Alzheimer's and other dementias

CHAPTER 9

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Definition and Aetiology

Dementia is a syndrome of marked cognitive impairment resulting from a decline in function from a previous level of performance to the extent the individual is no longer able to function independently in everyday activities. Dementia definitions differ slightly, with impairment in at least two cognitive domains being required for International Classification of Diseases Version 11 (ICD11) or at least one domain in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR).[1] In DSM-5-TR (Box 1), dementia is referred to as Major Neurocognitive Disorder (MNCD) and is differentiated from a Mild Neurocognitive Disorder by severity of cognitive impairment and its impact on function.

Diagnosis of a Neurocognitive Disorder (NCD) according to ICD-11 and DSM-5-TR criteria requires two assessment steps:

1. NCD classification: assessing the degree of cognitive impairment and functional decline
2. Causation: establishing a dementia subtype (which may be a working diagnosis).

Box 1: DSM-5-TR Diagnostic Criteria for Major Neurocognitive Disorder (Dementia)

A. Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on:

1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function; and

2. A substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.

B. The cognitive deficits interfere with independence in everyday activities (i.e., at a minimum, requiring assistance with complex instrumental activities of daily living such as paying bills or managing medications).

C. The cognitive deficits do not occur exclusively in the context of a delirium.

D. The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia).

Specify whether due to:

Alzheimer's disease

Frontotemporal degeneration

Lewy body disease

Vascular disease

Traumatic brain injury

Substance/medication use

HIV infection

Prion disease

Parkinson's disease

Huntington's disease

Another medical condition

Multiple etiologies

Unspecified etiology

Specify

Without behavioral disturbance: If the cognitive disturbance is not accompanied by any clinically significant behavioral disturbance.

With behavioral disturbance (specify disturbance): If the cognitive disturbance is accompanied by a clinically significant behavioral disturbance (e.g., psychotic symptoms, mood disturbance, agitation, apathy, or other behavioral symptoms).

Specify current severity:

Mild: Difficulties with instrumental activities of daily living (e.g., housework, managing money).

Moderate: Difficulties with basic activities of daily living (e.g., feeding, dressing).

Severe: Fully dependent.

Mild Neurocognitive Disorder is differentiated in that there is "evidence of *modest* cognitive decline" which does not result in loss of independent function, although the individual may be required to use compensatory strategies and accommodations to maintain independence. Mild Cognitive Impairment (MCI) is an alternative term commonly used in Neurology, and clinical practice in general.[2] Cognitive impairment should, in fact, be considered to be on a continuum, with MCI and dementia being categorical constructs imposed on that continuum. It is important to emphasise that a diagnosis of MCI or dementia does not necessarily imply that the impairment will worsen progressively, even though that is often the case for many of subtypes of these syndromes. The diagnosis of MCI does carry an increased risk of progression to dementia, but only ±15% progress to dementia (or MNCD) over the following two years, and some reverting to normal cognition.[2]

There are six key neurocognitive domains, defined in DSM-5-TR,[3] which can be remembered through the mnemonic: *SAMPLE* (see Figure 1).

Dementia subtypes include progressive diseases like Alzheimer's dementia (AD), Dementia with Lewy Bodies (DLB) and Frontotemporal dementia (FTD), or relatively static and chronic conditions such as with traumatic brain injury (Chapter 17) or treated HIV-associated Neurocognitive Disorder (HAND) (Chapter 22). The focus of this chapter is on AD, DLB, and FTD, with Vascular Dementia being covered in detail in the chapter on Cerebrovascular disease (Chapter 14). In older people, dementia commonly represents a mix of disease processes due to coexisting risk factors.

Epidemiology

The latest global estimate from the Global Burden of Disease Study 2019 is 57.4 million (95% CI: 50.4-65.1) cases worldwide in 2019, projected to increase to 152.8 million (95% CI: 130.8-175.6) in 2050. This rise in prevalence is attributable to the increase in the elderly population, with the age-standardized prevalence remaining stable.[4] There is much regional variation, with the smallest increases projected for Western Europe and high-income Asia-Pacific, and the largest

increases for North Africa, Middle East, and Eastern sub-Saharan Africa. Around 60% of people with dementia are living in low- and middle-income countries (LMIC).[5]

The incidence of dementia is showing a different trend, with several studies from high-income countries, and one from Nigeria, showing a decline in all-cause dementia incidence, especially in the last three decades.[6] While no specific cause for this decline has been found, changes in education, living conditions and health care are thought to have contributed.

Age is the biggest risk factor for developing dementia, with the rate of dementia doubling every five years from age 65.[5] Most dementias are *late onset*, occurring from age 65. The most common dementia is Alzheimer's Dementia (AD), being identified as the cause in about 60-70% of these late-onset cases, with 15-20% being Vascular Cognitive Impairment and Dementia (VCID).[8,9]

