, in particular THC (1.5 mg three times/day) and cannabis oil, reported no improvement in agitation, BPSDs, frequency of hallucinations, cognitive functions, along with no worsening of memory nor an increase in the frequency of adverse events in the intervention group compared to the control group.

Available evidence (from very low to moderate certainty) on ginkgo biloba (240 mg/day) reported an improvement of BPSDs, ADLs and quality of life in the intervention group compared to the control group.

Evidence on the use of methylphenidate reported conflicting results on apathy, depressive symptoms and IADLs, while evidence on the combination dextromethorphan/quinidine reported an improvement in BPSDs, agitation, depressive symptoms, along with an increase in the frequency of adverse events in the intervention group compared to the control group.

Some included studies investigated the efficacy and safety of AChEIs for the treatment of NCSDs in people with dementia. No substantial evidence supports the use of these molecules specifically for the treatment of BPSDs and agitation.

One study reported an improvement in BPSDs, apathy, and cognitive functions (ADAS-Cog and MMSE) in people with dementia treated with a combination of donepezil and choline alphoscerate compared to donepezil alone.

The WG, in line with the NICE guideline, considering the preliminary promising results from the included studies on Dextromethorphan quinidine and choline alphoscerate for the management of symptoms such as agitation and apathy, agreed that further research could be useful thus confirming the research recommendation.

Sleep disorders in people with dementia are characterized by daytime sleepiness and nighttime insomnia, and significantly affect the quality of life of both people with dementia and their caregivers. Within the overall assessment of these disorders, managing nighttime insomnia appears to be more relevant than managing daytime sleepiness, mainly due to affecting both people's quality of life of people suffering from it, and their caregivers' burden and stress. The analysis of one study on hypnotic agents reported no differences between groups in people treated with either zolpidem or zopiclone compared to placebo.

One study on trazodone, a molecule used at different doses as an antidepressant, anxiolytic and hypnotic agent, reported an increase in the mean total nighttime sleep time in people treated with 50 mg/day of this medication compared to placebo. Two studies investigating the use of either paracetamol or buprenorphine, though reporting a slight decrease in the mean total daytime sleep time in the intervention groups compared to placebo, reported no differences between groups in the mean total nighttime sleep time.

The WG confirmed the research recommendation from the NICE guideline to further explore the effectiveness of pharmacological treatments for sleep problems considering the relevance of these disorders and the lack of data.

A general consideration on the analysis of evidence from these studies is that they enrolled a population of older people with mild to moderate sleep disorders, likely due to the unfeasibility of carrying out trials on people with severe sleep problems. Therefore, recommendations should be considered as referring to a subgroup of people with dementia and sleep problems, and that clinical judgement is essential to manage those people that have symptoms requiring urgent nighttime care, mainly to prevent harms.

When considering available evidence on the use of ginkgo biloba for the treatment of psychological and behavioral symptoms in people with dementia, the NICE committee, despite acknowledging the positive results, underlines some concerns "that evidence from non-dementia specific populations had observed effects from drug interactions". Based on these considerations, and the note "that ginkgo biloba is on a list of items that currently cannot be prescribed in primary care", the NICE committee "agreed it was not appropriate to make any recommendations on its use". The WG, in line with the NICE committee and based on the certainty of included evidence, agreed to make any recommendations.

Non-pharmacological treatments

Review question 21b

The WG, as a first consideration, agreed on the need of specifically assessing people with dementia and NCSDs to identify possible causes of distress such as environmental or physical issues including pain, delirium, inappropriate medications, and inadequate care. These can cause severe distress, agitation, aggression, sleep disorders and other psychological and behavioral disorder that can further affect cognitive functions. Clinician should always consider that people with dementia can have troubles acknowledging and/or expressing their distress or discomfort in relation to a physical or environmental cause.

Based on the uncertain evidence from trials on pharmacological treatments for NCSDs in people with dementia, and their higher risk of causing adverse events, the WG agreed to confirm the recommendation to first ensure people with dementia their physical comfort, then offer psychosocial and environmental interventions as a first line treatment to reduce distress.

The analysis of evidence on psychosocial interventions for the management of agitation, aggression, distress and schizophrenia spectrum and other psychotic disorders raised some elements for discussion. Studies on multicomponent interventions based on participating in activities and group meetings compared to usual care reported no differences between groups in agitation and depressive symptoms. However, one trial on an intervention aimed at identifying determinants of stress on which to develop targeted intervention reported an improvement in quality of life and depressive symptoms in the intervention group compared to usual care. The WG underlined the relevance of this evidence and confirmed the recommendation to ensure

that people with dementia keep being offered access to tailored psychosocial and environmental interventions for distress both during and after treatment with antipsychotics.

Evidence on psychological treatments such as cognitive behavioral therapy and psychodynamic and interpersonal therapy for the management of psychological and behavioral symptoms reported an improvement in depressive symptoms and anxiety, but not in other studies reporting different outcomes, in the treatment group compared to usual care. Evidence of moderate certainty from studies on interventions based on counselling and structured support also reported an improvement in depressive symptoms in the intervention group compared to the control group. Three trials also reported an improvement in anxiety and depressive symptoms in the group treated with reminiscence therapy compared to usual care.

Based on analyzed evidence and considering that included studies enrolled people with mild to moderate dementia and mild to moderate depression, the WG agreed to confirm the recommendation from the NICE guideline to consider psychological treatments only in people with this level of severity of both cognitive and depressive symptoms. However, considering the relevance of this topic and the lack of evidence, the WG also included a research recommendation to investigate the most effective psychological treatments for the management of anxiety and depression in people with dementia at any stage.

When considering the management of distress, the WG underlined the importance of performing a structured and thorough assessment of people with dementia and their environment aimed at identifying and possibly removing the underlying causes of distress before considering any type of intervention.

In case the assessment failed to identify elements that could allow for a resolution of the issue, considering the already discussed higher risk of adverse events associated with the use of antipsychotics in people with dementia, the WG underlined that non-pharmacological (environmental and psychosocial) interventions should be offered as a first-line option, while psychotropic medications should be only considered as a second line option. In the analysis of evidence on staff training (Question 9) the WG discussed that the use of appropriate non-pharmacological interventions can be effective in reducing the use of antipsychotics without causing an increase in neuropsychiatric symptoms. Similarly, studies on staff training reported an improvement in agitation and aggression in the intervention group compared to the control group.

Evidence on individual or group interventions based on personalized activities, including games and art, reported an improvement in managing specific symptoms such as agitation, aggression, anxiety, and, as reported in one study, pain in the intervention group compared to usual care. Based on this evidence, the WG confirmed the recommendation from the NICE guideline to offer personalized activities to promote engagement, pleasure, and interest in people with dementia who experience agitation or aggression.

Evidence on interventions aimed at reorganizing and coordinating care, including the implementation of guidelines and interdisciplinary models for the management of neuropsychiatric symptoms reported an improvement of agitation in people with dementia compared enrolled in the treatment group compared to the usual care group.

Studies on aromatherapy reported conflicting results on the management of BPSDs in people with dementia, mainly due to the variable effect of the different tested aromas. Based on this preliminary evidence, the WG agreed to include a research recommendation on the possible effectiveness of aromatherapy in people with dementia who experience signs of agitation or aggression.

Only one study was included on animal-assisted therapy, with specifically trained dogs, to manage NCSDs in people with dementia reporting no differences between the intervention group and the control group in depressive symptoms and agitation.

One study on the use of a specifically adapted computer facilitating access to people with dementia reported an improvement in cognitive and depressive symptoms only in the subgroup of people with mild dementia.

Three studies on doll therapy in people with dementia reported no differences between the intervention group and the usual care group in anxiety (CMAI) and BPSDs.

Several studies on physical activity at different levels of intensity, specifically aimed at mimicking activities of daily life reported no differences between intervention groups and control groups in BPSDs and depressive symptoms. The WG, considering the relevance of this topic and the lack of available evidence, agreed to include and new research recommendation to investigate the effectiveness of physical activity in people with dementia who experience depressive symptoms, agitation, or apathy.

Only one study investigated the use of a therapeutic garden in people with dementia, reporting an improvement in BPSDs and a decrease in the mean dose of quetiapine prescribed to participants in the intervention group compared to controls. Based on this evidence and the relevance of the topic, the WG agreed to include a new recommendation to consider the use of therapeutic gardens to improve non-cognitive symptoms in people with dementia who experience neuropsychiatric symptoms.

Exposure to bright light was investigated in five studies reporting an improvement in confusion the intervention group compared to the control group, but no difference between groups in neuropsychiatric symptoms.

Available evidence on active, receptive, or the combination of active and receptive music therapy, including interventions based on assisted group session, singing, and playing instruments, reported an improvement in BPSDs, depressive symptoms, performance in the ADLs, quality of life, and agitation in the intervention groups compared to usual care (moderate certainty). Some studies reported conflicting results on symptoms such as agitation and anxiety when using different outcome measures. Evidence on interventions of receptive music therapy based on listening to music and songs, reported an overall improvement in BPSDs in intervention groups compared to usual therapy. Some studies on interventions tat combined active and receptive music therapy reported an improvement in depressive symptoms, agitation, psychological and behavioral symptoms, and quality of life, but not in cognitive symptoms and apathy, in the intervention groups compared to usual care. Based on this evidence, the WG included a new recommendation to consider intervention of active and/or receptive music therapy for the management of non-cognitive symptoms in people with dementia who experience neuropsychiatric symptoms.

Some studies on the use of an interactive therapeutic robot in the shape of a baby white seal reported an improvement in depressive symptoms and agitation in the intervention group. However, one single study on another therapeutic robot in the shape of a doll reported no differences between the intervention group and the usual care group. Evidence on anxiety were inconsistent. The WG included a recommendation to consider the use of therapeutic robots in people with dementia experiencing depressive symptoms, anxiety and agitation.

Evidence on personalized activities, tailored to disease severity, for the management sleep problems reported a decrease in mean total daytime sleep time in intervention groups compared to usual care, but no difference between groups in mean total nighttime sleep time. Evidence on targeted interventions for improving sleep hygiene, and interventions based on exposure to light and bright light, and physical activity, reported no differences between intervention groups and usual care in mean total nighttime sleep time and daytime sleepiness. Considering the relevance and difficulty of treating daytime sleepiness and nighttime insomnia in people with dementia, the WG confirmed the recommendation from the NICE guideline to consider a personalized multicomponent sleep management approach that includes sleep hygiene education, exposure to daylight, exercise, and personalized activities.

The WG, considering the very limited available evidence on specific interventions for the management of NCSDs in people with PDD or DLB, agreed to refer to the NICE guideline on PD, avoiding generalizing some of the proposed considerations.

Table 9. Summary of available evidence and indications reported in the summary of product characteristics/prescribing information of medications used for the management of non-cognitive symptoms of dementia.

Therapeutic category	Daily doses investigated	Main efficacy and safety outcomes	Population investigated	References	Therapeutic indications
Antidepressants Significant improvement in depressive symptoms as measured by GDS, but significant increase in adverse events (AEs)					
Sertraline	50-200mg	No significant effect on efficacy outcomes Significant increase in AEs	AD	Banerjee [2011] Finkel [2004] Lyketsos [2003] Weintraub [2010]	Major depressive episodes; Prevention of relapses of major depressive episodes; Panic attack disorder, whether or not associated with agoraphobia; Obsessive-compulsive disorder; Social anxiety disorder; Post-Traumatic Stress Disorder.
Escitalopram	5-15mg	No significant effect (study with small sample size)	AD	An [2017]	Major depressive episodes; Panic attack disorder, whether or not associated with agoraphobia; Social anxiety disorder; Generalized anxiety disorder Obsessive-compulsive disorder.
Mirtazapine	45mg	No significant effect	AD	Banerjee [2011] Banerjee [2021]	Major depressive episodes in adults.
Vortioxetine	5-20mg	Significant improvements in CSDD, GDS, ADL, MMSE No significant increase in AEs	AD	Jeong [2022]	Major depressive episodes.
Citalopram	10-30mg	Significant improvements in NPI No significant increase in AEs	AD, VaD	Nyth [1990] Pollock [2002] Porsteinsson [2014] Zhou [2019]	Endogenous depression and prevention of relapses of major depressive episodes; Panic attack disorder, whether or not associated with agoraphobia.
Bupropion	150-300mg	Significant worsening in NPI and MADRaS	AD	Maier [2020]	Major depressive episodes.
Fluoxetine	50-150mg	No significant effect (study with small sample size)	AD	Auchus [1997]	**Adults**: Major depressive episodes; Obsessive-compulsive disorder, Bulimia nervosa. **Children and adolescents aged ≥ 8 years**: Moderate to severe major depressive episodes who do not respond to psychotherapy in 4-6 weeks.
Fluvoxamine	50-150mg	No significant effect	AD, multi-infarct dementia	Olafsson [1992]	Major depressive episodes; Obsessive-compulsive disorder.
Trazodone	50-300mg	No significant effect	AD	Teri [2000]	Depressive disorders with or without anxiety component in adults.
Antipsicotici Significant improvement in symptoms of anxiety, agitation and neuropsychiatric symptoms as measured by CMAI, NPI, BPRS Significant increase in extrapyramidal events, somnolence, cerebrovascular events, and mortality Discontinuation of antipsychotic treatment is associated with a significant worsening of BPSDs					
Pimavanserin	34mg	Significant improvement in NPI-PS scores Increased risk of psychotic relapse upon treatment discontinuation	dementia (AD, PDD, DLB, FTD, VaD)	Ballard [2018] Tariot [2021]	Psychotic crises in people with Parkinson's disease (FDA approved only); Ongoing FDA regulatory process for AD. **Not approved in Italy.**
Brexpiprazol	0.5-2mg	Significant improvement in NPI-Agitation and CMAI Significant increase in AEs	AD	Grossberg [2020] Lee [2023]	Schizophrenia in adults; Agitation in people with AD (FDA approved only). **Not approved in Italy.**

Haloperidol	0.5-3mg (max 12mg)	No significant effect	AD	Auchus [1997] Tariot [2006] Teri [2000] De Deyn [1999]	**Persistent aggression and psychotic symptoms in patients with moderate to severe AD and VaD when non-pharmacological treatments fail and when there is a risk of harm to self or others.** Other indications in adults and pediatric population.
Aripiprazole	2-15mg	Significant improvement in CMAI, NPI (10mg/die) Significant increase in somnolence	AD	De Deyn [2005] Mintzer [2007] Streim [2008]	Schizophrenia in adults and adolescents aged ≥ 15 years; Moderate to severe manic episodes in people with Bipolar Disorder Type I and for the prevention of new manic episodes; Moderate to severe manic episodes in adolescents with Bipolar Disorder Type I aged ≥ 13 years, maximum duration of treatment 12 weeks.
Olanzapine	2.5-10mg	No significant effect Significant increase in somnolence	AD, VaD, mixed dementia	De Deyn [2004] Deberdt [2005] Schneider [2006] Street [2000]	Schizophrenia in adults; Moderate to severe manic episodes; Prevention of relapses in people with Bipolar Disorder.
Quetiapine	25-100mg	Significant improvement in NPI e BPRS Significant increase in somnolence	Dementia (AD, PDD, DLB)	Ballard [2005] Kurlan [2007] Paleacu [2008] Schneider [2006] Tariot [2006] Zhong [2007]	Schizophrenia; Bipolar disorder or treatment of moderate to severe manic episodes; Major depressive episodes in bipolar disorder or prevention of relapses of manic or depressive episodes in patients with bipolar disorder who have previously responded to quetiapine treatment; Major depressive episodes in people with Major Depressive Disorder with suboptimal response to antidepressant monotherapy.
Risperidone	0.5-2mg	Significant improvement in CMAI Significant increase in extrapyramidal events, cerebrovascular events, and somnolence	AD	Brodaty [2003] De Deyn [1999] Deberdt [2005] Katz [1999] Mintzer [2006] Schneider [2006]	Persistent aggression in people with moderate to severe AD who do not respond to non-pharmacological approaches, and when there is a risk of harming themselves or others, short-term treatment (up to 6 weeks); Schizophrenia; Moderate to severe mania episodes associated with bipolar disorder; Persistent aggression in behavior disorder in children from the age of 5 years and adolescents with intellectual functioning below average or mental retardation (DSM-IV criteria), short-term symptomatic treatment (up to 6 weeks).
Perphenazine	0.05-0.1mg/kg	No significant effect (study with small sample size)	AD	Pollock [2002]	Schizophrenia, paranoid states, and mania Toxic psychoses (amphetamines, LSD, cocaine, etc.); Organic mental syndromes with delirium; Anxiety disorders especially severe and resistant to treatment with typical anxiolytics; Depression accompanied by agitation and delirium, mostly in association with antidepressants; Vomiting and persistent hiccups; Intense pain usually in association with narcotic analgesics.
Mood stabilizers No benefit observed, worsening of cognitive symptoms with valproate					
Valproate	250-1500mg	Significant worsening in MMSE No significant improvement	AD	Herrmann [2007] Porsteinsson [2001] Profenno [2005] Tariot [2005]	Generalized seizure; partial seizure; Specific syndromes (West, Lennox-Gastaut).
Carbamazepine	100-300mg	Significant improvement in BPRS (study with small sample size)	AD	Olin [2001] Tariot [1998]	Seizures (psychomotor or temporal, generalized tonic-clonic seizures, mixed forms, focal seizures); Trigeminal neuralgia; Mania.

Modafinil	100-200mg	No significant effect	AD	Frakey [2012]	Excessive sleepiness associated with narcolepsy, with or without cataplexy in adults.
Drugs for sleep disturbances					
Lemborexant	2.5-15mg	No significant effect	AD	Moline [2021]	Sleep disturbances in adults (FDA approved only). **Not approved in Italy.**
Suvorexant	10-20mg	No significant effect	AD	Herring [2020]	Sleep disturbances in adults (FDA approved only). **Not approved in Italy.**
Zolpidem	10mg	No significant effect	AD	Louzada [2022]	Insomnia in adults (in older adults, a usual daily dose of 5mg is recommended), short-term treatment
Zopiclone	7.5mg	No significant effect	AD	Louzada [2022]	Insomnia in adults, short-term treatment
Trazodone	50mg	No significant effect	AD	Camargos [2014]	Depressive disorders with or without anxiety component in adults.
Paracetamol/ buprenorphine	-	Significant improvement in CSDD Significant reduction in daytime sleep duration	AD	Blytt [2018] Erdal [2018]	-
Melatonin	2-10mg	No significant effect	Dementia	Dowling [2008] Singer [2003] Wade [2014] van der Lek [2008] Delgado [2018]	Primary insomnia characterised by poor sleep quality in people aged ≥ 55 years, short-term treatment.
Psychostimulants					
Methylphenidate	10-20mg	Significant improvement in AES, CSDD, ADCS-CGIC, IADL	AD	Herrmann [2008] Rosenberg [2013] Padala [2018] Mintzer [2021]	Attention deficit hyperactivity disorder.
Acetylcholinesterase inhibitors/memantine					
Donepezil	10mg	Treatment continuation produces significant improvement in NPI, NPI-depression, MMSE scores	AD	Holmes [2004] Howard [2007]	Mild to moderate Alzheimer's dementia
Rivastigmine	3-9mg	No significant effect	AD	Mahlberg [2007] Ballard [2005]	Mild to moderate Alzheimer's dementia
Memantine	20mg	No significant effect	AD	Bakchine [2008] Fox [2012] Peskind [2006] Porsteinsson [2008]	Moderate to severe Alzheimer's dementia
Choline Alphoscerate					
Choline Alphoscerate	1200mg	Significant improvement in MMSE, ADAS-Cog, NPI, NPI-agitation	AD	Rea [2015]	Psycho-organic degenerative brain syndromes or those secondary to cerebrovascular insufficiency, i.e. primary or secondary cognitive disorders of the elderly characterised by memory deficits, confusion, and disorientation, decline in motivation and initiative and reduction in attentional capacity. Alterations in the affective sphere and senile behavior: emotional lability, irritability, indifference to surroundings. Pseudo-depression in the elderly.
Cannabinoids					
Cannabidiol	21 drops (11.8mg CBD + 0.5mg THC)	No significant effect	Dementia	Hermush [2022]	Crises associated with Lennox Gastaut or Dravet syndromes, in combination with clobazam, for people aged ≥ 2 years MS to relieve symptoms of spasticity
THC	4.5mg	No significant effect	Dementia (AD, VaD,	Van den Elsen [2015]	

			demenza mista)		
Others					
Dextromethorphan /quinidine	60mg/ 20mg	Significant improvement in NPI, NPI-agitation, CSDD Increased risk in AEs	AD	Cummings [2015]	Pseudobulbar syndrome in adults.
Prazosin	1-6mg	Significant improvement (study with small sample size)	AD	Wang [2009]	Hypertension. Benign prostatic hypertrophy.

Recommendations

Management of non-cognitive symptoms in people with dementia

132	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).	STRONG IN FAVOR
133	As initial and ongoing management, offer psychosocial and environmental interventions to reduce distress in people living with dementia.	STRONG IN FAVOR
134	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.	STRONG IN FAVOR
135	For people living with dementia who experience agitation or aggression, offer personalised activities to promote engagement, pleasure and interest.	STRONG IN FAVOR
136	Consider interventions aimed at specifically training staff for the management of non-cognitive symptoms in people living with dementia.	WEAK IN FAVOR
137	Consider providing access to therapeutic gardens for the management of non-cognitive symptoms in people living with dementia who experience BPSDs.	WEAK IN FAVOR
138	Consider interventions of active and/or receptive music therapy for the management of non-cognitive symptoms in people living with dementia who experience BPSDs.	WEAK IN FAVOR
139	Consider psychological treatments in people with mild to moderate dementia who experience mild to moderate depressive symptoms and/or anxiety.	WEAK IN FAVOR
140	Consider the use of therapeutic robots in people with dementia who experience depressive symptoms, anxiety and/or agitation.	WEAK IN FAVOR
141	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.	WEAK IN FAVOR
142	Before starting antipsychotics, discuss the benefits and harms with the person and their family members or caregivers (as appropriate). Consider using a decision aid to support this discussion.	STRONG IN FAVOR
143	When using antipsychotics: • use the lowest effective dose and use them for the shortest possible time;	STRONG IN FAVOR

	• reassess the person at least every four weeks, to check whether they still need medication.	
144	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.	STRONG IN FAVOR
145	Stop treatment with antipsychotics: • if 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 caregivers (as appropriate).	STRONG IN FAVOR
146	Do not offer valproate to manage agitation or aggression in people living with dementia, unless it is indicated for another condition.	STRONG AGAINST
147	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.	STRONG AGAINST
148	Do not offer bupropion to manage depressive symptoms in people living with dementia.	STRONG AGAINST
149	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 Table 6. Be aware that interventions may need to be modified for people living with dementia.	WEAK IN FAVOR

Research Recommendations

Treating non-cognitive symptoms in people with dementia

30R	What is the effectiveness and safety of citalopram for managing depressive symptoms in people living with dementia?
31R	What is the effectiveness and safety of vortioxetine for managing depressive symptoms in people living with dementia?
32R	What is the effectiveness of pharmacological treatments for managing sleep disorders in people living with dementia?
33R	What is the effectiveness and cost-effectiveness of dextromethorphan-quinidine for managing agitation in people living with dementia?
34R	What is the effectiveness and cost-effectiveness of choline alphoscerate for managing apathy in people living with dementia?
35R	What is the effectiveness of aromatherapy in people living with dementia experiencing agitation or aggression?
36R	What is the utility of physical exercise in people living with dementia experiencing depressive symptoms, agitation or apathy?
37R	What are the most effective psychological treatments for managing depression or anxiety in people living with dementia at each stage of the condition?

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Assessing and treating intercurrent illness in people living with dementia

Review question 22a	**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?**
Review question 22b	**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?**

Literature review

	22a	22b
Records identified from databases	16,169	16,169
Studies assessed for eligibility	8	8
Included studies	2	4
Studies included in the NICE GL	7	23
Total number of included studies	9	27

Eligibility criteria

Review question 22a

Population	People aged ≥40 years with or without a diagnosis of dementia.
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. • Usual care.
Outcomes	• Rates of accurately identified intercurrent illness in people living with dementia. • Diagnostic test accuracy (including sensitivity, specificity, predictive values). • Clinical outcomes including cognitive, functional, and behavioural ability. • Health-related quality of life of people living with dementia. • Resource use and cost.

Review question 22b

Population	People aged ≥40 years 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. • Usual care.
Outcomes	• Symptom resolution/reduction of non-cognitive symptoms. • Clinical outcomes including cognitive, functional, and behavioural ability. • Change in appropriate polypharmacy. • Intervention-related problems such as potentially avoidable hospital admissions and adverse effects. • Intervention related outcomes including concordance, compliance satisfaction of person living with dementia and their informal caregivers. • Health related quality of life of person living with dementia and his/her informal caregiver. • Resource use and cost.

Aim

The objective of the systematic literature review, in line with the strategy defined by the NICE Guideline, was to identify experimental and observational studies investigating the utility of tools for the assessment of the symptoms and severity of intercurrent conditions, and the effectiveness of available treatments for these conditions in people with dementia. We defined as intercurrent illnesses all conditions with an onset after the diagnosis of dementia. The literature review for both questions only included studies specifically aimed at identifying and assessing the effectiveness and utility of diagnostic and therapeutic interventions specific for people with dementia, thus different from those used in people without dementia.

Summary of evidence

Review question 22a

PAIN

Overall, six studies investigated the utility of specific tools for the assessment of pain. One study on 600 participants (Mosele 2012) investigated the performance of the PAINAD (Pain Assessment in Advanced Dementia) tool administered by a health professional compared with a self-reported Numerical Rating Scale (NRS). The study reported in the group with cognitive decline compared to the group with normal cognition a higher prevalence of pain both as measured with PAINAD (RR 1.39, 95% CI 1.20 – 1.62, I^2 n.a., low certainty) and as measured with the NRS (RR 1.19, 95% CI 1.00 – 1.41, I^2 n.a., low certainty). It also reported a higher mean frequency of pain reported through PAINAD (MD 0.70, 95% CI 0.26 – 1.14, I^2 n.a., low certainty), but not through NRS (MD 0.30, IC 95% CI -0.25 – 0.85, I^2 n.a., low certainty). Another study on 25 participants (DeWaters 2008) reported a correlation between PAINAD and NRS both in the group with cognitive decline ($p < 0.001$) and in the group with normal cognition ($p < 0.001$) (very low certainty).

One study on 40 participants (Horgas 2007) investigated the correlation between the NOPPAIN (Non-Communicative Patients Pain Assessment) tool and other two self-reported tools, one numerical rating scale (NRS) and a Verbal Descriptor Scale (VDS). The study reported no correlation between the severity of pain reported through the NOPPAIN tool and the other two tools for the group with cognitive decline, while it

reported a correlation between NOPPAIN e and the other two tools for the group with normal cognition (p < 0,001, low certainty). When considering the number of observed pain indicators, the study reported a correlation between NOPPAIN and the number of indicators both in the group with cognitive decline (p < 0.001, low certainty) and in the group with normal cognition (p < 0.001, low certainty).

One study on 174 participants (Van Herk 2009) compared the performance of the REPOS (Rotterdam Elderly Pain Observation Scale) compared to the scales PAINAD and NRS. The study reported a correlation between REPOS and PAINAD (rs = 0.75, 95% CI 0.66 – 0.82, very low certainty), but not between REPOS and NRS (rs = 0.19, 95% CI 0.01 – 0.35, very low certainty) the group with cognitive decline. However, it reported no correlation between REPOS and PAINAD (rs = 0,61, IC 95% 0,40 – 0,76, very low certainty) or NRS (rs = 0,36, IC 95% 0,09 – 0,58, very low certainty) in the group with normal cognition. The study also reported a difference between the median pain score between the group with cognitive decline and the group with normal cognition (p = 0,0002, very low certainty).

One study on 125 participants (Lukas 2013) compared the performance of the scales APS (Abbey Pain Scale for dementia patients), PAINAD, and NOPPAIN compared to a self-reported questionnaire. The study reported a correlation between the objective scales and the self-reported questionnaire (p < 0.001 for all scales, moderate certainty) both in the group with cognitive decline and in the group with normal cognition (APS p = 0.01, PAINAD p = 0.06, NOPPAIN p = 0.01, moderate certainty). It also reported a higher concordance between the objective tools and the self-reported questionnaire in the group with cognitive decline (APS 78.3%, PAINAD 73.3%, NOPPAIN 80.0%, moderate certainty) compared to the group with normal cognition (APS 66,1%, PAINAD 66,1%, NOPPAIN 69,2%, moderate certainty).

One study on 190 participants (Ersek 2019) compared the performance of the PIMD (Pain Intensity Measure for persons with Dementia) tool compared to the MOBID (Mobilization – Observation – Behaviour – Intensity – Dementia) and the ECPIR (Expert Clinician Pain Intensity Rating) tools. The study reported a correlation between the scales PIMD e MOBID in the assessment of pain severity at rest (p = 0.02, low certainty) and in movement (p < 0.001, low certainty). It also reported a correlation between the scales PIMD and ECPIR in assessing the severity of pain in movement (p < 0.001, low certainty), but not at rest (p = 0.8, low certainty).

FALLS

One study investigated the performance of the scale BBS (Berg Balance Scale) for the assessment of falls. The study (Kato-Narita 2011), on 88 participants, reported a difference in BBS scores between the group with cognitive decline and the group with normal cognition (MD -1.80, 95% CI -3.60 – -0.54, I^2 n.a., low certainty). It also reported a correlation between BBS scores and the number of falls within the last 12 months both in the group with cognitive decline (p = 0.045, low certainty) and in the group with normal cognition (p = 0.015, low certainty).

DELIRIUM

Two studies investigated the performance of different tools for the assessment of delirium. One study on 125 participants (Sepulveda 2015) investigated the accuracy of the DRS (Delirium Rating Scale) compared to standard criteria. The study reported a good accuracy of the tool in both the cognitive impairment group (CIg) and the normal cognition group (NCg) compared to DSM-5 (CIg: 87.03%; NCg: 98.86%; MD 11.83, 95% CI 3.07 – 20.59, low certainty), ICD-10 (CIg: 86.69%; NCg: 97.37%; MD 10.68, 95% CI 1.62 – 19.74, low certainty), DSM-III-R (CIg: 88.55%; NCg: 100%; MD 11.45, 95% CI 3.02 – 19.88, low certainty), and DSM-IV (CIg: 88.29%; NCg: 100%; MD 11.71, 95%CI 3.44 – 19.98, low certainty).

The second study investigated the accuracy of the Family Confusion Assessment Method (FAM-CAM) compared to the version of the CAM scale administered in the emergency setting. The study (Mailhot 2020), on 108 participants, reported a sensitivity of 56,7% and a specificity of 83,3% for the total sample (low

certainty), and values of sensitivity of 60,8% and 42,8%, and values of specificity of 74,3% and 90,7% in participants with dementia and participants without dementia respectively (low certainty).

Review question 22b

PAIN

Overall, six studies investigated the effectiveness of interventions aimed at the management of pain. One study on 173 participants (Fuchs-Lacelle 2008) investigated the implementation of a checklist for the structured assessment of pain (Pain Assessment Checklist for Seniors with Limited Ability to Communicate, PACSLAC) compared to standard assessment. The study reported an improvement in the intervention group compared to the control group in the PRN (Pro Re Nata) score for quantifying the number of drugs at three months (MD 0.005, p = 0.00, I^2 n.a., low certainty), and a decrease in stress related to care activities (MD -6.10, p = 0.04, I^2 n.a., low certainty).

Two studies investigated the effectiveness of the implementation of a structured protocol for treating pain (Stepwise Protocol of Treating Pain, SPTP) compared to standard treatment. One study on 241 participants (Husebo 2014) reported an improvement in the intervention group compared to the control group in psychological and behavioural symptoms (NPI: MD -9.60, 95% CI -15.68 – -3.52, I^2 n.a., moderate certainty). The second study (Sandvik 2014), on 327 participants, reported an improvement in the intervention group in overall pain (MD -3.40, 95% CI -6.42 – -0.38, I^2 n.a., moderate certainty), musculoskeletal pain (MOBID-2 part 1: MD -2.60, 95% CI -4.37 – -0.83, I^2 n.a., moderate certainty), and pain related to internal organs, head and skin (MOBID-2 part 2: MD -1.40, 95% CI -2.17 – -0.63, I^2 n.a., moderate certainty) measured with MOBID-2 (Mobilization-Observation-Behavior-IntensityDementia-2).