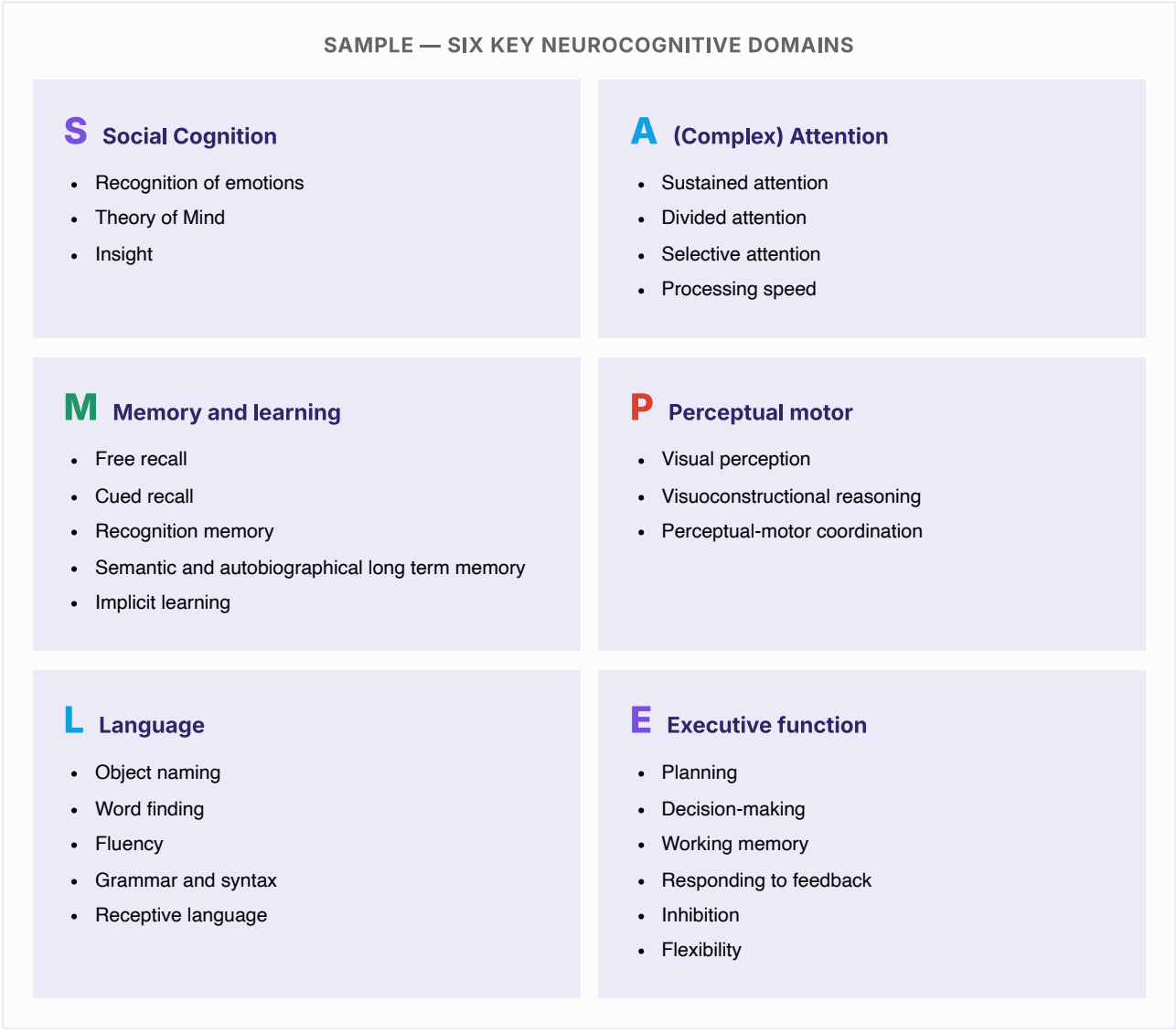


Figure 1: Cognitive domains and subdomains through the mnemonic: SAMPLE

Among early onset (young onset) dementias, occurring before age 65, are still most commonly caused by AD, but with other causes that feature prominently including frontotemporal dementia (FTD) or HIV-associated dementias. Among early onset dementia, FTD becomes a more common cause, making up between 3 and 26% of these cases, despite being frequently missed as a diagnosis.[10] DLB is similarly underrecognised, but is more common in late onset dementias,

with a higher incidence among men.[11] AD prevalence is 1.9 times higher in females, with the opposite trend in VCID, where prevalence is 1.8 times higher in males.[5]

Pathophysiology and Risk Factors

Alzheimer's Dementia

AD has a complex aetiopathogenesis that is not yet completely understood, but has a clear genetic risk with additional modifiable risk factors.[12] While the hallmark features of plaques and tangles in Alzheimer's disease have been known for over a century, the understanding of the detailed pathologies involved is more recent. The pathogenesis of the protein abnormalities, the β-amyloid (Aβ) peptides that aggregate to form the amyloid fibrils of the neuritic plaque, and the hyperphosphorylated tau that forms the neurofibrillary tangles, is now much better understood.[13]

With the recent development of biomarkers for amyloid (A), tau (T) and neurodegeneration (N), Alzheimer's disease has also been described using the AT(N) framework, with a diagnosis requiring the presence of both A and T.[14] This approach distinguishes the pathological process of the disease from the clinical syndrome, recognizing that pathology precedes the development of neurodegeneration and clinical features by several years, if not decades.

The amyloid cascade hypothesis is one of the more prominent hypotheses to explain the pathogenesis of AD. According to this hypothesis, amyloid precursor protein (APP) is cleaved into its fragments by either α-secretase or β-secretase, with subsequent cleavage by γ-secretase. This β-secretase pathway results in the development of 42-amino acid amyloid β (Aβ42), which accumulates in the brain over years to form plaques. This process has also been suggested to promote the hyperphosphorylation of the structural tau protein, leading to the formation of neurofibrillary tangles.[15] As the tau pathology spreads, it results in necroptosis. The tau pathology more closely tracks neurodegeneration and the clinical manifestations of dementia.

Neuroinflammatory changes are also an important part of the Alzheimer's disease process, and may be as a result of amyloid β accumulation, or precede and contribute its development.[13] Microglia seem to have particular role in AD pathogenesis and may help to maintain homeostasis despite amyloid accumulation.[13] Amyloid pathology can also cause vascular brain changes, such as through Cerebral Amyloid Angiopathy (CAA) and its resultant microhaemorrhages. Differentiating the exact role of amyloid β in the disease cascade has been an evolving area of the neuroscience, which may help to inform disease modifying treatments.

There are numerous genetic, environmental and potentially modifiable risk factors for dementia.[12] Genetically, up to 60-80% of AD can be related to heritable factors with APOE ε4 allele status being of particular importance, which increases risk by 2-3 fold in the heterozygous state and 10-12 fold in the homozygous condition.[13] There are more than 40 other genetic risk loci with small effect (odds ratios of 1.05 to 1.20) which together contribute to the genetic risk for AD pathology.[13] Three autosomal dominant genetic mutations, affecting the Presenilin (PSEN) 1, PSEN 2, and Amyloid Precursor Protein (APP) genes, are known to cause early-onset AD, Fortunately, these are rare and account for <1% of all cases of AD.

The Lancet Commission on Dementia[12] and the WHO Guidelines on Risk reduction of cognitive decline and dementia[16] have identified potentially modifiable risk factors for dementia (Figure 2). The 14 modifiable risk factors identified by the 2024 Lancet Commission were estimated to account for 45% of the population attributable risk of dementia, based on current evidence. Four additional risk factors, namely poverty, wealth shocks, income inequality, and HIV, have been proposed to further develop its global applicability for underrepresented regions.[58] Addressing modifiable risk factors in an individual across early life, middle life, and late life could potentially delay or prevent the onset of dementia and modify its course.[12]

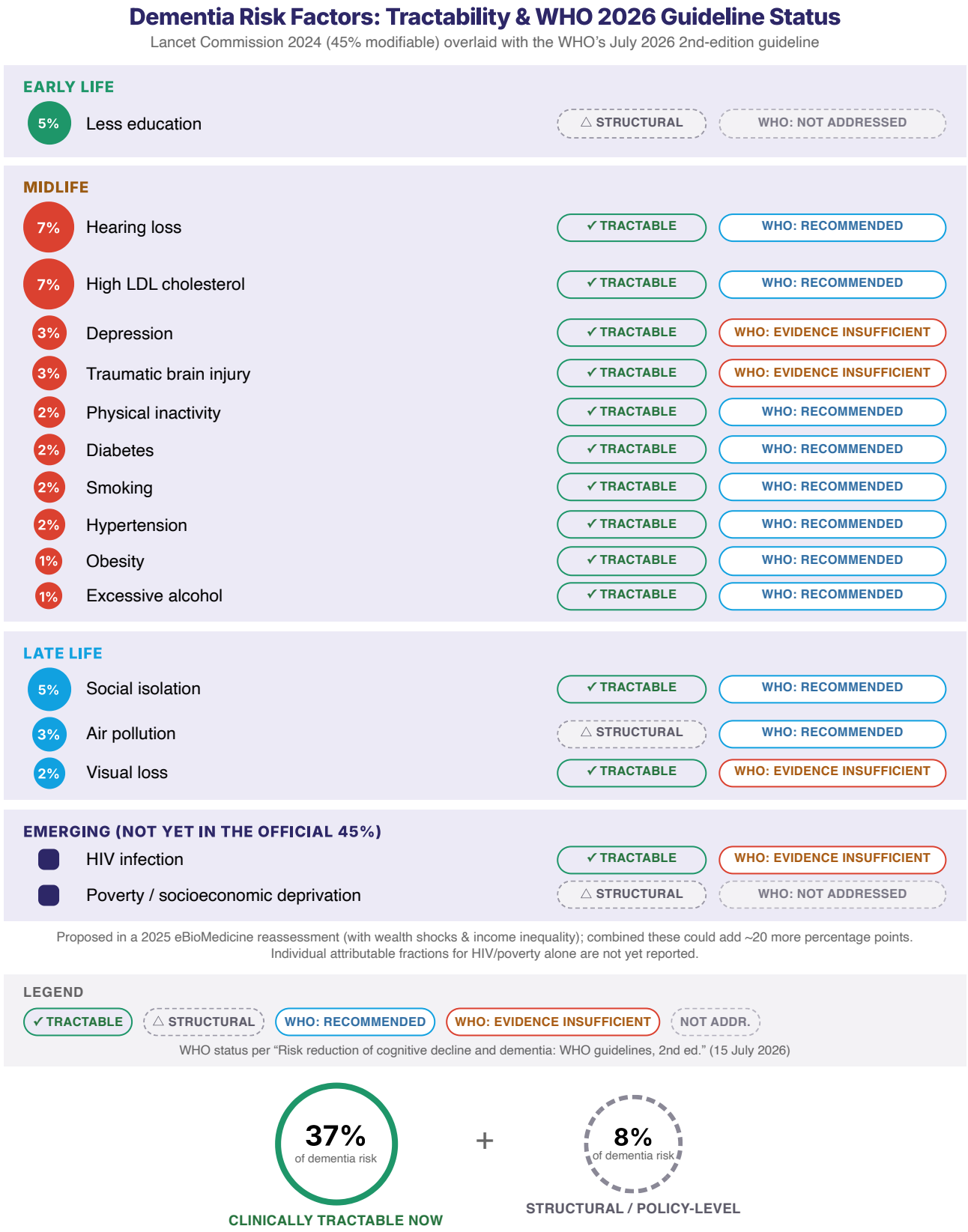


Figure 2: Dementia Risk Factors: Tractability and WHO 2026 Guideline Status (Claude for Mac v1.40609, Aug 2026)