One study investigated the effectiveness of a structured protocol for the identification and treatment of pain (Pain Recognition and Treatment, PRT) compared to a training intervention on the management of pain. The study (Chen 2016), on 195 participants, reported an improvement in the intervention group compared to the control group in the severity of weekly reported pain (PAINAD: MD -1.05, 95% CI -1.46 – -0.64, I^2 n.a., low certainty). However, it reported no differences between groups in the mean number of weekly pharmacological (MD -0.35, 95% CI -0.72 – 0.02, I^2 n.a., low certainty) and non-pharmacological treatments (MD 0.03, 95% CI -0.24 – 0.30, I^2 n.a., low certainty), and in agitation (CMAI: MD -0.10, 95% CI -2.46 – 2.26, I^2 n.a., low certainty).

One study investigated the effectiveness of the implementation of a specific protocol for the management of pain (Observational Pain Management Protocol, OPMP) compared to standard management. The study (Liu 2017), on 162 participants, reported an increase in the intervention group compared to the control group of the mean frequency of pharmacological treatments (MD 8.62, 95% CI 7.28 – 9.96, I^2 n.a., low certainty). It also reported a decrease in the intervention group of the reported pan severity (PAINAD: MD -1.69, IC 95% -2.57 – -0.81, I^2 n.a., low certainty). However, it reported no differences between groups in the mean quantity, measured with the MSQ (Medication Quantification Scale), of pain medications (MD -0.52, 95% CI-7.76 – 6.72, I^2 n.a., low certainty) and psychotropic agents (MD 4.28, 95% CI -9.32– 17.88, I^2 n.a., low certainty).

One last study investigated an intervention of Trans Cutaneous Electrical Nerve Stimulation (TENS) for pain management. The study (Hahm 2019), on 32 participants, reported no differences between groups in pain severity measured with algometry (MD 0.30, 95% CI -0.26 – 0.86, I^2 n.a., low certainty).

DELIRIUM

One study on 16 participants (Kolanowski 2011) investigated the effectiveness of an intervention of cognitive stimulation based on the participation to personalized recreational activities for the management of delirium.

The study reported no differences between groups in functional status (BI, Barthel Index: MD 4.33, 95% CI -12.64 – 21.30, I^2 n.a., very low certainty), confusion (CAM, Confusion Assessment Method: MD -0.17, 95% CI -0.70 – 0.36, I^2 n.a., very low certainty), and delirium (DRS, Dementia Rating Scale: MD -1.80, 95% CI -11.74 – 8.14, I^2 n.a., very low certainty). It also reported no differences in cognitive abilities (MMSE: MD 0.59, 95% CI -10.13 – 11.31, I^2 n.a., very low certainty).

HIP FRACTURE

Overall, nine studies investigated the effectiveness of interventions aimed at the management of people with dementia undergoing rehabilitation after hip fracture. One study on 199 participants (Stenvall 2007) investigated the effectiveness of an intervention of multidimensional management compared to standard care. The study reported a lower incidence of falls in the group with dementia compared to the overall group (tot: IRR 0.38, 95% CI 0.20 – 0.76; dementia: IRR 0.07, 95% CI 0.01 – 0.57, moderate certainty).

One study investigated the effectiveness of an intervention of enhancement of in-hospital care compared to standard care. Lo studio (Stenvall 2012), su 64 participants, reported no differences between groups in the rate of independence in ADL (RR 4.35, 95% CI 0.19 – 101.46, I^2 n.a., very low certainty) and in mortality rate (RR 2.25, 95% CI 0.73 – 6.93, I^2 n.a., very low certainty) at 12 months.

Five studies investigated the effectiveness of an intervention of enhancement of in-hospital and home care compared to standard care. Three studies (Freter 2017, Stenvall 2012, Uy 2008), on 152 participants, reported no differences between groups in mortality rate during hospitalisation (RR 0.63, 95% CI 0.21 – 1.91, I^2 17%, very low certainty).

When considering outcomes at 12 months, two studies on 177 participants (Huusko 2000, Shyu 2012) reported no differences between groups in mortality rate (RR1.06, 95% CI 0.53 – 2.13, I^2 n.a., very low certainty). One study on 36 participants (Shyu 2012) reported no differences between groups in the incidence of falls (RR 0.22, 95% CI 0.01 – 4.33, I^2 n.a., very low certainty). However, it reported a significant difference between groups in ADL (Chinese-BI: MD 25.40, 95% CI 10.89 – 39.91, I^2 n.a., very low certainty).

Two studies investigated the effectiveness of an in-hospital care management led by a geriatrician compared by an in-hospital care management led by an orthopedist. The two studies (Marcantonio 2001, Wyller 2012), on 212 participants, reported no differences between groups in the incidence of delirium during hospitalisation (RR 0.99, 95% CI 0.83 – 1.17, I^2 0%, very low certainty).

One study investigated the effectiveness of an intervention of interdisciplinary home-based rehabilitation compared to in-hospital standard care. The study (Karlsson 2020), on 103 participants, reported no differences between groups in incidence of falls (RR 0.90, 95% CI 0.62 – 1.31, I^2 n.a., very low certainty) and mortality rate after discharge (RR 0.81, 95% CI 0.42 – 1.57, I^2 n.a., very low certainty).

PHYSICAL EXERCISE FOR THE PREVENTION OF FALLS

Overall, 11 studies investigated the effectiveness of interventions based on physical activity and physical exercise to manage the risk of falls. Seven studies investigated the effectiveness of interventions based on physical exercise for fall prevention. The seven studies (Lord 2003, Moseley 2009, Pitkälä 2013, Rolland 2007, Rosendahl 2008, Toulotte 2003, Zieschang 2013), on 688 participants, reported a lower risk of falls in the intervention group compared to the control group (RR 0.68, 95% CI 0.51 – 0.92, I^2 79%, very low certainty). Two studies on 304 participants (Pitkälä 2013, Rolland 2007) reported no differences between groups in the risk of hip fracture (RR 1.46, 95% CI 0.58 – 3.70, I^2 0%, very low certainty).

Two studies investigated the effectiveness of an intervention of physical rehabilitation through home-based exercises compared to standard care. The two studies (Pitkälä 2013, Wesson 2013), on 148 participants, reported a decrease in the intervention group compared to the control group in the mean number of falls (MD -1.08, 95% CI -1.79 – -0.37, low certainty) and of the proportion of participants reporting at least one

fall (RR 0.69, 95% CI 0.51 – 0.93, low certainty). One study on 133 participants (Pitkälä 2013) reported in the intervention group (IG) compared to the control group (CT) a lower incidence of falls (IR: IG 1.35, 95% CI 1.07 – 1.67 versus CT 3.07, 95% CI 2.63 – 3.57, low certainty). However, it reported no differences between groups in the incidence of hip fractures (IR: IG 0.05, 95% CI 0.01 – 0.14 versus CT 0.05, 95% CI 0.01 – 0.15, low certainty) and overall fractures (IR: IG 0.06, 95% CI 0.02 – 0.17 versus CT 0.07, 95% CI 0.02 – 0.18, low certainty).

One study on 123 participants (Pitkälä 2013) investigated the effectiveness of a group intervention of physical rehabilitation based on personalized exercised. The study reported a decrease in the intervention group (IG) compared to the control group (CT) in the number of participants reporting at least one fall (RR 0.68, 95% CI 0.50 – 0.94, I^2 n.a., low certainty) and a lower incidence of falls (IR: IG 1.86, 95% CI 1.51 – 2.26 versus CT 3.07, 95% CI 2.63 – 3.57, low certainty). However, it reported no differences between groups in the mean number of falls (MD -1.03, 95% CI -2.19 – 0.13, I^2 n.a., low certainty). It also reported no differences in the incidence of hip fractures (IR: IG 0.04, 95% CI 0.00 – 0.13 versus CT 0.05, 95% CI 0.01 – 0.15, low certainty) and overall fractures (IR: IG 0.09, 95% CI 0.03 – 0.21 versus CT 0.07, 95% CI 0.02 – 0.18, low certainty).

One study on 274 participants (Shaw 2003) investigated the effectiveness of a multifactorial intervention, based on a multidisciplinary assessment and subsequent personalized intervention, in people referring to the ER after a fall. The study reported no differences between groups at 12 months in the risk of falls (RR0.92, 95% CI 0.81 – 1.05, I^2 n.a., very low certainty), femoral head fractures (RR 0.55, 95% CI 0.21 – 1.43, I^2 n.a., very low certainty), fall-related hospitalisations (RR 1.11, 95% CI 0.61 – 2.00, I^2 n.a., very low certainty). It also reported no differences in the mortality rate at 12 months (RR 1.03, 95% CI 0.65 – 1.64, I^2 n.a., very low certainty).

One study investigated the effectiveness of a program of group sessions of multimodal physical exercise in institutionalised people. The study (Puente-González 2021), on 72 participants, reported a lower incidence of falls in the intervention group compared to the control group (RR 0.36, 95% CI 0.16 – 0.82, I^2 n.a., low certainty). The study reported in improvement in stability (POMA-T, Tinetti's Performance-Oriented Mobility Assessment: MD 2.43, 95% CI 1.07 – 3.79, I^2 n.a., low certainty), balance (POMA-Balance: MD 0.63, IC 95% 0.12 – 1.14, I^2 n.a., low certainty), gait (POMA-Gait: MD 1.82, 95% CI 0.86 – 2.78, I^2 n.a., low certainty). It also reported an improvement in the intervention group in TUG scores (Timed Up and Go: MD -3.10, 95% CI -5.43 – -0.77, I^2 n.a., low certainty).

One last study investigated the effectiveness of an intervention involving the use of home-based technologies coupled with a tele-assistance service, including a nightlight path, an electronic bracelet and distance communication tools. The study (Tchalla 2012), on 96 participants, reported a decrease in the intervention group compared to the control group in the incidence of falls (RR 0.51, 95% CI 0.16 – 0.81, I^2 n.a., low certainty).

Analysis of evidence

The complex issue of comorbidities in people with dementia is also discussed in the analysis of the evidence retrieved for question 11, which considered evidence on the management of chronic physical conditions, comorbid to cognitive decline, whose onset precedes the diagnosis of dementia or mild cognitive impairment (MCI). The analysis of evidence for question 22 specifically focused on studies reporting data on available tools and methods for assessing the symptoms and severity of acute clinical conditions, unrelated to dementia, in people with a diagnosis of dementia. In particular, the NICE guideline (GL) focused on evidence on four acute clinical conditions including pain, falls and loss of mobility, delirium, and urinary tract infections. These conditions are usually considered as common in frail people, regardless their being comorbid with dementia, and can cause a worsening of the people's general health status and quality of life, increasing the

burden of care for caregivers. Outcome measures included the rate of intercurrent conditions, the accuracy of considered tests, clinical outcomes such as cognitive, functional and behavioural symptoms, and quality of life of people with dementia.

People with dementia experience pain like any other cognitively unimpaired person. However, assessing pain in people with dementia can be extremely difficult due to their inability to refer their discomfort both of their own accord and upon request from their caregivers or a health professional.

The WG discussed the issues related to an appropriate detection of pain in people with dementia. This difficulty, confirmed by both evidence and clinical practice, supports the hypothesis that pain in this population can either be largely underestimated, or be, on the other hand, largely overestimated leading to the inappropriate administration of pain medications.

Identifying tools for the objective assessment of pain and defining effective treatment protocols for people with dementia are a priority. Adequately detecting physical pain would be of invaluable support in the management not only of cases where pain is reported in an explicit way, but mainly of cases where indirect evidence of pain is available, such as behavioural disorders, which, if miscategorised, can lead to inappropriate treatments potentially affecting the quality of life of people with dementia and their carers.

The analysis of evidence reported no correlation between self-reported pain (self-reported assessments) and pain assessed by an observer in people with dementia compared to people without dementia.

Evidence underlined the importance of using objective tools for the assessment of pain (e.g., Pain Assessment in Advanced Dementia, PAINAD, including parameters such as breathing, vocalisation, facial expression, body language and consolability, or Pain Intensity Measure for Persons with Dementia, PIMD, based on bracing, rigid/stiff, sighing, complaining, grimacing, frowning, expressive eyes). In fact, these tools, by focusing on signs that are considered indicative of discomfort and of pain severity, allow detecting pain in people with dementia in the same way as in people without dementia, which is not possible when using self-reported tools.

This led the WG to highlight the situation of people with moderate to severe dementia, who might not be aware and/or able to refer their pain. Objective tools in these cases are the only reliable way to assess pain, along with the standard clinical evaluation. Moreover, the specificity of the situation also requires performing regular reassessments, both in case of persisting signs suggesting the presence of pain, especially behavioural disorders and agitation, and after treatment, to ensure the appropriate protocol phases are being followed.

The WG, based on available evidence, agreed with the NICE GL that sufficient evidence is available supporting a recommendation to use structured observational tools alongside self-reported pain assessment tools. The WG also confirmed the recommendation from the NICE GL agreeing that available evidence does not support any new indication to adopt specific strategies to manage pain in people with dementia that are different from the strategies adopted in people without dementia.

As mentioned, another relevant consideration was that people with dementia might be at a higher risk of being undertreated, thus receiving inappropriate or inadequate pain medications, than of being overtreated. This issue requires reaching a compromise that should be based on best clinical practices.

On this basis, the WG confirmed the recommendation from the NICE GL to consider, in people with dementia who experience pain, a stepwise treatment that balances pain management and potential adverse events. The WG underlined that pain should be managed with a gradual approach balancing the need for analgesia and any behavioural changes or other sign indicating pain.

Included studies did not report any longitudinal evidence supporting an indication to monitor pain with a specific frequency. Some cases require a periodic reassessment, which, however, could be unfeasible or inapplicable in clinical practice in all people with dementia. The WG, in line with the NICE GL, underlined that repeating pain assessment is appropriate in case of suspect persistence or relapse of the symptoms of pain.

When considering falls, only one case-control study was included investigating the performance of a scale estimating the risk of falls in people with dementia compared to people without dementia. The study reported a difference in scores between people with dementia and people without dementia, with equal correlation of BBS (Berg Balance Scale) scores and number of falls. Despite the limited evidence and based on general considerations derived from clinical practice, the WG agreed that the basic principles guiding the management of falls in people with dementia do not need to be different from those adopted in people without dementia.

The NICE GL referred for this topic to its guideline on assessing risk and prevention of falls in older people (CG161)[42]. The WG confirmed the recommendation from the NICE GL underlining that people with dementia might need additional support to participate effectively in any intervention. Some studies considered multifactorial interventions or multimodal physical exercise for preventing falls. However, these interventions might not be suitable for people with severe dementia due to the intensity of the activities and the number of needed tests, which may cause further distress. To this purpose, the included recommendation underlined that health professionals should consider individual needs of people with dementia when offering them interventions for preventing falls. The opportunity of specifically adapting interventions to ensure an appropriate participation should always be considered.

No relevant evidence was identified on the detection of delirium, and no evidence was identified on urinary tract infections in people with a diagnosis of dementia. Therefore, the WG, in line with the NICE GL, agreed not to include any recommendation on these topics. The NICE GL, due to the lack of evidence, included a research recommendation on the long-term recovery of functional abilities in people with dementia after an acute episode of delirium. However, the WG agreed on removing the recommendation and not including any research recommendation.

Recommendations

Assessing intercurrent illness in people living with dementia

150	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.	WEAK IN FAVOUR
151	For people living with dementia who are in pain, consider using a stepwise treatment protocol that balances pain management and potential adverse events.	WEAK IN FAVOUR
152	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.	STRONG IN FAVOUR

Treating intercurrent illness in people living with dementia

[42] NICE. Falls in older people: assessing risk and prevention Clinical guideline [CG161]. Last updated: June 2013. Available at: https://www.nice.org.uk/guidance/cg161/ (Last visited: 30/08/2023)

153	For managing the risk of falling for people living with dementia refer to the standard treatment for the prevention of falls (see Table 6). When using this guidance: • 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.	STRONG IN FAVOUR

Research Recommendations

No research recommendations were made.

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Caring for people living with dementia who are admitted to hospital

Review question 23	How should people living with dementia be cared for when admitted to hospital?

Literature review

Records identified from databases	8,019
Studies assessed for eligibility	4
Included studies	3
Studies included in the NICE GL	5
Total number of included studies	8

Eligibility criteria

Population	People aged ≥40 years living with dementia and admitted to hospital.
Interventions	Models of hospital care for people living with dementia, which may include elements such as: • additional support from hospital staff/others; • information needs (both information for the person living with dementia and the information needs of the hospital staff); • person-centred assessment; • assessment for hospital discharge (timing of discharge); • family/carer information needs, access and involvement in care; • types of wards; • environmental design; • comprehensive geriatric assessment; • medicines reconciliation and review.
Comparator	Standard care.
Outcomes	• Clinical outcomes including cognitive, functional and behavioural ability. • Process outcomes (e.g. adherence of staff to care protocols). • Access to health and social care support. • Experience and satisfaction of persons with dementia and their caregivers. • Health-related quality of life of persons with dementia and their caregivers. • Adverse events. • Equity of access to services. • Resources use and costs.

Aim

The objective of the systematic review of literature, according to the strategy defined in the NICE guideline, was to identify all comparative quantitative studies (e.g., randomized clinical trials, non-randomized experimental studies) investigating the utility and efficacy of different care models for people with dementia admitted to hospital.

Summary of evidence

Multicomponent strategies aimed at mental health

One study investigated the effectiveness of a multicomponent intervention based on an initial assessment by a specialist followed by personalized interventions and support strategies. The study (Baldwin 2004), enrolling 153 participants, did not report any difference between groups in depressive symptoms (GDS: MD -2.20, 95% CI -5.09 – 0.69, I^2 n.a., low certainty) and cognitive function (MMSE: MD -0.90, 95% CI -3.91 – 2.11, I^2 n.a., very low certainty). The study reported no differences in mean length of stay (MD -1.70, 95% CI -11.00 – 7.60, I^2 n.a., very low certainty), frequency of psychotropic drugs prescriptions at discharge (RR 1.04, 95% CI 0.70 – 1.57, I^2 n.a., very low certainty), and rate of hospital readmission after three months (RR 0.89, 95% CI 0.52 – 1.52, I^2 n.a., very low certainty). It also reported no differences in mortality rate (RR 1.29, 95% CI 0.67 – 2.47, I^2 n.a., very low certainty).

Family-centred function focused care models

One study investigated the effectiveness of an intervention based on a care model aimed at maximizing functional capacities and physical activity combined with a family-centred approach, which used hospitalization as an opportunity to strengthen the role of caregivers through educational and support strategies. The study (Bolt 2015), enrolling 86 participants, reported a reduction in the intervention group compared to the control group in the risk of readmission after 30 days (RR 0.29, 95% CI 0.08 – 0.97, I^2n.a., low certainty). However, the study reported no differences between groups in functional abilities (BI, Barthel Index: MD 13.50, 95% CI -1.64 – 28.64, I^2 n.a., very low certainty), balance and gait (Tinetti scale: MD 0.00, 95% CI -5.23 – 5.23, I^2 n.a., very low certainty). It also reported no differences in anxiety (HAS, Hospital Anxiety Scale: MD -2.40, 95% CI -5.03 –0.23, I^2 n.a., very low certainty), depression (HAD, Hospital Depression Scale: MD -1.60, 95% CI -3.87 – 0.67, I^2 n.a., very low certainty), and severity of delirium (DSS, Delirium Severity Scale: MD -2.70, 95% CI -6.31 – 0.91, I^2 n.a., very low certainty). No differences were reported also in the mean length of stay (MD -0.40, 95% CI -1.27 – 0.47, I^2 n.a., low certainty) and in the rate of discharge to nursing homes (RR 1.04, 95% CI 0.52 – 2.10, I^2 n.a., very low certainty).

Proactive case finding with palliative care service

One study on 52 participants (Campbell 2004) investigated the effectiveness of an intervention of proactive case finding and collaboration between a palliative care service and staff from intensive care units. Palliative care interventions included communication of the prognosis to family members/caregivers and activation of palliative care services, support in identifying advanced care plans or preferences for end-of-life care, and implementation of palliative care. The study reported a decrease in the intervention group compared to usual care of the mean length of stay in hospital (MD -4.70, 95% CI -8.87 – -0.53, I^2 n.a., low certainty) and in the intensive care unit (MD -3.30, 95% CI -5.46 – -1, 14, I^2 n.a., low certainty). The study reported no differences between groups in mortality rate during hospitalization (RR 1.21, 95% CI 0.77 – 1.91, I2 n.a., very low certainty), and in the rate of discharge to nursing homes (RR 0.60, 95% CI 0.26 – 1 ,41, I^2 n.a., very low certainty).

Management of mental health in specialist units

One study on 600 participants (Goldberg 2013) investigated the effectiveness of an intervention based on the management of delirium and psychological and behavioural symptoms within a specialist mental health unit. The study reported no differences between groups in the rates of mortality (RR 0.90, 95% CI 0.67 – 1.20, I^2 n.a., low certainty), readmission (RR 0.92, 95% CI 0.73 – 1.15, I^2 n.a., low certainty), discharge at home (RR 1.06, 95% CI 0.95 – 1.17, I^2 n.a., low certainty), and institutionalization (RR 0.72, 95% CI 0.51 – 1.00, I^2 n.a., low certainty). However, it reported a higher caregiver satisfaction in care in the intervention group compared to the control group (RR 1.10, 95% CI 1.03 – 1.18, I^2 n.a., low certainty).

Follow-up individualized care plan

One study on 558 participants (Villars 2013) investigated the effectiveness of the implementation of an individualized care plane after discharge, including follow-up visits and telephone support from a multidisciplinary team and social health care professionals. The study reported no differences between groups in the rates of readmission to ER (RR 0.91, 95% CI 0.49 – 1.69, I^2 n.a., very low certainty) or to any other hospital ward (RR 0.81, 95% CI 0.52 – 1.23, I^2 n.a., very low certainty) at 1 month. It also reported no differences in the rates of readmission to ER (RR 0.80, 95% CI 0.58 – 1.09, I^2 n.a., very low certainty) or to any other hospital ward (RR 0.76, 95% CI 0.48 – 1.21, I^2 n.a., very low certainty) at 3 months.

Multidimensional nutritional assessment

One study investigated the effectiveness of a multidimensional assessment intervention aimed at the identification and structured and personalized management of nutritional aspects. The study (Arahata 2017), enrolling 214 participants, reported a higher frequency in the intervention group compared to control group in the frequency of discontinuation of artificial hydration and/or nutrition (AHN: RR 2.07, 95% CI 1.47 – 2.90, I^2 n.a., low certainty). The study also reported a higher survival rate without AHN (RR 2.57, 95% CI 1.46 – 4.53, I^2 n.a., low certainty), a higher frequency of people without AHN (RR 1.77, 95% CI 1.25 – 2.51, I^2 n.a., low certainty), and a lower frequency of nasogastric tube and PEG insertions (Percutaneous Endoscopic Gastrostomy) (RR 0.21, 95% CI 0.08 – 0.59, I^2 n.a., low certainty). However, the study reported no differences between groups in frequency of central or peripheral venous catheter insertions (RR 0.90, 95% CI 0.67 – 1.19, I^2 n.a., low certainty), mean length of stay (MD 14.00, 95% CI -0.11 – 28.11, I^2 n.a., low certainty), and mortality rate at discharge (RR 0.95, 95% CI 0.65 – 1.40, I^2 n.a., low certainty)

Physical activity

One study investigated the effectiveness of an intervention based on a group exercise program aimed at the strengthening of both upper and lower limbs. The study (Fleiner 2017), on 85 participants, reported no differences between groups in psychological and behavioural symptoms (NPI: MD -5.90, 95% CI -12.46 – 0.66, I^2 n.a., low certainty) and agitation (CMAI: MD -3.90, 95% CI -10.63 – 2.83, I^2 n.a., low certainty).

Involvement of a pharmacist or pharmacologist in the hospital team

One study investigated the effectiveness of involving a pharmacist or pharmacologist in the care team to manage the reconciliation and optimization of medicines and monitor pharmacological therapies. The study (Gustafsson 2017), on 429 participants, reported a lower risk of hospital readmission due to issues related to the pharmacological treatment after 30 days in the intervention group compared to the control group (RR 0.47, 95% CI 0.24 – 0.93, I^2 n.a., moderate certainty). However, it reported no differences between groups in the overall rates of readmission (RR 0.79, 95% CI 0.52 – 1.22, I^2 n.a., low certainty) and mortality (RR 1.32, 95% CI 0.88 – 1.99, I^2 n.a., low certainty) at 30 days.

Analysis of evidence

The objective of this systematic review was to define the most appropriate ways to manage people with dementia when they are admitted to hospital, and to identify potential harms caused by inappropriate care models within the hospital setting.

While analysing evidence for question 13 the Working Group (WG) discussed the main issues that people with dementia and their caregivers deal with when transferring between settings, mainly due to an inadequate communication about changes in the environment and care, a scarce contact with health professionals, and a lack of communication about care protocols among different professionals. This is particularly relevant for people with dementia considering their vulnerability and the higher risk of complications due to inadequate communication of information on pharmacological and non-pharmacological treatments during the process of transferring the person between settings. The WG underlined that this is particularly relevant in case of acute conditions requiring hospitalization in people with pre-existing comorbidities.

Hospitalization is a sudden and traumatic change often causing distress, confusion, and the onset of delirium. These conditions can further affect global functions and decrease the person's ability to be discharged back home while still being independent or after having recovered their independence. Maintaining global functions, if not reaching a better performance, should be the minimum goal after a hospitalization when considering globally a care plan for people with dementia and their caregivers.

Moreover, hospitalizations due to acute conditions could be a unique opportunity for people with undiagnosed dementia to receive an assessment and diagnosis. This could be a key element not only to improve treatments and the whole care path during the hospitalization allowing also to reduce the time to discharge, but also to provide an essential support to define the best care path possible allowing to plan the access to post-diagnostic interventions and support.

Evidence included studies on care models for people with dementia admitted to hospital reporting information on the type of ward and organization of its environment, the need of additional support from hospital staff and/or other professionals, the need of individual assessments, considerations on time to discharge, and the use of multidimensional assessments and protocols for medicine reconciliation and optimization. These interventions were measured in relation to clinical, functional, and behavioural outcomes, staff compliance to care protocols, access to health and social care, experience, and satisfaction of people with dementia and their caregivers, equity in the access to services, and adverse events.

Very few studies were included compared to the number of retrieved records, investigating mainly multicomponent strategies aimed at mental health, family-cantered care model aimed at maximizing functional capacities, follow-up individualized care plans, multidimensional nutritional assessment, physical activity, and involvement of a pharmacist or pharmacologist in the hospital team.

One study investigated a model for the management of mental health in specialist units, and one study investigated case finding strategies for the activation of palliative care. Evidence from epidemiological studies showed that people with dementia have a longer length of stay, delays in time to discharge, and lower functional abilities and level of independence. Moreover, evidence, along with clinical practice, show that people with dementia have a higher risk of delirium when hospitalized, as also reported in the guideline sections dedicated to diagnosis and treatment of delirium.

The WG agreed that none of the considered interventions was supported by high-level evidence (overall low and very low certainty) for people with dementia and their caregivers. On this basis, in accordance with the approach adopted by NICE, no specific clinical practice recommendations were made.

However, indications on how to manage in-hospital care for people with dementia is essential. In particular, the WG highlighted some specific opportunities, such as hospitalizing people with dementia in wards, such as geriatric wards, where the probability of having specialized staff with a specific expertise in managing people with dementia or with frailty or comorbidities/multimorbidity is higher. As discussed in the NICE

guideline, this should not lead to iniquities towards people who cannot benefit from this opportunity. The most appropriate approach is to identity the best practices in each different specialist wards and apply them in all wards admitting people with dementia. This led to confirming the recommendation to consider, in case of people with dementia admitted to hospital, involving a multidisciplinary team to ensure tailored interventions based on a multidimensional assessment of their overall health, including their nutritional status.

The WG also discussed a further relevant issue referring to differences in healthcare systems across different countries and different regions. This strongly affects how to generalize and consider care models, as most of the evidence comes from studies carried out in the UK or the USA whose structures are difficult to generalize globally. Based on clinical experience, the WG underlined the need to ensure, in case of admission of people with dementia to hospital, a multidimensional assessment, the monitoring and review of all drug treatments, and the reconciliation of pharmacological treatments, as discussed in the section referring to the transition between settings. Issues relating to the safety of drug treatments should always be taken into special consideration, considering the involvement of a pharmacist or pharmacologist. As for the optimization and reconciliation of pharmacological treatments the NICE guideline refers to the document QS120 (NG5)[43] (see Table 7).

Recommendations

Caring for people living with dementia who are admitted to hospital

154	Be aware of the increased risk of delirium in people living with dementia who are admitted to hospital. See Table 6 for interventions to identify and treat delirium.	WEAK IN FAVOR
155	In case of people with dementia admitted to hospital, ensure the availability of a multidimensional assessment, the monitoring and review of all pharmacological treatments, and the reconciliation of pharmacological treatment plans, and any possible issues related to safety, considering the involvement of a pharmacist or pharmacologist. For further indications on the optimization and reconciliation of pharmacological treatments see Table 7 and the recommendation on the reconciliation of pharmacological treatments provided by the Ministry of Health[44].	STRONG IN FAVOR
156	Consider the involvement of a multidisciplinary team in case of people with dementia admitted to hospital to ensure personalized interventions based on a multidimensional assessment of their overall health, including their nutritional status.	WEAK IN FAVOR

Research Recommendations

No research recommendations were made.

[43] NICE. Medicines optimisation. [QS120] Published: 24 March 2016. https://www.nice.org.uk/guidance/qs120 (Last visited: 30/08/2023).

[44] Ministero della Salute - D.G. Programmazione sanitaria. Raccomandazione n. 17 - Riconciliazione della terapia farmacologica. Available at: https://www.salute.gov.it/portale/sicurezzaCure/dettaglioPubblicazioniSicurezzaCure.jsp?id=2354 (Last visited: 30/08/2023).

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Palliative care

Review question 24	What models of palliative care are effective for people with dementia?

Literature review

	Quantitative evidence	Qualitative evidence
Records identified from databases	3,402	21,475
Studies assessed for eligibility	26	4
Included studies	9	1
Studies included in the NICE GL	3	8
Total number of included studies	12	9

Eligibility criteria

Quantitative evidence

Population	• People aged ≥40 years living with dementia. • Caregivers of people (aged ≥40 years) living with dementia.
Interventions	• Defined models of palliative care. • Enteral tube feeding interventions.
Comparator	• Alternative models of palliative care. • No enteral tube feeding. • Standard care.
Outcomes	• Improvements in care. • Nutritional status. • Pain. • Patient satisfaction and quality of life. • Carer burden, satisfaction and quality of life. • Adverse events. • Resource use and costs.

Qualitative evidence

A single literature search was conducted for all the qualitative questions referring to people with dementia included in this Guideline (GL) (Review questions 6, 7c, 10a, 10b, 24).

Population	• People aged ≥40 years living with dementia. • Caregivers of people (aged ≥40 years) living with dementia.

Phenomena of interest	Aspects of palliative care approaches impacting on people living with dementia, which may include: • meeting physical care needs; • psychological, social and spiritual care needs; • planning; • communication.
Outcomes	• Experiences and satisfaction of people living with dementia. • Experiences and satisfaction of caregivers of people living with dementia. • Experiences of health and social care professionals.

Aim

The objective of the systematic literature review, in line with the strategy defined by the NICE Guideline, was to identify comparative studies (e.g., Randomised Controlled Trials, RCT; non-randomised experimental studies) or qualitative studies investigating the effectiveness of different palliative care models for people with dementia. Only qualitative studies reporting the opinions and/or experiences of people with dementia and/or their caregivers were included.

Summary of evidence

QUANTITATIVE EVIDENCE

Specialist palliative care team

One study (Ahronheim 2000) on 99 participants investigated the effectiveness of consultation by a specialised palliative care team compared to standard care in hospitalised people with advanced dementia. The study reported a higher probability of developing an overall palliative care plan in the intervention group compared to the control group (RR 5.84, 95% CI 1.37 – 25.02, I^2 n.a., low certainty). However, it reported no differences between groups in the frequency of new feeding tubes (RR 1.06, 95% CI 0.68 – 1.65, I^2 n.a., low certainty) or in the total number of feeding tubes (RR 1.06, 95% CI 0.81 – 1.39, I^2 n.a., low certainty). It also reported no differences in the frequency of mechanical ventilation (RR 0.53, 95% CI 0.10 – 2.77, I^2 n.a., low certainty), tracheostomy (RR 0.35, 95% CI 0.01 – 8.48, I^2 n.a., low certainty), and cardiopulmonary resuscitation (RR 0.15, 95% CI 0.01 – 2.86, I^2 n.a., low certainty). No differences were reported in mortality rate during hospitalisation (RR 1.06, 95% CI 0.53 – 2.13, I^2 n.a., low certainty).