Vascular cognitive impairment and dementia (VCID)

Vascular dementia has seen a broadening of the concept to vascular cognitive impairment and dementia,[17] and new diagnostic criteria[18] have been proposed. VCID is the second most common form of dementia, accounting for about 15-20% of all cases. Vascular contributions to dementia are, however, much more common in autopsy studies, with up to 75% having some vascular pathology and about one-third having significant vascular pathology.[19]

Recently, international collaborations, such as the Stroke and Cognition Consortium (STROKOG)[20] and the METACOHORTS Consortium,[21] have been formed to expedite the development of new treatments and prevention efforts. A framework for research priorities in the cerebrovascular biology of cognitive decline has been proposed.[22] The priorities include the development and validation of imaging and biospecimen-based biomarkers, better experimental models, and increased understanding of the underlying molecular and physiological mechanisms – white matter disease, infarction, microhaemorrhage, vascular autoregulation, glymphatic flow, inflammation, metabolic processes, and the interaction between vascular and Alzheimer pathologies. For further details on VCID, see Chapter 15 on Cerebrovascular Diseases.

Frontotemporal Dementia

Frontotemporal Dementia (FTD) is a group of clinical syndromes that occur when there is frontotemporal lobar degeneration (FTLD). The clinical syndromes known as FTD can be primarily behavioural (behavioural variant FTD) or language-related (primary progressive aphasias, PPA)[10], (Figure 3).

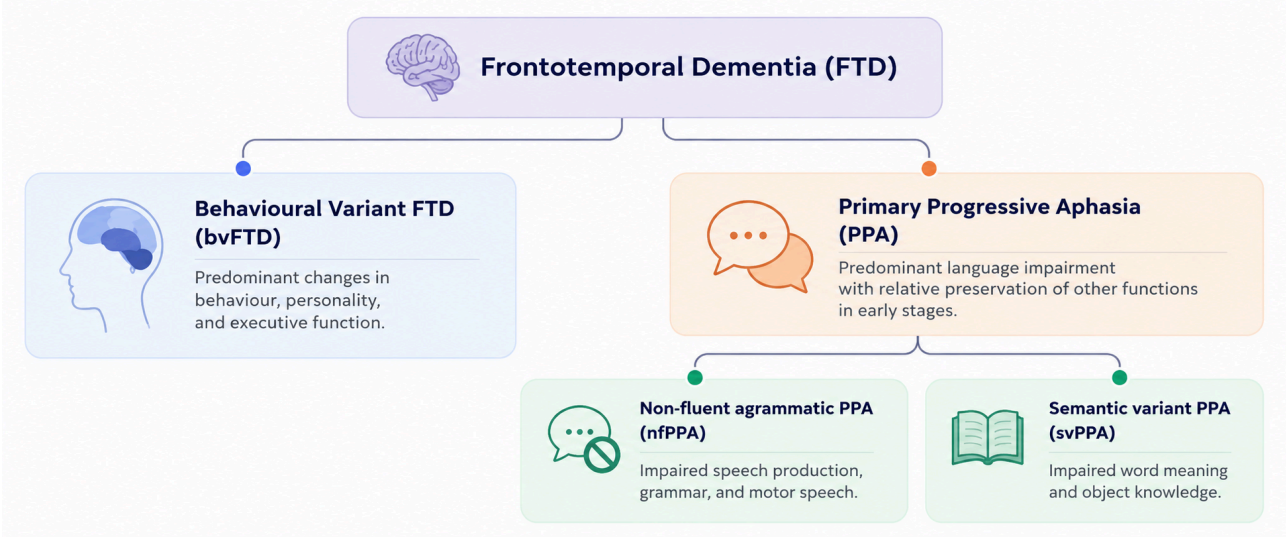


Figure 3: Subtypes of Frontotemporal Dementia

There are various neuropathological processes that can lead to FTD, with genetics playing an important role.[10] FTD can result from genetic mutations in C9orf72 (chromosome 9 open reading frame 72), MAPT (microtubule-associated protein tau) and GRN (progranulin), with C9orf72 being the commonest inherited cause of FTD-Motor Neuron Disease (MND).

The FTLD can result from various proteinopathies, including tau pathology, TDP-43 (TAR DNA-binding protein 43), FUS (fused-in sarcoma) or VCP (valosin-containing protein), with varying prevalence in the clinical syndromes according to these underlying pathologies.[10] These can also give risk to FTLD within Parkinson's plus syndromes, such as corticobasal degeneration and progressive supranuclear palsy.[10]

Dementia with Lewy Bodies

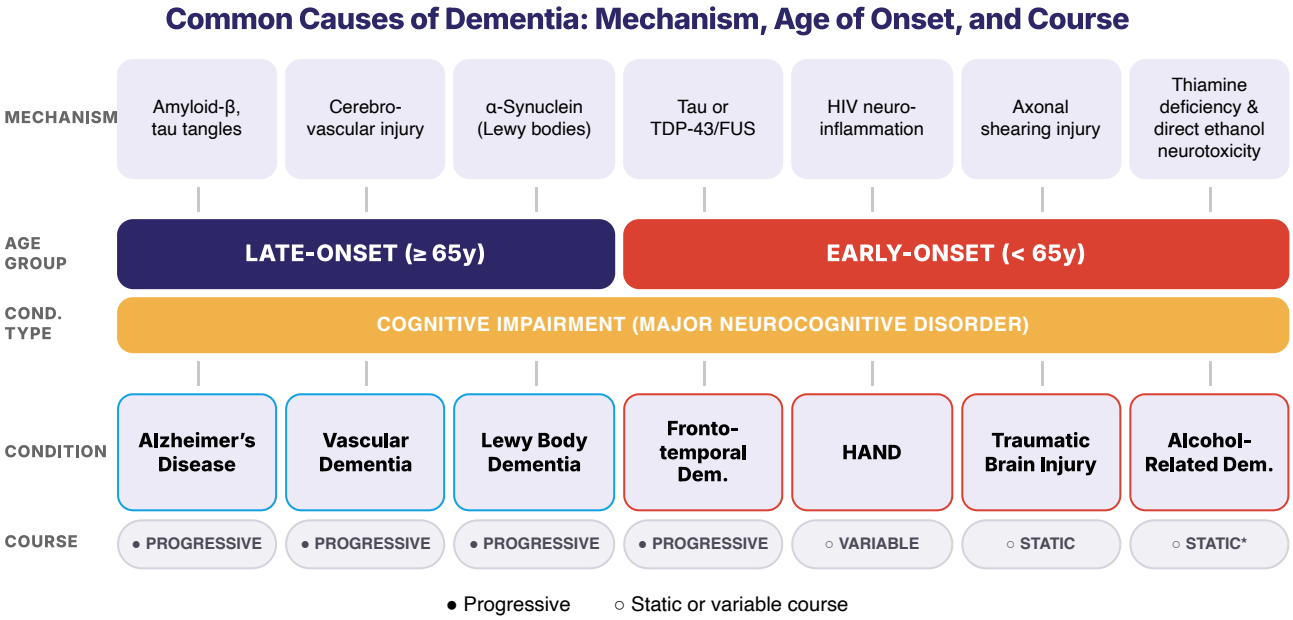
Dementia with Lewy Bodies (DLB) and Parkinson's disease dementia (PDD) lie on a pathological continuum.[23] The core feature of these dementias is α-synuclein neuronal inclusions, known as Lewy bodies.[24] Although α-synucleinopathy can be the singular pathology, it is often coexisting with amyloid β and vascular pathology in DLB.[24] According to the Fourth Consensus Report of the DLB Consortium,[25] the core features of DLB are fluctuating cognition, attention or alertness; recurrent, well-formed visual hallucinations; REM sleep behaviour disorder (RBD) and spontaneous parkinsonism requiring only of the three cardinal features – bradykinesia, rest tremor or rigidity.