Decision aids on feeding options

One study (Hanson 2011) on 254 participants investigated the effectiveness of an intervention for caregivers of people with advanced dementia, based on structured decision aids providing information about dementia, and feeding options and their outcomes, advantages, and disadvantages. The study reported a lower decisional conflict at three months (MD -0.47, $p < 0.001$, low certainty) and a lower risk of weight loss at nine months (RR 0.37, 95% CI 0.15 – 0.91, I^2 n.a., low certainty) in the intervention group compared to the control group. However, it reported no differences between groups at three months in the need for any modified diet (RR 1.08, 95% CI 0.92 – 1.26, I^2 n.a., low certainty), specialised dysphagia diet (RR 1.17, 95% CI 0.98 – 1.41, I^2 n.a., low certainty), specialised staff assistance (RR 2.00, 95% CI 0.98 – 4.10, I^2 n.a., low certainty). It also reported no differences at three months in the need for specialised utensils (RR 0.60, 95% CI 0.22 – 1.60, I^2 n.a., low certainty), and head and body positioning (RR 2.00, 95% CI 0.18 – 21.78, I^2 n.a., low certainty). The study also reported no differences between groups at nine months in the frequency of new feeding tubes

(RR 0.33, 95% CI 0.03 – 3.12, I^2 n.a., low certainty) and do-not-feed orders (RR 1.98, 95% CI 0.37 – 10.57, I^2 n.a., low certainty), and in mortality rate (RR 0.92, 95% CI 0.59 – 1.44, I^2 n.a., low certainty).

Goals of care intervention

One study (Hanson 2017) investigated the effectiveness of an intervention based on the definition of Goals of Care (GOC), dedicated to nursing home care staff who was provided with decision aids, training sessions on dementia and end-of-life management, and structured discussion with the nursing home care team. The study, on 299 participants, reported a higher family-healthcare provider concordance in primary care goals of care in the intervention group compared to the control group (RR 3.12, 95% CI 1.68 – 5.78, I^2 n.a., moderate certainty). However, it reported no differences between groups in family reported quality of general communication (QoC, Quality of Communication: MD -0.40, 95% CI -1.02 – 0.22, I^2 n.a., low certainty) and end-of-life communication (QoC: MD 1.00, 95% CI 0.17 – 1.83, I^2 n.a., low certainty). It also reported no differences in perceived quality of end-of-life symptom management (SM-EOLD, Symptom Management at the End of Life in Dementia: MD -0.30, 95% CI -3.14 – 2.54, I^2n.a., low certainty) and quality of care (SWC-EOLD, Satisfaction With Care at the End of Life in Dementia: MD -1.30, 95% CI -3.03 – 0.43, I^2 n.a., low certainty). No differences were also reported in the mean number of palliative care domains considered in care plans (PCTPD, Palliative Care Treatment Plan Domain score: MD 0.30, 95% CI -0.35 – 0.95, I^2 n.a., low certainty).

Facilitated case conferencing

One study (Agar 2017) on 131 participants investigated the effectiveness of a facilitated case conferencing (FCC) led by a specialist multidisciplinary team. The study reported no differences between groups in the family-rated quality of end-of-life comfort (CAD-EOLD, Comfort Assessment in Dying with Dementia: MD -0.80, 95% CI -2.82 – 1.22, I^2 n.a., low certainty), symptom management (SM-EOLD:MD -2.70, 95% CI -5.61 – 0.21, I^2 n.a., low certainty) and global care (SWC-EOLD: MD 0.70, 95% CI -0.93 – 2.33, I^2 n.a., low certainty). It also reported no differences between groups in the nurse-related quality of end-of-life comfort (CAD-EOLD: MD -1.20, 95% CI -3.22 – 0.82, I^2 n.a., low certainty a) and symptom management (SM-EOLD: MD -0.80, 95% CI -3.87 – 2.27, I^2 n.a., low certainty).

Generic and patient-specific feedback strategies

One study (Boogaard 2018) investigated the effectiveness of two strategies to gather feedback using two different scales, the SWC-EOLD (Satisfaction With Care at the End of Life in Dementia) and the CAD-EOLD (Comfort Assessment in Dying at the End of Life in Dementia) allowing caregivers to report their perceived quality of end-of-life care (SWC-EOLD) and quality of dying (comfort) (CAD-EOLD) in dying people with dementia. The study compared two different strategies of using these scales. One group used a generic feedback strategy and was compared to a group using a patient-specific strategy tailored to the individual needs. In the generic strategy group, scale scores were reported in a digital importing system, while in the patient-centred strategy caregivers' answers to the scales, gathered at baseline, were discussed in the multidisciplinary team meetings. Based on discussions on each participant, the team drafted a document including all suggestions to improve care. The study, on 287 participants, reported, an improvement in the quality of comfort assessed by caregivers in the patient-centred feedback group compared to the control group (CAD-EOLD: MD 2.20, 95% CI 0.04 – 4.36, I^2 n.a., moderate certainty). However, it reported no differences between groups in the quality of care assessed by caregivers (SWC-EOLD: MD -0.20, 95% CI -1.88 – 1.48, I^2 n.a., low certainty). The study also reported a lower satisfaction with quality of care assessed by caregivers in the generic feedback group compared to the control group (SWC-EOLD: MD -1.70, 95% CI -3.24 – -0.16, I^2n.a., moderate certainty). However, it reported no differences between groups in the quality of comfort assessed by caregivers (CAD-EOLD: MD 1.00, 95% CI -1.12 – 3.12, I^2 n.a., low certainty).

Triggered palliative care by hospitalisation

One study (Hanson 2019) investigated the effectiveness of activating a protocol of specialty palliative care consultation while hospitalised plus post-discharge transitional telephone support by a palliative care nurse practitioner. The study, on 62 participants, reported a higher mean number of palliative care domains considered in care plans in the intervention group compared to the control group (PDCI, Palliative Care Domain Index: MD 4.90, 95% CI 3.83 – 5.97, I^2 n.a., moderate certainty). It also reported a higher frequency of documented discussions about prognosis (RR 28.80, 95% CI 4.17 – 198.97, I^2 n.a., low certainty) and goals of care (RR 3.60, 95% CI 1.95 – 6.64, I^2 n.a., moderate certainty), and a higher percentage of decisions not to tube feed (RR 8.53, 95% CI 2.14 – 34.02, I^2 n.a., low certainty). However, reported no differences between groups in the quality of comfort assessed by caregivers (CAD-EOLD: MD 0.80, 95% CI -1.27 – 2.87, I^2 n.a., low certainty), and in the frequency of decisions not to re-hospitalise (RR 9.58, 95% CI 0.54 – 170.73, I^2 n.a., very low certainty).

Decision support tools

One study (Loizeau 2019) investigated the effectiveness of two structured tools to support physicians in reducing decisional conflict about administering antibiotics and artificial hydration in people with advanced dementia. When considering decisions on antibiotics, the study reported a lower decisional conflict in the subgroup of formal caregivers in intervention group compared to the control group (DCS, Decisional Conflict Scale: MD -12.10, 95% CI -23.86 – -0.34, I^2 n.a., low certainty). However, it reported no differences between groups in decisional conflict in the subgroups of clinicians (DCS: MD-5.80, 95% CI -14.59 – 2.99, I^2 n.a., very low certainty) and family members (DCS: MD -6.10, 95% CI -16.90 – 4.70, I^2 n.a., very low certainty). When considering decisions on artificial hydration, the study reported no differences between groups in decisional conflict in the subgroups of clinicians (DCS: MD-5.50, 95% CI -15.33 – 4.33, I^2 n.a., very low certainty), family members (DCS: MD -6.4, 95% CI -15.77 – 2.97, I^2 n.a., very low certainty), and formal caregivers (DCS: MD-0.40, 95% CI -12.90 – 12.10, I^2 n.a., very low certainty).

Programmes based on multicomponent interventions

One study (Van den Block 2020) investigated the effectiveness of a multicomponent intervention aimed at the implementation of non-specialist palliative care in residential structures through specific training interventions for structured staff. The study, on 940 participants, reported no differences between groups in the quality of comfort assessed by caregiver (CAD-EOLD: MD -0.14, 95% CI -1.89 – 1.61, I^2 n.a., very low certainty). It also reported no differences in the quality of care during the last month of life (QoL-LTC, Quality of Dying in Long Term Care: MD 2.21, 95% CI -1.09 – 5.51, I^2 n.a., very low certainty).

Specific training programmes

One study (Tropea 2022) investigated the effectiveness of implementing a specific training program for nursing home staff aimed at improving the outcomes of people with dementia during end of life, especially in decreasing the rate of unplanned hospitalisations and in-hospital mortality. The study, on 1.304 participants, reported no differences between groups in the frequency of unplanned hospitalisations at six months (RR 1.11, 95% CI 0.89 – 1.38, I^2 n.a., very low certainty) and at 12 months (RR 1.12, 95% CI 0.95 – 1.31, I^2 n.a., very low certainty). It also reported no differences in the rate of in-hospital mortality at six months (RR 1.14, 95% CI 0.55 – 2.38, I^2 n.a., very low certainty) and at 12 months (RR 0.90, 95% CI 0.52 – 1.56, I^2 n.a., very low certainty).

Multidimensional and multidisciplinary training interventions for end-of-life care

Two studies investigated the effectiveness of multidimensional interventions for the management or people with dementia at the end of their life. One study (Verreault 2018) investigated an intervention, facilitated by specialised personnel, including staff training, structured pain assessment, and regular communication with caregivers. The second study (Brazil 2018) investigated an advance care planning intervention managed by

specialised personnel including the training and involvement of caregiver in decision-making. The two studies on 254 participants, reported an improvement in the intervention group compared to the control group in the quality of care perceived by family members (FPCS, Family Perception of Care Scale: MD 9.37, 95% CI 3.42 – 15.31, I^2 0%, low certainty). The first study (Verreault 2018), on 124 participants, reported an improvement in the intervention group compared to the control group in the quality of the management of comfort (CAD-EOLD: MD 2.70, 95% CI 0.55 – 4.85, I^2 n.a., low certainty) and symptoms (SM-EOLD: MD 4.90, 95% CI 1.15 – 8.65, I^2 n.a., low certainty). The second study (Brazil 2018), on 143 participants, reported no differences between groups in decisional conflict (DCS, Decisional Conflict Scale: MD -6.00, 95% CI -15.95 – 3.95, I^2 n.a., very low certainty) and distress (GHQ, General Health Questionnaire: MD -0.50, 95% CI -3.18 – 2.18, I^2 n.a., low certainty) of family members/caregivers.

Advance care planning

One study (Mitchell 2018) investigated the effectiveness of using written and video materials from specialists in geriatrics and palliative care to support caregivers in decision-making on end-of-life care options. The study, on 400 participants, reported a higher number of no tube feeding directives in the intervention group compared to the control group (RR 1.19, 95% CI 1.05 – 1.36, I^2 n.a., moderate certainty). However, it reported no differences between groups in the number of no hospitalization (RR 1.02, 95% CI 0.89 – 1.17, I^2 n.a., low certainty) and no intravenous hydration directives (RR 1.20, 95% CI 0.94 – 1.53, I^2 n.a., low certainty), and in the frequency of goal-of-care discussions (RR 1.34, 95% CI 0.99 – 1.83, I^2 n.a., low certainty).

QUALITATIVE EVIDENCE

Carer identified issues

Seven studies, including one with a mixed methodology, explored the opinions on palliative care of current or grieving caregivers of people with dementia (Crowther 2013, Dening 2012, Lamahewa 2017, Lawrence 2011, Moore 2017, Poole 2018, Treloar 2009). Overall, considered studies included: 11 participants with dementia, 158 current or grieving caregivers, and 66 palliative care professionals. Data were gathered through unstructured interviews, semi-structured interviews, and focus groups.

Interviewed caregivers identified the following issues in relation to palliative care for people with dementia.

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 informal caregivers 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-interest 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)
- Informal carers reported often having to retell the same information to different health-care professionals (high confidence)
- Informal carers sometimes had doubts making decisions, particularly if there was not an up-to-date living will (high confidence)

- Informal carers valued continuity in their relationship with professionals 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)
- Informal 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)
- Informal 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)

Professional identified issues

Five studies explored the perceived barriers to high-quality palliative care for people with dementia (Davies 2014, Dening 2012, Grisaffi 2010, Lawrence 2011, Poole 2018). Considered studies included 102 palliative care professionals and 59 current or grieving caregivers. Data were gathered through semi-structured interviews, unstructured interviews, and focus groups.

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 several 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[45] 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 professionals, 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).

[45] Primary Care Trust (PCT) are the statutory bodies of the NHS and are responsible for providing most health services and improving public health. https://www.nhsconfed.org/system/files/2021-07/The_legacy_of_PCTs. pdf (Last visited: 30/08/2023).

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).

Analysis of evidence

The World Health Organization (WHO) defines palliative care as "an approach that improves the quality of life of patients (adults and children) and their families who are facing problems associated with life-threatening illness. It prevents and relieves suffering through the early identification, correct assessment and treatment of pain and other problems, whether physical, psychosocial, or spiritual." The WHO also underlines that "palliative care does not replace your usual care: it can be provided alongside regular medical care" and that "palliative care is not a luxury, it is essential" and "should be available and affordable to each and every person who needs it" (WHO 2020)[46].

Palliative care can be needed for several different conditions, including dementia, cancer, heart diseases, lung diseases, HIV/AIDS, other neurological diseases, and liver or kidney diseases. However, guidelines and position papers based on expert consensus from different scientific societies focusing on palliative care and end of life often lack precise and complete reference to the specific conditions of people with dementia.

The analysis of evidence for this question included both quantitative and qualitative studies. Only qualitative studies reporting the experiences of people with dementia and/or their caregivers and/or health or social care professionals on effective palliative care models for people with dementia were included.

The systematic review only included evidence analysing palliative care models, including enteral feeding, and considering outcomes such as improving quality of care, pain assessment and management, nutritional status, satisfaction and quality of life of people with dementia, burden, satisfaction and quality of life of caregivers, adverse events.

The working group (WG) discussed on the applicability of the guidelines on end-of-life care (End of life care for adults – QS13)[47] referred to by the NICE GL on this topic.

The WG agreed on the relevance of the recommendations on general principles included by the NICE GL on palliative care. The specificity of the conditions of people with dementia was considered by the WG as a particularly relevant issue. The WG underlined the need to focus on those areas that appear as more relevant in this people, such as the difficulties in assessing pain and distress, the impossibility of predicting the time of death, the ability to decide for themselves on palliative and end-of-life care.

The WG discussed the relevance of determining when to initiate palliative care in people with dementia. The course and characteristics of dementia, along with the individual clinical variability, require considering a flexible approach, that takes into account the individual needs emerging from each disease trajectory. This condition, in fact, unlike other conditions, does not allow the definition of a specific period identifiable as the start of the end-of-life phase. This difficulty in identifying the end-of-life phase, and thus knowing when to initiate a palliative care approach, can increase the variability in quality of care and access to palliative care for people with dementia.

On this basis, palliative care planning should be started from post diagnosis, due to the wide variability of the moment of death, thus the difficulty in recognizing when end-of-life care is required. This issue is even more relevant considering that people with dementia usually have comorbidities that can contribute to, or be

[46] WHO. Palliative care. Last updated: August 2020. Available at: https://www.who.int/news-room/fact-sheets/detail/palliative-care (Last visited: 30/08/2023).
[47] NICE. End of life care for adults. Quality standard [QS13]. Last updated: September 2021. Available at: https://www.nice.org.uk/guidance/qs13 (Last visited: 30/08/2023).

directly responsible for, a sometimes-unpredictable worsening of their clinical conditions, impairing their ability to express themselves faster that previously hypothesised. Based on these potential unplanned changes in the progression of the disease, the WG agreed to confirm the recommendation from the NICE GL to offer, from diagnosis, people with dementia flexible, needs-based palliative care.

This also suggests considering planning the steps of the care process in advance, to facilitate the transition of the clinical condition, allowing for the most important element, which is involving people with dementia and their caregivers in decision making.

In particular, the process should be tailored to each individual situation, underlining the importance, towards the end of life, to follow the processes of advance care planning with both people with dementia, and that their caregivers respect the principles of best-interest decision making, especially in case they are incapable of deciding for themselves. The complexity of advance care planning and its adequate application starts from the identification of the most appropriate time to start sharing and discussing this topic with people with dementia and their caregivers.

One study investigated the utility of targeted interventions to support caregivers in decision making on advance care planning using written and video materials from specialists in geriatrics and palliative care. The study reported a higher frequency of no tube feeding directives in the intervention group, but no differences between groups in the number of no hospitalization and no intravenous hydration directives.

The WG underlined several times the importance of training health and social care professionals who care for people with dementia. Quantitative evidence specific for the end of life in people with dementia are lacking. One study investigated the implementation of a specific training program for nursing home staff aimed at improving the outcomes of people with dementia at the end of their life. However, it reported no differences between groups in the rates of unplanned hospitalization and mortality.

Some studies specifically investigated the effectiveness of multidimensional and multidisciplinary training interventions on end-of-life care. One study investigated an intervention, facilitated by specialised personnel, including staff training, structured pain assessment, and regular communication with caregivers. Another study investigated an advance care planning intervention managed by specialised personnel including the training and involvement of caregiver in decision-making. Both studies reported an improvement in the intervention group of the quality of care perceived by caregivers, and the first study also reported an improvement in comfort and symptom management.

The analysis of evidence highlighted the importance of providing supportive tools for the assessment of people with advanced dementia, allowing to personalized care based on personal history, physical and environmental conditions, preferences, emotional aspects, cultural attitudes, religious beliefs, and spiritual needs.

One study investigating the implementation of structured tools to support physicians in reducing decisional conflict about administering antibiotics and artificial hydration in people with advanced dementia reported a lower frequency of antibiotics prescriptions in the intervention group compared to the control group, and a lower decisional conflict among formal caregivers. No differences were reported in decisional conflict among physicians, family members and formal caregivers on decisions about artificial hydration.

Several interventions based on the definition of Goals of Care (GOC) were considered. One study investigating a goal-oriented intervention for nursing home staff reported a higher agreement between health professionals and caregivers on the primary GOC in the intervention group. However, no differences between groups were reported on communication, and satisfaction with end-of-life symptom management and care. One study investigating a facilitated case-conferencing intervention reported no differences between groups on the management of comfort, symptoms and quality of care as perceived by both caregivers and health professionals.

One study investigating the use of personalized feedback, provided by caregivers of people with dementia who are at the end of their life, compared to generic feedback. The study reported better in perceived comfort in the intervention group compared to the control group, while it reported a lower caregiver-reported satisfaction with quality of care.

One study investigated the effectiveness of activating a protocol of specialty palliative care consultation while hospitalised plus post-discharge transitional telephone support by a palliative care nurse practitioner. The study reported a higher frequency in the intervention group of palliative care domains in care plans, discussions about prognosis and care goals, and a higher percentage of decisions not to tube feed.

The decision whether to hospitalise people with severe dementia is critical. Several aspects should be considered, all aiming at identifying the best option for each person. Hospital wards who manage people with acute conditions are not organized to manage the typical frailty, especially behavioural and cognitive, of people with dementia. The WG discussed the need of performing an assessment considering the balance between clinical needs and potential harms during hospitalisation, some of which associated to the effects of an impersonal environment that is not organised to account for individual conditions. Evidence and clinical practice suggest a higher risk of disorientation and delirium in people with dementia who are hospitalised, along with a longer length of stay, higher risk of infection, and higher risk of in-hospital and post-discharge death. On this basis the WG agreed to confirm the recommendations from the NICE GL. One specific recommendation underlines the need, when thinking about hospitalisation, of always considering advance care plans and decisions, underlining the value of maintaining, when possible, people in a family environment, which seem to prevent several adverse effects associated with hospitalisation. Any decision to hospitalise should be based on an objective assessment of the balance between potential benefits and harms.

The only study investigating the effectiveness of a specialised palliative care team consultation compared to standard care in hospitalised people with advanced dementia showed a higher frequency in the intervention group of palliative care plans, but no differences between groups in other procedures, such as tube feeding, mechanical ventilation, tracheostomy, cardiopulmonary resuscitation, and mortality during hospitalisation.

The WG discussed another crucial issue related to decisions on feeding options. The choice to consider alternative feeding options in relation to dysphagia and/or limited patient compliance remains a crucial element in caring for people with advanced dementia. On this basis providing caregivers adequate and appropriate information and training is essential. One study investigated the effectiveness of an intervention for caregivers of people with advanced dementia, based on structured decision aids providing information about dementia, and nutritional options and their outcomes, advantages, and disadvantages. The study reported a lower decisional conflict and a lower risk of weight loss in the intervention group compared to the control group. However, there were no differences between groups in the need for any specific dysphagia diet, specialised staff assistance, head and body positioning, placement of new feeding tubes, do-not-feed orders, and mortality rate.

The WG confirmed the recommendation from the NICE GL to encourage and support, for as long as possible, people with dementia to eat and drink, considering their nutritional needs, and considering involving a speech and language therapist to assess and treat dysphagia. Potential concerns about a person's safety when eating and drinking should be identified as early as possible.

Available evidence on tube feeding in people with severe dementia reported no significant results. Eating difficulties can vary across the different dementia subtypes, mainly in terms of time of onset of dysphagia and/or behavioural disorders.

The WG agreed to confirm the recommendation from the NICE GL not to routinely use enteral feeding in people living with severe dementia, unless indicated for a potentially reversible comorbidity.

Overall, the WG, considered the lack of quantitative evidence on specific palliative care interventions, agreed to confirm the research recommendation from the NICE GL on the most effective palliative care models and and-of-life interventions.

Qualitative evidence was analysed by considering separately the themes identified by caregivers and those identified by the professionals. Overall, this evidence was considered of moderate certainty.

The analysis of qualitative evidence on the themes identified by caregiver highlighted that the main issues about palliative care for people with dementia were related to the difficulty of satisfying the need for physical care, including the possibility of ensuring an adequate food and fluid intake, which, in relation to care facilities, received a negative evaluation by caregivers. The indication to consider other aspects besides care remains crucial. Informal caregivers often experienced grief before the death of their family member. Studies showed their need to have their grief acknowledged, and to receive information on how to obtain support.

The WG underlined the importance of considering individuals' interests, sensitivities, and preferences, recognising their personal and social identity. Caregivers' dissatisfaction with the lack of interaction and communication between them and healthcare professional remains a critical issue, along with the small amount of time dedicated to involving family members. Caregivers felt satisfied with end-of-life care if adequately informed and involved, even when end-of-life care was not in accordance with advance care plans. Studies reported that caregivers asked to receive timely information from an expert professional.

When considering advance care planning and advance directives, caregivers reported how unfrequently these were offered in routine clinical practice, and how they often had to initiate and then “push” for services to be provided, due to the offer being unpredictable and fragmented.

As discussed about considering admission to hospital for people living with severe dementia, caregivers confirmed that they did not like the hospital environment and found it an uncomfortable experience and place to be. Hospital staff in the wards caring for people with acute conditions struggled to provide basic care to people with dementia and their caregivers, who referred to perceive a lack of understanding, little compassion, and, sometimes, low staffing levels. Another extremely relevant issue was caregivers reporting to perceive a lack of dignity in dying in a ward.

Themes identified by caregiver caring for people with dementia at the end of their life were more complex. One relevant issue was the difficulty to identify the most appropriate moment to start end-of-life care, due to the unpredictability and fluctuation of clinical conditions.

Studies reported that professionals were concerned about being able to answer the needs for physical care, such as pain management, requiring specific medical and nursing skills, and the need to define complex care paths. Complex paths are needed as people with advanced dementia have complex health and social needs, which professionals are not always able to answer due to their programmed shifts and the inadequate care settings. The difficulty of managing care besides physical needs, such as individuals' interests, sensitivities, and preferences, and the risk of perceiving little empathy, were reported as critical issues by health professionals. They also agreed that hospitalisation was often inappropriate. Palliative care staff also 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.

Moreover, some health and social care professionals reported that the growing number of guidelines, standards, rules, and regulations makes palliative care standardised leaving no room for flexibility. One study underlined that general practitioners' (GPs) prior knowledge of the person living with dementia is important in informing decisions. Caregivers were seen by professionals as an expert source of information regarding people's wishes, in case of inability to or difficulties in expressing them.

Qualitative studies on the level of staff training explored the opinions of health professionals. Studies reported a need to improve staff training, who often acknowledged they had received little or no training on

dementia, especially on the specific needs of people with severe dementia. This need was also underlined by health professionals, to decrease the need to refer to specialist care. However, some professionals also reported to feel that palliative care should be left to specialists.

The management of real and perceived risks was also reported as a difficult challenge, due to lack of trust, and fear of litigation or blame.

Overall, the analysis of evidence on palliative care for people with dementia underlined how care should be person-centred, accounting for all individual aspects, including all physical, psychological, social, and spiritual aspects of each person's life. The WG confirmed the crucial role of informal caregivers, who should be involved in decision-making and in all phases of the disease, providing adequate support. Advance care planning should consider the needs and preferences of people with dementia and their caregivers to help them in programming their future. Obtaining appropriate tools to assess people with dementia, training health and social care professionals on end-of-life and palliative care and agreeing on a targeted and effective care planning at each stage of the disease are all crucial requirements to preserve people's dignity as a substantial and inalienable value.

Recommendations

Palliative care

157	From diagnosis, offer people living with dementia flexible, needs-based palliative care that takes into account how unpredictable dementia progression can be.	STRONG IN FAVOR
158	Encourage and support people living with dementia to eat and drink, taking into account their nutritional needs.	STRONG IN FAVOR
159	Consider involving a speech and language therapist if there are concerns about a person’s safety when eating and drinking.	WEAK IN FAVOR
160	Do not routinely use enteral feeding in people living with severe dementia, unless indicated for a potentially reversible comorbidity.	STRONG AGAINST
161	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.	STRONG IN FAVOR
162	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.	STRONG IN FAVOR
163	For standards and measures on palliative care, see Table 10.	STRONG IN FAVOR
164	For guidance on care for people in the last days of life, see Table 11.	STRONG IN FAVOR
165	For guidance, on best interest decision-making, see Table 12	STRONG IN FAVOR

166	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.	WEAK IN FAVOR
167	Consider using a structured tool to assess the likes and dislikes, routines and personal history of a person living with dementia.	WEAK IN FAVOR

Research Recommendations

Palliative care

38R	What are the most effective models of general and specialist palliative care support to meet the needs of people with advanced dementia?
39R	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?

Table 10. Quality standard [QS13][48] End of life care for adults.

Quality statement 1. Adults who are likely to be approaching the end of their life are identified using a systematic approach.
Quality statement 2. Adults approaching the end of their life have opportunities to discuss advance care planning.
Quality statement 3. Adults approaching the end of their life receive care that is coordinated between health and social care practitioners within and across different services and organisations.
Quality statement 4. Adults approaching the end of their life and their carers have access to support 24 hours a day, 7 days a week.
Quality statement 5. Carers providing end of life care to people at home are supported to access local services that can provide assistance.

Table 11. Quality standard [QS144][49] Care of dying adults in the last days of life.

Quality statement 1. Adults who have signs and symptoms that suggest they may be in the last days of life are monitored for further changes to help determine if they are nearing death, stabilising or recovering.
Quality statement 2. Adults in the last days of life, and the people important to them, are given opportunities to discuss, develop and review an individualised care plan.
Quality statement 3. Adults in the last days of life who are likely to need symptom control are prescribed anticipatory medicines with individualised indications for use, dosage and route of administration.
Quality statement 4. Adults in the last days of life have their hydration status assessed daily, and have a discussion about the risks and benefits of hydration options.

[48] https://www.nice.org.uk/guidance/qs13
[49] https://www.nice.org.uk/guidance/qs144

Table 12. Quality standard [QS194][50] Decision making and mental capacity.

Quality statement 1. People aged 16 and over who may lack capacity to make decisions are supported with decision making in a way that reflects their individual circumstances and meets their particular needs.
Quality statement 2. People aged 16 and over at risk of losing capacity to make decisions, and those with fluctuating capacity, are given the opportunity to discuss advance care planning at each health and social care review.
Quality statement 3. People aged 16 and over who are assessed as lacking capacity to make a particular decision at the time that decision needs to be made, have a clear record of the reasons why they lack capacity and the practicable steps taken to support them.
Quality statement 4. People aged 16 and over who lack capacity to make a particular decision at the time that decision needs to be made have their wishes, feelings, values and beliefs accounted for in best interests decisions.

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[50] https://www.nice.org.uk/guidance/qs194

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Cost of illness and cost-consequences analysis of dementia in Italy

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Introduction

Concerns regarding the quality of healthcare services and budget constraints require healthcare providers to identify and implement strategies to improve service delivery. It should be underlined that the implementation of any strategy requires costs. Failure to assess the economic implications of implementing such strategies can lead to inefficiencies, such as overutilisation of unnecessary services or underutilisation of useful interventions, thus risk causing inequalities that could undermine the quality and accessibility of healthcare services (Hoomans 2014). In this context, the economic assessment within a Health Technology Assessment (HTA), aims to measure the efficiency and allocation of healthcare resources and interventions to improve health outcomes. It is a valuable decision-support tool for all healthcare stakeholders, ensuring informed decision-making.

All forms of economic assessments involve cost analysis, which requires adequately collecting information on relevant resources and allocating costs to each resource (Hoomans 2014). Cost analysis can support decision makers in assessing the financial impact of implementing health services or interventions. The type of economic evaluation to be performed (*Cost-Consequences Analysis, Cost-Effectiveness Analysis, Cost-Utility Analysis, Cost-Benefit Analysis, Cost Minimization Analysis*) is selected based on the information required to make a specific decision and on the healthcare interventions or services that are being evaluated and compared.

For the purposes of this guideline (LG) on the diagnosis and treatment of dementia and Mild Cognitive Impairment (MCI), understanding the costs associated with the management and treatment of people with dementia (PwD) in Italy could help decision makers in developing and prioritizing policies and interventions for both PwD and their families/caregivers. Understanding the costs associated with a specific condition or disease allows for the proper allocation of healthcare resources, enabling efficient implementation of health policies within budgetary constraints (Jo 2014). Specifically, Cost of Illness (COI) analysis (Burden of Disease, BoD) is defined as the methodology that aims to identify and assess the costs associated with a specific condition. COI provides an overview of the costs associated with dementia, serving as a tool to support health policies for a better management of people with dementia in Italy in terms of access to services and their quality. COI studies are an initial step in performing economic assessments aimed at measuring not only the costs related to a specific disease or condition but also the effectiveness of a health program or intervention compared to existing options at a national level.

At the time of the present analysis, some COI studies on dementia in Italy were already available in published literature. These studies primarily aimed to estimate the average annual cost per patient using a cross-sectional approach (Bruno 2018, Chiatti 2015, Handels 2018). Bruno and colleagues (Bruno 2018) conducted

a study on 198 participants with Alzheimer's disease (AD) enrolled between April 2013 and January 2014 in Centres for Cognitive Disorders and Dementia (CCDDs), estimating an annual cost per person with mild, moderate, and severe AD of €22,200, €18,624, and €32,736, respectively. These estimates were obtained by using the Resource Utilization in Dementia (RUD) questionnaire, a widely used and validated tool for data collection on resource use in dementia. The cost related to informal care, calculated as the free time and work lost due non-professional caring activities for people with AD, results as 74% of the average annual cost for people with mild AD, 79% for people with moderate AD, and 81% for people with severe AD. The study by Handels and colleagues (Handels 2018) also used the RUR questionnaire in 53 participants with mostly mild dementia enrolled from 2014 to 2015 in several European countries, including Italy. It estimated an average annual cost per PwD of €13.835, with approximately 69% of the costs attributed to informal care. The study by Chiatti and colleagues (Chiatti 2015) on the analysis of costs due to AD was based on data from a multicenter randomized clinical trial performed in five districts in the Marche region (UP-TECH). This study enrolled 438 people with moderate AD and assessed the effectiveness of innovative interventions. The baseline evaluation considered the resources used by PwD in the six months before the first interview, which was carried out between January 2013 and July 2013. The resources included healthcare services, informal care, and welfare benefits provided by the National Institute for the Italian Social Security Administration (Istituto Nazionale della Previdenza Sociale, INPS), such as attendance allowance. The study estimated that the average annual cost per person with moderate AD was €20,128 of which 68% was associated with informal care. Another COI study (Meijer 2022) carried out in several European countries, including Italy, using data from the SHARE (Survey of Health, Ageing and Retirement in Europe), estimated the total costs attributable to dementia, that results almost €18.4 billion of which 92% were associated with informal care (cost calculated using the opportunity cost approach, which considers the average wage in the reference country that participants would have earned if they had spent their time performing a payed job instead of providing informal care).

The purpose of this section is to provide an updated estimate of the total costs related to dementia in Italy. The main objective is to provide healthcare decision makers a comprehensive overview of the health and social care and of the informal care currently dedicated to PwD and their caregivers. Additionally, a cost-consequence analysis was carried out to evaluate the overall impact on total expenditure resulting from changes in certain variables within the cost-analysis model.