Limbic-predominant age-related TDP-43 encephalopathy (LATE)

LATE is a recently described entity which affects older people and presents with an amnestic picture resembling Alzheimer's disease,[26] Its pathology – which typically involves the amygdala, hippocampus and middle frontal gyrus – is common in older brains, seen in nearly 25% of brains at autopsy in a community cohort.[27] The pathogenesis and clinical picture of this condition, and its status in relation to Alzheimer's disease and frontotemporal dementia, are only beginning to be understood.

Summary of select subtypes

See below for a summary of the core mechanisms of dementia subtypes according to age of onset (Figure 4) and their presentations and biomarkers (Box 2).



*Static if abstinent from alcohol. HAND = HIV-Associated Neurocognitive Disorder. Both Alzheimer's disease and vascular dementia can also present with early onset (<65y), though they are more common later in life.

Figure 4: Common causes of dementia: mechanism, age of onset, and course. (Claude for Mac v1.40609, Aug 2026)

Box 2: Subtype pathophysiology, presentation, and biomarkers

Subtype	Pathophysiology	Presentation	Potential Biomarkers[28]
AD	Dual proteinopathy (amyloid and tau), with microglial and neuroinflammatory roles.	Learning and memory (typically amnestic) and language. Possible atypical presentations e.g. Posterior cortical atrophy or frontal subtypes	**CSF:** amyloid β1–42, amyloid β1–40, phosphorylated tau 181 and 217, and total tau; NfL and GFAP. **Plasma:** phosphorylated tau 181 and 217 **Supportive imaging:** MTA atrophy on MRI, amyloid-PET
VCID	Subcortical ischaemic vs strategic infarct vs multi-infarct	Processing speed, executive function, memory (strategic retrieval)	Only **non-specific markers of brain injury**, particularly raised in acute injury: NfL, tau and GFAP. **Supportive imaging**: significant stroke/s, extensive small vessel disease
FTD	Tauopathy, TDP, FUS	Three clinical syndromes: bvFTD, nfPPA, svPPA	**Plasma:** potential for p-TDP-43 **Genetic markers:** e.g. C9orf72 **Supportive imaging:** 18-FDG-PET and MRI show hypometabolism/atrophy in frontal and temporal lobes, but variation

DLB	Alpha-synucleinopathy, often with mixed disease	Marked cognitive fluctuations, spontaneous parkinsonism or severe neuroleptic sensitivity, visual hallucinations, REM sleep behaviour disorder, non-motor signs (constipation, anosmia, autonomic symptoms)	**CSF:** potential for α-synuclein seed amplification assays **Supportive Imaging:** 18-FDG-PET (e.g. cingulate island sign), DAT-PET **Others:** Low uptake on MIBG myocardial scintigraphy; RBD on polysomnography; posterior slow wave activity and periodic fluctuations in the pre-alpha and theta range on EEG[25]

Presentation and Course of Illness

Dementia may present with symptoms across the range of neuropsychiatric clusters, with presentation depending on disease stage, patient related factors, and their sociocultural context, including the context of their roles in the home environment and whether they are employed.

At their core, dementias are cognitive syndromes and presentation will most commonly include a history of these cognitive difficulties, such as misplacing items, forgetting conversations, and word-finding difficulties. Difficulties with executive function and social cognition are often more challenging for the person to identify in themselves and can benefit from collateral information. History may, however, be unreliable in the case of estrangement from family or limited recent contact.

Neuropsychiatric symptoms, such as apathy or depression, can result in increasing withdrawal and mood changes, which could prompt family to facilitate help-seeking. New onset mental health symptoms in later life should be considered a flag for a possible neurodegenerative process.[29] Similarly, destabilisation of a well-controlled mental disorder should prompt further enquiry.

Dementia presentation and course may be variable between individuals even within the same subtype. In general, AD tends to be insidious in onset, and progress gradually and slowly. Late-onset AD progresses through the preclinical stages in about 10 years, prodromal stages (MCI) in about 4 years, and dementia to death in about six years.[13] Course may have marked steps with pure or mixed VCID or if there are other brain insults, such as falls with head injuries or delirium episodes due to a urinary tract infection.

History alone is not enough to rule in or rule out a vascular component to the dementia. Many older people may have a degree of small vessel disease in their brains that is visible on modern neuroimaging, which needs to be differentiated from a significant cause of their presenting dementia syndrome. VCID can also be of insidious onset and gradual progression in the case of subcortical ischaemic vascular dementia (SiVaD),[30] but has a different clinical phenotype on the neurological examination and cognitive profile (more marked in working memory and executive function.

Assessment and Diagnosis

The assessment of patients with possible dementia depends on context and will be practically different in low-resource and high-resource settings. Irrespective of setting clinical assessment is the foundation of the diagnosis.

Clinicians should explore baseline educational and functional levels, the onset and course of the symptoms, and potential for temporal relation to any other potential brain insult or changes in psychosocial context. Changes to their level of function are indicated through exploring instrumental activities of daily living (such as through increasing compensation or loss of function in their work tasks, or managing finances, shopping, and driving) or as the condition progresses, basic activities of daily living (such as dressing, washing, and continence).

A thorough history includes gathering information from patient and ideally, their care partner that will help to formulate a working diagnosis, as well as appropriately assess risk to and by the person. Medical history would include the presence of potentially modifiable risk factors. While vascular risk factors do not equate to a diagnosis of vascular dementia, as these also occur in AD and other dementia subtypes, their treatment should be optimised. Risk may be particularly influenced by fall risk and frailty, suicidality, psychotic symptoms, interpersonal vulnerability, and their financial and legal situation. Assessment may specifically need to explore their current ability to work, driving capacity, financial capacity, and testamentary capacity.

A focussed but considered neurological examination is essential. This would help to identify if there is significant cerebrovascular disease that could be resulting in a VCID, as well as identifying neurodegenerative conditions, such as Parkinson's plus syndromes. In particular, key components to take note of include focal neurological signs that would suggest upper motor neuron fallout (e.g. abnormal power, tone, or plantar response), subtle parkinsonism, abnormal gait, eye signs (nystagmus and vertical gaze palsy), and frontal release signs (including grasp reflex). Cardiovascular examination should take particular note of the pulse rate and blood pressure.