Objectives of the economic analysis

This economic analysis had the following objectives:

- estimating the economic impact of dementia in Italy to provide potentially useful information for planning and allocating health and social care resources for the identification, management, and treatment of PwD (*Cost-of-Illness study*).
- assessing the economic impact of new diagnostic, therapeutic, and organizational strategies (*Cost-Consequence Analysis study*) on the total expenditure associated with dementia.

As previously mentioned, COI studies are the initial step in performing an economic assessment, as they can provide an overview of the costs associated with a specific disease. Identifying and measuring the costs related to the identification, management, and treatment of people with dementia allow, in a subsequent phase, to assess the impact on the *status quo* of potential changes in diagnostic, therapeutic, and organizational processes aimed at the management and treatment of PwD (CCA).

Methods

Performing a COI analysis requires defining the following aspects (Costa 2012):

- the disease;
- the epidemiological approach;
- the type of costs to be included in the analysis and the method for the estimate;
- the study perspective.

Defining the disease is essential because the associated costs depend on the severity of the disease or, in the case of PwD, their living conditions (home or nursing home) (Small 2002, Zhu 2006). The epidemiological approach refers to the decision to perform a COI study based on the prevalence or incidence of the disease. The first approach aims to estimate the economic burden associated with the disease during a specific period (e.g., one year). The second approach aims to estimate the costs of a disease starting from the diagnosis up to a specific endpoint (e.g., recovery, death) (Costa 2012).

To obtain an overall estimate of the costs of dementia in Italy, the COI analysis was conducted based on prevalent cases (prevalence-based approach) of dementia diagnosed according to the DSM-IV clinical criteria.

The type of costs to be included within the COI also defines the perspective of the analysis. If only direct costs are considered, which are those paid by the National Health Service (NHS) when providing healthcare services for management and trearment of each condition, then the COI analysis will be from the perspective of the NHS. If indirect costs, such as the loss of productivity of PwD or their caregvers due to the disease or to their caregiving activities, and/or out-of-pocket expenditures are included in the analysis, then the the COI analysis will have a social perspective. For purpose of this GL, the COI analysis was carried out from a social perspective. Therefore, in addition to direct costs, indirect costs, out-of-pocket costs, and welfare costs (INPS) were also considered.

When considering the method used to estimate direct costs, to assess healthcare resources and associated costs a bottom-up approach was adopted, which requires estimating the cost associated to a specific healthcare service by registering all healthcare resources used for each individua patient. When identifying health resources and cost components, when possible, a micro-costing approach was used. This approach requires estimating the expenses associated to a specific intervention by assigning a unitary cost to each cost input, with the total cost of the intervention determined by the subsequent aggregation of the single unitary costs. A gross-costing approach was used for health services for which the detail of provided resources could not be identified. This approach requires estimating individual health services in a highly aggregated way, (e.g., the cost per hospital stay, the cost of a health program). The volumes of provided healthcare services were identified using three sources: the national surveys carried out as part of the 2022-2023 Fund for Alzheimer's and Other Dementias by the Istituto Superiore di Sanità (ISS) in memory clinics (Centres for Cognitive Disorders and Dementia, CCDD), nursing homes (NHs), and daycare centres (DCC), the national database of the Hospital Discharge Records (HDR), and available literature. The costs associated with each healthcare service were calculated using the following sources: the national HDR database, the national price list for outpatient specialist services updated based on the agreement between State and Regions (effective since January 1, 2024)[51], and based on available literature.

[51] Ministero della Salute. Decreto Tariffe 12 Aprile 2023. Available at: https://www.quotidianosanita.it/allegati/allegato1681723698.pdf. (Last visit: 30/08/2023).

The out-of-pocket costs was calculated using data from the national survey on the socio-economic conditions of caregivers of PwD, based on what reported by caregivers on their monthly expenses for the management and treatment of the disease.

The indirect costs were estimated using the human capital approach. This method estimates the loss of productivity due to a specific illness by calculating the daily or hourly income that the PwD lost due to the disease, and/or by calculating the income lost by their caregivers due to their caregiving activities. In this analysis, indirect costs were estimated using data from the national survey on the socio-economic conditions of caregivers of PwD, considering the hourly income estimated by ISTAT[52].

Welfare costs covered by INPS were estimated only for people with a diagnosis of Alzheimer's dementia (AD), as data for people with other dementia subtypes were not available. This estimate was based on the number of approved requests for 100% disability and attendance allowances for people who received a diagnosis of AD in 2021.

When possible, each cost component was estimated based on prevalent dementia cases (target population). However, when data were unavailable, healthcare resources and costs were identified only for the subgroup of PwD for which data were available (e.g., welfare costs were calculated only for people with AD). Details on the estimate of prevalent cases of dementia, resource use, and costs used within the COI model are reported in the following paragraphs.

Prevalence of dementia and patient care

The prevalence of dementia was estimated for both people aged ≥65 years (late-onset) and people aged 35 to 64 years (early-onset). The prevalence of dementia in the late-onset group was estimated by applying the sex- and age-specific rates reported in a study by Bacigalupo (2018) to the Italian population aged ≥65 years as of January 1, 2023, according to ISTAT[53] (rates per 100 inhabitants) (**Table 13**). The prevalence of dementia in the early-onset group was estimated by applying the sex- and age-specific rates reported by a study by Chiari (2021) to the Italian population aged 35 to 64 as of January 1, 2023 (rates per 100,000 inhabitants) (**Table 14**). When considering both cases of late-onset and early-onset dementia, the overall number of cases of dementita in Italy was 1,150,691.

The number of prevalent cases of Mild Cognitive Impairment (MCI) was estimated using the sex- and age-specific rates reported by the COSMIC study (Sachdev 2015). Overall, 952,101 cases of MCI were estimated (**Table 15**).

Table 13. Prevalence of late-onset dementia (≥65 years)

Age class	Males			Females			Total	
	Population	Rates x 100	Cases n (95%CI)	Population	Rates x 100	Cases n (95%CI)	Population	Cases n (95%CI)
65-69	1.713.300	0.9	15.420	1.875.973	1.1	20.636	3.589.273	36.055
70-74	1.546.347	2.1	32.473	1.757.524	2.2	38.666	3.303.871	71.139
75-79	1.244.111	4.6	57.229	1.510.746	5.6	84.602	2.754.857	141.831
80-84	952.465	9.0	85.722	1.307.563	13.3	173.906	2.260.028	259.628
85-89	538.083	13.9	74.794	889.663	26.4	234.871	1.427.746	309.665

[52] ISTAT. Average hourly earnings for employee jobs in the private sector. 2020. Available at: http://dati.istat.it/Index.aspx?QueryId=33484&lang=en. (Last visit: 30/08/2023).
[53] ISTAT. Popolazione residente al 1° gennaio 2023. Available at: http://dati.istat.it/Index.aspx?DataSetCode=DCIS_POPRES1. (Last visit: 30/08/2023).

90+	243.710	31.2	76.038	597.960	38.9	232.606	841.670	308.644
Total	**6.238.016**		**341.675**	**7.939.429**		**785.286**	**14.177.445**	**1.126.961**

Table 14. **Prevalence of young-onset dementia (35-64 years)**

Age class	Males			Females			Total	
	Population	Rates x 100	Cases n (95%CI)	Population	Rates x 100	Cases n (95%CI)	Population	Cases n (95%CI)
35-69	1.686.199	0	0	1.661.407	4.6	76	3.347.606	76
40-44	1.880.664	3.7	70	1.876.439	11.1	208	3.757.103	278
45-49	2.232.491	23.5	525	2.256.376	10.2	230	4.488.867	755
50-54	2.362.175	38.4	907	2.414.762	63.2	1.526	4.776.937	2.433
55-59	2.355.923	177.1	4.172	2.439.739	152.5	3.721	4.795.662	7.893
60-64	2.009.181	285.3	5.732	2.139.733	306.7	6.563	4.148.914	12.295
Total	**12.526.633**		**11.406**	**12.788.456**		**12.324**	**25.315.089**	**23.730**

Table 15. **Prevalence of Mild cognitive impairment (≥60 years)**

Age class	Males			Females			Total	
	Population	Rates x 100	Cases n (95%CI)	Population	Rates x 100	Cases n (95%CI)	Population	Cases n (95%CI)
60-69	3.722.481	4.0	148.899	4.015.706	4.8	192.754	7.738.187	341.653
70-79	2.790.458	5.7	159.056	3.268.270	5.8	189.560	6.058.728	348.616
80-89	1.490.548	7.1	105.829	2.197.226	7.1	156.003	3.687.774	261.832
Total	**8.003.487**		**413.784**	**9.481.202**		**538.317**	**17.484.689**	**952.101**

Healthcare resources dedicated to the management and treatment of PwD in specific stages of the disease and in specific living conditions were identified by stratifying the overall number of prevalent cases of dementia according to these characteristics. Specifically, when considering disease severity, the World Health Organisation (WHO) reported that 49% of prevalent cases have mild dementia (563,839 cases when applying this percentage to the the estimated number of prevalent cases in Italy), 27% have moderate dementia (310,687 cases in Italy), and the remaining 24% have severe dementia (276,166 cases in Italy)[54]. When considering living conditions, since no data were available on the number of institutionalised PwD, data from a published report on Marche region were used, reporting that 41% of available beds in NHs were dedicated to PwD. The NHs considered in the analysis were nursing homes for dependent elderly people (code R2), nursing homes for dependent elderly people with dementia (code R2D), care homes for dependent elderly (code R3) and care homes for dependent elderly people with dementia (R3D)[55]. No official data are available at a national level on the specific number of beds according to the codes R1, R2, R2D, and R3. However, an estimate was published by the National Commission of the Ministry of Health for the definition and updating of the Essential Levels of Assistance in May 2007 of the number of beds that could be activated over five years according to each code[56]. Applying the percentage of institutionalized PwD out of the total number of available beds with codes R2, R2D, R3, and R3D estimated by the Marche Region (41%) to the estimated

[54] WHO, Global status report on the public health response to dementia. Available at: https://www.who.int/publications/i/item/9789240033245 (Last visit: 30/08/2023).

[55] Interrogazione n. 778, a risposta scritta, presentata in data 6 aprile 2023 ad iniziativa del Consigliere Mastrovincenzo: "Assistenza residenziale anziani: posti effettivi dedicati alle persone con demenza". Available at: https://www.consiglio.marche.it/banche_dati_e_documentazione/atti_di_indirizzo_e_controllo/interrogazioni/risposte_pdf/rispinter778_11.pdf (Last visit: 30/08/2023).

[56] Ministero della Salute. Commissione nazionale per la definizione e l'aggiornamento dei livelli essenziali di assistenza. Prestazioni residenziali e semiresidenziali, 2007. Available at: https://www.salute.gov.it/imgs/C_17_pubblicazioni_733_allegato.pdf (Last visit: 30/08/2023).

number of beds that could be activated over five years with the codes R2, R2D, R3, the resulting overall number of institutionalised PwD at a national level was 141,994 (12% of prevalent cases) (**Table 16**).

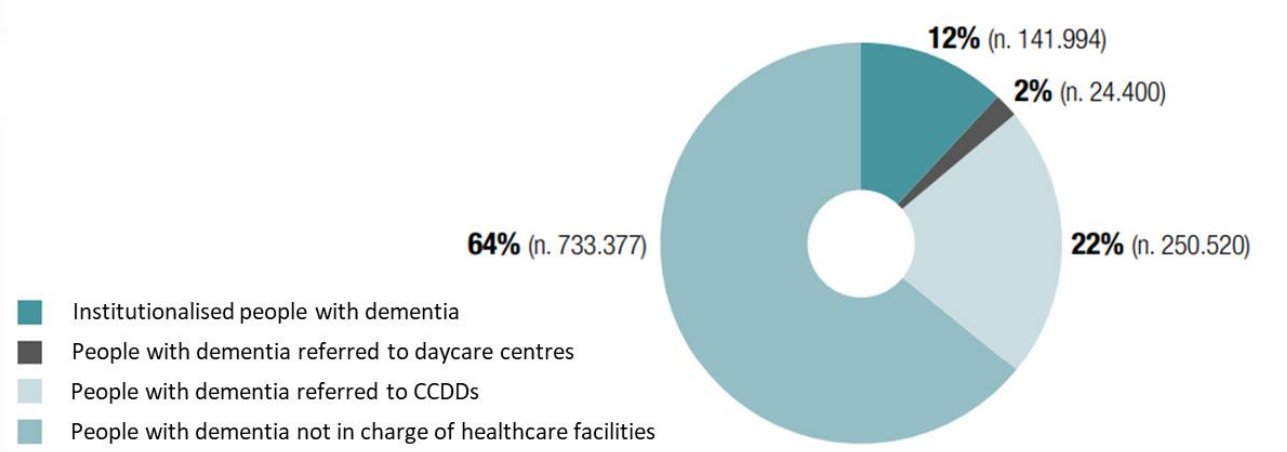
Table 16. Estimated number of institutionalized PwD at a national level

Parameter	Estimate	Source
Number of beds (code R2D) – Italy (n)	54.507	National Commission of the Ministry of Health for the definition and updating of the Essential Levels of Care (May 2007)
Number of beds (code R2) – Italy (n)	73.039	
Number of beds (code R3) – Italy (n)	218.026	
Total number of beds (R2, R2D, R3) – Italy (n)	345.572	
Institutionalized PwD out of the total of available beds with codes R2, R2D, R3, R3D – Marche Region (%)	41	Marche Region
Institutionalized PwD out of the total of available beds with codes R2, R2D, R3, R3D – Marche Region (n)	141.994	Obtained by applying 41% to the number of beds with code R2, R2D, R3 at a national level

It should be noted that, according to the indications from the Ministry of Health, only code R3 is present at a national level, while code R3D for PwD is only specified within the Marche region.

When considering non-institutionalized PwD, data from the national surveys carried out by the ISS[57] within the DDCs and CCDDs were used to estimate the number of PwD referred to each health and social care facility. Based on the survey of DCCs, a mean of 25 PwD per single DCC was estimated. Applying this estimate to the 976 DCCs distributed over the Italian terrotory (excluding DCCs that do not admit PwD), 24,400 PwD were estimated to refer to DCCs. Based on data from the national survey of CCDDs, a total of 149,400 PwD were estimated to refeto to CCDDs that responded to the survey, while 101,520 PwD were estimated, based on data from responder CCDDs, to refer to CCDDs that did not provide this information. Based on both information, an overall number of 250,920 PwD was estimated to refer to CCDDs at a national level. In addition, 96.626 individuals with a diagnosis of MCI were estimated to refer to the 534 CCDDs that responded to the survey (**Figure 1**).

Figure 1. Distribution of PwD concerning caretaking by social and healthcare facilities at the national level



CCDDs: Centres for Cognitive Disorders and Dementias

[57] https://www.iss.it/le-demenze-survey

Estimates of the direct costs

The COI analysis attempted to estimate the direct costs paid by the NHS for:

- diagnostic services;
- health and social facilities (nursing homes and daycare centres);
- monitoring;
- antidementia and antipsychotics drugs;
- hospitalisations and admissions emergency services;
- non-pharmacological interventions

DIAGNOSTIC SERVICES COSTS

Data from the survey dedicated to caregivers of PwD were used to identify the diagnostic services that PwD access to to receive the diagnosis and the proportion of PwD undergoing each service (**Table 17**). The frequency of use associated with each diagnostic diagnostic service were attributed to incident cases of dementia (about 300,000 cases) (**Qiu 2006**) and to incident cases of MCI (around 290,000 cases) (**Gillis 2019**). We assumed that 100% of incident cases of dementia underwent neuropsychological assessment. Specifically, based on data from the survey on CCDDs, we assumed that 100% of incident cases received a multidisciplinary neuropsychological evaluation (first level) and 57.7% underwent a comprehensive neuropsychological evaluation (second level). We also assumed that all people with MCI underwent first and second level neuropsychological evaluations.

We assumed that genetic testing was performed in cases of familial AD (approximately 8% of cases of AD [41% of incident cases of dementia], based on data from the survey on CCDDs) and in cases of frontotemporal dementia (7% of incident cases, based on a data from the survey on CCDDs).

Most of the unitary costs for each diagnostic service were determined the national price list for outpatient specialist services[58]. Since no specific codes for genetic tests were identified in the national price list, the costs for these tests were determined using the price list for genetic analysis applied in Tuscany[59].

Tables 17 and **18** report the utilization frequencies and unit costs associated with each diagnostic service.

Table 17. Diagnostic services considered and the proportion of patient users

Diagnostic service	Frequency of use among incident cases of dementia and MCI (%)	Source
Cerebrospinal fluid (CSF) tests	6.9	survey on CCDDs
Cerebral CT/MRI	80.2	
Blood tests	55.0	
EEG	23.5	
FDG-PET	13.6	
Amyloid-PET	10.2	
SPECT	3.5	
Genetic tests	Applied to cases of familial AD (approximately 8% of cases of AD [41% of incident cases]) and to cases of frontotemporal dementia (7% of incident cases of dementia).	

[58] Ministero della Salute. Decreto Tariffe 12 Aprile 2023. Available at: https://www.quotidianosanita.it/allegati/allegato1681723698.pdf (Last visited: 30/08/2023).

[59] Prestazioni di Struttura di Genetica Clinica. Regione Toscana. Available at: https://www.regione.toscana.it/documents/10180/12147059/Allegato+2+Parere+n.+26-2013+(Autore+Bailo+29-01-2013).pdf/e99ab077-9735-4f89-9eed-336147a1a87c;jsessionid=35C4101691C598BD9C6C8A8BE8CEB5F2.web-rt-as01-p2?version=1.0 (Last visited: 30/08/2023).

Table 18. Unitary costs of diagnostic services

Cerebral CT/MRI			
Code	**Description**	**Price**	**Source**
88.91.1	BRAIN MRI, CRANIOCERVICAL JUNCTION AND RELATED VASCULAR DISTRICT	€ 166.55	National price list for outpatient specialist services*
88.91.2	BRAIN MRI, CRANIOCERVICAL JUNCTION AND RELATED VASCULAR DISTRICT WITH OR WITHOUT CONTRAST AGENT	€ 247.50	
Cost included in the model for brain CT/MRI.		€ 207.03	Mean of the previous codes
Blood tests			
Code	**Description**	**Price**	**Source**
90.09.2	ASPARTATE TRANSAMINASE (AST) (GOT) [S]	€ 1.05	National price list for outpatient specialist services*
90.39.1	URINARY PROTEIN (ELECTROPHORESIS OF). Included: total protein assay 90.38.5	€ 3.25	
90.10.5	BILIRUBIN TOTAL WITH REFLEX (cut-off >1 mg/dL unless more restrictive regional cut-offs are defined. Included: Direct and Indirect Bilirubin	€ 1.05	
90.10.7	BILIRUBIN DIRECT. Not cumulable with 90.10.5	€ 1.15	
90.13.B	LDL CHOLESTEROL. Indirect determination. Available only in association with HDL cholesterol (90.14.1), total cholesterol (90.14.3) and triglycerides (90.43.2)	€ 1.75	
90.13.C	LDL CHOLESTEROL. Direct determination	€ 1.75	
90.14.1	HDL CHOLESTEROL	€ 1.40	
90.14.3	TOTAL CHOLESTEROL	€ 1.05	
90.43.2	TRIGLYCERIDES	€ 1.10	
90.27.1	Glucose	€ 1.00	
90.28.1	Hb – GLYCATED HEMOGLOBIN	€ 3.35	
91.10.B	TREPONEMA PALLIDUM Syphilis serology. EIA/CLIA and/or TPHA antibodies [TPPA] plus VDRL [RPR]. Included: possible titration and possible immunoblotting	€ 6.65	
90.11.4	TOTAL CALCIUM	€ 0.95	
90.13.3	CHLORIDE	€ 0.90	
90.24.3	INORGANIC PHOSPHATE (PHOSPHORUS)	€ 1.00	
90.32.5	TOTAL MAGNESIUM	€ 1.10	
90.37.4	POTASSIUM	€ 1.00	
90.40.4	SODIUM	€ 0.85	
90.43.5	URATE	€ 1.05	
90.16.3	CREATININE. Not cumulable with 90.16.4	€ 1.10	
90.16.4	CREATININE CLEARANCE. Not cumulable with CREATININ (90.16.3)	€ 1.90	
90.44.1	UREA	€ 1.00	
90.06.5	ALPHA AMYLASE ISOENZYMES (Pancreatic Fraction)	€ 1.50	
90.23.2	FOLATE	€ 3.05	
90.13.5	COBALAMIN (VITAMINE B12)	€ 2.95	
90.41.8	THYROID-STIMULATING HORMONE [TSH] REFLEX TEST. If TSH ≥ 0.45 mU/L and ≤ 3.5 mU/L: report of TSH only; If TSH < 0.45 mU/L or > 3.5 mU/L: automatic run of FT4; If FT4 ≥ 3.5, report of TSH + FT4; If FT4 < 3.5, automatic run of FT3 and report of TSH + FT4 + FT3. Not cumulable with: TSH, FT3, FT4. Unless more restrictive regional cut-offs are defined.	€ 4.60	
90.42.1	THYROID-STIMULATING HORMONE [TSH]. Not cumulable with 90.41.8	€ 2.55	
90.42.3	FREE THYROXINE (FT4). Not cumulable with 90.41.8	€ 2.60	
90.43.3	FREE TRIIODOTHYRONINE (FT3). Not cumulable with 90.41.8	€ 2.65	
Cost included in the model for blood tests		€ 55.30	Sum of the previous codes
EEG			
Code	**Description**	**Price**	**Source**

89.14	ELECTROENCEPHALOGRAPHY. Excluding: EEG with polysomnography (89.17)	€ 23.20	National price list for outpatient specialist services*
FDG-PET			
Code	**Description**	**Price**	**Source**
92.11.6	BRAIN POSITRON EMISSION TOMOGRAPHY WITH FDG	€ 939.95	National price list for outpatient specialist services*
Amyloid-PET			
Code	**Description**	**Price**	**Source**
92.11.A	BRAIN POSITRON EMISSION TOMOGRAPHY WITH OTHER RADIOTRACERS	€ 1267.90	National price list for outpatient specialist services*
SPECT			
Code	**Description**	**Price**	**Source**
92.11.5	BRAIN PERFUSION SPECT. Basal conditions, with pharmacological stimulation or activation	€ 257.75	National price list for outpatient specialist services*
Cerebrospinal fluid (CSF) analysis			
Code	**Description**	**Price**	**Source**
03.31	CSF tests	€ 187.50	National price list for outpatient specialist services*
Genetic tests			
Code	**Description**	**Price**	**Source**
91.30.3	FTD I level. PGRN gene SEQUENCING (c.a. 400 bp blocks)	€ 156.00	Tuscany region price list §
91.30.3	FTD II level. MAPT gene SEQUENCING (c.a. 400 bp blocks)	€ 156.00	
91.29.2	FTD III level. Quantitative PCR (Real-time PCR) Amplification and quantification of nucleic acids with fluorescence measurement of APOE gene	€ 65.00	
91.30.3	Familial AD I level. PSEN1 gene SEQUENCING (c.a. 400 bp blocks)	€ 156.00	Tuscany region price list §
91.30.3	Familial AD II level. APP gene SEQUENCING (c.a. 400 bp blocks)	€ 156.00	
91.30.2	Familial AD III level. Study of the size of fragments of DNA from different restriction enzymes of the APOE gene	€ 128.00	
Neuropsychological assessment I level			
Code	**Description**	**Price**	**Source**
89.07	MULTIDISCIPLINARY ASSESSMENT. Included: possible elaboration of MULTIDISCIPLINARY INDIVIDUAL REHABILITATION PLAN.	€ 46.00	National price list for outpatient specialist services*
Neuropsychological assessment II level			
Code	**Description**	**Price**	**Source**
94.01.1	ADMINISTRATION AND INTERPRETATION OF INTELLIGENCE TESTS	€ 9.70	National price list for outpatient specialist services*
94.01.2	ADMINISTRATION AND INTERPRETATION OF COGNITIVE DETERIORATION OR DEVELOPMENT TESTS, M.D.B., MODA, WAIS, STANFORD BINET, psychomotor development tests	€ 15.45	
94.02.1	ADMINISTRATION AND INTERPRETATION OF MEMORY TESTS Implicit, explicit, short- and long-term memory, attention tests, reading ability tests	€ 5.80	
94.08.1	ADMINISTRATION AND INTERPRETATION OF TESTS FOR EXECUTIVE FUNCTIONS	€ 5.95	
94.08.2	ADMINISTRATION AND INTERPRETATION OF TESTS FOR VISUOSPATIAL ABILITIES	€ 5.80	
94.08.4	ASSESSMENT FOR APHASIA. With standardized battery (Boston A.B., Aachen A.B., ENPA)	€ 27.10	
94.08.5	ADMINISTRATION AND INTERPRETATION TESTS FOR SOCIAL DYSFUNCTION ASSESSMENT	€ 5.80	
94.09	CLINICAL PSYCHOLOGICAL INTERVIEW	€ 22.00	
Cost included in the model for neuropsychological evaluation (level II)		€ 97.60	Sum of the previous codes

* Source: Ministero della Salute. Decreto Tariffe 12 April 2023.
§ Source: Prestazioni di Struttura di Genetica Clinica. Regione Toscana.

COSTS OF HEALTH AND SOCIAL CARE FACILITIES

The model for COI analysis included costs associated with residential and semi-residential facilities. Surveys conducted by ISS in NHs and DCCs were used to estimate these costs. These costs were estimated based on data from the surveys carried out by the ISS on NHs and DCCs. Specifically, for NHs, the survey allowed to gather information on length of stay, type of facility (public or private facilities operating in agreement with the NHS), and daily fees along with the portion of costs covered by the NHS (**Table 19**). The annual costs covered by the NHS for each institutionalized person with dementia was estimated by multiplying the portion of the mean daily fee covered by the NHS (72% for public facilities and 46% for private facilities operating in agreement with the NHS) by 365 days (1 year). The annual cost for each person with dementia institutionalised in a public facility was €19,973 and was €13,852 for each person with dementia institutionalized in private facilities operating in agreement with the NHS. A mean portion of costs covered by the NHS per year of €14,041 for each person with dementia was estimated by weighting these annual costs according to the portion of of public facilities (3.1%) and private facilities operating in agreement with the NHS (96.9%) that responded to the survey.

Table 19. Data used to estimate costs of residential facilities (data from the ISS survey on NHs)

Length of stay	
Mean (months)	35
Median (months)	42
Public facilities (n=33)	
Minimum daily fee, mean (min-max) (€)	68.0 (28-148)
Maximum daily fee, mean (min-max) (€)	84.0 (28-148)
Mean daily fee (€)	76.0
Costs covered by regional health service, mean (min-max) (%)	59.0 (0-100)
Costs covered by social and health service, mean (min-max) (%)	13.0 (0-100)
Costs covered by the customer, mean (min-max) (%)	26.0 (0-58)
Other, mean (min-max) (%)	1.6 (0-50)
Private facilities operating in agreement with the NHS (n=1,033)	
Minimum daily fee, mean (min-max) (€)	75.0 (15-168)
Maximum daily fee, mean (min-max) (€)	90.0 (27-450)
Mean daily fee (€)	82.5
Costs covered by regional health service, mean (min-max) (%)	36.0 (0-100)
Costs covered by social and health service, mean (min-max) (%)	10.0 (0-100)
Costs covered by the customer, mean (min-max) (%)	52.9 (0-100)
Other, mean (min-max) (%)	1.0 (0-100)

The same information collected for residential facilities were also collected for daycare centres (DCCs) through a specific survey. Data from the surveys used to calculate the portion of costs of daycare centres covered by the NHS are reported in Table 20.

The annual portion of costs covered by the NHS for each person with dementia referring to a DCC was estimated by multiplying the mean daily portion of costs covered by the NHS (62% for public facilities and 50% for private facilities operating in agreement with the NHS) for 365 days (1 year). The annual cost for each person with dementia referring to a public facility was €7,858 and was €6,388 for each person with dementia referring to a private facilities operating in agreement with the NHS. A mean portion of costs covered by the

NHS per year of €6.638 for each person with dementia refering to a DCC was estimated by weighting these annual costs according to the portion of of public facilities (17.0%) and private facilities operating in agreement with the NHS (83.0%) that responded to the survey.

Table 20. Data used to estimate costs of residential facilities (data from the ISS survey on DCCs)

Length of stay	
Mean (months)	21
Median (months)	18
Public facilities (n=33)	
Minimum daily fee, mean (min-max) (€)	29.0
Maximum daily fee, mean (min-max) (€)	40.0
Mean daily fee (€)	34.5
Costs covered by regional health service, mean (min-max) (%)	46.4 (0-100)
Costs covered by social and health service, mean (min-max) (%)	16.0 (0-50)
Costs covered by the customer, mean (min-max) (%)	8.5 (0-58)
Other, mean (min-max) (%)	11.9 (0-50)
Private facilities operating in agreement with the NHS (n=1,033)	
Minimum daily fee, mean (min-max) (€)	30.0
Maximum daily fee, mean (min-max) (€)	40.0
Mean daily fee (€)	35.0
Costs covered by regional health service, mean (min-max) (%)	33.9 (0-100)
Costs covered by social and health service, mean (min-max) (%)	16.1 (0-100)
Costs covered by the customer, mean (min-max) (%)	40.2 (0-100)
Other, mean (min-max) (%)	2.5 (0-100)

MONITORING COSTS

We assumed that the monitoring of people with dementia would require one neurological assessment, one ECG and blood tests onece a year. The cost for each of these services was quantifies using the national price list for outpatient specialist care services[60], specifically using the codes 89.01.C (NEUROLOGICAL EXAMINATION), 89.52 (ELECTROCARDIOGRAPHY) and the codes reported in **Table 17** for blood tests. Monitoring costs were only associated with people with a diagnosis of dementia, whose number was estimated by subtracting the number of incident cases from the total number of prevalent cases.

Table 21. Expenditure charged to the NHS for antidementia drugs by age categories

Age classes	Prevalence of use*/ Prevalence of AD (Ippoliti 2023)	People with AD taking anti-AD drugs (prevalence estimates of AD from Tognoni 2005 applied to prevalent cases of dementia estimated in the COI study)	Portion of costs of antidementia drugs covered by the NHS
65-69	38.00%	8.184	€ 596.678
70-74	70.00%	20.814	€ 1.517.619
75-79	43.00%	41.461	€ 3.022.975
80-84	34.00%	61.473	€ 4.482.102
85-89	20.00%	45.117	€ 3.289.554
>90	8.00%	14.073	€ 1.026.070

* Year 2019

[60] Ministero della Salute. Decreto Tariffe 12 Aprile 2023. Available at: https://www.quotidianosanita.it/allegati/allegato1681723698.pdf (Last visit: 30/08/2023).

COST OF ANTIDEMENTIA DRUGS AND ANTIPSYCHOTIC DRUGS

Information on the prevalence of antidementia drugs (ADDs) use was obtained based on data from the study by Ippoliti (2023), which estimated the prevalence of use of ADD in 2018-2020 by analyzing all prescriptions refunded by the NHS and provided by community pharmacies to people aged ≥65 years (**Table 21**). Specifically, the prevalence of use of ADDs was estimated by considering the prevalence of use of ADDs per age class and the prevalence of AD per age class. The number of PwD taking ADDs was estimated by applying the prevalece of use of ADDs per age class reported by Ippoliti (2023) to the number of cases of AD calculated by applying the estimates of prevalence of AD per age class reported by Tognoni (2005) to the number of prevalent cases of dementia per age class estimated in the COI study (**Table 21**). An estimate of the cost of ADDs was obtained based on the OSMED 2021 Report[61] that calculated a cost per ADDs user of € 117.60 for a mean treatment length of eight months. Since the study by Ippoliti (2023) reportd that around 38% of the costs for ADDs are out-of-pocket (thus with no refund by the NHS), the portion of costs for ADDs covered by the NHS was calsulate by considering the cost per user reported by the OSMED Report was considered excluding the 38% portion that was exclusively out-of-pocket.

The COI analysis did not account for the costs for ADDs in PwD aged <65 years. However, this estimate can be considered as irrelevant, as reported to be cose to 0% in the OSMED 2021 Report.

Overall, 36.1% of prevalent PwD were reported as using antipsychotic medications (data from the survey on CCDDs and referring to the proportion of PwD who received a prescription for antipsychotic medications). The annual cost per person with dementia taking antipsychotic medications was estimated by multiplying the mean cost per defined daily dose (DDD) estimated for antipsychotics by the OSMED 2021 Report per 365 days (1 year).

COSTS ASSOCIATED TO HOSPITALIZATIONS AND ADMISSIONS TO EMERGENCY SERVICES

The use of hospital services by PwD was analysed based on information from the Ministry of Health database of Hospital Discharge Records (HDRs) for 2019.