Red flags for further investigation into rarer neurodegenerative conditions or other reversible causes may include:

- Atypical course
    - Early onset
    - Acuity of onset
    - Rapid progression
    - Fluctuating or episodic course

- Neurological signs and symptoms
  - Abnormal neurological exam e.g. abnormal movements, parkinsonism
  - Falls, particularly backwards falls due to postural instability
  - Significant autonomic dysfunction
  - Gait disturbance
  - Early incontinence
  - New onset seizures
- Family history
  - Autosomal dominant pattern of inheritance
  - Other neurodegenerative conditions, such as Parkinson's disease or MND
- Potential signs and symptoms of other causes of cognitive impairment
  - Unexplained/severe weight loss or other clinical suspicions for cancer
  - Signs of malnourishment
  - New onset headaches
  - Significant mood component
  - Other functional neurological symptoms

Cognitive testing should be conducted in the clinical assessment through brief bedside/office cognitive tests, unless the severity or clinical condition renders the patient relatively untestable. These tools may include the Mini-Mental State Examination (MMSE),[31] Montreal Cognitive Assessment (MOCA),[32] Addenbrooke's Cognitive Examination (ACE),[33] Frontal Assessment Battery (FAB),[34] and International HIV Dementia Scale (IHDS).[35] Formal and in-depth neuropsychological testing may be indicated and is often more beneficial earlier on in the disease process.

Assess for neuropsychiatric conditions includes a systematic enquiry about behavioural and psychological symptoms of dementia (BPSD), their triggers, their intensity, and the distress they cause in the patient and their care partners. The first step in managing BPSD is conducting a proper assessment of the behaviour, such as through the framework, BPSD-DATE (Figure 5)[36]

Neuropsychiatric symptoms can include apathy, agitation, aggression, anxiety, depression, mood lability, sleep disturbances, eating disturbances, compulsions, hallucinations, and delusions. The Neuropsychiatric Inventory – Caregiver Distress Scale is a useful measure to explore the presence of these symptoms and how they are impacting the care partner.[37]

Collateral information of withdrawal, significant tearfulness or irritability can raise suspicion for depression. However, differentiating apathy from depression is needed to guide management decisions, with symptoms of low mood, guilt, and thoughts of death helping to make a diagnosis of depression.[38]

Paranoia can occur in the context of memory lapses (misplaced items being stolen), and assessment should determine the severity and the context of paranoia and hallucinations, including how distressing or behaviourally problematic these are, or if these are well-systematised and fixed.

The presence of significant neuropsychiatric symptom burden should trigger diagnostic consideration, as differentiating a neurocognitive disorder from a suspected or established primary psychiatric disorder can, at times, be challenging. Functional cognitive impairment through significant

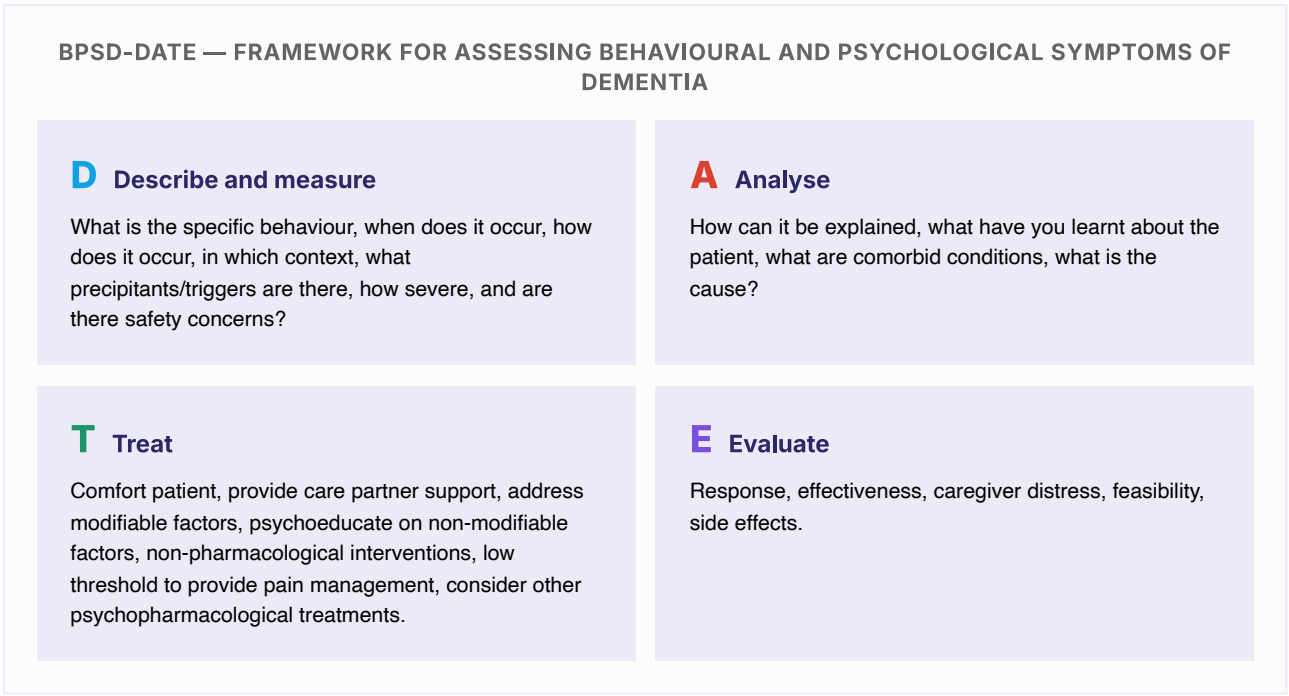


Figure 5: framework for assessment of BPSD using BSPD-DATE[36]

anxiety or depression ('pseudodementia'), or a functional cognitive disorder, can mimic a dementia presentation. Cognitive symptoms in these conditions typically have internal inconsistency and result from dysregulated attention.[39]

People with psychiatric conditions do have higher rates of dementia, including those with depression, bipolar disorder and psychotic disorders.[40] As a result, neuropsychiatrists will often be asked to help assess for dementia in the course of primary psychotic disorders, such as schizophrenia. In schizophrenia, cognitive impairment is present early in the disorder and does not necessarily progress faster than the ageing process over the life course.[41] However, with this lower cognitive baseline and the health and lifestyle factors that are commonly comorbid in primary psychotic disorders, there is a higher risk for developing dementia.[41] Late-onset psychiatric presentations should appropriately treated and closely monitored for emergence of a dementia syndrome.

Another common clinical challenge in neuropsychiatry is assessment of cognitive impairment in the context of significant alcohol use. A sustained period of sobriety over at least three months helps to elucidate if there is a reversible component to the conditions, but diagnostic clarity often requires ongoing monitoring to determine if there is progression.

Excluding the reversible causes of dementia is of utmost importance, as these treatment of these mimickers may dramatically improve symptoms and function. Often, these can precipitate the emergence or progression of cognitive symptoms in a patient with underlying vulnerability in their brain, such as through prodromal AD or a dysexecutive MCI from vascular pathology.

Investigations

While dementia is fundamentally a clinical diagnosis and syndrome, there have been significant advances in the evidence and availability of biomarkers. Investigations serve three purposes: to support or confirm pathology, to exclude other causes of cognitive

impairment, and to provide baseline investigations before starting treatments. The exact investigations will depend on clinical context, availability, and affordability.

Suggested basic workup for dementia

Blood workup

- Full blood count; Haemoglobin level
- Sodium and electrolytes
- Renal function: urea and creatinine
- Liver function tests
- Thyroid function: TSH
- Vitamin B12
- Calcium
- HIV
- Syphilis screen
- Fasting glucose and HbA1c
- Total cholesterol and full lipid profile

Urine

- Dipsticks ± culture

Imaging

- Chest X-Ray (particularly if smoking history)
- Strong consideration of structural imaging (CT Brain or MRI Brain)

Cerebrospinal fluid

- If there is suspicion for inflammatory or infectious disease process (e.g. autoimmune encephalitis): cells, protein, IgG CSF:serum index, syphilis screening, autoimmune encephalitis panels, and others as indicated.

Biomarkers

For some dementias, there are neuroimaging biomarkers, CSF biomarkers, and blood biomarkers (Box 2). For AD, CSF biomarkers include amyloid β1–42, amyloid β1–40, phosphorylated tau 181, and total tau. Highly sensitive plasma panels now are able to identify plasma phosphorylated tau 181 and 217.[13]

There are some additional biomarker modalities in the case of DLB.[25] These include on MIBG myocardial scintigraphy, which can show low uptake and abnormal cardiac sympathetic innervation, polysomnography, which can demonstrate REM Sleep Behaviour Disorder (RBD), and EEG can show prominent posterior slow wave activity and periodic fluctuations in the pre-alpha and theta range.