The HDR database is used to register all hospital and day hospital admissions throughout the Italian territory in public hospitals and private hospitals operating in an agreement with the NHS. The HDR includes personal and clinical information for each patient, for whom an anonymized identification code is provided. The diagnoses and procedures performed during hospitalization are classified using the international classification of diseases (ICD9CM).

Specifically, the number of PwD hospitalised during 2019 and the mean number of admissions were estimated by selecting from the HDR database all discharges for acute conditions between January 1, 2019 and December 31, 2019 and a primary or secondary diagnosis of Dementia (ICD9CM 290.xx) or Alcohol-induced persisting dementia (ICD9CM 291.2) or Drug-induced persistent dementia (ICD9CM 292.82) or Amnestic disorder in conditions classified elsewhere (ICD9CM 294.0) or Dementia in conditions classified elsewhere (ICD9CM 294.1) or Alzheimer's disease (ICD9CM 331.0) or Frontotemporal dementia (ICD9CM 331.1x) or Senile degeneration of brain (ICD9CM 331.2) or Cerebral degeneration in diseases classified elsewhere

[61] AIFA. Rapporto OSMED 2021. Available at: https://www.aifa.gov.it/documents/20142/1740782/Rapporto- OsMed-2021.pdf (Last visit: 30/08/2023).

(ICD9CM 331.7) or Other cerebral degeneration (ICD9CM 331.8x) or Cerebral degeneration, unspecified (ICD9CM 331.9) or Jakob-Creutzfeldt disease (ICD9CM 046.1).

The cost for considered hospital admissions was estimated assuming that admissions in each region were refunded based on the national price list (Decreto Ministeriale 18/10/2012) and that cases were classified according to the Diagnosis Related Groups (DRG) system version 24.

On this basis, the number of PwD discharged in 2019 was 115,936 (around 10% of prevalent cases) for a total of 130,592 discharges and a portion of costs covered by the NHS of € 445,387,511. Therefore, the mean hospitalisation cost per person was € 3,842.

The number of admissions to the emergency department (ED) of people with dementia was estimated, since no data were available at a national level, based on a cross-sectional study carried out on admissions to the ED of people aged ≥ 65 years registered in 2016 to 2019 within the National Hospital Ambulatory Medical Care Survey (NHAMCS) of the Centers for Disease Control and Prevention (CDC) (**Gerlach 2023**). The study reported that approximately 7% of admissions to the ED were people with AD and other dementias. Applying this estimate from the US population to the number of admissions to the ED reported in Italy in 2017 (19.727.801, AGENAS),[62] a total of 1.336.176 admissions of PwD to the ED were estimated. The cost of admissions to the ED, obtained based on data from the *Progetto Mattoni*[63] of the Ministry of Health, was € 307.03 (estimate updated to 2022).

COSTS FOR NON-PHARMACOLOGICAL INTERVENTIONS

The non-pharmacological interventions included in the COI study refer to training for cognitive symptoms and individual motor rehabilitation. The cost of these interventions was calculated based on the national price list for for outpatient specialist services using codes 93.89.2 (TRAINING FOR COGNITIVE SYMPTOMS. Rehabilitation of memory functions, gnosis, and praxis. Cycle of 10 sessions) and 93.11.1 (INDIVIDUAL MOTOR REHABILITATION referring to "functions of joints, bones, reflexes and muscles" according to the WHO ICF and mainly characterized by therapeutic motor exercise, irrespective of the technique used, the means it is performed in, the prosthetics, orthotics, and assistive technology, and the manual therapeutic activities. For each 30-minute session. Maximum cycle of 10 sessions). These services were considered only for people with a confirmed diagnosis of dementia who received psychosocial, educational, and rehabilitative treatments and interventions within CCDDs (25.5% of PwD referring to national CCDDs - data from the ISS survey of CCDDs).

Estimates of the indirect costs

The indirect costs included in the COI study were estimated by calculating the costs from the loss of productivity of caregivers of PwD due to caring activities. Specifically, the national survey on caregivers of PwD reportd that 84% of caregivers caring for PwD living at home, and 16% of caregivers of institutionalized PwD still had an occupation. Information from the survey on caregiver that was used to estimate the costs

[62] AGENAS, Caratteristiche delle strutture sede di Pronto Soccorso. Fonte: PNE 2018 (Dati 2017).
[63] https://www.salute.gov.it/portale/prontoSoccorso/dettaglioContenutiProntoSoccorso.jsp?lingua=italiano&id=1131&area=118%20Pronto%20Soccorso&menu=vuoto

related to the loss of productivity of caregivers is reported in **Table 22**. The cost of daily loss of productivity was calculated by applying the cost of care hours per day to the proportion of caregivers who still had an occupation. This cost was estimated by multiplying the houly wage reported by ISTAT (€11.70)[64] by the median number of care hours per day provided by the caregiver as reported in the survey. The indirect costs associated with the loss of productivity of caregivers were estimated for institutionalized PwD and PwD with moderate to severe dementia living at home.

Table 22. Data used to estimate the loss of productivity of caregivers – ISS survey on caregivers

Parameters	PwD living at home		Institutionalized PwD	
Caregivers who still have an occupation (%)	84%		16%	
	With caregiver	Without caregiver	With caregiver	Without caregiver
	48.80%	51.20%	21.40%	78.60%
Care hours per day (median)	4.0	7.0	2.9	2.0

Estimated costs of for social security and welfare

Social security and welfare costs were estimated using information from the database of the National Social Scurity Administration (Istituto Nazionale della Previdenza Sociale, INPS). Specifically, data used in the COI study refer to the social security and wefare services provided by INPS, which are universal and funded by the tax system. Type of services differ from social security, which aims to protect workers and is primarily funded by social contributions. Consulting the INPS database for 2021 allowed to identify 8,730 accepted applications for 100% disability and attendance allowance for people with AD. Welfare costs associated with the number of accepted applications was estimated assuming a monthly attendance allowance of approximately € 520.00. Since no information was available on accepted applications for types of dementia other than AD, the number of identified applications is an underestimation of the total number of applications submitted to the INPS.

A more realistic estimate was obtained based on data from the survey on caregivers of PwD, which reported that 56.4% of PwD receive an attendance allowance.

Welfare costs were calculated accounting for the number of applications for attendance allowance for people with AD accepted by the INPS. Data from the survey of caregivers were used, as reported in the following chapter, to calculate out-of-pocket costs excluding attendance allowance.

Estimated out-of-pocket costs

Out-of-pocket costs were estimated based on data from the survey on caregivers of PwD. The survey reported that the average costs per month associated to the disease is €1,142.00 for PwD living at home (approximately 60% for formal caregivers) and is €1,792.00 for institutionalised PwD (approximately 58% for care). In people receiving attendance allowance (56.4%, estimate applied to all PwD except those with mild dementia) out-of-pocket costs were adjusted to exclude the attendance allowance, thus avoiding counting it twice.

[64] ISTAT. Average hourly earnings for employee jobs in the private sector. 2020. Available at: http://dati.istat.it/Index.aspx?QueryId=33484&lang=en (Last visit: 30/08/2023).

Results

Cost of illness

When considering direct costs, based oin previously reportd information on costs related to use and healthcare resources, an overall total cost per year covered by the NHS for dementia of approximately €3.8 billion was estimated, approximately 53% of which is related to residential facilities (assuming approximately 141,994 institutionalized PwD, which would be 12% of prevalent cases of dementia (**Figure 2**).

When considering indirect costs, calculated in terms of loss of productivity of caregivers who still had an occupation due to caring for PwD, the COI model allowed to estimate a total expenditure of around € 5 billion (of which € 4.8 billion were related to people with moderate to severe dementia living at home).

Available information from the INPS database referring only to people with AD allowed to estimate an estimated welfare expenditure for attendance allowance of approximately € 54.5 million.

The annual out-of-pocket expenditure for treating and managing the disease was estimated to be approximately € 14.8 billion. In particular, the mean out-of-pocket expenditure per year for non-institutionalized PwD was € 12.3 billion (approximately 60% for formal caregivers), while the mean out-of-pocket expenditure per year for institutionalized PwD was € 2.5 billion (approximately 58% for residential care, likely intended as the portion of the fee for residential facilities covered by the resident) (**Figure 3**).

The total annual expenditure for the management and treatment dementia in Italy, calculated by summing all the previously reported direct, indirect, and out-of-pocket costs, was estimated to be approximately €23.6 billion (**Table 23**). The distribution of the total annual expenditure accoding to tyoe of costs is reported in **Figure 4**, which shows that approximately 63% of costs are covered by PwD and their families/caregivers.

Figure 2. Direct costs for the NHS

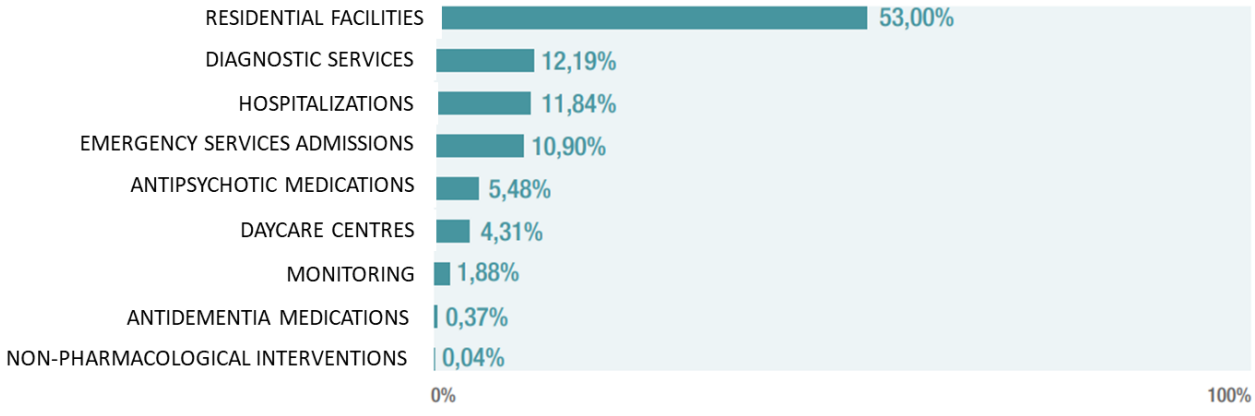
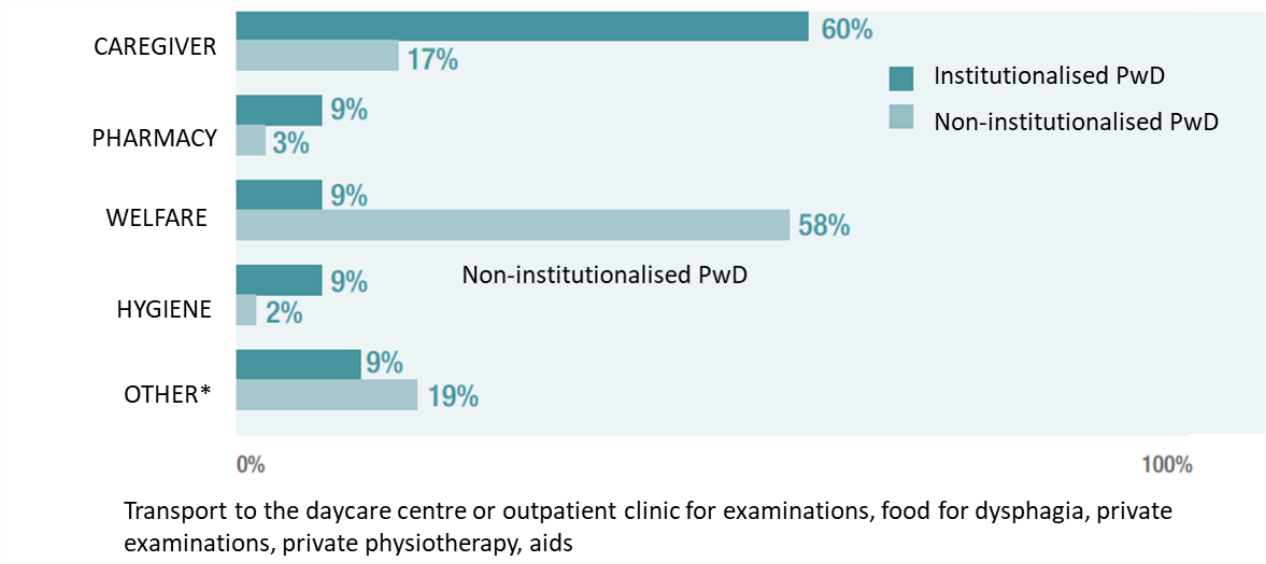


Figure 3. Distribution of out-of-pocket costs for institutionalized and non-institutionalized PwD



Transport to the daycare centre or outpatient clinic for examinations, food for dysphagia, private examinations, private physiotherapy, aids

Figure 4. Distribution of total costs per year for the management and treatment of people with dementia in Italy

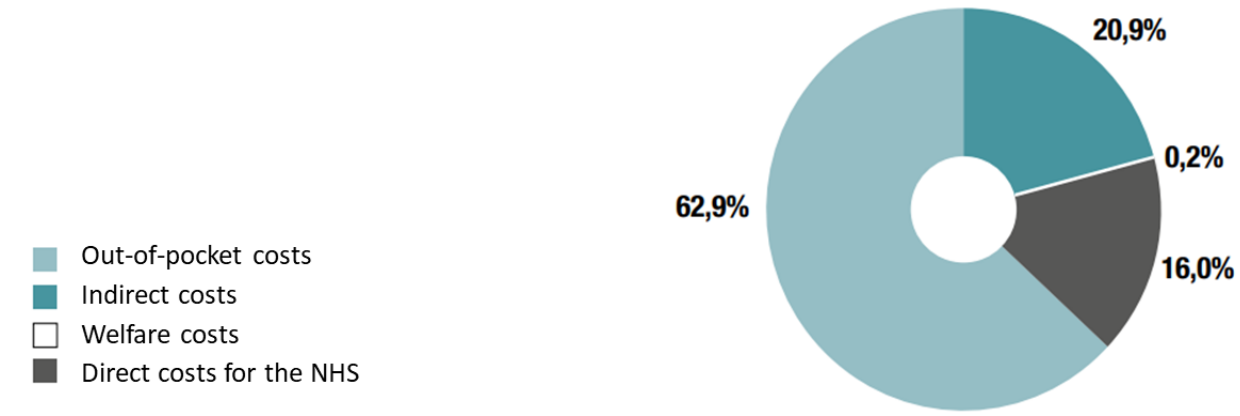


Table 23. Total costs per year for the management and treatment of dementia in Italy stratified per type of costs

Type of costs	Mean cost per year
Direct costs for the NHS	**€ 3,762,156,734**
Diagnostic services	€ 458,478,234
Monitoring	€ 70,692,450
Antidementia drugs	€ 13,934,999
Antipsychotic drugs	€ 206,204,348
Hospitalizations	€ 445,387,511
Emergency Room admissions	€ 410,251,354
Non-pharmacological interventions	€ 1,465,247
Nursing homes	€ 1,993,772,812
Daycare centres	€ 161,969,779
Indirect costs	**€ 4,930,797,637**
Loss of productivity of caregivers – not institutionalized PwD	€ 4,794,222,870
Loss of productivity of caregivers – institutionalized PwD	€ 136,574,768
Welfare costs	**€ 54,475,200**
Out-of-pocket costs	**€ 14,811,282,468**
Formal caregivers	€ 7,847,145,228
Pharmacy	€ 1,192,617,251
Care	€ 2,560,747,878
Hygiene	€ 1,119,707,054
Other	€ 2,091,065,058
Total costs	**€ 23,558,712,039**

Cost-Consequences Analysis

Using a Cost-Consequence Analysis (CCA), based on results from the COI analysis, we test different potential scenarios to assess their economic impact.

Specifically, the following scenarios were assessed:

- reduction in the number of institutionalised PwD (base-case = 41.1% institutionalized PwD on the total number of available beds, min = 22.7% institutionalized PwD, equivalent to the minimum value reported by the districs of the Marche region as part of the survey on available beds for PwD);
- reduction in the use of antipsychotic medications in PwD (base-case = 36.1% of PwD using antipsychotic medications, min = 20%);
- all PwD referring to CDCDs receiving psychosocial, educational and rehabilitative treatments and interventions (base-case = 25.5%, max = 100%).

Assuming approximately 23% of available beds are occupied by institutionalized PwD, costs for the NHS would decrease by around 24% (- €891.5 million), out-of-pocket costs would decrease by around 3% (- €495.2 million), and indirect costs would increase by around 5% (+ €240.7 million) (**Table 24**). When considering the use of antipsychotic medications, a 20% reduction in the number of PwD using antipsychotic medications (20% of users versus a base-case of 36.1%) would lead to an approximate 2.4% decrease in NHS expenditure (- €92 million) (**Table 24**).
Assuming all PwD received psychosocial, educational, and rehabilitative treatments and interventions, the NHS expenditure would increase by approximately 0.1% (+ €4.3 million) (**Table 24**).

Table 24. Results of the Cost-Consequences Analysis

	Direct costs for the NHS		Out-of-pocket costs		Indirect costs	
	Scenario (Δ vs base- case, €)	Scenario (Δ vs base-case, %)	Scenario (Δ vs base- case, €)	Scenario (Δ vs base-case, %)	Scenario (Δ vs base- case, €)	Scenario (Δ vs base-case, %)
Proportion of institutionalized PwD on the total number of available beds (base-case = 41.1%, min = 22.7%)	-891,512,265	-23.7	-495,240,908	-3.3	+240,703,058	+4.9
Proportion of PwD receiving antipsychotic drugs (base-case = 36.1%, min = 20.0%)	-91,963,712	-2,4	0	0	0	0
Proportion of PwD referring to CDCDs who receive psychosocial, educational and rehabilitative treatments and interventions (base-case = 25.5%, min = 100%)	+4,280,821	+0.1	0	0	0	0

Conclusions

The economic analysis developed for this guideline (GL) aimed to provide an updated overview, based on available data sources, of the current management of people with dementia (PwD) in Italy from an organizational and economic perspective.

The total costs for the management and treatment of PwD were approximately €23.6 billion, with 63% being out-of-pocket costs covered by families of PwD.

Reducing the number of institutionalized PwD would result in an increase of the estimated welfare costs in terms of loss of caregivers' productivity, and in a reduction in both costs covered by the NHS and out-of-pocket costs covered by PwD.

Assuming an approximate 45% reduction in the number of PwD using antipsychotic medication would lead to reduction in costs for the NHS of approximately €92 million. Assuming all PwD referring to CDCDs received psychosocial, educational and rehabilitative treatments and interventions, the costs for the NHS would by approximately €4.3 million.

This economic analysis has some limitations. Specifically, having to make assumptions when national data were unavailable could have led to overestimating or underestimating the costs for specific health services. To reduce the risk of bias, analyses were performed adopting a conservative approach.

When estimating costs for diagnosis, the cost of the neuropsychological assessment was estimated for incident cases of dementia and for prevalent cases of MCI. Prevalent cases of MCI were included because people with isolated cognitive disorders are constantly monitored through cognitive assessment to detect the possible onset of dementia.

When considering welfare costs, as we had no direct access to the INPS database, we could not select ad hoc the ICD9CM codes of interest. All considered services refer only to people with a diagnosis of AD, an therefore are an underestimation of the total amount of services provided to PwD. Moreover, the COI analysis did not account for relevant aspects including comorbidities in PwD and home care services. The inclusion of these aspects in the analyses could be considered in future economic assessments to provide a more comprehensive estimate of the total costs associated to the management and care of PwD in Italy.

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Bioethical aspects

The methodological handbook (MH) for the development of clinical practice guidelines (GL) (CNEC 2019) indicates that "the ISS Bioethics Unit participates in the development of GL by evaluating the ethical implications of implementing the recommended interventions". However, the SNLG MH does not provide structured methodological indications on how some specific ethical issues should be identified and addressed within the GL. In drafting this LG, when these issues were not explicitly identified and classified, they were widely discussed by all professionals involved in developing the recommendations by a process of analysis and summary, which led to defining an operational direction.

As reported by the large amount of available literature, there are several complex ethical issues and real practical dilemmas when considering the integrated management of people with major and minor neurocognitive disorders. Specific issues are peculiar to each phase of the disease, and the possibility of solving them all, permanently, within a however detailed GL, is unlikely.

Any ethical issue that may arise, for example, in cases when values and principles guiding the actions of healthcare professionals are inconsistent, even concerning the choices of people with dementia and their family members, lies in the specific space of real life, where a shared and thoughtful approach should be adopted. In this relational space, ethical problems should be addressed carefully by clinicians and all those involved in the care relationship, with specific attention to the participation, dignity, and rights of the most vulnerable person and all involved people.

While developing this guideline, which is the first of its type ever made in Italy, several ethical issues were discussed among the working group (WG) and taken into account when making decisions on each recommendation. The discussion is based on the ongoing activities of the Permanent Table on Dementia, coordinated by the Ministry of Health, which developed a document, approved by the State Regions Conference in 2020, providing indications for the governance and clinical practice in dementia[65].

This Guidance document is an important basis to better understand some aspects of this GL. However, a further document should also be underlined, developed by the National Committee for Bioethics (NCB) in 2014, providing indications on ethical aspects of dementia and Alzheimer's disease[66]. This document explores several bioethical issues, such as personal identity, communication of the diagnosis, therapeutic relationship, symptomatic treatments, social and health care, social information and training, and legal issues.

As highlighted by these documents and by national and international literature, the discussion on bioethical aspects is far from over. It instead needs an increasingly rigorous and effective synergistic approach. To this purpose, in Italy, the commitment of many professionals involved in the governance and clinical management of dementia shows the desire to build an institutional, cultural, and scientific path aimed at developing a fair system of care, management, and protection of people, with particular attention to the relation between socioeconomic conditions and inequalities in health.

There are several complex and multifaceted issues to be addressed, starting from primary prevention, which is an essential and urgent aspect from a public health point of view. Theoretical models indicate that appropriate interventions on risk factors could prevent up to 40% of dementia cases worldwide, leading a commission of experts established in 2020 by the Lancet to state that it is necessary to "be ambitious about prevention" (Livingston 2020).

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65 https://www.iss.it/documents/20126/5783571/Raccomandazioni+per+la+governance+e+la+clinica+nel+settore+delle+demenze.pdf/dbf0d6d5-6360-41d9-aa51-74b18f62dad8?t=1626171914860 (Last visited: 30/08/2023)

66 NCB. https://bioetica.governo.it/it/documenti/pareri/le-demenze-e-la-malattia-di-alzheimer/ (Last visited: 30/08/2023).

We believe this slogan represents and should continue representing to the fullest of its potential a guiding light for innovative paths and strategies.

When considering therapeutic alliance, the approach to care and palliative care is also extremely important. Limited data are still available in Italy on the application of Law N. 219 of 2017, providing regulations in matter of informed consent and advance care directives[67], which harmonized all requirements on consent in clinical practice, placing a strong emphasis on the protection and promotion of individual autonomy and self-determination.

The approach proposed by Law N. 219 implies the involvement of people in decisions about their care from the very early stages of the disease and requires a paradigm shift from the disability model to the valorization of residual skills and abilities. Law No. 219 provided two legal institutes: advance healthcare directives (AHD) and advance care planning (ACP). APC was especially introduced to enable people with chronic and disabling pathologies to share with professionals every decision about their present and future care in a continuous process of information, reflection, and choice. However, for this intention to be effectively implemented, reference models and shared good practices should be developed. In particular, in case of multimorbidity, disability, and limited capacity, where gathering the individual wishes appears to be more complex, specific attention should be placed to guarantee equality and equal treatment for both people with the capacity to discern and people with impaired capacity.

Palliative care is provided within the ACP. As many have already underlined, in Italy, as in other countries, it is not uncommon for people with clinical and social frailty not to be appropriately referred to palliative care. Treatments are often delivered in a fragmented and uncoordinated way, with repeated hospitalisations that can even result in inappropriate treatments. The need for palliative care in people with neurological diseases is not yet managed the same way as for other diseases. The NCB in 2014 had already underlined the need to guarantee appropriate access to palliative care for people with neurocognitive disorders.

It is essential to underline the need to implement a structured approach to overcome the different barriers that still hinder the adequate implementation of Law n. 38 of 2010: «Provisions to ensure access to palliative care and pain management"[68] to people with dementia. Palliative care approaches are not exclusively focused on the end of life, they are also a peculiar method for taking care globally of people and their family members, aimed at identifying their needs throughout the clinical path. For this reason, as recommended in this GL, this approach should be initiated starting from the diagnosis and should be carried out throughout the course of the disease within the care relationship and shared planning.

Another relevant ethical issue that was discussed within the WG was the use of restraints in managing people with dementia, a practice that is currently generally rejected by international policies. As for physical restraints, pharmacological restraints using benzodiazepines and antipsychotics, if deemed necessary and prescribed by the responsible specialist, should only be used after adequate information detailing all associated risks. From an ethical point of view, it is important to underline that the use of restraints is only justified in case of proven necessity and should always be documented and periodically reassessed based on shared and explicit standards. To this purpose, starting a careful monitoring of the phenomenon throughout the national territory could be useful.

The primary recommendation from NBC, namely that people with dementia should be recognized as a person throughout every stage of the disease, is still valid to this day, after over ten years, and represents both a starting point and, in a certain sense, the objective of the clinical and institutional path.

The condition of unawareness or relational difficulty of people with dementia does not justify any form of discrimination and stigmatization. Research (including research in palliative care), prevention, treatments, and care should be included as having a relevant role in health policies.

[67] Law n. 219 of 2017. https://www.gazzettaufficiale.it/eli/id/2018/1/16/18G00006/sg. (Last visited:30/08/2023).
[68] https://www.gazzettaufficiale.it/gunewsletter/dettaglio.jsp?service=1&datagu=2010-03-19&task=dettaglio&numgu=65&redaz=010G0056&tmstp=1269600292070 (Last visited: 30/08/2023)

SUMMARY OF RECOMMENDATIONS

Clinical practice recommendations

IDENTIFICATION, DIAGNOSIS AND POST-DIAGNOSTIC SUPPORT

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 cognitive decline and • if possible, from someone who knows the person well (such as a family member).	**STRONG IN FAVOR** Adapted
2	If cognitive decline 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 and • prescribe brain CT and/or MRI to exclude secondary causes of cognitive decline.	**STRONG IN FAVOR** Adapted
3	When using cognitive testing to assess people with dementia or someone who knows the person well (such as a family member), use a validated brief structured cognitive instrument such as: • 10-point cognitive screener (10-CS); • 6-item cognitive impairment test (6CIT) [§]; • 6-item screener (6-IS); • Memory Impairment Screen (MIS); • Mini-Cog; • Test Your Memory (TYM) [§]; • General Practitioner Assessment of Cognition (GPCOG)[§§].	**STRONG IN FAVOR** Adapted
4	Do not rule out cognitive decline solely because the person has a normal score on a cognitive instrument and plan a monitoring of cognitive functions in time.	**STRONG AGAINST** Adapted
5	Refer the person to a specialist dementia diagnostic service (Centre for Cognitive Disorders and Dementias) 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.	**STRONG IN FAVOR** Adapted
6	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.	**STRONG IN FAVOR** Adopted
7	For more guidance on assessing for dementia in people with learning disabilities, see Table 6 in the Full Guideline.	**STRONG IN FAVOR** Adapted

Diagnosis of dementia in specialist settings

8	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.	**WEAK IN FAVOR** Adopted
9	If Alzheimer's disease is suspected, include a test of verbal episodic memory in the assessment.	**STRONG IN FAVOR** Adopted
10	Offer neuropsychological testing with validated neuropsychological tests as an essential part of the diagnostic process for dementia and dementia subtypes.	**STRONG IN FAVOR** New
11	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 for vascular dementia; • NIA-AA criteria for Alzheimer's disease; • Movement Disorders Society criteria for Parkinson's disease dementia; • WHO and International criteria for Creutzfeldt-Jakob disease.	**STRONG IN FAVOR** Adopted
12	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.	**STRONG IN FAVOR** Adopted
13	Only consider further diagnostic tests if: • it would help to diagnose a dementia subtype and • knowing more about the dementia subtype would change management.	**WEAK IN FAVOR** Adopted

Further tests for Alzheimer's disease

14	If the diagnosis is uncertain (see recommendation 13) and Alzheimer's disease is suspected, consider either: • ^{18}F-FDG PET, or perfusion SPECT if ^{18}F-FDG PET is unavailable or • examining cerebrospinal fluid for: – total Tau and phosphorylated-Tau 181 and – amyloid β 1-42/amyloid β 1-40 ratio or amyloid β 1-42 If a diagnosis cannot be made after one of these tests, consider using the other one.	**WEAK IN FAVOR** Adapted
15	Be aware that the older a person is, more likely they are to get a false positive with cerebrospinal fluid examination.	**WEAK IN FAVOR** Adopted
16	Do not rule out Alzheimer's disease based solely on the results of CT or MRI scans.	**STRONG AGAINST** Adopted
17	Do not use *ApoE* ε4 genotyping or electroencephalography to diagnose Alzheimer's disease.	**STRONG AGAINST** Adopted
18	Be aware that young-onset Alzheimer's disease has a genetic cause in some people.	**WEAK IN FAVOR** Adopted

Further tests for dementia with Lewy bodies

19	If the diagnosis is uncertain (see recommendation 13) and dementia with Lewy bodies is suspected, use ^{123}I-FP-CIT SPECT.	**STRONG IN FAVOR** Adopted
20	If ^{123}I-FP-CIT SPECT is unavailable, consider as an alternative: • ^{123}I-MIBG cardiac scintigraphy or • polysomnography with EEG	**WEAK IN FAVOR** Adapted
21	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.	**STRONG AGAINST** Adopted

Further tests for frontotemporal dementia

22	If the diagnosis is uncertain (see recommendation 13) and frontotemporal dementia is suspected, use, with semi-quantitative reading, either: • ^{18}F-FDG PET or • perfusion SPECT.	**STRONG IN FAVOR** Adapted
23	Do not rule out frontotemporal dementia based solely on the results of structural, perfusion or metabolic imaging tests.	**STRONG AGAINST** Adopted
24	Be aware that frontotemporal dementia has a genetic cause in some people.	**WEAK IN FAVOR** Adopted

Further tests for vascular dementia

25	If the dementia subtype is uncertain (see recommendation 13) and vascular dementia is suspected, use MRI. If MRI is unavailable or contraindicated, use CT.	**STRONG IN FAVOR** Adopted
26	Do not diagnose vascular dementia based solely on vascular lesion burden.	**STRONG AGAINST** Adopted
27	Be aware that young-onset vascular dementia has a genetic cause in some people.	**WEAK IN FAVOR** Adopted

Diagnosis of Mild Cognitive Impairment in specialist settings

28	Offer a neuropsychological assessment using validated neuropsychological tests, including specific tests for episodic memory, as part of the diagnostic process for MCI and its subtypes.	**STRONG IN FAVOR** New
29	Do not offer biomarkers for the diagnosis and differential diagnosis of MCI.	**STRONG AGAINST** New
30	Offer people with a diagnosis of MCI regular neuropsychological assessments over time to monitor possible changes in cognitive functions.	**STRONG IN FAVOR** New

Drugs that may worsen cognitive decline

31	Be aware that some commonly prescribed medicines are associated with increased anticholinergic burden, and therefore cognitive impairment.	**WEAK IN FAVOR** Adopted
32	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	**WEAK IN FAVOR** Adopted
33	Consider that there are validated tools for assessing anticholinergic burden (for example, the Anticholinergic Cognitive Burden Scale).	**WEAK IN FAVOR** Adapted
34	For guidance on carrying out medication reviews, see the indications reported in Table 7 in the Full Guideline.	**STRONG IN FAVOR** Adopted

Distinguishing dementia from dementia with delirium or delirium alone

35	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) • 4-A's Test (4AT).	**WEAK IN FAVOR** Adapted
36	Do not use standardised instruments (including cognitive instruments) alone to distinguish delirium from delirium superimposed on dementia.	**STRONG AGAINST** Adopted
37	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 the identification and treatment of delirium, see Table 6 in the Full Guideline.	**STRONG IN FAVOR** Adopted

Pre-, peri- and post-diagnostic counselling

38	Consider offering people with dementia and their caregivers peri- and post-diagnostic counselling targeted to the specific conditions of each patient (including symptom severity).	**WEAK IN FAVOR** New
39	For the communication of diagnosis and post-diagnostic support see the section "Communication of the diagnosis of dementia" of the document "Recommendations for the governance and clinical management in dementia"[69] issued by the National Committee for dementia.	**STRONG IN FAVOR** New

[69] Available at: https://www.iss.it/documents/20126/5783571/Raccomandazioni+per+la+governance+e+la+clinica+nel+settore+delle+demenze.pdf/dbf0d6d5-6360-41d9-aa51-74b18f62dad8?t=1626171914860 (Last visited: 30/08/2023)

CARE MODELS AND COORDINATION OF CARE

Care planning, review and coordination

40	Provide people living with dementia with a single named health or social care professional who is responsible for their Personalized Care Plan (PAI) within an integrated care pathway. For further indications on how to organize a PAI, see: • indication 6 from the document "National Guidance for the Clinical Governance of Dementia"[70] issued by the National Committee on Dementia; • the document "National Guidance for the definition of Integrated Care Pathways for dementia"[71] issued by the National Committee on Dementia.	**STRONG IN FAVOR** Adapted
41	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 document "National Guidance for the Clinical Governance of Dementia" issued by the National Committee on Dementia; • ensure that people are aware of their rights to and the availability of local advocacy services, in line with the document "National Guidance for the Clinical Governance of Dementia" issued by the National Committee on Dementia; • 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).	**WEAK IN FAVOR** Adapted
42	When developing care and support plans and advance care and support plans, request consent to transfer these to different care settings as needed.	**STRONG IN FAVOR** Adopted
43	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).	**WEAK IN FAVOR** Adopted
44	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.	**WEAK IN FAVOR** Adopted
45	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 minorities*.	**WEAK IN FAVOR** Adapted

[70] Available at: https://www.iss.it/documents/20126/5783571/Raccomandazioni+per+la+governance+e+la+clinica+nel+settore+delle+demenze.pdf/dbf0d6d5-6360-41d9-aa51-74b18f62dad8?t=1626171914860 (Last visited: 30/08/2023)
[71] Available at: https://www.iss.it/documents/20126/5783571/Testo+Linee+di+indirizzo+Nazionali+sui+Percorsi+Diagnostico+Terapeutici+Assistenziali+%28PDTA%29+per+le+demenze.pdf/d5123f6a-2161-6c42-5377-8796cce29fe0?t=1626170681347 (Last visited: 30/08/2023)

Post diagnosis review for people living with dementia

46	After a person is diagnosed with dementia or Mild Cognitive Impairment, ensure they and their carers have access to specialist multidisciplinary dementia services (Centres for Cognitive Disorders and Dementias, CCDDs).	**STRONG IN FAVOR** Adapted
47	Specialist multidisciplinary dementia services (Centres for Cognitive Disorders and Dementias, CCDDs) should offer a choice of flexible access or prescheduled monitoring appointments.	**WEAK IN FAVOR** Adapted
48	General practitioners, when visiting people living with dementia or Mild Cognitive Impairment, or their carers, should assess for any emerging dementia-related needs and ask them if they need any more support.	**WEAK IN FAVOR** Adapted

Staff training

49	Care and support providers should provide all staff with appropriate 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.	**WEAK IN FAVOR** Adapted
50	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; • 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; the specific needs of younger people living with dementia and people who are working or looking for work.	**WEAK IN FAVOR** Adapted
51	Consider giving carers and/or family members the opportunity to attend and take part in staff dementia training sessions.	**WEAK IN FAVOR** Adopted
52	Consider training staff to provide multi-sensory stimulation for people with moderate to severe dementia and communication difficulties.	**WEAK IN FAVOR** Adopted

Involving people living with dementia in decisions about care

53	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.	**STRONG IN FAVOR** Adopted
54	Be aware of the obligation to provide accessible information. For more guidance on providing information and discussing people's preferences with them, see the document "National Guidance for the Clinical Governance of Dementia" issued by the National Committee on Dementia.	**STRONG IN FAVOR** Adapted
55	Throughout the diagnostic process, 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 health and social are professionals will be involved in their care and how to contact them; • if appropriate, how dementia affects driving, and that they need to tell the general practitioner and healthcare staff involved in renewing their licence about their dementia diagnosis; • their legal rights and responsibilities, see the document "National Guidance for the Clinical Governance of Dementia" issued by the National Committee on Dementia; • their right to reasonable adjustments (law 68/99[72] with modifications according to the Legislative Decree 151/2015[73]) 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.	**STRONG IN FAVOR** Adapted
56	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.	**STRONG IN FAVOR** Adopted
57	After diagnosis, direct people and their family members or carers (as appropriate) to relevant services for information and support (see recommendations 40 and 41 on care coordination).	**STRONG IN FAVOR** Adopted
58	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.	**STRONG IN FAVOR** Adopted
59	Ensure that people living with dementia and their carers know how to get more information and who from if their needs change.	**STRONG IN FAVOR** Adopted
60	Tell people living with dementia (at all stages of the condition) about research studies they could participate in.	**STRONG IN FAVOR** Adopted
61	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);	**STRONG IN FAVOR** Adopted

[72] Law, March 12, 1999, n. 68 (https://www.gazzettaufficiale.it/eli/id/1999/03/23/099G0123/sg) (Last visited: 30/08/2023).
[73] Legislative Decree, September 14, 2015, n. 151 (https://www.gazzettaufficiale.it/eli/id/2015/09/23/15G00164/sg) (Last visited: 30/08/2023).

	• 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.	
62	Explain that they will be given chances to review and change any advance statements and decisions they have made.	**STRONG IN FAVOR** Adopted
63	At each care review, offer people the chance to review and change any advance statements and decisions they have made.	**STRONG IN FAVOR** Adopted
64	Encourage and enable people living with dementia to give their own views and opinions about their care.	**STRONG IN FAVOR** Adopted
65	If needed, use additional or modified ways of communicating (for example visual aids or simplified text).	**STRONG IN FAVOR** Adopted
66	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 41).	**STRONG IN FAVOR** Adopted
67	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.	**WEAK IN FAVOR** Adopted

Management strategies for people living with dementia/Mild Cognitive Impairment and co-existing physical long-term conditions

68	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 Table 6 in the Full Guideline.	**STRONG IN FAVOR** Adopted
69	For people with dementia or Mild Cognitive Impairment and at least one chronic physical comorbidity, when managing comorbidities (e.g., hypertension, cardiovascular diseases, type 2 diabetes, sensory deficits, urinary tract conditions) refer to the best practices for each condition, considering each person's specific clinical conditions and except in case the administration of standard care could cause more harm that benefit (see Table 6 in the Full Guideline).	**STRONG IN FAVOR** Adapted

Care setting transitions

70	When managing transition between care settings consider that: • in case of hospitalisation, a comprehensive geriatric assessment should be performed on people with dementia on admission to hospital, and any care plan should be shared with the admitting team, while, at discharge, continuity of care should be ensured; • the NICE guideline on transition between inpatient mental health settings and community or care home settings.	**STRONG IN FAVOR** Adapted
71	For guidance on medicine optimisation and reconciliation, see Table 8 in the Full Guideline. Follow the principles in these guidelines for transitions between other settings (for example from home to a care home or respite care).	**STRONG IN FAVOR** Adapted
72	Review the needs and wishes of people with dementia and their caregivers (including any care and support plans referring to current and future care) after every transition.	**STRONG IN FAVOR** Adapted

Supporting caregivers of people with dementia

73	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.	**STRONG IN FAVOR** Adopted
74	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.	**STRONG IN FAVOR** Adopted
75	Advise carers about their right to the following and how to get them: • a formal assessment of their own needs, including their physical and mental health; • an assessment of their need for short breaks and other respite care.	**STRONG IN FAVOR** Adopted
76	Be aware that carers of people living with dementia are at an increased risk of depression. For guidance on identifying and managing depression, see Table 6 in the Full Guideline.	**WEAK IN FAVOR** Adopted

PHARMACOLOGICAL TREATMENTS FOR COGNITIVE SYMPTOMS

Acetylcholinesterase inhibitors, memantine, and new biological treatments for Alzheimer's dementia and Mild Cognitive Impairment

77	The three acetylcholinesterase (AChE) inhibitors donepezil, galantamine and rivastigmine as monotherapies are recommended as options for managing mild to moderate Alzheimer's dementia under all of the conditions specified in recommendations 82 and 83.	**STRONG IN FAVOR** Adopted
78	Offer donepezil as monotherapy for managing moderate to severe Alzheimer's dementia based on the conditions specified in recommendations 82 and 83.	**WEAK IN FAVOR** New
79	Memantine monotherapy is recommended as an option for managing Alzheimer's dementia for people with: • moderate Alzheimer's dementia who are intolerant of or have a contraindication to AChE inhibitors or • severe Alzheimer's dementia. Treatment should be under the conditions specified in recommendation 82.	**WEAK IN FAVOR** Adopted
80	For people who are not taking an AChE inhibitor or memantine, prescribers should only start treatment with these on the advice of a specialist (neurologist, geriatrician, psychiatrist) who has the necessary knowledge and skills. Only specialists in Centres for Cognitive Disorders and Dementias (CCDDs) can provide refundable prescriptions for these drugs within the National Health System.	**WEAK IN FAVOR** Adapted
81	If prescribing an AChE inhibitor, 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.	**WEAK IN FAVOR** Adopted
82	When using assessment scales to determine the severity of Alzheimer's dementia, 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.	**WEAK IN FAVOR** Adopted
83	When assessing the severity of Alzheimer's dementia 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 person's dementia because of the person'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 person 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.	**WEAK AGAINST** Adopted

Acetylcholinesterase inhibitors and memantine in people with mild cognitive impairment

84	Do not offer AChE inhibitors (donepezil, galantamine, and rivastigmine) and memantine for the treatment of Mild Cognitive Impairment.	**STRONG AGAINST** New

Biological drugs in people with Alzheimer's dementia and Mild Cognitive Impairment

85	Do not offer monoclonal antibodies against the different forms of amyloid β as a treatment for Alzheimer's dementia or Mild Cognitive Impairment.	**STRONG AGAINST** New

Repurposing of pharmacological interventions

86	Do not offer the following treatments specifically to slow the progression of Alzheimer's disease or to slow or stop the conversion from Mild Cognitive Impairment to dementia: • antidiabetic drugs; • antihypertensive drugs; • statins; • non-steroidal anti-inflammatory drugs (NSAIDs), including acetylsalicylic acid.	**STRONG AGAINST** Adapted

Co-prescription of acetylcholinesterase inhibitors and memantine in Alzheimer's dementia

87	For people with moderate Alzheimer's dementia who are already taking an AChE inhibitor consider memantine in addition to the AChE inhibitor.	**WEAK IN FAVOR** Adapted
88	For people with severe Alzheimer's dementia who are already taking an AChE inhibitor offer memantine in addition to the AChE inhibitor.	**STRONG IN FAVOR** Adapted

Discontinuation of acetylcholinesterase inhibitors and memantine in Alzheimer's dementia

89	Do not stop AChE inhibitors or memantine in people with Alzheimer's dementia because of disease severity alone.	**STRONG AGAINST** Adopted

Acetylcholinesterase inhibitors and memantine for Parkinson's disease dementia

90	Offer AChE inhibitors[74] for people with mild or moderate Parkinson's disease dementia.	**STRONG IN FAVOR** Adopted
91	Consider AChE inhibitors[75] for people with severe Parkinson's disease dementia.	**WEAK IN FAVOR** Adopted
92	Consider memantine[76] for people with Parkinson's disease dementia, only if AChE inhibitors are not tolerated or are contraindicated.	**WEAK IN FAVOR** Adopted

Acetylcholinesterase inhibitors for dementia with Lewy bodies

93	Offer donepezil or to people with mild to moderate dementia with Lewy bodies.	**STRONG IN FAVOR** Adopted
94	Only consider galantamine for people with mild to moderate dementia with Lewy bodies if donepezil and rivastigmine are not tolerated.	**WEAK IN FAVOR** Adopted

[74] Rivastigmine capsules is currently the only AChEI with an indication for the treatment of mild to moderate PDD. Use of donepezil, galantamine and rivastigmine patches is off label.
[75] Use of AChEI, including rivastigmine capsules, for the treatment of severe PDD is off label.
[76] Use of memantine for the treatment of PDD is off label.

95	Consider donepezil or rivastigmine for people with severe dementia with Lewy bodies.	**WEAK IN FAVOR** Adopted
96	Consider memantine for people with dementia with Lewy bodies if cholinesterase inhibitors are not tolerated or are contraindicated.	**WEAK IN FAVOR** Adopted

Acetylcholinesterase inhibitors and memantine for types of dementia other than Alzheimer's disease

97	Only consider cholinesterase inhibitors or memantine for people with vascular dementia if they have suspected comorbid Alzheimer's disease, Parkinson's disease dementia or dementia with Lewy bodies.	**WEAK IN FAVOR** Adopted
98	Do not offer cholinesterase inhibitors or memantine to people with frontotemporal dementia.	**STRONG AGAINST** Adopted
99	Do not offer cholinesterase inhibitors or memantine to people with cognitive impairment caused by multiple sclerosis.	**STRONG AGAINST** Adopted

NON-PHARMACOLOGICAL INTERVENTIONS FOR COGNITIVE SYMPTOMS

Non-pharmacological interventions for cognitive symptoms in dementia

100	Do not offer acupuncture to treat cognitive symptoms in dementia.	**STRONG AGAINST** Adopted
101	Consider aerobic physical exercise to treat cognitive symptoms in people with mild Alzheimer's dementia.	**WEAK IN FAVOR** New
102	Consider non-aerobic physical exercise to treat cognitive symptoms in people with mild to moderate dementia.	**WEAK IN FAVOR** New
103	Consider the combination of aerobic and non-aerobic physical exercise to treat cognitive symptoms in people with moderate dementia.	**WEAK IN FAVOR** New
104	Do not offer specific formulas, including the combinations of supplements containing omega 3 fatty acids, phospholipids, choline, uridine monophosphate, vitamin E, vitamin C, vitamin B6, vitamin B12, folic acid, and selenium to treat cognitive symptoms in people with dementia in absence of documented deficiencies.	**STRONG AGAINST** New
105	Do not offer vitamin E and folic acid supplements to treat cognitive symptoms in people with dementia in absence of documented deficiencies.	**STRONG AGAINST** Adapted
106	Do not offer ginseng, ginkgo biloba, huperzine A, and other herbal supplements, antioxidants such as omega-3, selenium and sodium oligomannate to treat cognitive symptoms in people with dementia.	**STRONG AGAINST** Adapted
107	Do not offer ketogenic dietary interventions to treat cognitive symptoms in people with dementia.	**STRONG AGAINST** New
108	Do not offer light therapy to treat cognitive symptoms in people with moderate to severe dementia.	**STRONG AGAINST** New
109	Consider music therapy to treat cognitive symptoms in people with mild to severe dementia.	**WEAK IN FAVOR** New

110	Do not offer psychotherapy to treat cognitive symptoms in people with mild to moderate dementia.	**STRONG AGAINST** Adapted
111	Consider reminiscence therapy to treat cognitive symptoms in people with moderate dementia.	**WEAK IN FAVOR** Adapted
112	Do not offer therapeutic robots to treat cognitive symptoms in people with dementia.	**STRONG AGAINST** New
113	Consider occupational therapy to support functional abilities in people with mild to moderate dementia.	**WEAK IN FAVOR** Adapted
114	Consider cognitive rehabilitation to support functional abilities in people with mild to moderate dementia.	**WEAK IN FAVOR** Adapted
115	Offer cognitive stimulation to treat cognitive symptoms in people with mild to moderate dementia.	**STRONG IN FAVOR** Adapted
116	Consider cognitive training to treat cognitive symptoms in people with mild Alzheimer's dementia.	**WEAK IN FAVOR** New
117	Offer a range of activities to promote wellbeing and autonomy that are tailored to the person’s individual preferences.	**STRONG IN FAVOR** Adapted

Non-pharmacological interventions for cognitive symptoms in Mild Cognitive Impairment

118	Do not consider acupuncture to treat cognitive symptoms in people with Mild Cognitive Impairment.	**WEAK AGAINST** New
119	Do not offer aromatherapy to treat cognitive symptoms in people with Mild Cognitive Impairment.	**STRONG AGAINST** New
120	Consider art therapy to treat cognitive symptoms and improve depressive symptoms and anxiety in people with Mild Cognitive Impairment.	**WEAK IN FAVOR** New
121	Consider physical exercise to treat cognitive symptoms and promote independence in people with Mild Cognitive Impairment.	**WEAK IN FAVOR** New
122	Consider dance to treat of cognitive symptoms and improve depressive symptoms in people with Mild Cognitive Impairment.	**WEAK IN FAVOR** New
123	Consider games (e.g., cards, board games) to treat cognitive symptoms and improve depressive symptoms in people with Mild Cognitive Impairment.	**WEAK IN FAVOR** New
124	Consider cognitive rehabilitation to treat cognitive symptoms and promote independence in people with Mild Cognitive Impairment.	**WEAK IN FAVOR** New
125	Offer cognitive training to treat cognitive symptoms in people with Mild Cognitive Impairment.	**STRONG IN FAVOR** New
126	Do not offer specific formulas, including combinations of supplements containing omega 3 fatty acids, phospholipids, choline, uridine monophosphate, vitamin E, vitamin C, vitamin B6, vitamin B12, folic acid and selenium, supplements based on combinations of fatty acids polyunsaturated, such as omega-3 and omega-6, and monounsaturated and multivitamins and/or antioxidants supplements to treat cognitive symptoms in people with Mild Cognitive Impairment in absence of documented deficiencies.	**STRONG AGAINST** New
127	Do not offer ginkgo biloba, ginseng, omega 3, resveratrol or other antioxidants to treat cognitive symptoms in people with Mild Cognitive Impairment.	**STRONG AGAINST** New
128	Do not offer vitamin B and vitamin E supplements to treat cognitive symptoms in people with Mild Cognitive Impairment in absence of documented deficiencies.	**STRONG AGAINST** New
129	Do not offer ketogenic dietary interventions to treat cognitive symptoms in people with Mild Cognitive Impairment.	**STRONG AGAINST** New
130	Do not consider transcranial stimulation interventions to treat people with Mild Cognitive Impairment.	**WEAK AGAINST** New
131	Consider music therapy to treat cognitive symptoms and improve depressive symptoms and anxiety in people with Mild Cognitive Impairment.	**WEAK IN FAVOR** New

NON-COGNITIVE SYMPTOMS, INTERCURRENT ILLNESSES AND PALLIATIVE CARE

Management of non-cognitive symptoms in people with dementia

132	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).	**STRONG IN FAVOR** Adopted
133	As initial and ongoing management, offer psychosocial and environmental interventions to reduce distress in people living with dementia.	**STRONG IN FAVOR** Adapted
134	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.	**STRONG IN FAVOR** Adopted
135	For people living with dementia who experience agitation or aggression, offer personalised activities to promote engagement, pleasure and interest.	**STRONG IN FAVOR** Adopted
136	Consider interventions aimed at specifically training staff for the management of non-cognitive symptoms in people living with dementia.	**WEAK IN FAVOR** New
137	Consider providing access to therapeutic gardens for the management of non-cognitive symptoms in people living with dementia who experience BPSDs.	**WEAK IN FAVOR** New
138	Consider interventions of active and/or receptive music therapy for the management of non-cognitive symptoms in people living with dementia who experience BPSDs.	**WEAK IN FAVOR** New
139	Consider psychological treatments in people with mild to moderate dementia who experience mild to moderate depressive symptoms and/or anxiety.	**WEAK IN FAVOR** New
140	Consider the use of therapeutic robots in people with dementia who experience depressive symptoms, anxiety and/or agitation.	**WEAK IN FAVOR** New
141	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.	**WEAK IN FAVOR** Adopted
142	Before starting antipsychotics, discuss the benefits and harms with the person and their family members or caregivers (as appropriate). Consider using a decision aid to support this discussion.	**STRONG IN FAVOR** Adopted
143	When using antipsychotics: • use the lowest effective dose and use them for the shortest possible time; • reassess the person at least every four weeks, to check whether they still need medication.	**STRONG IN FAVOR** Adapted
144	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.	**STRONG IN FAVOR** Adopted
145	Stop treatment with antipsychotics: • if 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 caregivers (as appropriate).	**STRONG IN FAVOR** Adopted
146	Do not offer valproate to manage agitation or aggression in people living with dementia, unless it is indicated for another condition.	**STRONG AGAINST** Adopted

147	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.	**STRONG AGAINST** Adopted
148	Do not offer bupropion to manage depressive symptoms in people living with dementia.	**STRONG AGAINST** New
149	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 Table 6 in the Full Guideline. Be aware that interventions may need to be modified for people living with dementia.	**WEAK IN FAVOR** Adopted

Assessing intercurrent illness in people living with dementia

150	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.	**WEAK IN FAVOR** Adopted
151	For people living with dementia who are in pain, consider using a stepwise treatment protocol that balances pain management and potential adverse events.	**WEAK IN FAVOR** Adopted
152	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.	**STRONG IN FAVOR** Adopted

Treating intercurrent illness in people living with dementia

153	For managing the risk of falling for people living with dementia refer to the standard treatment for the prevention of falls (see Table 6 in the Full Guideline). When using this guidance: • 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.	**STRONG IN FAVOR** Adopted

Caring for people living with dementia who are admitted to hospital

154	Be aware of the increased risk of delirium in people living with dementia who are admitted to hospital. See Table 6 in the Full Guideline for interventions to identify and treat delirium.	**WEAK IN FAVOR** Adopted
155	In case of people with dementia admitted to hospital, ensure the availability of a multidimensional assessment, the monitoring and review of all pharmacological treatments, and the reconciliation of pharmacological treatment plans, and any possible issues related to safety, considering the involvement of a pharmacist or pharmacologist. For further indications on the optimization and reconciliation of pharmacological treatments see Table 7 in the Full Guideline and the recommendation on the reconciliation of pharmacological treatments provided by the Ministry of Health[77].	**STRONG IN FAVOR** New

[77] Ministero della Salute - D.G. Programmazione sanitaria. Raccomandazione n. 17 - Riconciliazione della terapia farmacologica. Available at: https://www.salute.gov.it/portale/sicurezzaCure/dettaglioPubblicazioniSicurezzaCure.jsp?id=2354 (Last visited: 30/08/2023).

156	Consider the involvement of a multidisciplinary team in case of people with dementia admitted to hospital to ensure personalized interventions based on a multidimensional assessment of their overall health, including their nutritional status.	**WEAK IN FAVOR** New

Palliative care

157	From diagnosis, offer people living with dementia flexible, needs-based palliative care that takes into account how unpredictable dementia progression can be.	**STRONG IN FAVOR** Adopted
158	Encourage and support people living with dementia to eat and drink, taking into account their nutritional needs.	**STRONG IN FAVOR** Adopted
159	Consider involving a speech and language therapist if there are concerns about a person's safety when eating and drinking.	**WEAK IN FAVOR** Adopted
160	Do not routinely use enteral feeding in people living with severe dementia, unless indicated for a potentially reversible comorbidity.	**STRONG AGAINST** Adopted
161	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.	**STRONG IN FAVOR** Adopted
162	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.	**STRONG IN FAVOR** Adopted
163	For standards and measures on palliative care, see Table 10 in the Full Guideline.	**STRONG IN FAVOR** Adopted
164	For guidance on care for people in the last days of life, see Table 11 in the Full Guideline.	**STRONG IN FAVOR** Adopted
165	For guidance, on best interest decision-making, see Table 12 in the Full Guideline.	**STRONG IN FAVOR** Adopted
166	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.	**WEAK IN FAVOR** Adopted
167	Consider using a structured tool to assess the likes and dislikes, routines and personal history of a person living with dementia.	**WEAK IN FAVOR** Adopted

Research recommendations

IDENTIFICATION, DIAGNOSIS AND POST-DIAGNOSTIC SUPPORT

Case finding for people at high risk of dementia

1R	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?	Adopted

Diagnosis and differential diagnosis of dementia and Mild Cognitive Impairment

2R	What is the utility and cost effectiveness of amyloid PET imaging as an additional test to support the diagnosis of Alzheimer's disease and other dementias when compared with standard diagnostic procedures and other imaging or biomarker tests?	Adapted
3R	What is the utility of plasma biomarkers as additional tests to support the diagnosis of Alzheimer's disease and other dementias when compared with standard diagnostic procedures and other imaging or biomarker tests?	New
4R	What is the utility of biomarkers within the diagnostic process, and for the differential diagnosis and prognosis of MCI?	New

Drugs that may worsen cognitive decline

5R	Does actively reducing anticholinergic burden in people living with dementia or Mild Cognitive Impairment improve cognitive outcomes compared with usual care?	Adopted

Distinguishing dementia from dementia with delirium or delirium alone

6R	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?	Adopted
7R	What is the accuracy of 4-A's Test (4AT) and Confusion Assessment Method (CAM) in distinguishing people with delirium or delirium superimposed on dementia from dementia alone in a primary care setting or in a residential care setting?	New

CARE MODELS AND COORDINATION OF CARE

Care planning, review and coordination

8R	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?	Adopted
9R	What are the most effective methods of care planning for people in residential care settings?	Adopted
10R	What are the most effective methods of care planning for people who do not have regular contact with an informal carer?	Adopted

Post diagnosis review for people living with dementia

11R	What is the effectiveness of telemedicine interventions for the post diagnosis review of people with dementia?	New
12R	What is the effectiveness of an interdisciplinary review from general practitioners in collaboration with other healthcare professionals in assessing for interventions for any emerging dementia-related needs?	New

Staff training

13R	What is the cost effectiveness of implementing a dementia-specific addition to training for community staff, including dementia-specific elements on managing anxiety, communication, nutritional status, personal care, and environment adaptation?	Adapted
14R	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?	Adopted

Managing mental health conditions alongside dementia/Mild Cognitive Impairment

15R	What are the optimal management strategies for people with enduring mental health problems (including schizophrenia and other psychotic disorders) who subsequently develop dementia or Mild Cognitive Impairment?	Adapted

Supporting caregivers of people with dementia

16R	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?	Adopted

PHARMACOLOGICAL TREATMENTS FOR COGNITIVE SYMPTOMS

Acetylcholinesterase inhibitors and memantine in people with Mild Cognitive Impairment

17R	What is the efficacy of AChE inhibitors and memantine for the treatment of the different subtypes of Mild Cognitive Impairment?	New

Biological drugs in people with Alzheimer's dementia and mild cognitive impairment

18R	What is the safety and efficacy of monoclonal antibodies targeted to the different forms of amyloid β for the treatment of Alzheimer's dementia or Mild Cognitive Impairment in terms of: • long-term safety and efficacy (e.g., ARIA events), • generalizability of results (e.g., interactions with other treatments for comorbidities), • choice of outcomes proving the clinical relevance of treatment effects?	New

Acetylcholinesterase inhibitors for the treatment of DLB

19R	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?	Adopted

NON-PHARMACOLOGICAL INTERVENTIONS FOR COGNITIVE SYMPTOMS

Non-pharmacological interventions for cognitive symptoms in dementia

20R	What is the effectiveness of art therapy for improving cognition in people with dementia?	New
21R	What is the effectiveness of dance for improving cognition in people with dementia?	New
22R	What is the effectiveness of pet therapy for improving cognition in people with dementia?	New
23R	What is the effectiveness of cognitive training for improving cognition in people with moderate Alzheimer's dementia or other types of dementia?	New
24R	What is the effectiveness of interventions targeted at promoting cognitive, communication, and linguistic abilities in people with dementia?	New

Non-pharmacological interventions for cognitive symptoms in Mild Cognitive Impairment

25R	What is the effectiveness of specific memory interventions for the treatment of people with Mild Cognitive Impairment?	New
26R	What is the effectiveness of transcranial stimulation for the treatment of people with Mild Cognitive Impairment?	New
27R	What is the effectiveness of psychosocial interventions for the treatment of people with Mild Cognitive Impairment?	New
28R	What is the effectiveness of rehabilitative interventions based on serious games or virtual reality for improving cognition in people with Mild Cognitive Impairment?	New
29R	What is the effectiveness of interventions targeted at promoting cognitive, communication, and linguistic abilities in people with Mild Cognitive Impairment?	New

NON-COGNITIVE SYMPTOMS, INTERCURRENT ILLNESSES AND PALLIATIVE CARE

Treating non-cognitive symptoms in people with dementia

30R	What is the effectiveness and safety of citalopram for managing depressive symptoms in people living with dementia?	New
31R	What is the effectiveness and safety of vortioxetine for managing depressive symptoms in people living with dementia?	New
32R	What is the effectiveness of pharmacological treatments for managing sleep disorders in people living with dementia?	Adapted
33R	What is the effectiveness and cost-effectiveness of dextromethorphan-quinidine for managing agitation in people living with dementia?	Adopted
34R	What is the effectiveness and cost-effectiveness of choline alphoscerate for managing apathy in people living with dementia?	Adopted
35R	What is the effectiveness of aromatherapy in people living with dementia experiencing agitation or aggression?	New
36R	What is the utility of physical exercise in people living with dementia experiencing depressive symptoms, agitation or apathy?	New
37R	What are the most effective psychological treatments for managing depression or anxiety in people living with dementia at each stage of the condition?	Adopted

Palliative care

38R	What are the most effective models of general and specialist palliative care support to meet the needs of people with advanced dementia?	Adopted
39R	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?	Adapted

APPENDIX

Glossary

4 A's test (4AT): Screening tool designed for the rapid assessment of delirium and cognitive impairment. Scores > 4 suggest the presence of delirium. However, a more comprehensive assessment of mental status is required to obtain the diagnosis. Scores ranging from 1 to 3 suggest cognitive impairment and require a more comprehensive assessment of cognitive status along with an additional interview with family members or caregivers. A score of 0 does not categorically rule out the presence of delirium or cognitive impairment. Items 1-3 are evaluated solely based on observation at the time of assessment. Item 4 requires information from one or more sources (nurses, other staff members, general practitioner, family member/caregiver, etc.).

5-word test: It consists of five words presented to the person. The person needs to memorize and repeat the words in the same order they were presented to them. Presented words have a difficulty ranging from simplest to the complex. An interference test can be used before asking to repeat the five words.

6-item Cognitive Impairment Test (6-CIT): rapid test to assess cognitive status. It requires less than 5 minutes. It consists of 3 orientation items: counting backwards starting from 20, listing the months of the year in backwards, and memorising an address.

6-item Screener (6-IS): developed to be administered in person or by phone, it is useful for clinicians or researchers who need a rapid and accurate screening test for cognitive decline. It consists of three questions for temporal orientation (year, month, and day of the week) and three-word recall. Each correct answer is scored one point, for a maximum score of 6 points. Two or more mistakes are considered a high risk of cognitive impairment.

10-point Cognitive Screener (10-CS): it consists of three questions for temporal orientation (year, month, and date), a three-word recall, and an animal naming task with a four-point scale. Each correct answer for temporal orientation questions and word recall is scored one point, while scores for the animal naming tasks range from zero points for 0-5 remembered animals to four points for 15 or more remembered animals. Scores ≥ 8 are normal, scores ranging from 6 to 7 suggest possible cognitive impairment, and scores ranging from 0 to 5 suggest probable cognitive impairment.

11C-Pittsburgh compound B (11C-PiB): radioactive analog of thioflavin T used only for research purposes in PET as a tracer of amyloid β plaques in neuronal tissues. It is largely used in studies on Alzheimer's dementia. Other radiotracers labelled with fluoride (florbetaben and flutemetamol) are approved for the same purpose in amyloid PET.

95% Confidence Interval (95% CI): range of values accompaning an estimate and providing an indication of its accuracy. Indicates the level of confidence that the interval obtained for the estimate includes the true value.

^{99}mTc-hexamethyl propylene amine oxime (^{99}m Tc-HMPAO): gamma-emitting tracer used in SPECT to analyse cerebral blood flow.

^{99}mTc-ethyl-cysteinate-dimer (^{99}mTc-ECD): neutral lipophilic agent, which passively diffuses across the blood-brain barrier as the ^{99}mTc-HMPAO. These agents are distributed proportionally to blood flow, providing a representation of regional cerebral perfusion.

[^{123}I]FP-CIT (DaTSCAN) SPECT: Single Photon Emission Computed Tomography (SPECT) con ^{123}I-ioflupan (ioflupane labelled with iodine-123, a radioactive form of iodine) is a nuclear medicine test consisting in acquiring images of the brain three hours after the administration of the radiopharmaceutical, which reversibly binds the presynaptic transporter of dopamine at the nerve endings in the neurons of the striatum that are responsible for transporting the neurotransmitter. This test allows to evaluate the functionality of the nigrostriatal dopaminergic circuit, which is characteristically altered in Parkinson's disease and in other primary degenerative parkinsonisms that share the neuropathological alteration of this circuit. Specifically, this method supports the differential diagnosis between Parkinson's disease and essential tremor or forms of secondary parkinsonism where the functional integrity at the level of the striatum is preserved, and the differential diagnosis between dementia with Lewy bodies and other forms of dementia, such as Alzheimer's dementia.

Abbey Pain Scale for people with dementia (APS): tool designed to support pain assessment in people who have lost the ability to verbally express their needs, such as people with dementia or with cognitive or communication disorders. Higer scores indicate higher levels of pain (range 0-14).