Neuroimaging

For a detailed understanding of the different neuroimaging modalities, see Chapter 4.

Structural imaging of the brain, through MRI or CT will depend on setting and the purpose of the investigation. While MRI is considered the gold-standard for assessing dementia, CT scans can often provide a pragmatic second best to visualise the brain and ensure no gross abnormalities are missed. Functional imaging may be considered, such as with FDG-PET or other radioisotopes. Hypometabolism in certain patterns can occur prior to the development of atrophy, such as with frontotemporal hypometabolism in FTD or temporoparietal hypometabolism in AD.

In assessing AD, structural neuroimaging typically shows cerebral atrophy, predominantly of the temporoparietal cortex and the hippocampus. Medial Temporal Atrophy (MTA) is a radiological scale from 0-4 suggesting progressively more significant atrophy of the hippocampus and can be supportive of a diagnosis of AD. It is visualised on coronal section at the level of the anterior pons where the cerebral peduncles come together (Figure 6). Variants of AD may have different presentations and atypical patterns of atrophy, including frontal variant AD, Posterior Cortical Atrophy (PCA), and logopaenic PPA.

Where there is potential for anti-amyloid treatments or diagnostic uncertainty, the amyloid burden can be quantified through amyloid PET imaging. Amyloid PET, FDG-PET, and MRI are considered neuroimaging biomarkers in AD.[13]

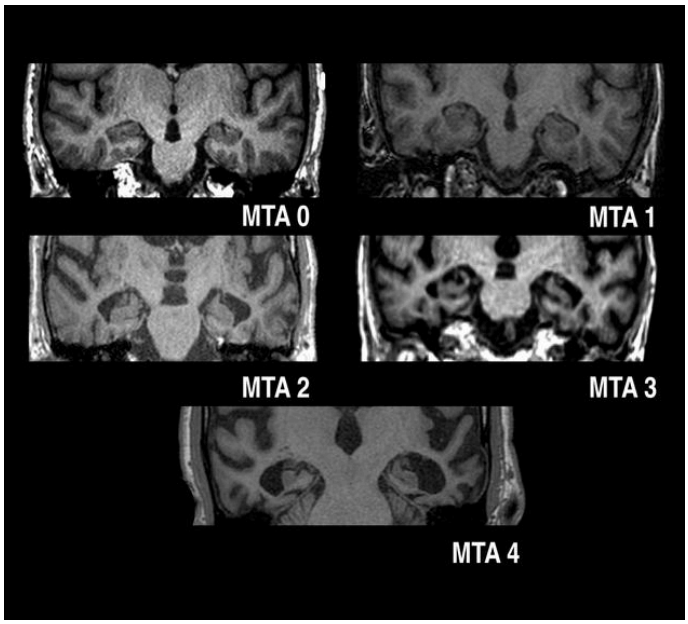


Figure 6 - courtesy of Di Muzio B, Medial temporal lobe atrophy score. Case study, Radiopaedia.org (Accessed on 12 Jul 2026) https://doi.org/10.53347/rID-42027

In assessing VCID, imaging should look for evidence of infarcts, lacunes, and microhaemorrhages, as well as the extent of the white matter pathology. Background atherosclerosis can also be seen. White matter pathology is described radiologically using the Fazekas scale, which summarises the size and confluence of lesions in the periventricular white matter and deep white matter (Figure 7).

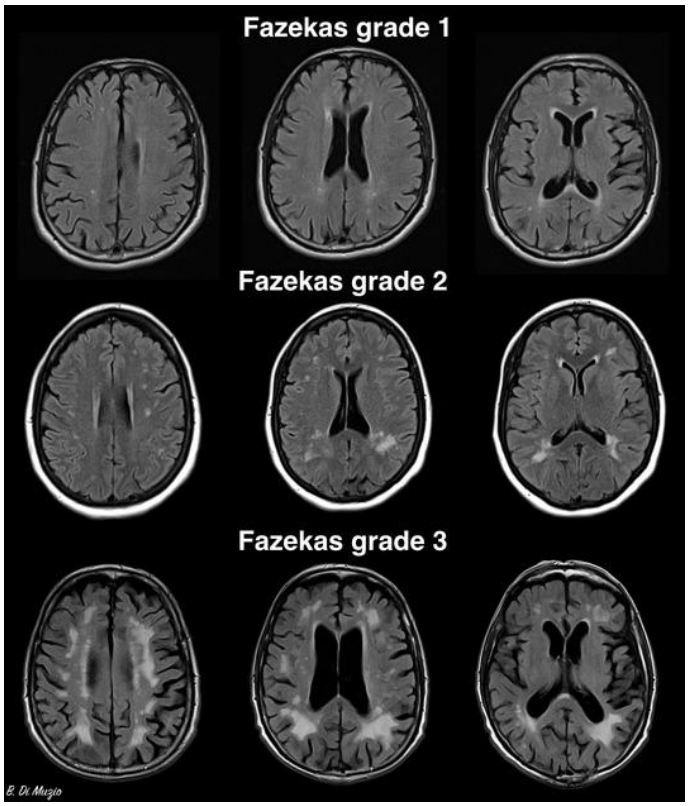


Figure 7 - courtesy of Di Muzio B, Fazekas scale for white matter lesions. Case study, Radiopaedia.org (Accessed on 12 Jul 2026) https://doi.org/10.53347/rID-36927

The following case is courtesy of Radiopaedia, with progressive impairment in short term memory, but preserved remote and autobiographical memory. Try to identify the MTA level on this coronal MRI image (Figure 8), and look through the linked scans of the coronal and T2 FLAIR sequences to try identify the pathology.

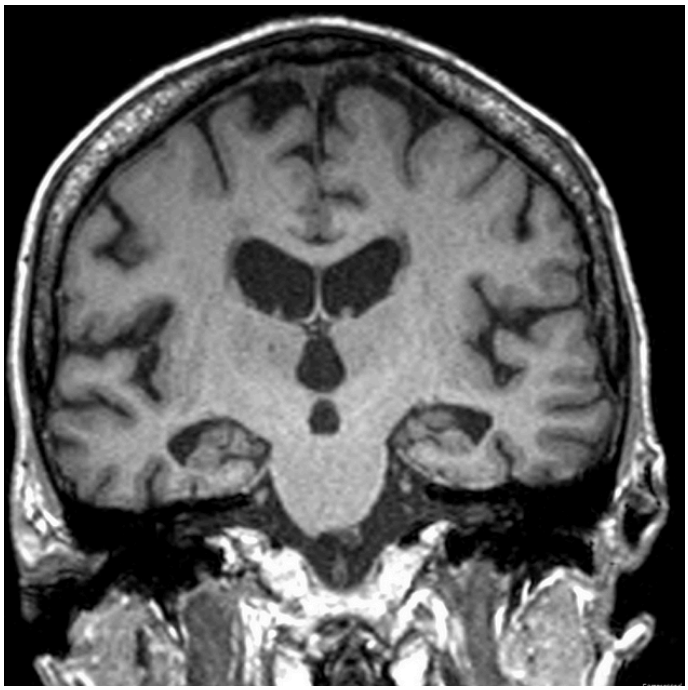


Figure 8 - Courtesy of Gaillard F, Alzheimer disease. Case study, Radiopaedia.org (Accessed on 12 Jul 2026) https://doi.org/10.53347/rID-22196

For DLB, CT and MRI are not particularly helpful in differentiating out the disease. Low dopamine uptake in basal ganglia can be demonstrated on functional imaging (PET or SPECT), which is an indicative biomarker. FDG-PET can show occipital hypometabolism in addition to the temporoparietal hypometabolism, which helps to differentiate it from AD in some cases. The cingulate island sign (preserved metabolism in posterior cingulate region compared to adjacent parietal and occipital lobes) can similarly help to differentiate as a supportive feature (Figure 9).