Abbreviated Mental Test (AMT): screening test developed in 1972. Its use is currently limited as it is considered to have low sensitivity because its results could potentially be confused with poor intellect, age, social class, hearing sensitivity, and a history of stroke. Lower scores indicate impairment of cognitive functions (range 0-10).

Acetylcholinesterase inhibitors (AChEI): including donepezil, galantamine, and rivastigmine. They are the only currently available medications for the treatment of cognitive symptoms in Alzheimer's dementia.

Activities of Daily Living (ADL): six-item scale for the assessment of the level of depencency in performing activities of daily living. Lower scores indicate higher dependency (range 0-10).

AD8 Dementia Screening Interview (AD8): test developed as a brief and easy-to-use tool to distinguish the signs of normal ageing from symptoms of mild dementia. It consists of 8 items assessing memory, orientation, judgment, and functioning. The scale cut-offs are the folloging: normal 0-1; impairment of cognitive abilities ≥ 2. This test assesses intra-individual changes in some cognitive domains compared to previous levels of functioning and is sensitive to early signs of dementia, irrespective of its causes.

Addenbrooke's Cognitive Examination – Revised (ACE-R): test developed to distinguish Mild Cognitive Impairment from cognitive changes typical of normal aging and from the different subtypes of dementia. This test was then revised (ACE-R) and abbreviated versions were also developed (Mini-ACE). It is a brief cognitive battery (15-20 minutes) including the MMSE along with other tasks allowing to calculate five subscores, each for one single cognitive domain including attention/orientation; memory; fluence; language; visuo-spatial skills. Lower scores indicate higher impairment of cognitive functions (range 0-100).

Advance care planning: a document designed within the relationship between patient and physician relating to the evolution of the consequences of a chronic and disabling disease, or of a disease characterised by an unstoppable evolution and a poor prognosis. Patients and, with their consent, their family members or a trusted person are adequately informed about the possible evolution of the disease, about what patients can realistically expect in terms of quality of life, about the clinical opportunities of interventions, and about palliative care. Patients expresses their consent on what the physician proposes and their intentions for future care, including the opportunity of appointing a power of attorney. In case of people who are unable to give their consent, physicians and the healthcare team are required to comply with the wishes expressed in the advanced care plan. [78]

Advance healthcare directives: document in which an adult, capable, person can exopress their wishes and preferences about health care interventions, as well as agreeing to or refusing diagnostic tests or treatments, before they are no longer capable to make decisions for themselves. The document identifies a trusted person, defined as "power of attorney" who can make decision n their behalf and represent them in the relations with the physicians and health facilities.[79]

Agitated Behaviors Mapping Instrument (ABMI): tool to assess agitation and environmental conditions in residential facilities including the direct observation of behaviors indicative of physical and verbal/vocal agitation. Higher score values indicate a higher frequency of agitated behaviours (range 0-140).

Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog): tool aimed at assessing the severity of cognitive symptoms in people with dementia. Higher score values indicate higher impairment of cognitive functions (range 0-70).

Alzheimer's Disease Assessment Scale-Cognitive Subscale-11 item (ADAS-Cog11): cognitive efficiency test based on the performance in nine cognitive tests: impairment and comprehension of spoken language, recall of instructions, difficulty in word retrieval, orders, the naming of objects and fingers, constructional praxia, ideational praxia, orientation. It also includes two tasks of immediate word recall and recognition. Higher scores indicate higher impairment of cognitive functions (range 0-70).

Alzheimer's Disease Assessment Scale-Cognitive Subscale-13 item (ADAS-Cog13): test including all items of the ADAS-Cog-11 along with a delayed word recall test, and a number cancellation task or a maze task. Higher scores indicate higher impairment of cognitive functions (range 0-85).

Alzheimer's Disease Composite Score (ADCOMS): tool including four items from the ADAS-Cog, two items from the MMSE, and six items from the CDR-SB. Higher scores indicate higher impairment of cognitive functions (range 0-1.97).

Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale (ADCS-ADL): 23-item scale with 6 items assessing basic activities of daily living (BADL) and 17 items assessing instrumental activities of daily living (IADL). Lower scores indicate higher severity (range 0-78).

[78] Source: Law 22 December 2017, no. 2019, art. 5 para 1. Available at: https://www.gazzettaufficiale.it/eli/id/2018/1/16/18G00006/sg (Last visited: 30/08/2023)
[79] Source: Law 22 December 2017, no. 219, art. 4 para 1. Available at: https://www.gazzettaufficiale.it/eli/id/2018/1/16/18G00006/sg (Last visited: 30/08/2023).

Alzheimer's Disease Cooperative Study-Clinical Global Impression Clinician Rated (ADCS-CGIC): tool for the assessment of the global cognitive, functional, and behavioural performance of people with Alzheimer's dementia. Higher scores indicate to higher severity (range 1-7).

Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC) Criteria: criteria for the diagnosis of ischemic vascular dementia published by the Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC) of California (United States).

Alzheimer's Disease Related Quality of Life (ADRQL/ADRQoL): multidimensional tool for the assessment of health-related quality of life in people with Alzheimer's dementia and other cognitive disorders. Higher scores indicate better quality of life (range 1-100).

Alzheimer's Disease (AD) Scale: 17-item tool used for the identification, diagnosis, and differential diagnosis of Alzheimer's dementia. Higher scores indicate a higher probability of disease (range 1-17).

Amyloid-Related Imaging Abnormalities (ARIA): abnormalities detectable with nuclear magnetic resonance imaging in the brain of people with Alzheimer's dementia. ARIA events were first characterised in people receiving treatment with monoclonal antibodies targeted against amyloid β (Aβ). ARIA events can occur in as ARIA with oedema (ARIA-E) or ARIA with microhaemorrhage (ARIA-H). These events have a high incidence in people receiving monoclonal antibodies, especially aducanumab, donanemab, and lecanemab, and mainly occur in ApoE ε4 carriers.

Amyloid PET: nuclear investigation using radiotracers (PiB, flutemetamol, florbetaben) able to identify the presence of amyloid plaques in brain tissues. It is a test used mainly to support the diagnosis of Alzheimer's dementia and Mild Cognitive Impairment due to Alzheimer's dementia.

Amyloid Precursor Protein (APP): a transmembrane protein known to be the precursor of amyloid β, a protein thought to be the neuropathological hallmark of Alzheimer's dementia.

Anticholinergic Cognitive Burden Scale (ACB): cholinergic burden is the cumulative effect on person taking one or more drugs with anticholinergic activity. The ACB classifies anticholinergic activity with a score ranging from 0 (drugs without anticholinergic activity) to 3 (drugs with high anticholinergic activity). ACB scores ≥ 3 may increase the risk of cognitive decline, functional decline, falls, and death in older adults.

Anticholinergic Loading Scale (ACL): tool developed based on expert consensus and aimed at classifying drugs with anticholinergic properties in levels ranging from 0 (no known anticholinergic activity) up to 3 (high anticholinergic activity).

Anticholinergic Risk Scale (ARS): tool aimed at classifying drugs according to their anticholinergic potential on a three-point scale (0, no risk or low risk; 3, high anticholinergic potential). Each person's ARS score is the sum of of the scores related to the number of medications they take.

Apathy Evaluation Scale (AES): Semi-structured test that quantitatively assesses general apathy and its cognitive, emotional and behavioural aspects. It consists of 18 questions, with a 4-point scale ranging from 1 (not at all) to 4 (very much). AES scores on range from 18 to 72. Lower scores indicate apathy (range 18-72).

Applause sign (AS): The test requires the examiner to ask the person to applaude with their hands three times. Three applauses correspond to a score of 3 (normal), 4 applauses to a score of 2 (abnormal), 5-10 applauses to a score of 1 (abnormal), > 10 applauses to a score of 0 (abnormal). The test was first used in people with progressive supranuclear palsy, and has since been used in other neurodegenerative conditions, including parkinsonisms (Parkinson's disease and Lewy body dementia), corticobasal degeneration and other dementia subtypes including frontotemporal dementia and Alzheimer's dementia. The test may indicate an alteration in basal ganglia, which are structures involved in voluntary movements.

Artificial hydration and/or nutrition (AHN): medical treatments that allows people to receive nutrition and hydration when they are no longer able to take them by mouth. These treatments are only provided to people who are no longer able eat and drink enough to ensure survival.

Attention Test (AT): vigilance test which consisting in pronouncing a sequence of letters ('S-A-V-E-A-H-A-A-R-T') and requesting participants to note whenever they hear an 'A'. Higher scores indicate better performance (range 0-4).

Barthel Index (BI): tool for the assessment of dependency, specifically the degree of assistance required by the person in 10 items related to mobility and personal care. Lower scores indicate higher dependency (range 0-100).

Basic Activities of Daily Living (BADL): tool aimed at assessing the degree of dependency in performing specific basic activities of daily living such as personal care, mobility, and eating. Higher scores indicate higher dependency (range0-6).

Bayer Activities of Daily Living (B-ADL): 25-item questionnaire, administered by the interviewer, developed as a brief tool for the assessment of functional disabilities. Its target population are people with neurocognitive disorders. Higher scores indicate higher disability (range 25-250).

Beck Anxiety Inventory (BAI): self- Self-administered tool consisting of 21 questions to measure the severity of anxiety. Higher scores indicate higher levels of anxiety (range 0-63).

Beck Depression Inventory (BDI): self-administered tool consisting of 21 questions used to measure the severity of depressive symptoms. Higher scores indicate higher severity of depressive symptoms (range 0-63).

Behavioural Assessment Scale of Later Life (BASOLL): composite tool for the identification of behavioural problems and symptoms in older people aimed at alerting healthcare professionals of the need for a specialist assessment. Lower scores indicate fewer behavioral problems (range 0-105).

Behavioural Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD): tool used to identify and assess potentially treatable behavioural symptoms in people with Alzheimer's dementia. Higher scores indicate lower symptom severity (range 0-36).

Berg Balance Scale (BBS): tool for the objective assessment of the person's ability to maintain balance safely during a predefined set of tasks. Higher scores indicate a higher level of ability to maintain balance (range 0-56).

Berlin Inventory of Caregivers' Burden with Dementia Patients (BIZA-D): tool for the subjective and objective assessment of the burden of informal caregivers of people with dementia. Lower scores indicate lower burden (range 0-16).

β amiloide (Aβ): peptide that can be made of 36 to 43 amino acids. It is produced when beta- and gamma-secretase cuts the amyloid β precursor protein (APP). Aβ is the main component of extracellular amyloid plaques in the brain, which are considered as one of the main factors underlying the etiopathogenesis of Alzheimer's dementia.

Bias: systematic error in the process of designing a study or collecting, analysing, interpreting, or publishing data, leading to a distortion in the results or conclusions of the study.

Body Mass Index (BMI): is the reference indicator for epidemiological and screening studies on obesity. It should be noted that BMI, being an indicator for population studies, is not capable to assess the actual body composition, and it does not allow knowing body fat distribution.

Boston Naming Test (BNT): 60-item test based on figures with a degree of difficulty ranging from simple to complex. It is a useful tool for measuring word retrieval in people with aphasia or other stroke-related language disorders, Alzheimer's dementia, or other dementia-related disorders. Short versions of the BNT are also available. This type of test is also used to assess learning disabilities in children and adults with brain injuries.

Brief Agitation Rating Scale (BARS): 10-item tool used to assess agitation in institutionalized people based on the presence and frequency of behaviours indicative of agitation or physical and verbal aggression. Higher scores indicate a higher level of agitation (range 10-70).

Brief Neuropsychological Test Battery (BNTB): tool consisting of tests for logical memory, clock drawing, digit span, semantic fluency, and the MMSE used for the diagnosis of Mild Cognitive Impairment and dementia.

Brief Psychiatric Rating Scale (BPRS): tool used to assess psychopathological symptoms in people with psychotic disorders. Higher scores indicate higher symptom severity (range 18-126).

Brief Symptom Inventory (BSI): tool to assess the presence, intensity, and frequency of psychopathological symptoms and distress. Higher scores indicate higher frequency and severity of symptoms (range 0-212).

Bristol Activities of Daily Living Scale (BADLS): 20-item tool used to assess the level of dependency in performing ADL in people with dementia. Higher scores indicate dependency (range 0-60).

Burden: level of stress or physical and emotional burden perceived by a person caring for another person who is elderly or has a chronic condition or disability.

Burden Scale for Family Caregivers (BSFC): tool designed to assess the subjective burden perceived by informal caregivers. Higher scores indicate higher perceived load (range 0-30).

California Verbal Learning Test (CVLT): one of the most frequently used neuropsychological tests to assess memory and episodic verbal learning.

Cambridge Cognition Examination (CAMCOG): standardized tool used to measure the severity of dementia and to assess the level of cognitive impairment. The tool measures orientation, language, memory, praxis, attention, abstract thinking, perception, and calculation. Administering the scale takes around 20 to 30 minutes. Lower scores indicate higher impairment of cognitive functions (range 0-107).

Canadian Occupational Performance Measure (COPM): questionnaire used to measure people's perception of the importance, performance, and satisfaction in relation to their occupational problems. Higher scores indicate better performance and higher levels of importance and satisfaction.

Care pathway: diagnostic or management path. The objective is to provide a methodology for organising the management of a defined group of patients in a defined period of time.

Caregiver Perceived Stress Scale (CPSS): tool used to measure individual levels of perceived stress. Higher scores indicate a higher level of perceived stress (range 0-40).

Caregiver Burden Inventory (CBI): tool to measure the caregiver's perceived support load. It consists of 24 items assessed via a 5-point scale, and higher scores indicate a higher perceived care burden (range 0-96).

Caregiver Self-Efficacy Scale (CSES): tool measuring self-efficacy in care management (4 items, range 4-40) and self-efficacy in service use (5 items, range 5-50). Higher scores in CSES indicate higher levels of self-efficacy.

Caregiver Strain Scale (CSS): 41-item tool used to assess the frequency of specific behaviours and the impact of these behaviours on caregivers. Higher scores indicate a higher level of caregivers' stress ('strain') (range 0-164).

Case conferencing: formal, planned and structured method for the clinical discussion of each individual case, aimed at providing coordinated and integrated services reducing variability and inappropriateness.

Center for Epidemiologic Studies Depression Scale (CES-D): self-administered scale used to assess depressive symptoms. Higher scores indicate higher frequency and severity of symptoms (range 0-60).

Centres for Cognitive Disorders and Dementia (CDCD): specialised centers focused on the prevention, diagnosis and treatment of people with dementia.

Cerebral Autosomal Dominant Arteriopathy with Sub-cortical Infarcts and Leukoencephalopathy (CADASIL): rare genetic disorder with high penetrance characterised by the occlusion of cerebral arterioles, causing recurrent ischemic strokes. The etiology of this disease, whose most common symptomatology is stroke, is likely attributable to a mutation in the NOTCH3 gene.

Cerebrospinal fluid (CSF): clear and colourless fluid present in the cerebral ventricles, in the subarachnoid spaces of the meninges, and in the dural sac of the spinal cord. It has several important biological functions, both mechanical by protecting the delicate structures of the central nervous system, and metabolic by acting as a vehicle for various nutrients and for the byproducts of catabolism of the nervous tissue. The analysis of the alteration of certain proteins within the CSF can be useful in the diagnosis or differential diagnosis of different neurodegenerative diseases.

Challenging Behaviour Scale (CBS): 25-item tool that identifies the incidence, frequency, and severity of behaviours that nursing home staff finds difficult to manage. Higher scores indigate higher levels of behavioural problems (range 0-400).

Chinese Version of the Verbal Learning Test (CVVLT): Chinese version of the California Verbal Learning Test (see CVLT).

Clearance: parameter indicating how efficient is the elimination of a substance from the body.

Clinical Dementia Rating (CDR): tool used to assess the stage of dementia consisting of six areas: memory, orientation, judgment and problem-solving, community affairs, home and hobbies, and personal care. The scores from each area are combined to form a final composite score. Higher scores indicate higher impairment of cognitive functions.

Clinical Dementia Rating-Sum of Boxes (CDR-SB): scale used to assess dementia severity. Unlike the CDR scale, it is more sensitive to changes over time. Higher scores indicate higher impairment of cognitive function (range 0-18).

Clinical Global Impression (CGI): scale used to assess disease severity (CGI-S) and global improvement or change (change, CGI-C). This scale does not provide a global score but separate scores for CGI-S (range 1-7) and CGI-C (range 1-7) with higher scores indicating more severe worsening.

Clinical Global Impression of Change (CGIC): tool used to determine the level of change in terms of clinician-perceived improvement or worsening in specific clinical or global patient outcomes. Higher scores idicate higher improvement (range -5 – 5).

Clinician's rated Anticholinergic Scale: tool used to quantify the potential anticholinergic effects of each investigated drug.

Clock Drawing Test (CDT): test that allows the overall assessment of executive functions, praxic-constructive skills and visuospatial skills. It consists of correctly drawing the time of 11:10 a.m. on a pre-printed sheet. The test can identify visual-constructive deficits, visuospatial deficits, altered mental representation, and deficits in executive functions. This test is also included in neuropsychological tests such as MoCA and ACE-R. The score of the Clock Drawing Test is calculated considering the items referring to: outline, numbers, hands, centre. The maximum score is 61. Scores are adjusted for age in subjects aged 20 to 89 years, and for years of education ranging from 5 to over 13.

Cognitive Test for Delirium (CTD): tool specially designed to assess the presence of delirium in hospitalized people, specifically in hospitalized people who are unable to speak and write. Higher scores indicate better cognitive function (range 0-30).

Cohen-Mansfield Agitation Inventory (CMAI): scale used for the assessment of the frequency of episodes of physical aggression and agitation in people with dementia. Higher scores indicate higher frequency of symptoms (range 29-203).

Comfort Assessment in Dying with Dementia (CAD- EOLD): scale used to assess end-of-life quality. Higher scores indicate higher intensity of symptoms (range 14-24).

Comprehensive Assessment of Prospective Memory (CAPM): self-administered scale used to measure the loss of prospective memory in relation to activities of daily living. Lower scores indicate a lower frequency of memory loss (range 1-5).

Computed Tomography (CT): diagnostic imaging technique based on obtaining croiss-sectional or three-dimensional images by combining of a series of X-ray scans through a computerised analysis.

Confidence in the Evidence from Reviews of Qualitative Research (CERQual): approach for the systematic and transparent assessment of the certainty of evidence from qualitative studies.

Confounders (residual): presence of potential confounders, not included among those considered in the analyses carried out within the published study, which are believed to have led to an underestimation of the effect reported by study results.

Confusion Assessment Method (CAM): standard tool used to identify the presence of delirium in clinical and research settings and to determine the severity of symptoms (CAM-severity). Higher scores indicate higher symptom severity (range 0-19).

Consortium to Establish a Registry for Alzheimer's Disease (CERAD): consortium established in 1986 by a grant from the National Institute of Aging (NIA) to standardise the procedures for the assessment and diagnosis in people with Alzheimer's dementia.

Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery: battery of neuropsychological tests aimed at assessing cognitive functions in people with Alzheimer's dementia. Higher scores indicate better cognitive function (range 0-100).

Coping: term used to define the strategies that each person adopts to face and manage problems and difficulties.

Cornell Scale for Depression in Dementia (CSDD): tool specifically used to assess the signs and symptoms of major depression in people with dementia. Higher scores indicate higher severity of depressive symptoms (range 0-38).

COVID-19: respiratory infectious disease caused by the SARS-CoV-2 virus of the family of coronaviruses.

Critical Appraisal Skills Programme (CASP): international program aimed at supporting the dissemination and implementation of Evidence Based Medicine (EBM), which provides checklists for the structured assessment of the quality and certainty of evidence.

Decisional Conflict Scale (DCS): tool to assess the level of decisional conflict defined as the perceived uncertainty about choosing options, factors contributing to uncertainty and satisfaction with the choice. Higher scores indicate higher decisional conflict (range 0-100).

Delirium Rating Scale (DRS): tool adopted by specialists or specially trained personnel to measure symptoms of delirium. Higher scores indicate higher symptom severity (range 0-32).

Delirium Rating Scale Revised 98 (DRS-R98): tool used to assess the presence and severity of symptoms of delirium. Higher scores indicate higher symptom severity (range 0-46).

Delirium Severity Scale (DSS): scale measuring the level of severity of delirium based on 17 items. Higher scores indicate more severe delirium (range 0-21).

DEMentia Digital Interactive Social Chart (DEM-DISC): digital tool aimed at providing personalized information about the diagnostic process, management and support of dementia.

Dem-QoL: 28-item scale used to assess health-related quality of life in people with dementia, considering their cognitive status, positive and negative emotions, social relationships, and loneliness. Higher scores indicate better quality of life (range 28-112).

Detection Rate: proportion of people with a specific condition reporting a positive result at a diagnostic test.

Diagnostic and Statistical Manual of mental disorders (DSM): nosographic system developed by the American Psychiatric Association for mental or psychopathological disorders. It is one the most widely used tools by psychiatrists, psychologists and physicians, both in clinical practice and for research purposes. The most recent version is the DSM-5-TR. **Diagnostic impact:** effect size of a diagnostic test or a diagnostic strategy (e.g. sequential testing).

Digit span test: test measuring verbal and working memory. People are required to recall a sequence of numbers that they see or hear in the same order as they are presented or opposite order. After each correctly repeated sequence, a new sequence including one more number is proposed.

Distress: state of intense mental or physical distress, such as extreme levels of anxiety, sadness, or grief, accompanied by the inability to cope with it.

Dose-response gradient: or biological gradient, when a higher exposure results in a higher likelihood of outcome (e.g., in case of drug treatments, increading the drug dose increases the magnitude of the effect).

Double-blind: experimental study, most commonly pharmacological, in which both participants and investigators are blind to treatment allocation, to avoid any influence of knowing this information on investigators' behaviours and participants' response to treatment.

Edinburgh Feeding Evaluation in Dementia (EdFED): screening tool to assess feeding difficulties in people with dementia. Higher scores indicate higher symptom severity (range 0-20).

Electroencephalography (EEG): instrumental examination consisting in recording and studying the electrical activity of the brain using electrodes.

Epworth Sleepiness Scale (ESS): self-administered questionnaire used to assess the presence and severity of sleep disorders. Higher scores indicating higher severity of sleep disorders (range 0-24).

EQ-5D/Euro-QoL/EuroQoL-5D: standardised questionnaire used to measure health-related quality of life. Higher scores indicate better quality of life (range 0-100).

Essential Levels of Care (ELC): services that the National Health System is required to provide to all citizens, free of charge or upon payment of a contribution (ticket), with public resources collected through the tax system.

European Medicines Agency (EMA): the regulatory agency that ensures the scientific evaluation, supervision and control of the safety of medicinal products for human and veterinary use in the European Union.[80]

European Pathway Association (EPA): an international non-profit organisation that gathers different care networks, user groups, academic institutions, support organisations, and people who wish to support the development, implementation, and evaluation of clinical/care pathways.

Evidence-Based Medicine (EBM): the conscious and contextualised use of the best available scientific evidence as a basis for clinical decision-making.[81] The goal of EBMs is to integrate the best scientific evidence, clinical experience, and patient values and preferences to guide clinical decision-making.

Expert Clinician Pain Intensity Rating (ECPIR): pain assessment performed by specialised clinicians through a multidimensional assessment based on a standardised protocol.

Facilitated Case Conferencing (FCC): case conferencing implemented with the participation of a facilitator.

Family Confusion Assessment Method (FAM-CAM): tool based on the CAM scale and optimised to be administered to family members and caregivers to assess the presence of symptoms of delirium in people in different care settings.

Family Perception of Care Scale (FPCS): tool assessing informal caregivers' perception of the care provided to their family members during their last four weeks of life. It includes 25 items rated using a 7-point Likert scale. Higher total scores indicate higher satisfaction with care.

Fluorodeoxyglucose (^{18}F-FDG): 18F-labeled glucose analog used as a tracer for PET imaging in several fields, including oncology, cardiology, and neurology. In neurology is used for dementias and neurodegenerative diseases for the identification of regions with abnormal glucose metabolism.

Food and Drug Administration (FDA): the government agency that is responsible for the regulation of food and drugs for human and veterinary consuption in the United States of America.

Free recall score of 5-word test: test assessing episodic verbal memory through free immediate and delayed recall. It consists of five items that are also used to control the learning of the five words and to facilitate their retrieval if free recall is incomplete. (range 0-10).

Frontal Assessment Battery (FAB): brief tool used for the differential diagnosis between dementias with dysexecutive frontal phenotype and Alzheimer's dementia in a clinical setting. Higher scores indicate better performance (range 0-18).

Frontal Systems Behavior Scale (FrSBe): brief tool used to measure three behavioural disorders (apathy, disinhibition, and executive dysfunction), aimed at quantifying behavioural changes over time.

[80] Source: European Medicines Agency (EMA). Available at: https://www.ema.europa.eu/en/homepage (Last visited: 30/08/2023)
[81] Sackett DL, Rosenberg WM, Gray JA et al. Evidence based medicine: what it is and what it isn't. BMJ 1996; 312(7023): 71-2.

FTD Scale: 17-item tool to support the identification, diagnosis, and differential diagnosis of frontotemporal dementia.

Functional Activities Questionnaire (FAQ): test that measures Instrumental Activities of Daily Living (IADLs) such as preparing a meal or managing finances. Useful to monitor these functional changes over time. The FAQ questionnaire can be used to distinguish people with Mild Cognitive Impairment from those with mild Alzheimer's dementia. The test consists of 10 tasks with a score ranging from 3 'fully dependent' to 0 'normal'. A score of 3 on at least three tasks is indicative of cognitive decline. Higher scores indicate higher impairment of cognitive functions (range 0-30).

General Health Questionnaire (GHQ): tool consisting of 30, 28 or 12 items used to assess, based on a Likert scale ranging from 0 to 3, the severity of mental disorders suring the two weeks prior to the administration of the test. Higher scores indicate worse mental condition.

General Perceived Self-Efficacy Scale (GPSE): self-administered tool assessing individual perception of self-efficacy. It consists of 10 items that are assessed based on a scale ranging from 1 to 4. Higher scores indicate higher self-efficacy (range 10-40).

General Practitioner (GP): health professional operating in an agreement with the NHS chosen the citizen. They provide primary care in their medical office, at home, and in nursing homes. GPs are responsible for delivering integrated and continuous care to every person requiring medical care.

General Practitioner assessment of Cognition (GPCOG): brief tool for the assessment of cognitive impairment. It was developed for primary care medicine, including general practitioners. It is an easy-to-use test requiring a short time to be administered, approximately four minutes for people with suspected cognitive decline and two minutes for their family members/caregivers. Lower scores indicate higher impairment of cognitive functions (range 0-15).

Geriatric Depression Scale (GDS): 30-item or 15-item (GDS-15 short form) screening tool used to identify the presence and severity of depressive symptoms. Higher scores indicate higher frequency and severity of depressive symptoms (range 0-15).

Neurofibrillary tangle (NFT): abnormal accumulations of hyperphosphorylated Tau protein in the brain.

Guidelines International Network (GIN): network of organisations and individual entities interested in evidence-based guidelines.

Guy's Advanced Dementia Schedule (GADS): consists of a number of objects presented to participants (the words 'table' and 'stand', a pencil and sheet of paper, a baby's rattle, a tennis ball, a comb, a cup, a knife, a matchbox containing used matches, a whistle, an harmonica, a party mask). The first two verbal elements aim to determine whether people can spontaneously read words. The second word is presented upside down to assess if they reorient the paper. The remaining items are presented to participants and each type of response is recorded. Total scores range from 0 to 40.

Hachinski ischemic score (HIS): simple clinical tool currently used to differentiate the main types of dementia, such as primary degenerative, vascular or multi-infarct, and mixed dementia. People with a score ≥7 are classified as subjects with 'multi-infarct dementia', while people with a score ≤4 are classified as

subjects with 'primary degenerative dementia'. A score of 5 or 6 is considered an intermediate value and is usually referred to as 'mixed dementia'.

Hamilton Anxiety Rating Scale (HAMA): scale used to assess the severity of symptoms of psychic and somatic anxiety. Higher scores indicate higher symptom severity (range 0-51).

Hamilton Depression Rating Scale (HDRS): 17-item tool used for assessing of the presence of depressive symptoms. Higher scores indicate a higher frequency of symptoms (range 0-51).

Hazard ratio (HR): ratio, used in survival analyses, between incidence rates of an event in people exposed and non-exposed to the investigated risk factor.

Health-Related Quality of Life (HR-QoL): measure used to assess the if and how individual wellbeing can be affected over time by a disease or condition of disability.

Health Technology Assessment (HTA): the multidisciplinary process that summarises information on clinical, economic, social, and ethical issues related to the use of a specific health technology in a systematic, transparent, impartial and robust way. Its objective is to support to the identificationhealthcare policies that are safe, effective, patient-centred and aimed at achieving the best quality of care.[82]

Health Utilities Index Mark 3 (HUIM-3): tool developed by McMaster University and used to measure health-related quality of life by analysing eight health states (vision, hearing, speech, ambulation, dexterity, emotion, cognition, pain). Higher scores indicate a higher quality of life (range -0.36 – 1.00).

Hospital Anxiety and Depression Scale (HADS): 14-item self-administered tool used to measure the presence and severity of anxiety and depressive symptoms. Higher scores indicate a higher frequency and severity of symptoms (range 0-42).

Hospital Anxiety Scale (HAS): section of the “HADS scale” consisting of the seven items related to anxiety.

Hospital Depression Scale (HAD): section of the “HADS scale” consisting of the seven items related to depressive symptoms.

Hyperphosphorylated Tau protein (p-Tau): protein that consitutes the intracellular neurofibrillary tangles that are one of the main hallmarks of several neurodegenerative diseases including Alzheimer's dementia and other tauopathies.

I^2: commonly used measure of heterogeneity in meta-analyses that provides an estimate of the proportion of variability explained by differences among the results of the included studies.

Imprecision: imprecision of the estimates obtained by studies with small sample size and/or that observe a small number of events.

[82] Source: Italian Ministry of Health. Dispositivi medici. Il processo di Health Technology Assessment (HTA). Available at: https://www.salute.gov.it/portale/dispositiviMedici/dettaglioContenutiDispositiviMedici.jsp?lingua=italiano&id=5199&area=dispositivi-medici&menu=tecnologie (Last visited: 30/08/2023).

Incidence Rate Ratio (IRR): ratio of two incidence rates, where the incidence rate is defined as the number of events per person/time at risk.

Inconsistency: variability in estimates of frequency of included studies. It refers to an unexplained heterogeneity in the results observed by considered studies.

Indirectness: non-direct transferability of results to the context of interest. It refers to the non-transferability of results from considered studies to the target context of the guideline.

Informant Questionnaire on Cognitive Decline in the Elderly – 26 items version (IQCODE26-item): test administered to relatives or friends of the person with suspected cognitive decline. The score calculated by summing the 26 items (score ranging from 1 to 5 for each question) divided by the number of items (26). Lower scores indicate higher impairment of cognitive function (range 0-5).

Instrumental Activities of Daily Living (IADL): skills and abilities needed to perform specific daily activities associated with an independent lifestyle. These activities are not considered essential for basic functioning, but they are considered important for assessing quality of daily life and relative independence.

Integrated Alzheimer's Disease Rating Scale (iADRS): composite tool including the ADAS-Cog scale and the ADCS-ADL scale, adopted to assess disease progression in people with Alzheimer's dementia. Lower scores indicate a worse performance (range 0-146).

Integrated Care Pathway (ICP): a predefined, articulated, and coordinated sequence of services provided at outpatient and/or inpatient and/or territorial level, which requires the integrated participation of different specialists and professionals (and of patients themsenves), at a hospital and/or territorial level, in order to achieve the most appropriate diagnosis and therapy for a specific condition or even the health care needed in particular life circumstances, such as pregnancy and childbirth[83].

Intention-to-treat (ITT): statistical method that, when applied in the analysis of data from an experimental study, considers information from each participant based on the group they were initially allocated to rather that based on the treatment they received.

International Classification of Diseases (ICD): diagnostic tool used in epidemiology, public health, and for clinical purposes.

International Working Group (IWG): International Expert Group on Dementia that produced the recommendations for the clinical diagnosis of Alzheimer's dementia.

Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA): national regulatory authority for drug treatments in Italy. It is a public body that operates operating according to the principles of autonomy, transparency and efficiency, under the direction of the Ministry of Health and the supervision of the Ministry of Health and the Ministry of Economy.[84]

[83] from "Piano Nazionale per il Governo delle Liste d'Attesa 2012-2014". Italian Ministry of Health.
[84] Source: AIFA. Available at: https://www.aifa.gov.it/web/guest/l-agenzia (Last visited: 30/08/2023).

Letter Sorting Test (LST): test requiring participants to pronounce a 5-letter word forward, backwards, and in alphabetical order. The score is calculated by assigning 1 point for each correct pronunciation.