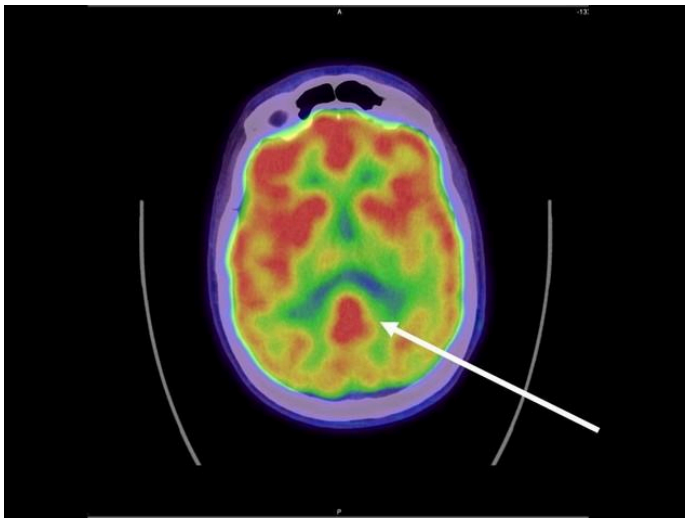


Figure 9 - Ayesa S, Cingulate island sign. Case study, Radiopaedia.org (Accessed on 01 Sep 2026) https://doi.org/10.53347/rID-93710

Neuropsychiatric aspects of treatment

Holistic management of AD and other dementias is patient-centred, individualised, and follows a biopsychosocial approach. Multidomain interventions, which address multiple components to health in the individual, have been used as early interventions to try prevent progression from prodromal conditions to dementia.[42] Multidisciplinary team members, such as occupational therapists, psychiatrists, psychologists geriatric physicians, dieticians, physiotherapists, and other colleagues all have roles to play at various points in their care.

Non-pharmacological management

A key management step is the initial counselling and psychoeducation. Due to the ubiquitous use of the term 'dementia', it is important to address the patient and care partner's understanding of this term and the meaning it carries. Clinicians may need to manage grief reactions and provide psychosocial support. Knowledge of local resources and non-governmental organisations can assist for initial and ongoing support.

The clinician, guided by the risk assessment, can help the patient and care partners explore options for the best environment for the patient's care and living arrangements. Care support, through community based services, such as community health workers and carers, can help the patient and family to cope in their home environment. Having health consultations and delivering interventions in the form of home based care can be considered in severe dementia or where there are mobility issues.

Fragmentation in families and communities can make creating a coherent social plan effortful, particularly if there is a history of relationship breakdown from premorbid personality styles and conflict. Having access to a skilled social worker is crucial and highly beneficial, although the entire MDT should have an active role in managing the psychosocial context of patients with dementia.

Future planning is best facilitated early on in the disease process while capacity is maintained, so that autonomy can be preserved where possible. Throughout assessment and management, the clinician should find opportunities to enhance autonomy and support self-efficacy, even in the context of established dementia. Mechanisms to protect patients who have lost their financial capacity to manage their estates, such as through curatorship, are often a source of tension and conflict, but may be required to manage risk.

Non-pharmacological treatments include appropriate cognitive and environmental stimulation to minimise the distress from overstimulation. This may include limiting visitor numbers at one time point, reducing competing stimuli (e.g. TV and conversation), and choosing appropriate timing for activities.

Motivational interviewing for substance use, such as for alcohol or smoking, should be an ongoing process, potentially with pharmacological support where indicated.

Management should involve encouraging movement and exercise, which has shown the potential to help prevent AD and dementias[43] through effects on amyloid β, inflammations, neurotrophins, and cerebral blood flow.[44] Additionally, exercise can have important psychological and social

benefits, including feelings of autonomy and competence, enhanced motivation, self-esteem, and improvement in social relationships.[45] For those with an established diagnosis of dementia, improving cardiorespiratory fitness would be associated with lower dementia mortality.[46] While evidence is mixed on the best exercise type and dose, multicomponent exercise is perhaps the most effective for preserving global cognition and executive function.[47]

Psychosocial interventions have been found to be effective in the management of BPSD.[48] Music therapy has evidence for anxiety and agitation in dementia[48] and is often recommended more broadly for other BPSD such as apathy.[38]

Apathy can be a challenge to manage, but is best managed behaviourally through structure, routine, and behavioural activation. Comorbid apathy and depression may benefit from a trial of an antidepressant. However, particularly with the potential for SSRIs to worsen apathy in some older individuals, these should be discontinued where ineffective.[38] There may be some improvement on apathy in AD with AChEi's, and there are some limited preliminary data on dopaminergic medications and psychostimulants in dementia.[49] The mainstay of treatment, however, is behavioural and psychosocial.

Supplementation

While patients often have interest in dietary supplementation, there is no substantial evidence at this stage. Vitamin E does not have convincing evidence of effect, but is low risk for harm.[50] While Omega 3 has had some preliminary evidence it can help prevent dementia, this has not translated into an evidence based therapeutic intervention for dementia.[51] Creatine monohydrate is gaining popularity for its established benefits in muscle strength and anti-frailty, but is unproven in terms of benefits for cognition in dementia.[52]

Pharmacological management

Particularly with the high medication burden that older people are often negotiating, the first step in pharmacological management is to review and rationalise current treatments. If possible, wean to stop all potential contributors to cognitive impairment, such as those with anticholinergic effects. Benzodiazepines contribute to fall risk and have been implicated in dementias, and where possible should be rationalised and stopped. Weaning these often chronic medications requires buy-in from the patient and appropriate counselling, together with a plan on how to manage the symptoms for which they were initiated. Management of vascular risk factors, but without overtreating blood pressure and blood glucose, is a key element of the treatment of dementias.

Cognitive enhancers

Acetylcholinesterase inhibitors (AChEi), such as donepezil and rivastigmine, can help combat the reductions in cholinergic activity associated with AD pathology. AChEi's are indicated in mild to moderate AD, having been shown to modestly slow decline in function. They are indicated in DLB or Parkinson's Disease Dementia, as well as in those with Vascular dementia that is mixed with Alzheimer's dementia. However, they

are not recommended in FTD. Prescription in amnestic MCI/mild NCD is debated and can be considered, but it does not convincingly prevent conversion to dementia.[2]

The most common side effects are gastrointestinal side (GI) effects, dizziness, and sleep related effects including vivid dreams or insomnia. Pulse checks are required to evaluate for bradycardia in all patients, which may be more common in conditions associated with autonomic symptoms, such as DLB. Severe or symptomatic bradycardia should warrant withholding the AChEi and seeking cardiology opinion.

Most patients tolerate donepezil at its standard starting dose of 5mg/day, with uptitration to the target dose of 10mg/day after a month. It is typically dosed at night, to ease GI side effects, but may be moved to the morning if dreams present a challenge. Side effects often abate with time. When tolerated, there is benefit in ongoing prescription even into advanced disease.

Memantine is a N-methyl-D-aspartate (NMDA) receptor antagonist, which aims to limit excitotoxic damage from pathologic overstimulation of glutaminergic neurons. It is indicated in moderate to severe AD from a cognitive indication. Additionally, there may be some modest benefits in agitation, delusions, and other neuropsychiatric symptoms. Although there is theoretical indication for prescription in earlier disease stages, there is no current evidence that this improves outcomes. It is considered at an earlier stage if AChEi's are not tolerated. Dosing is increased weekly by 5mg/day to its target dose of 10mg twice daily.