Lewy Body Composite Risk Score (LBCRS): 10-item questionnaire investigating the presence/absence of four motor signs and six non-motor symptoms that are characteristic to dementia with Lewy body. Scores ≥ 3 indicate a high probability that Lewy bodies are the condition contributing to the underlying cognitive decline.

Magnetic Resonance Imaging (RM): structural neuroimaging technique used as an appropriate support in the diagnostic workup and to exclude secondary causes of dementia (e.g., vascular lesions, inflammatory diases, tumors, etc.). This test can require measuring volumetric or linear indices of brain atrophy, such as the identification of areas of atrophy such as hippocampal or temporo-medial and parietal atrophy, characteristic of Alzheimer's dementia.

Manchester and Oxford Universities Scale for the Psychopathological Assessment of Dementia (MOU-SEPAD): tool used to assess behavioural and psychopathological changes in people with dementia. Higher scores indicate higher frequency and severity of symptoms.

Mass spectrometry: instrumental examination based on measuring the ratio between mass and charge of one or more molecules in a sample, often used to calculate the molecular weight of the components of the sample.

Mattis Dementia Rating Scale (MDRS): originally developed for the diagnosis of Alzheimer's dementia, it has also been used for the early detection of dementia, for the differential diagnosis between Alzheimer's dementia and other dementias, and for the staging of dementia. The scale's tasks are classified in five subdomains, each assessing different cognitive areas, including attention, initiation/perseverance, construction, conceptualization, and memory.

Mean Difference (MD): statistical measure indicating the absolute difference between the mean values observed in two groups within a clinical trial.

Medication Appropriateness Index (MAI): tool used to measure the appropriateness of prescriptions of pharmacological treatments in older people. Lower scores indicate higher appropriateness (range 0-18).

Medication Quantification Scale (MSQ): tool used to quantify, based on three relevant aspects (pharmaceutical class, dose, and risk profile), the drug treatment plans used in populations with chronic pain. Higher scores indicate higher risk (range 0-6).

Memory Impairment Screen (MIS): test assessing episodic memory. It consists of a phase in which the person is required to remember a series of four words that belong to different semantic categories. After a two-to-three-minute phase during which the person is asked to perform different tasks (e.g., counting backwards from 20 to 0), the examiner goes back to the four words previously shown through a free recall. In case of inability to remember a word, the examiner supports the person through a guided recall. Lower scores indicate higher impairment of cognitive functions (range 0-8).

Mental Health Inventory-5 (MH-5): international brief, valid, and reliable tool for assessing mental health in adults. The tool includes five questions. There are six possible answers to each question, with scores ranging

from 1 to 6. Scores therefore range from 5 to 30 and are then transformed into a score ranging from 0 to 100. Higher scores indicate better mental health (range 0-100).

Meta-analysis: a statistical method for the quantitative summary of results from by different studies on the same topic.

Mini-Cog: test requiring a short time to be administered (approximately three minutes) used to identify cognitive impairment in older people. The test consists of a three-word recall part (score from 0 to 3) and a second part based on clock drawing (score from 0 to 2). Lower scores indicate higher impairment of cognitive function (range 0-5).

Mini Mental State Examination (MMSE): easy-to-administer neuropsychological test consisting of simple questions and small graphic tasks, allowing to assess different aspects of brain function such as orientation, memory, attention, calculation, recall, and language. Lower scores indicate higher impairment of cognitive functions (range 0-30).

Measure of effectiveness: effect size of an intervention or treatment strategy.

Mobilisation Observation Behaviour Intensity Dementia Pain Scale (MOBID): observational pain scale by which assessors observe pain-related behaviours (e.g., facial expressions, defence movements) and assess pain intensity at rest and during a standardized protocol in which the patient is guided through five movements. The overall pain intensity is assessed using a scale ranging from 0 to 10, with 0 meaning no pain and 10 indicating the strongest possible pain.

Mobilisation Observation Behaviour Intensity Dementia 2 Pain Scale (MOBID-2): scale used to assess pain intensity. Unlike the version described above, it consists of two parts. Part 1 assesses musculoskeletal pain when performing standardised, guided movements during morning care (five items). Part 2 assesses pain that might be related to internal organs, head, and skin and is monitored over time (five items). The overall pain intensity is assessed using a scale ranging from 0 to 10, with 0 meaning no pain and 10 indicating the strongest possible pain.

Modified Crichton Royal Behavioural Rating Scale (CRBRS): scale measuring a range of behaviours and activities (e.g. mobility, communication, cooperation, restlessness, eating, incontinence, sleep, mood, and orientation) on a five-point scale. Higher scores indicate better functioning (range 0-38).

Modified Richmond Agitation Sedation Scale (mRASS): tool to assess the level of sedation and agitation. The score ranges from -5 (unarausable) to +4 (combative).

Monoclonal antibodies (mAbs): biological drugs mainly acting on amyloid β plaques or on the isoforms of the Tau protein. They are currently being tested for the treatment of Mild Cognitive Impairment due to Alzheimer's dementia and mild Alzheimer's dementia.

Montgomery – Åsberg Depression Rating Scale (MA-DRS): tool used to assess the severity of depressive episodes and symptoms consisting of 10 items rated on a scale ranging from 0 to 6. Higher scores indicate of higher severity of depressive symptoms (range 0-60).

Montreal Cognitive Assessment (MoCA): rapid tool designed for the identification of Mild Cognitive Impairment in response to the low sensitivity of the MMSE test. The items included in the MoCA measure

attention, concentration, executive functions, memory, language, visualspatial skills, abstraction, calculation, and orientation. Lower scores indicate higher impairment of cognitive function (range 0-30).

Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS): tool for assessing people with Parkinson's disease. It consists of four parts: i) nonmotor experiences of daily living, ii) motor experiences of daily living, iii) motor examination; iv) motor complications.

Multifactorial Memory Questionnaire (MMQ): Self-administered questionnaire used to assess memory in adults. Consisting of three scales measuring satisfaction with memory functioning, self-appraisal of memory ability, and self-reported use of memory strategies. Higher scores indicate higher satisfaction and perceived memory abilities and frequent use of memory aids and strategies.

Multimorbidity: condition in which a person is affected by two or more chronic clinical conditions.

Multiple Affect Adjective Checklist (MAACL): self-administered questionnaire aimed at identifying positive and negative affects by assessing subjective levels of anxiety, depression, and hostility through 132 adjectives.

Myocardial innervation scintigraphy (^{123}I-MIBG): nuclear medicine test examining the distribution and integrity of adrenergic endings at a myocardial level through intravenous administration of the radiopharmaceutical metaiodobenzylguanidine (MIBG) labelled with I^{123}. This technique is used to support the diagnosis of Parkinson's disease and Lewy body dementia.

National Collaborating Centre for Mental Health (NCCMH): established in 2001 based on collaboration between the Royal College of Psychiatrists and University College London, it produces documents and guidelines on mental health issues.

National Institute for Health and Care Excellence (NICE): public entity gioverned by the UK Ministry of Health, it manages the evaluation of literature in the biomedical and biotechnological fields, with a specific focus to the assessment of the cost/effectiveness.

National Institute of Aging (NIA): cantre referring to the National Institutes of Health (NIH), established in 1974. Its focus is the overall health of adults and older people. It is the leading centre in the United States on Alzheimer's dementia and other dementias.

National Institute of Neurological and Communicative Disorders e Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA): working group that defined the criteria for the presence of cognitive impairment and suspected dementia syndrome for a clinical diagnosis of possible or probable Alzheimer's dementia in 1984 and the revised criteria in 2011.

National Institute of Neurological Disorders and Stroke e Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN): international workshop that drafted the criteria for the diagnosis of vascular dementia in 1993.

Neurobehavioral Cognitive Status Examination (NCSE): tool for the assessment of neurocognitive functions exploring three general factors (consciousness, orientation, and attention) and using independent tests to assess the functioning of five main domains (language, spatial skills, memory, calculations, and reasoning). It includes 62 items, and the total score ranges from 0 to 12.

Neurobehavioral Rating Scale (NBRS): multidimensional tool used to measure changes in neurobehavioral symptoms. Higher scores indicate higher symptom severity.

Neuropsychiatry Inventory (NPI): test including 10 behavioural domains with 7-8 subdomains. It measures the severity (3-point scale) and frequency (4-point scale) of symptoms. Categories include delusions, hallucinations, dysphoria, anxiety, agitation/aggression, euphoria, disinhibition, irritability, apathy, and aberrant motor activity. The total score is the sum of the subdomain scores. Higher scores indicate a more severe behavioural disorder (range 0-144).

Neuropsychological Test Battery (NTB): battery of neuropsychoilogical tests including nine validated components: Wechsler Memory Scale visual immediate (score range, 0-18), Wechsler Memory Scale verbal immediate (score range, 0-24), Rey Auditory Verbal Learning Test (RAVLT) immediate (score range, 0-105), Wechsler Memory Digit Span (score range, 0-24), Controlled Word Association Test (COWAT), Category Fluency Test (CFT), Wechsler Memory Scale visual delayed (score range, 0-6), Wechsler Memory Scale verbal delayed (score range, 0-8), and RAVLT delayed (score range, 0-30).

New York University delayed paragraph recall test: test used to measure verbal memory based on the administration of a short paragraph presented verbally. Higher scores indicate better performance (range 0-21).

Non Communicative Patients Pain Assessment (NOP-PAIN): tool used to assess the presence and intensity of pain at rest and in movement in people with dementia, based on the observation of specific behaviours suggestive of the presence of pain. Higher scores indicate higher frequency and intensity of pain (range 0-55).

Nottingham Health Profile (NHP): self-administered questionnaire used to measure subjective health status, in terms of frequency and severity of any health problem, based on questions related to different aspects of daily life. Higher scores indicating higher frequency and severity of health problems (range 0-100).

Numeric Rating Scale (NRS): scale used in verbal or written form to determine the level of pain. Higher scores (range 0-10).

Nursing Home Behaviour Problem Scale (NHBPS): 29-item tool to assess the frequency of behavioural disorders in people in nursing homes. Higher scores indicate a higher frequency of behavioural disorders (range 0-116).

Observational Pain Management Protocol (OPMP): protocol designed to to guide the care flow related to pain management in nursing homes, which includes indications for pain assessment, implementation of any interventions, and subsequent monitoring.

Observational Scale of Level of Arousal (OSLA): brief tool to assess the presence and severity of abnormalities in the state of arousal associated with the presence of delirium. Higher scores indicate higher symptom severity (range 0-15).

Odds Ratio (OR): measure of risk calculated as the ratio of two probabilities of an event estimated in two different groups (e.g., intervention versus placebo). An OR value > 1 indicates that the intervention group has a higher risk of an event compared to the placebo group; an OR value < 1 indicates that the intervention

group has a lower risk of an event compared to the placebo group; an OR = 1 indicates that there are no differences between groups.

Olfactory test: test based on the administration of dispensers containing a set of predefined smells that the person is required to identify. The test requires to initially identify the presence of a smell and then to correctly identify it based on a set of options.

Open label (study): clinical trial that does not maintain information about the blinded treatment and in which participants and healthcare professionals are, therefore, aware of treatment allocation.

Orientation (OR): subscale belonging to the ADAS-Cog test. Eight questions are asked related to time, place, and situation. One point is awarded for each correct answer.

Outcome/Surrogate Outcome: clinical/functional outcome of people enrolled in an epidemiological study, used to measure the effectiveness of a health intervention.

p value: also referred to as the level of significance, it indicates the probability that the difference between the hypothesized result and observed result is due to chance.

Pain Assessment Checklist for Seniors with Limited Ability to Communicate (PACSLAC): tool used to assess the presence of behaviours suggestive of pain in elderly people with a limited ability to communicate. Higher scores indicate higher pain intensity (range 0-60).

Pain Assessment in Advanced Dementia (PAINAD): tool used to assess the presence of pain in people with dementia, based on the observation of behaviours and gestures suggestive of pain. Higher scores indicate higher pain intensity (range 0-10).

Pain Intensity Measure for Persons with Dementia (PIMD): observational tool used to assess the presence and intensity of pain in people with dementia, based on the observation of behaviours indicating the presence of pain. Higher scores indicate higher pain intensity (range 0-21).

Pain Recognition and Treatment (PRT): protocol for Pain Identification, Assessment, and Treatment that includes indications to guide decision-making for pain assessment, management, and monitoring.

Palliative Care Domain Index (PDCI): tool used to assess the level of treatment required in ten domains related to palliative care. Higher scores indicate higher treatment of symptoms (range 0-10).

Palliative Care Treatment Plan Domain score (PCTPD): tool used to collect the general content of treatment plans of people in nursing homes. Higher scores indicate a higher number of required treatments (range 0-10).

Palmomental Reflex (PMR) or Marinesco-Radovici sign: superficial primitive reflex consisting of a unilateral contraction of the chin muscle elicited by rubbing a specific part of the palm under the thumb. It is present in early childhood and disappears with brain maturation but can reappear due to brain disease causing damages disrupting normal cortical inhibitory pathways.

Patient Health Questionnaire-4 item (PHQ-4): brief tool, based on four questions, for the assessment of mental health, in particular symptoms of anxiety and depression. Llower scores indicate better mental status (range 0-12).

Perceived Health Status (PHS): tool that measures the perceived health status based on three items that assess current health status, health status compared to others of the same age, and satisfaction with one's health status compared to one year earlier. Each item is measured with a 3-point Likert scale, with higher scores indicating better perceived health status.

Perceived Stress Scale (PSS): tool used to assess the level of perceived stress. Higher scores indicate a higher level of perceived stress (range 0-40).

Personalised Care Plan (PCP)[85]: the appropriate tool to define a shared advance care plan. It identifies the interventions that the multidisciplinary team considers as ethical and appropriate to pursue and must be considered as a flexible tool whose objectives are subject to periodic review and adjustment. Particularly important is the approach of PCP to the end-of-life phase.

PET: see Positron Emission Tomography.

Phototest: brief cognitive test that assesses the ability of the person to recall six objects that had been previously shown them with the request of naming them. Between naming and remembering, a verbal fluency task is performed where the person is required to evoke names of people cloassified by gender. Lower scores indicate higher impairment of cognitive function (range 0-60).

Physical Self-Maintenance Scale (PSMS): scale used to assess the presence and level of dependence or disability in older people, based on six ADL-based items and eight IADL-based items. The score ranges from 6 to 30, with higher scores indicating a higher level of dependence (range 6-30).

Physically Aggressive Behaviour (PAB): Likert scale for assessing the presence and frequency of physical behaviours indicative of aggression. Higher scores indicate a higher frequency of aggressive behaviour.

Pittsburgh Agitation Scale (PAS): tool used to measure the level of agitation based on four specific behavioural dimensions (persistent vocalisations, motor agitation, aggression, and resistance to care). Higher scores indicate higher levels of agitation (range 0-16).

Pittsburgh Sleep Quality Index (PSQI): 19-item self-administered questionnaire assessing sleep quality over one month. Lower total scores indicate better sleep quality (range 0-21).

Positive Response Schedule (PRS): tool to assess wellbeing in people with severe dementia.

Predictive values: negative predictive value (NPV) corresponds to the proportion of people with a negative test result who do not have the target condition and is therefore correctly classified. Positive predictive value

[85] Source: 'Recommendations for Governance and Clinic in the Field of Dementia' by the National Committee for Dementia. Available at: https://www.iss.it/documents/20126/5783571/Raccomandazioni+per+la+governance+e+la+clinica+nel+settore+delle+demenze.pdf/dbf0d6d5-6360-41dù1-74b18f62dad8?t=1626171914860 (Last visited: 30/08/2023)

(PPV) corresponds to the proportion of people with a positive test result who have the target condition and is therefore correctly classified.

Presenilin genes (PSEN1, PSEN2): genes encoding specific membrane proteins that are involved in the γ-secretase enzyme, the enzyme responsible for degrading the amyloid precursor protein, from which the β amyloid peptide, a hallmark of Alzheimer's dementia, is formed. The autosomal dominant mutations of these genes are associated with mostly early-onset familial forms of the disease, as they increase the production of the neurotoxic form of the β amyloid protein.

Proteinopathies: a generic term used to define neurodegenerative diseases characterised by the deposition of abnormal aggregates of 'misfolded' proteins in the brain, at an intra and/or extraneuronal level. Examples of proteinopathies are Alzheimer's dementia, characterized by the accumulation of amyloid β in amyloid plaques, and of hyperphosphorylated Tau protein in neurofibrillary tangles, or Parkinson's disease, whose neuropathological hallmark is the deposition of α-synuclein in Lewy bodies.

Proxy: an individual entity actingon behalf of another entity who is unable to act to to unavoidable reasons.

Publication bias: potential systematic overestimation or underestimation of the benefits or risks due to the selective lack of published studies.

QUALIDEM: tool used for informant-reported assessment of the quality of life of people with dementia throughout the different stages of the disease, based on their ability to adapt to the physical, psychological, and social consequences of the disease. Higher scores indicate higher quality of life (range 0-111).

Quality of Communication (QoC) questionnaire: questionnaire consisting of 13 items assessing the quality of communication. Higher scores indicate better quality (range 0-10).

Quality of Life in Alzheimer's Disease (QoL-AD): scale used for the assessment of the quality of life of people with dementia. It is a 13-item scale with scores for each iterm ranging from 1 to 4. Lower scores indicate worse quality of life

Quality of Dying in Long-Term Care (QoL-LTC): tool designed to assess the quality of care during the last month of life, often used to assess care during the end of life in nursing homes. Higher scores indicate better quality of care (range 11-55).

Quality of Life in Late-Stage Dementia (QUALID): 11-item tool designed to assess differences between healthcare professionals and caregivers in how they perceive the quality of life of people with dementia. Lower scores indicate higher quality of life (range 11-55).

Quality of Life Scale (QOLS): 16-item questionnaire used to measure quality of life by assessing material and physical wellbeing, quality of relationships, social and recreational activities, and personal development and satisfaction. Higher scores indicate better quality of life (range 16-112).

Randomised Controlled Trial (RCT): experimental epidemiological studies in which participants are enrolled and randomly allocated (i.e. destined) to receive one or more treatments.

Rating Anxiety in Dementia (RAID): tool used to assess the presence and severity of signs and symptoms of anxiety in people with dementia based on self-reported or caregiver-reported information. Higher scores indicate higher levels of anxiety (range 0-54).

Real-Time Quaking-Induced Conversion (RT-QuIC): technique used for the identification of prions in CSF. This technique is based on the ability of the misfolised pathological form of prion protein (PrP) to induce the conversion of normal PrP into its misfolded form, amplifying its quantity up to detectable levels.

Repeatable Battery for Assessment of Neuropsychological Status (RBANS): five-domain tool aimed at measuring immediate and delayed memory, visuospatial/constructional skills, language, and attention. Higher scores indicate better cognitive functions (range 40-160).

Residential Care Transition Module (RCTM): psychosocial intervention designed to support families in managing emotional and psychological stress following the institutionalisation of a family member with cognitive impairment.

Revised Memory and Behavior Problem Checklist (RMBPC): tool used to assess how upsetting is the burden of care perceived by careguvers in presence of 24 memory and behavioural problems. Higher scores indicate more problematic behaviours (range 0-24).

Revised Scale for Caregiving Self-Efficacy (RSCSE): tool including three domains scored separately used to assess how caregivers perceive their ability to manage and overcome difficulties related to care. Higher scores indicate a higher confidence in their abilities (range 0-100 for each domain, total 0-300).

Rey Auditory Verbal Learning (RAVL): test for verbal memory based on 15 words learned therough 5 taskes, where the total number of correct words is the total recall score (range 0-75), while the number of recalled words after a 30-minute breack is the total delayed recall score (range 0-15).

Rey Complex Figure Test (RCFT): tool used to assess visuospatial functions. Hgher scores indicate a better performance (range 0-36).

Relative risk (RR): measure of the association of being exposed to a specific risk factor with the onset of a specific condition, calculated as the ratio of the incidence rates in the exposed cohort (numerator) and the non-exposed cohort (denominator).

Rivermead Behavioural Memory Test (RBMT): battery of tests used to assess ecological memory, based on tasks involved in everyday life aimed at measuring daily life memory functions. Higher scores indicate better performance (range 0-12).

Rotterdam Elderly Pain Observation Scale (REPOS): observational scale for the assessment of pain in institutionalized people who are unable to independently report the presence of pain. Higher scores indicate higher pain frequency and severity (range 0-42).

Rowland Universal Dementia Assessment Scale (RUDAS): cognitive test used to minimize the effect of cultural and linguistic differences. The test includes items such as memory, visuospatial orientation, praxis, visuoconstructive skills, memory recall, language. The higher possible score is 30, lower scores indicate higher impairment.

Satisfaction With Care at the End of Life in Dementia (SWC-EOLD): scale that measures satisfaction with care received in the previous 90 days. It consists of 10 items, with higher scores indicating higher satisfaction (range 10-40).

Scale for the Assessment of Positive Symptoms (SAPS): tool that measures positive symptoms of schizophrenia. It includes 34 items organized into four domains (hallucinations, delusions, bizarre behaviour, and formal thought disorders). Higher scores indicate higher symptom severity (range 0-170).

Selection bias: bias introduced in a clinical trial subjects the allocations of participants to a treatment arm is not entirely random but is chosen by the people involved in the trial or is due to other uncontrolled factors that may affect the outcome of the study.

Self Efficacy Questionnaire Symptom Management (SEQ-SM): questionnaire that measures the perceived competence of informal caregivers in caring for their family member with dementia. It consists of five items, with higher scores indicating a higher perceived competence.

Self-Management Ability Scale (SMAS): scale that measures cognitive and behavioral skills that are thought to contribute to a successful self-management of aging. It consists of 30 items, with higher scores indicating to higher levels of self-management.

Self-Perceived Pressure by Informal Care (SPPIC): scale that measures the pressure perceived by informal caregivers in relation to their caring situation and in relation to their own needs, such as the time dedicated to other activities. It includes nine items, with higher scores indicating a higher perceived care burden (range 9-45).

Sense of Competence Questionnaire (SCQ): 27-item questionnaire assessing caregivers' sense of competence. Higher scores indicate a better sense of competence (range 27-135).

Seoul Verbal Learning Test (SVLT): see CVLT.

Serum Anticholinergic Activity (SAA): method for determining the anticholinergic activity of a drug based on a plasma radioreceptor assay aimed at quantifying drug-induced muscarinic blockade.

Setting: place or type of environment in which an event takes place, specifically, in the healthcare, activities related to interventions and care.

Seven Minute Screen (SMS): tool that consists of four short cognitive tests. 1. Benton temporal orientation, assessing temporal orientation, with a higher possible score of 113. 2. Enhanced cued recall, requiring the identification of 16 figures that are recalled immediately or after a short interval, with a higher possible score of 16. 3. Clock drawing, requiring to a clock with the hands positioned at a given time, with a higher possible score of 7. 4. Verbal fluency, requiring remembering as many animals as possible in one minute, with a higher possible score of 45.

Short Form Health Survey (SF-36, SF-12): self-administered questionnaire measuring health-related quality of life. It consists of 36 (or 12 in the short version) questions organized into eight scales (physical functioning, limitations due to physical health, limitations due to emotional problems, energy and fatigue, emotional well-being, social activities, pain and general health perception). Total score ranges from 0 to 100 with higher scores indicating better health status.

Short Portable Mental Status Questionnaire (SPMSQ): brief test consisting of a list of ten questions investigating some aspects of cognitive abilities: seven items assessing orientation, two items assessing long-term memory, and one item assessing the ability to focus. For orientation, scores range from 0 to 10, with higher scores indicating higher cognitive impairment.

Short Smell Test (SST): test based on the recognition of familiar smells. This test is used for the assessment of people with cognitive decline due to dementia.

Standard error (SE): statistical measure defined as the estimation of the standard deviation, therefore the variability and imprecision, of an estimator, such as a sample's mean.

Statistical significance: it refers to the probability that a given result from an epidemiological study occurred due to chance. Conventionally, the probability below which the outcome is considered as not due to chance, therefore not statistically significant, is $p < 0.05$.

Single-Photon Emission Computed Tomography (SPECT): tomographic technique of nuclear medicine imaging that uses gamma rays to generate images after administration of a radiopharmaceutical. It is used for the functional study of the brain in case of suspected brain and neurodegenerative diseases (Alzheimer's dementia and other dementias, Parkinson's disease and other movement disorders, epilepsy, etc.).

Spatial Orientation Subscale (SOS): item of the Abilities Assessment Instrument (used to assess self-care, social, interactional, and interpretive abilities in people with cognitive impairment) used to assess environmental orientation. Higher scores indicate better performance.

Standardised Mean Difference (SMD): summary statistics used in meta-analyses when included studies repord data on the same outcome but using different measures, which makes it necessary to standardise results on a uniform scale to allow for a cumulative analysis of the estimates.

Standardised Uptake Value ratio (SUVr): measure used in nuclear medicine for the physiological quantification of regional concentrations of radioactivity, which describes in a semi-quantitative way the regional glucose metabolism within the analysis of images acquired through instrumental examinations such as PET and SPECT with 18F-FDG.

State-Trait Anxiety Inventory (STAI): test that measures state and trait anxiety. It consists of 40 items, with higher scores indicating higher levels of anxiety (range 20-80).

Stepwise Protocol of Treating Pain (SPTP): pain management protocol, based on recommendations from the American Geriatrics Society in 2009. According to this protocol, after an initial assessment of their current treatments, patients can receive pain therapy with oral paracetamol, morphine and/or pregabalin, or, in case of difficultis swallowing, with buprenorphine patch, with the possibility of adjusting doses or combining treatments based on tolerability.

Subjective Cognitive Decline (SCD) or Subjective Cognitive Impairment (SCI): self-reported deterioration in memory, which is different from before, even if the overall cognitive performance is still in the range considered as normal according to objective tests.

Suicidal Ideation Scale (SIS): scale that measures the level of suicidal ideation. It consists of five items with higher scores indicating higher levels of suicidal ideation.

Symptom Management at the End of Life in Demetia (SM-EOLD): scale that measures how often a person experienced the following nine symptoms and signs during the previous 90 days: pain, shortness of breath, depression, fear, anxiety, agitation, calm, skin lesions, and resistance to treatment. THigher scores indicate better symptom management (range 0-45).

Syndrome Kurztest (SK): battery of tests including nine subtests aimed at assessint memory and attention deficits. Subtest 1 consists in naming 12 objects. Subtest 2 consists in recalling the objects from subtest 1. Subtest 3 consists in naming numerals. Subtest 4 consists in arranging blocks in numerical order. Subtest 5 consists in replacing blocks in their original position. Subtest 6 consists in identifying and counting symbols. Subtest 7 consists in reading reversing couples of letters. Subtest 8 consists in the delayed recall of objects from subtest 1. Subtest 9 consists in a recognition memory test using objects from subtest 1.

Systematic review (SR): review of scientific literature summarising results from primary studies (e.g., a series of randomised controlled trials). Systematic reviews use a methodology and approach that is reproducible and standardised.

Taupathy: see Proteinopathies.

Tau-PET: see Positron Emission Tomography.

Taylor Manifest Anxiety Scale (TMAS): scale that measures symptoms of anxiety. Higher scores indicate higher levels of anxiety (range 0-50).

Test Your Memory (TYM): cognitive screening test considered as valid, especially in primary care. It examines orientation, ability to copy a sentence, semantic knowledge, calculation, verbal fluency, similarities, naming, visuospatial abilities, and recall of the copied sentence. Higher scores indicate higher impairment of cognitive functions (range 0-50).

Timed Up and Go (TUG): screening tests to identify people at risk of falling. It measures the time in seconds that people need to get up from a chair, walk three meters, turn around, return to the chair, and sit down. Lower scores indicate a better performance.

Tinetti scales: scale assessing balance (nine items) and gait (seven items). Higher scores indicate a lower risk of falls (range 0-28).

The Clinician's Interview Based Impression of Change – Plus Caregiver Input (CIBIC+): tool used to measure the global impression of change based on interviewing both the person and their caregiver. Lower scores indicate higher improvement (range 1-7).

Positron Emission Tomography (PET): diagnostic nuclear imaging technique that allows, using radiotracers, to visualize and measure changes in different biological activities such as perfusion, metabolic processes, or absorption, depending on the specific tracer used. Some examples are tracers for Tau protein (Tau-PET) or for amyloid (amyloid PET) to assess their accumulation in the brain as a support for the diagnosis of AD. Other examples are the intravenous administration of a substance that is normally present in the body labelled with a radioactive molecule (radiopharmaceutical), as in the case of glucose in [^{18}F]-FDG (fluorodeoxyglucose) PET scans, or dopamine, in fluorodopa (^{18}F) PET. These are defined as functional tests as the labelled molecule allows the detection of their normal distribution, or their increase or decrease in the target structures.

Total Tau protein (t-Tau): protein associated with microtubules, whose main function is to modulate the stability of axonal microtubules. Under physiological conditions, Tau is abundant in neurons, while its expression in glial cells is low and is limited to astrocytes and oligodendrocytes. The hyperphosphorylation of the Tau protein is responsible for its insolubility by promoting its aggregation into neurofibrillary or glial fibrillary tangles, responsible for the destabilization of microtubules. These neurofibrillary tangles represent a neuropathological hallmark of tauopathies.

Trail Making Test A-B (TMT-A, TMT-B): test that assesses attention, graphomotor speed, and executive functions. It consists of two parts: TMT-A and TMT-B. Part A consists in drawing a line connecting numbers from 1 to 25 in numerical order. Part B consists in connecting a series of letters and numbers alternating them. The total score corresponds to the time required to complete each task.

Unified Parkinson's Disease Rating Scale (UPDRS): scale that assesses different aspects of Parkinson's disease. It consists of six parts: i) evaluation of mentation, behavior, and mood; ii) self-evaluation of the activities of daily life; iii) clinician-scored monitored motor evaluation; iv) complications of therapy; v) Hoehn and Yahr Scales staging of severity; vi) Schwab and England ADL scale. See also Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS).

Verbal Descriptor Scale (VDS): tool that measures the intensity of perceived pain. It is structured as a thermometer with the following possible answers: no pain, mild pain, moderate pain, severe pain, extreme pain, pain as bad ad could be.

Visual Analogue Scale (VAS): visual analogue tool providing a visual representation of the categorical values that the measured phenomenon can assume. For example, in case of the VAS scale used for pain assessment, a series of images suggestive of the different degrees of pain.

WebNeuro test battery: test is primarily designe for neurocognitive assessment, also used to measure outcomes related to emotional status, emotional resilience, symptoms of depression or anxiety, cognitive performance including speed of psychomotor response, impulsivity, attention, and concentration, efficiency of information processing, working memory, and executive functions.

Wechsler Adult Intelligence Scale (WAIS): test that measures intelligence and cognitive abilities in adults and includes six verbal subtests (information, similarities, vocabulary, comprehension, arithmetic, and digit span) and five performance subtests: block design, picture completion, digit symbol coding, object assembly, and picture arrangement.

Wechsler Memory Scale-Revised Logical Memory (WMS-R LM): subtest of the Wechsler Memory Scale-revised which consist in telling two short stories (each containing 25 units of ideas) and asking the person to remember them. The score is calculated based on the total number of recalled ideas for both stories. (range 0-50).

WHO-QoL: tool assessing people's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, and concerns. It includes 100 items categorised into six domains related to quality of life and rated on a 5-point scale.

Zarit Burden Interview (ZBI): scale used to assess the impact of the burden of caring for people with chronic or degenerative conditions on their caregivers. It includes 22 items and that can be used either as a structured interview or as a self-administered tool. The scale is short, easy to admister, and requires caregivers to

answer a series of questions based on a Likert scale ranging from 0 (never) to 4 (almost always). The items ask caregivers how the disability of the person they care for affects their quality of life, and investigate their psychological suffering, guilt, financial difficulties, and other difficulties of the family member/caregiver. Higher scores indicate a higher burden (range 0-88).

z-score: the measure indicating the distance in terms of standard deviations of a raw score from the mean of the population and allowing to compare obtained results to a 'normal' population.

Zung Depression Scale (ZDS): self-administered scale that measures the level of depression. It consists of 20 items assessing the following four characteristics of depression: the pervasive effect, the physiological equivalents, other disturbances, and psychomotor activities. Higher scores indicate a severe level of depression (range 25-100).

Supplementary Materials

Below is the list of appendixes, available at the following link:

https://www.demenze.it/it-schede-18-documentazione_sulle_demenze

Appendix 1. Scope

Appendix 2. Report of the open consultation of the Scope document

Appendix 3. Conflict of Interests of the Working Group

Appendix 4. Review search strategies

Appendix 5. GRADE and CERQual tables

Appendix 6. Meta-analysis

Appendix 7. OSMED analysis – Review Question 3a

Appendix 8. Evidence to Decision Tables

Appendix 9. Report of the open consultation of the draft guideline