Anti-amyloid treatments

With the need for disease-modifying treatments, immunotherapies that target amyloid have developed. These include lecanemab and donanemab. While they have been shown to clear amyloid on functional imaging and modestly reduce progression in early cognitive decline, the extent of their risk-benefit impact remains contentious. With the risk of Amyloid Related Imaging Abnormalities (ARIA) like haemorrhages and oedema, together with the current lack of long term data, offering these medications should be done with a thorough informed consent process.

Other emerging treatments

There is a potential role for herpes virus vaccinations as a preventative strategy, with the growing evidence of the role that Herpes Simplex Virus 1 and Varicella Zoster Virus can play in AD, particularly among APOE ε4 carriers.[53] However, this is not currently established as a treatment option for those with dementia.

Managing common neuropsychiatric conditions

We recommend adopting good psychiatric principles of rational prescribing and deprescribing, starting low, going slow, and minimising the number of changes that are attempted simultaneously.

When prescribing in older age, there are additional pharmacokinetic considerations, such as the predicted reductions in kidney and liver function.

It is prudent to have a low threshold for treating depression, as it can impact function and quality of life. Common antidepressants to be considered include selective serotonin reuptake inhibitors (SSRIs) like citalopram or sertraline, which do not have significant anticholinergic symptoms like the tricyclics. Clinicians should consider the addition of a proton pump inhibitor if initiating SSRIs and there is bleeding risk. Mirtazepine can be attractive at low doses due to its potential to improve sleep, but daytime somnolescence can be a barrier. Serotonin noradrenaline reuptake inhibitors (SNRIs) can be useful in comorbid pain syndromes.

For mild or infrequent agitation, consideration of the cognitive enhancers or an SSRI like citalopram would be first line. If there is significant aggression, risk, or distress, atypical (second-generation) antipsychotics like risperidone or olanzapine can be considered. However, this medication class carries risk for increased all-cause mortality, with a hazard ratio of around 2, particularly within the first six months after initiating.[54] They are also associated with higher rates of hospitalisation and insitutionalisation.[55] However, there may be an indication bias present due to these medications being typically reserved for when there are significant behavioural challenges and potentially more severe disease.

Sleep is often a challenge that causes frustration for patients and care partners. It requires careful elucidation to determine the pattern of sleep, actual number of hours in bed and asleep, barriers to sleep, and explore for potential comorbid mental health conditions. Sleep hygiene and cognitive behavioural therapy for insomnia should be considered. Low risk pharmacological options such as melatonin and magnesium supplementation are reasonable first line agents. Other agents that could be considered are trazodone or low-dose quetiapine.

Care for the mental health of care partners is a fundamental component to management of neuropsychiatric symptoms in dementia. This includes appropriate psychoeducation and counselling, linking with local dementia resources, facilitating future planning discussions, and furthering their existing skills for managing cognitive impairment and behaviours that challenge.

Prevention

The evidence that the modification of lifestyle and other risk factors can slow cognitive decline and potentially delay the onset of dementia, or prevent it, is gradually accumulating. For most risk factors, the evidence comes largely from observational studies, although some controlled trials are also available. While individual factors – such as education, physical activity, and control of vascular risk factors – are important to address, it is the lifelong cumulation of risk that appears to be most potent. Multimodal interventions over long periods have therefore been investigated.

The best-known investigation is the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER Trial),[56] a 2-year multi-domain randomized controlled trial in which the active arm included dietary counselling, physical exercise, cognitive training, and vascular and metabolic risk monitoring. Over 24 months, the improvement in global cognition was 25% higher in the intervention group compared to the general health advice control group. The improvement was observed regardless of demographic and socioeconomic factors, and was also seen in people with genetic susceptibility (APOE*4 positive) to Alzheimer's disease. Long-term data from this trial, to explore whether the intervention did indeed prevent dementia, are not yet available.

While the FINGER trial generated much enthusiasm, two other large multi-domain trials, the Multi-domain Alzheimer Preventive Trial (MAPT) from France and the Dementia by Intensive Vascular Care (PreDIVA) from the Netherlands, were negative on their primary outcomes (respectively, cognitive decline and all-cause dementia). Sub-analyses of these trials, however, revealed that there was benefit in people with increased risk of dementia.

This highlighted the need for further research and resulted in the development of an international network of trials called the World-Wide FINGERS (WW-FINGERS),[42] which encompasses 25 countries, including some LMIC. Some of the trials, such as the Maintain Your Brain Trial in Australia,[57] are completely online.

With the current evidence, it is reasonable to advise older people at risk of cognitive decline to implement the measures of controlling vascular risk factors, optimising their physical, mental and social activities, reducing stress, treating depression if present, and following a balanced Mediterranean-like diet. Indeed, it would be reasonable to argue that dementia prevention is a lifelong endeavour, the seeds of which are sown in childhood with good education and a nurturing environment.

Chapter Summary

- **Definition and Aetiology:** Dementia is a clinical syndrome of neurocognitive impairment that causes loss of independence in daily functioning. Disease subtypes include the progressive disorders of Alzheimer's Dementia (AD), Frontotemporal Dementia (FTD), and Dementia with Lewy Bodies (DLB).
- **Epidemiology:** Dementia prevalence is rising mainly due to population ageing, and is expected to triple by 2050, with 60% predicted to be in developing countries. Age is the most significant risk factor, with risk doubling every 5 years from 65 years old. AD causes up to 70% of late onset dementia (≥65 years old). Mixed pathology is common among older persons. In young people, causes are more diverse.
- **Pathophysiology:** *AD:* amyloid-β + phosphorylated tau → neurodegeneration, with microglial/neuroinflammatory involvement; APOE ε4 is an important genetic risk factor. *FTD:* Frontotemporal lobar degeneration due to tau, TDP-43 or FUS proteinopathies. C9orf72, MAPT and GRN mutations are important genetic causes. *DLB:* α-synuclein/Lewy body pathology.
- **Presentation and Course of Illness:** Any of the six cognitive domains can be affected in dementia, although most commonly learning and memory. AD has an insidious onset with gradual progression. VCID can be either acute and stepwise or insidious and gradual in its progression, but often with a characteristic neurological examination or dysexecutive neurocognitive profile. DLB classically presents with marked fluctuations in cognition, parkinsonism, visual hallucinations, REM-sleep behaviour disorder, and other supportive features. FTD can present in three clinical syndromes that affect behaviour and/or language.
- **Assessment and Diagnosis:** Clinical assessment is the foundation to making a dementia diagnosis, with understanding of the patient context, baseline, onset and course of symptoms, neurocognitive profile, and impact of the symptoms on function. Quality collateral is key. Assessment of the diagnosis, risk factors, neuropsychiatric symptoms, risk and safety guides treatment. Clinicians should conduct brief cognitive tests ± refer for full neuropsychological batteries. There should be clinical exclusion of delirium and reversible causes, including both medical and psychiatric.
- **Investigations:** Structural imaging, using MRI or CT, can identify atrophy patterns, vascular lesions, and alternate pathology. Functional imaging can provide further information, such as with 18-FDG-PET for hypometabolism or amyloid-PET for amyloid burden. Plasma and urine investigations exclude other reversible causes of cognitive impairment. Specific biomarkers are becoming available, now including plasma biomarkers such as plasma p-tau181 and 217 for AD.
- **Neuropsychiatric aspects of treatment:** Treatment should be through a holistic and person-centred biopsychosocial approach. This involves psychoeducation, caregiver support, supporting appropriate autonomy, and future planning. Physical activity, music therapy, and other modalities may be helpful. Clinicians should adopt rational prescribing and deprescribing, and start low, go slow with pharmacological agents. Anticholinergics should be weaned and stopped where at all possible. Cognitive enhancers with AChEi's and memantine can be considered. Anti-amyloid treatments are still contentious but increasingly used. Antipsychotics should be reserved for severe presentations due to their mortality risks.

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